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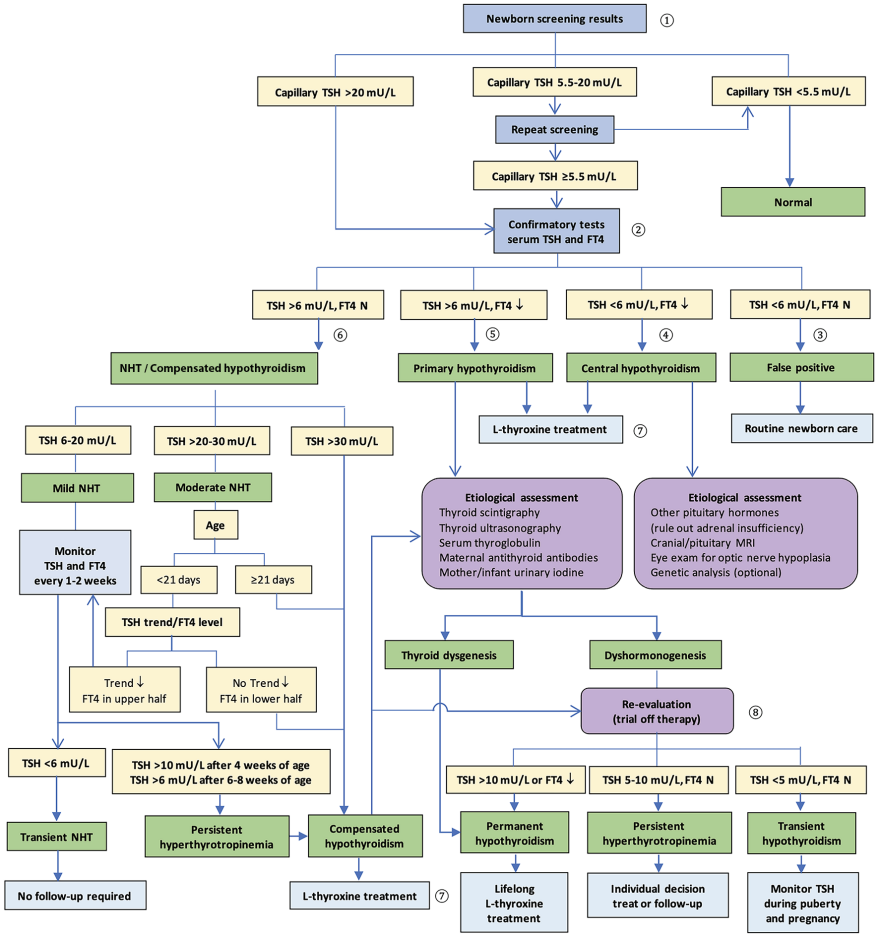

Approach to Newborns with Elevated TSH: A Different Perspective from the International Guidelines for Iodine-deficient Countries

Kara C and Korkmaz HA.

Page: 242-255

Official Journal of Turkish Society for Pediatric Endocrinology and Diabetes

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MANUSCRIPT PREPARATION

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What is already known on this topic?

What this study adds?

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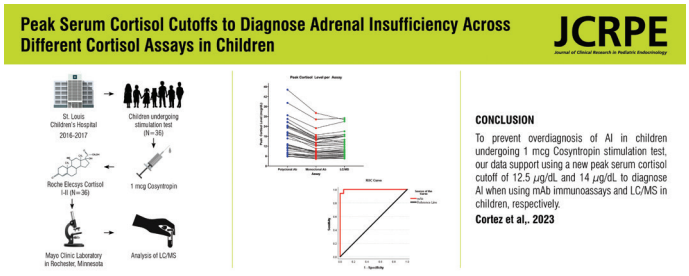

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Book Chapters: Darendeliler F. Growth Hormone Treatment in Rare Disorders: The KIGS Experience. In: Ranke MB, Price DA, Reiter EO (eds). Growth Hormone Therapy in Pediatrics: 20 Years of KIGS. Basel, Karger, 2007;213-239.

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FAREWELL

Dear Colleagues,

After serving for 17 years as Editor in Chief of the Journal of Clinical Research in Pediatric Endocrinology (JCRPE), the time has come for me to step down and pass the flag to the new Editor in Chief, Prof. Dr. Adullah Bereket.

It has been a great privilage and an honour for me in my academic career to initiate and to guide the development of JCRPE from its earliest days to its current standing position as a respected platform for scientific exchange in the field of pediatric endocrinology. When we started this journey, we had a vision to create a journal that would cover high quality research, increase collaboration and support clinicians in understanding and treating pediatric endocrine disorders. Thanks to the dedication of the authors who submitted their studies, reviewers, editorial board members and our readers - that vision became a reality.

I would also like to thank Galenos Publishing House that has supported us from the beginning and Jeremy Jones who has done a comprehensive work in the editing process.

I would like to express my special thanks to the Associate Editors who have worked very hard in continuing to increasing the high standards of JCRPE.

I am also deeply grateful to the many researchers, clinicians and international opinion leaders who supported us with their work, as well as to the peer reviewers whoso expertise made it possible to maintain our high standards.

Throughout these years, I have had the honour of witnessing the remarkable growth of our journal and the pediatric endocrinology community it serves.

I thank you all who made this possible with continuing support and commitment. Without the collective team work this would not have been possible.

As I step down, I know with confidence that the journal is in good hands and will continue to evolve with the needs of the international medical community.

I look forward to seeing JCRPE reach new milestones under Prof. Dr Abdullah Bereket's new leadership and I am proud to be part of its story and history.

Best Regards,

Feyza Darendeliler
Former Editor in Chief

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A NEW CHAPTER

It is with a great sense of honour and humility that I step into the role of Editor-in-Chief of the Journal of Clinical Research in Pediatric Endocrinology. It is a challenging mission for me to succeed Professor Feyza Darendeliler as Editor-in-Chief who drove the journal forward from the very beginning. JCRPE became one of the outstanding journals in Pediatric Endocrinology field under her visionary leadership.

I wish to express my sincere thanks to her for nearly two decades of dedication in guiding the JCRPE from its first issue to the excellent reputation it has today. We will continue to benefit her wisdom as she accepted to function as "honorary EIC".

I approach the role of EIC with gratitude for her and excitement for what lies ahead. My goal is to further develop the JCRPE as a unique and powerful platform for the European and the world-wide clinical research to strengthen expertise and visibility in key areas of Pediatric Endocrinology.

I am very fortunate to work with an established, excellent team of associate editors who are all committed to contribute to the successful development of JCRPE. I trust their continuing support in taking this responsibility.

I take this opportunity to thank also editorial board members, Galenos Publishing House, managing editorial staff and Jeremy Jones for their meticulous work for each article to be published and generous support of Turkish Society for Pediatric Endocrinology and Diabetes. Your contributions are greatly acknowledged, and I look forward to continuing our successful and pleasant collaboration.

Aside from that, we would not even exist without our esteemed authors and reviewers. So, I am excited about receiving more of your excellent pediatric endocrinology research articles to the JCRPE in the future, and I count on all clinicans/researchers to offer their valuable time acting as reviewers.

Although replacing someone who has founded and represented the Journal for so long is a major task, I believe that serving as an Associate Editor for years has prepared me to take over the EIC role, so the transition should go smoothly.

I am looking forward to working with all reserchers and clinicians in the field throughout the world to make JCRPE a truely global platform and a flagship journal in Pediatric Endocrinology.

Prof. Abdullah Bereket, MD

REVIEW

DOI: 10.4274/jcrpe.galenos.2024.2024-4-15

J Clin Res Pediatr Endocrinol 2025;17(3):242-255

Approach to Newborns with Elevated TSH: A Different Perspective from the International Guidelines for Iodine-deficient Countries

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Abstract

Lowering of thyroid-stimulating hormone (TSH) cutoffs in newborn screening programs has created a management dilemma by leading to more frequent detection of neonates with elevated TSH concentrations due to false-positive results, transient neonatal hyperthyrotropinemia (NHT), and milder forms of congenital hypothyroidism. Current consensus guidelines recommend starting treatment if the venous TSH level is >20 mU/L in the face of a normal free thyroxine (FT4) level, which is an arbitrary threshold for treatment decisions. In countries such as Türkiye, where transient NHT may be more common due to iodine deficiency (ID) and/or overload, putting this recommendation into daily practice may lead to unnecessary or over treatment, time-consuming long-term follow-up, and increased workload and costs. In this review, we addressed alternative approaches for infants with elevated TSH concentrations detected at newborn screening. The suggested management approach can be summarized as: Infants with mild NHT (venous TSH <20 mU/L) should be followed without treatment. In moderate NHT (venous TSH 20-30 mU/L), treatment or monitoring decisions can be made according to age, TSH trend and absolute FT4 level. Moderate cases of NHT should be treated if age at confirmatory testing is >21 days or if there is no downward trend in TSH and FT4 level is in the lower half of age-specific reference range in the first 21 days. In in-between cases of moderate NHT, thyroid ultrasound may guide treatment decision by determining mild cases of thyroid dysgenesis that require life-long treatment. Otherwise, monitoring is a reasonable option. Infants with compensated hypothyroidism (venous TSH >30 mU/L and normal FT4) or persistent hyperthyrotropinemia (>6-10 mU/L after the neonatal period) should receive L-thyroxine treatment. However, all treated cases of isolated TSH elevation should be closely monitored to avoid overtreatment, and re-evaluated by a trial off therapy. This alternative approach will largely eliminate unnecessary treatment of infants with transient NHT, mostly caused by ID or excess in Türkiye, and will reduce workload and costs by preventing unwarranted investigation and long-term follow-up.

Keywords: Congenital hypothyroidism, neonatal hyperthyrotropinemia, newborn screening

Introduction

Congenital hypothyroidism (CH) refers to thyroid hormone deficiency present at birth, resulting from an impairment of the thyroid axis at the hypothalamic-pituitary (central) or thyroid (primary) level. Primary CH occurs mainly due to developmental defects of the thyroid gland (dysgenesis) or insufficient thyroid hormone biosynthesis (dyshormonogenesis). Thyroid dysgenesis includes ectopy, athyreosis, orthotopic hypoplasia and hemiagenesis (1). Dyshormonogenesis refers to impaired biosynthesis of thyroid hormones in a normally located gland, usually with compensatory goiter (2). Resistance to thyroid-stimulating hormone (TSH) has a special place in the etiology of primary CH, with a phenotypic spectrum varying from severe hypothyroidism with hypoplastic thyroid to mild persistent hyperthyrotropinemia (PHT) with a normal-sized gland (3,4). Central CH is caused by defective stimulation of a normal thyroid gland by TSH due to hypothalamic or pituitary pathologies (5). Since isolated TSH deficiency

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is a rare condition, central CH occurs mostly as part of hypopituitarism (multiple pituitary hormone deficiencies). In addition, CH can be classified as permanent and transient. Permanent CH is a condition of thyroid hormone deficiency that requires lifelong treatment. Transient CH is a temporary deficiency of thyroid hormone production that recovers in the first few months or years of life (1,2). The classification and etiology of CH are given in Table 1.

The term "congenital hypothyroidism" was first introduced by Radwin et al. (6) in 1949 to describe children with severe intellectual disability and growth retardation due to hypothyroidism. In the early 1970s, Klein et al. (7) showed that clinical diagnosis and adequate treatment before three months of age could prevent mental retardation in children with CH, and then successfully implemented laboratory screening for CH, involving the determination of TSH in samples of cord blood (8). Anecdotally, Dussault and Laberge (9) developed a radioimmunoassay for the measurement of thyroxine (T4) on filter paper blood spots, and subsequently initiated the first neonatal mass screening for CH in Quebec in 1973 (10). The introduction of newborn screening programs (NSPs) enabled early diagnosis before the onset of clinical symptoms based on biochemical measurements of TSH and T4 (11). However, the gradual lowering of TSH cutoff levels over time by screening programs has led to the detection of mild cases that exhibit elevated serum TSH concentrations with normal peripheral thyroid hormone [T4 and triiodothyronine (T3)] levels. This condition has been termed compensated or subclinical hypothyroidism (SCH) (12,13,14,15,16). On the other hand, "isolated hyperthyrotropinemia" has been suggested as a more accurate term to describe elevated TSH levels in the presence of normal T4 levels, which does not reflect a true state of hypothyroidism (17,18). Thus, the terms SCH and hyperthyrotropinemia (isolated, neonatal, or persistent) are often used interchangeably (12,19). Herein, we refer to the state of low serum free T4 (FT4) levels as hypothyroidism (20). We believe that when FT4 levels are normal, severe TSH elevation (>30 mU/L for newborns) can be defined as compensated hypothyroidism (or SCH), requiring immediate treatment, whereas mild to moderate TSH elevation (6-30 mU/L for newborns) can be defined as isolated neonatal hyperthyrotropinemia (NHT). Considering literature data (21,22,23), we choose a TSH threshold value of 30 mU/L as the most inclusive definition for NHT given the conditions found in Türkiye, as will be discussed in detail below. No doubt, this definition of NHT includes mild compensated hypothyroidism that can spontaneously resolve during the neonatal period due to iodine deficiency (ID) or overload, but it expresses an approach in favor of the option of monitoring without treatment.

Current consensus guidelines recommend starting treatment if the venous TSH level is >20 mU/L in the face of a normal FT4 level, which is an arbitrary threshold for treatment decisions (14,15,16). Due to the lack of sufficient evidence, this recommendation is based on expert opinion and has the potential to lead to unnecessary treatments in cases of transient NHT. In countries such as Türkiye, where transient NHT may be more common due to ID and/or overload (24,25,26,27,28,29), putting this recommendation into daily practice may lead to unnecessary treatment, long-term follow-up, and increased workload and costs. Therefore, in this review, we propose an alternative approach for infants with elevated TSH on neonatal screening. To explain the reasons for this alternative approach, we will first discuss the national NSP data and current iodine nutrition status in Türkiye. Next, we focus on the issue of NHT as an unintended consequence of current NSPs. We then present a comprehensive algorithmic approach for the management of newborns with NHT and CH, taking into account both international guidelines (14,15,16) and regional conditions (24-44).

National NSP for CH in Türkiye

The Turkish Directorate of Public Health launched the national NSP for CH in December 2006 (30). In 81 provinces, more than 100 pediatric endocrinology clinics serve as reference centers and deal with the management of newborns referred from the NSP. At the beginning, the cutoff point for capillary TSH was 20 mU/L (serum equivalent). The capillary TSH cutoff value was reduced to 15 mU/L in 2008 and to 5.5 mU/L whole blood (equivalent to 12 mU/L in serum, assuming an average hematocrit of 55%) in 2013 (Table 2). In the current program, the heel-prick blood specimens are routinely collected on filter paper between days 3 and 5 of life. If capillary TSH is ≥20 mU/L whole blood in the first screening specimen, a venous sample is taken immediately for confirmation. When it is between 5.5 and 20 mU/L, a second heel-prick test is performed. A sample taken in the first 48 hours of life before hospital discharge was formerly defined as "early sample", and a new dried blood specimen was requested from these babies (30). However, these early samples were stopped in 2015 due to the high costs and increased workload (31). If capillary TSH is ≥5.5 mU/L for repeat samples, the newborn is recalled for confirmatory tests (Figure 1). The decision whether to treat the babies and to perform further diagnostic tests are at the discretion of the clinician at the referral center.

Although this program has largely eliminated cases of severe mental and growth retardation due to CH, it has also led to the detection of many mild or transient cases

Table 1. Classification and etiology of congenital hypothyroidism

Permanent congenital hypothyroidism

1. Primary hypothyroidism
 a) Thyroid dysgenesis: ectopia, athyreosis, hypoplasia, hemiagenesis
  i) Familial or genetic (2-5% of dygenesis cases): syndrome or associated features
   (1) NKX2.1: Brain-lung-thyroid syndrome (respiratory distress, choreatetosis)
   (2) FOXE1: Bamforth-Lazarus syndrome (cleft palate, chonal atresia, spiky hair)
   (3) PAX8: Hypoplasia, genitourinary anomalies (rare)
   (4) GLIS3: Athyreosis, neonatal diabetes, cystic kidneys, cholestasis
   (5) NKX2.5: Athyreosis/ectopy, congenital heart malformations
   (6) JAG1: Hypoplasia/ectopy, Alagille syndrome type 1
   (7) CDC8 (BOREALIN): Ectopy, athyreosis, hemiagenesis
   (8) NTN1 (Netrin1), TUBB1 (Tubulin1): Ectopy
  ii) Sporadic (95-98% unknown etiology)
 b) Dyshormonogenesis: impaired hormone production (±goiter) due to defects in
  i) Iodide uptake by sodium-iodide symporter (NIS-SLC5A5)
  ii) Iodide transport from follicular cell into colloid
   (1) SLC26A4 (PDS): Pendred syndrome (deafness with goiter)
   (2) SLC26A7: Normal hearing
  iii) Iodide organification by TPO
  iv) Hydrogen peroxide generation
   (1) Dual oxidase 2 (DUOX2) or activator/maturation factor 2 (DUOXA2)
   (2) Dual oxidase 1 (DUOX1) or activator/maturation factor 1 (DUOXA1)
  v) Thyroglobulin synthesis (TG)
  vi) Deiodination by iodotyrosine deiodinase/dehalogenase (IYD-DEHAL1)
 c) TSH resistance
  i) Defect in TSH receptor (TSHR): Normal-sized thyroid to severe hypoplasia
  ii) Defect in G-protein signalling (GNAS): Pseudohypoparathyroidism type 1a
 d) Syndromic primary hypothyroidism (usually with normal thyroid morphology)
  i) TBX1: Di George syndorme
  ii) ELN: Williams-Beuren syndrome
  iii) DYRK1A: Down syndrome
  iv) SALL1 (Townes-Brocks), URB1 (Johanson-Blizzard), KMT2D, KDM6A (Kabuki)

2. Central hypothyroidism
 a) Secondary (pituitary) hypothyroidism
  i) Isolated TSH deficiency (TSHβ): Low TSH, pitutary hyperplasia
  ii) TRH receptor resistance (TRHR): Low TSH and prolactin
  iii) Combined pituitary deficiencies (HESX1, LHX3, LHX4, PIT1, PROP1, SOX3, OTX2)
 b) Tertiary (hypothalamic) hypothyroidism
  i) IGSF1: X-linked, low TSH/prolactin, delayed puberty, postpubertal macroorchidism
  ii) TBLX1, IRS4: X-linked, inappropriately normal TSH, sensorineural deafness
  iii) Combined pituitary deficiencies (LEPR, PROK2, FGF8, FGFR1, SOX2, CHD7)

Transient congenital hypothyroidism

1) Primary hypothyroidism
 a) Maternal iodine deficiency (endemic goiter)
 b) Maternal and neonatal iodine exposure
 c) Maternal antithyroid medications (methimazole, propylthiouracil)
 d) Maternal TSH receptor-blocking antibodies
 e) Genetic defects *(DUOX2, DUOXA2, TPO)*

2) Central hypothyroidism
 a) Maternal hyperthyroidism
 b) Prematurity (particularly <27 weeks of gestation)
 c) Drugs: Dopamin, steroids

TPO: thyroid peroxidase, TSH: thyroid-stimulating hormone, FT4: free thyroxine, NHT: neonatal hyperthyrotropinemia

of CH and NHT (27,29). The first published data from the national NSP in Türkiye showed very high incidence rates of possible CH at birth (1:888 in 2008, 1:592 in 2009 and 1:469 in 2010). The recall rates were also high, ranging from 1.9% in 2008 to 3.8% in 2010 (30). However, regional and nationwide studies have shown that more than half of the CH cases were transient (27,29). According to the 2014 NSP data, 7.2% of 1,270,311 newborns screened after 48 hours of life had a capillary TSH level above 5 mU/L (31). This rate was 40.6% among 660,946 newborns screened within the first 48 hours after birth. While the authors emphasized justifiably that mild ID was an ongoing problem in Türkiye [see Table 3 for assessment of iodine status according to World Health Organization (WHO) criteria], these data revealed the existence of a much greater problem for pediatric endocrinologists: tens of thousands of newborn

Table 2. Changes in TSH cutoff values in the Turkish National NSP

Starting date	Borderline TSH cutoff†	High TSH cutoff†	Reporting unit*
December 2006	20 mU/L	50 mU/L	Serum
July 2008	15 mU/L	50 mU/L	Serum
February 2013	5.5 mU/L	20 mU/L	Whole blood*

†When TSH level is between the borderline and high cutoff points, screening is repeated. When TSH level is above the high cutoff or repeat screening is abnormal, venous sampling is performed for confirmatory testing.
*Filter-paper TSH screening results can be reported per unit of serum or whole blood. Serum equivalent is calculated as 2.2 times the whole blood TSH value, assuming an average hematocrit of 55% for the first days of life. Therefore, a borderline TSH cutoff of 5.5 mU/L whole blood is equivalent to 12 mU/L in serum.
NSP: newborn screening program, TSH: thyroid-stimulating hormone

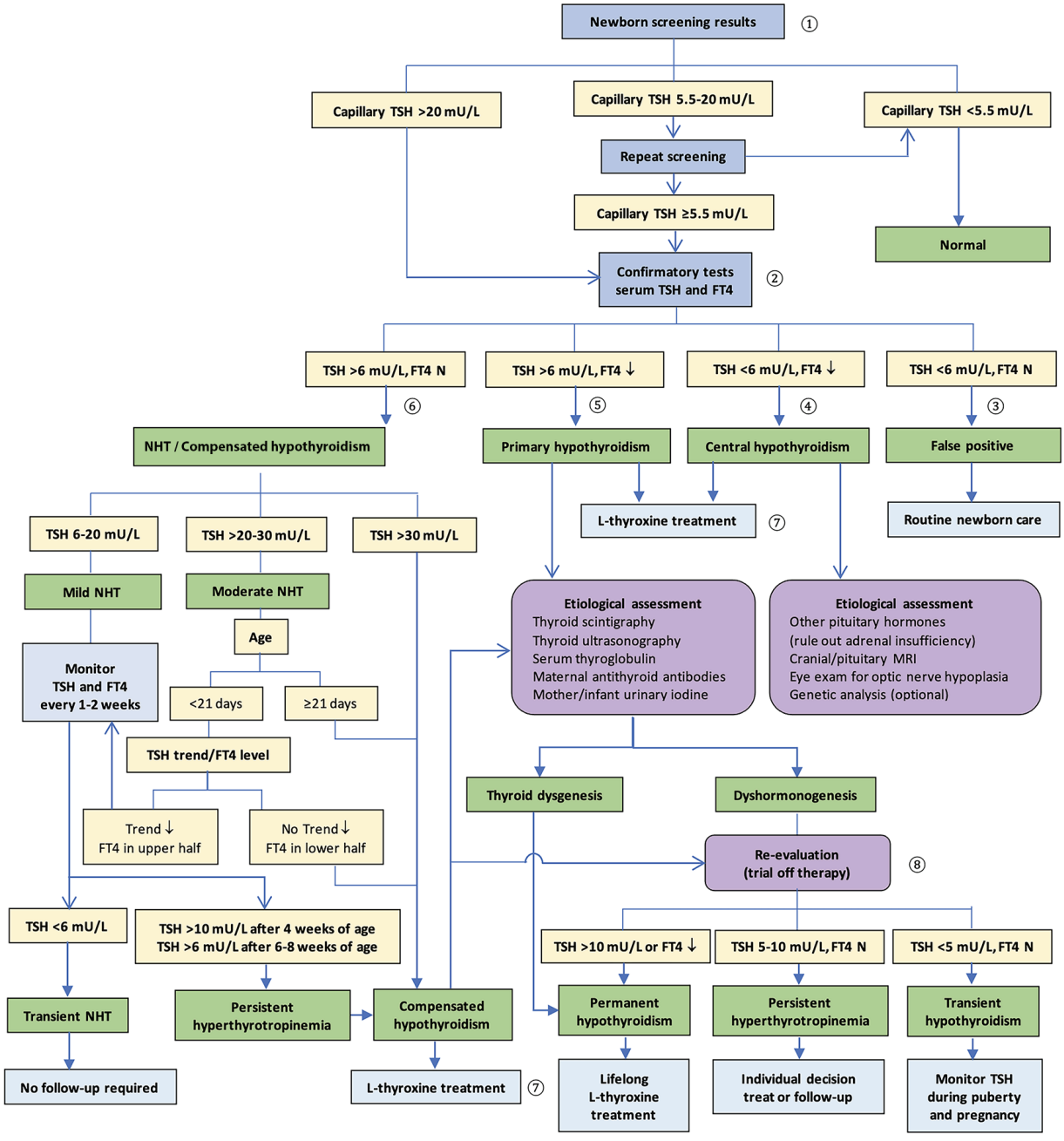

Figure 1. The approach to an infant with TSH elevation on newborn screening (numbers 1 to 8 in the flow diagram refer to the subheadings under the title "An Alternative Approach to the Infants with Neonatal TSH Elevation")

TSH: thyroid-stimulating hormone, FT4: free thyroxine, NHT: neonatal hyperthyrotropinemia

babies are referred to outpatient clinics due to elevated TSH levels. Therefore, an important question was raised: how should we manage newborns with elevated TSH detected by NSP using the low TSH cutoff level of 5.5 mU/L in an iodine-deficient country?

Iodine Problem in Türkiye

WHO and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) recommend four methods for assessing and monitoring iodine intake in a population: urinary iodine concentration (UIC), goiter prevalence, serum/dried blood thyroglobulin and neonatal TSH levels (45,46). Table 3 shows the epidemiological criteria for assessing iodine status based on WHO/ICCIDD recommended indicators in target populations, including school-age children (SAC), pregnant women and newborn infants. The key data from studies of UIC in various target populations in Türkiye are given in Table 4. UIC data for schoolchildren and pregnant women in Table 4 will be discussed together with screening TSH data for newborns.

The largest pilot study on neonatal TSH screening in Türkiye was conducted in the early 1990s. When the TSH cutoff was 20 mU/L whole blood, the recall rate and CH incidence were reported as 2.3%, and 1/2736 live births, respectively (32). The high prevalence of elevated TSH levels was attributed to endemic ID in Türkiye. Another regional study found that the incidence of CH at birth was 1/840 using a TSH cutoff of 20 mU/L (37). After the exclusion of transient CH cases, the incidence of permanent CH was 1/2354. The major causes of transient CH are ID and iodine excess (37). The studies by Erdoğan et al. (34) and Erdoğan et al. (35) on goiter prevalence and UIC in SAC before 2000 reported that Türkiye was a moderately ID country, with some severely affected regions (Table 4), which confirmed the data obtained from the previous studies of neonatal TSH screening (32,37).

For correcting ID in Türkiye, a salt iodization program was initiated in 1968 on a voluntary basis. Legislation for mandatory iodization of table salt was passed in 1998, and strictly enforced in 2000. The use of iodized salt corrected ID within a decade in SAC representative of the general population (39), but mild ID persisted in vulnerable groups of the population, such as pregnant women, lactating mothers, and newborn babies (25,26,28,36,38,41,42,43). As noted above, the national NSP data indicate that an ID problem continues (30,31) despite improved iodine intake among the SAC in Türkiye (Table 4) (39,44). A study by Oguz Kutlu and Kara (25) focusing on iodine intake of pregnant women explained the reason for the discrepancy between neonatal TSH levels and UICs in SAC, both of which are indicators of iodine status at the population level (Table 3) (45,46). This study showed that pregnant women living in Ankara, an apparently iodine-sufficient capital city, had a high prevalence of goiter (15%) and a low median UIC (80.5 µg/L), indicating insufficient iodine intake (25). These interesting data demonstrated that iodine nutritional status of SAC does not reflect the iodine supply for pregnant

Table 3. Epidemiological criteria for assessing iodine nutrition of a population based on WHO/ICCIDD recommended indicators (45,46)

Iodine intake	Iodine status	Median UIC (µg/L)	Total goiter rate (%)	Thyroglobulin (ng/mL, DBS)	TSH > 5 mU/L whole blood
School-age children (≥6 years)*					**Newborns**
Insufficient	Iodine deficiency	< 100	≥5	> 40	≥3%
Severity of public health problem	Mild iodine deficiency	50-99	≥30		3-19.9%
	Moderate iodine deficiency	20-49	20-29.9		20-39.9%
	Severe iodine deficiency	< 20	5-19.9		≥40%
Adequate	Adequate iodine nutrition	100-199	< 5	4-40	< 3%
Above requirements	More than adequate†	200-299			
Excessive	Excessive‡	≥300			
Pregnant women**					
Insufficient	Iodine deficiency	< 150			
Adequate	Adequate iodine nutrition	150-249			
Above requirements	More than adequate	250-499			
Excessive	Excessive‡‡	≥500			

*Applies to adults, but not to pregnant and lactating women.
**For lactating women and children < 2 years of age a median UIC of 100 µg/L can be used to define adequate iodine intake, but no other categories of iodine intake are defined. Although lactating women have the same requirement as pregnant women, the median UIC is lower because iodine is excreted in breast milk.
†Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk of more than adequate intake in the overall population.
‡Risk of adverse health consequences including iodine-induced hyperthyroidism, autoimmune thyroid diseases.
‡‡The term "excessive" for pregnant women means in excess of the amount required to prevent and control iodine deficiency.
DBS: dried whole blood spots, ICCIDD: International Council for Control of Iodine Deficiency Disorders, TSH: thyroid-stimulating hormone, UIC: urinary iodine concentration, WHO: World Health Organization

women. The finding of inadequate iodine nutrition in pregnant women and their offspring was later confirmed in national, multicenter, and large-scale studies (28,42,43).

Although the use of iodized salt in the Turkish population has reached adequate (≥90%) levels (Table 4), salt intake alone has not been enough to meet the increased iodine requirement in pregnant women. Possible reasons for this might be inadequate iodine content of table salts, erroneous consumption of iodized salt, and/or insufficient salt intake. In fact, a surveillance study revealed that only 56.5% of salt samples at the home level had adequate (>15 ppm) iodine content (39), which was well below the minimum target level of 90% recommended by WHO/ICCIDD (46). Another study focusing on the knowledge, attitudes, and behaviors of pregnant women regarding iodized salt consumption found that only 19% stored iodized salt appropriately in lightproof containers and that only 16% added iodized salt properly after cooking into the stewpot or their plate (38). Even if the women correctly consumed adequately (15-40 ppm) iodized salts, their daily salt intake may not be enough to meet the daily iodine requirement. In fact, a person should consume approximately 6-15 g per day of adequately iodized salt to receive the 250-µg iodine recommended by WHO for pregnant women (46). Paradoxically, the WHO recommends a salt intake per person of <5 g/day to reduce the risk of cardiovascular diseases (47). A salt intake below 5 g/day during pregnancy may cause insufficient iodine intake. For this reason, the American Thyroid Association recommends a supplement of 150 µg iodine per day during pregnancy and lactation, in addition to the use of iodized salt (48), but only 5% of pregnant women in our country take iodine supplements (28).

Another important problem in Türkiye is perinatal iodine exposure due to the use of iodine-containing antiseptics for cleaning the perineum before delivery or the umbilical area of the baby. Iodine excess increases neonatal TSH levels and can even induce transient hypothyroidism through the Wolff-Chaikoff effect, usually lasting about 10 days (49). Newborns in iodine-deficient regions may be more susceptible to the Wolff-Chaikoff effect from topical iodine exposure (49). For example, Zonguldak is an iodine-deficient province and povidone-iodine is widely used for antisepsis during delivery. A study conducted in Zonguldak revealed that 61% of 116 newborn babies had iodine excess, even

Table 4. Iodine nutrition status in Türkiye: summary of key studies on urinary iodine concentrations of vulnerable populations

Authors	Study year	Study area	Target population	Number of subjects	Use of iodized salt	Use of iodine supplement	Median UIC (µg/L)	Reference range of UIC	Prevalence of iodine deficiency
Yordam et al. (33)	1997	Yahyalı Ankara	5-24 years 6-15 years	232 2155	None	None	15.7 62.7	100-199	NA
Erdoğan et al. (34)	1997	Black Sea and Ankara	SAC 9-11 years	1226	None	None	21 (14 to 30)	100-199	95%
Erdoğan et al. (35)	1997-1999	Türkiye (20 cities)	SAC 9-11 years	5948	None	None	36 (14 to 78)	100-199	NA
Kurtoglu et al. (36)	2003	Kayseri	Mothers† Newborns	70 70	NA	NA	30.2 23.8	100-199	90% 100%
Kut et al. (38)	2006	Adana	Pregnant w.	141	95%	None	149.7	150-249	50%
Erdoğan et al. (39)	2007	Türkiye (30 cities)	SAC 6-14 years	900	73%‡	None	107 (21 to 338)	100-199	47%
Egri et al. (40)	2007	Malatya	Pregnant w.	824	43%	None	72.3	150-249	99%
Oguz Kutlu and Kara (25)	2008	Ankara	Pregnant w.	168	80%	None	80.5	150-249	73%
Yaman et al. (26)	2012	Zonguldak	Mothers* Newborns	116 116	99%	None	84 279*	100-199	57% 10%*
Celik et al. (41)	2013	Edirne	Pregnant w.	275	97%	None	77	150-249	88%
Oral et al. (42)	2014	İstanbul	Pregnant w.	3487	69%	None	73	150-249	91%
Anaforoğlu et al. (43)	2015	Trabzon	Pregnant w.	864	91%	None	102	150-249	78%
Çelmeli et al. (44)	2015	Antalya	SAC 6-14 years	1594	NA	NA	174.7	100-199	19%
Vural et al. (28)	2018 2020	Türkiye All regions	Pregnant w. Newborns	1444 1444	89%	5.5%	94 96	150-249 100-199	74% 51%

†The median iodine content of breast-milk was 73 µg/L, with 72.9% for the values <100 µg/L. All women delivered spontaneously and had no iodine exposure.
‡Of the 900 household salt samples; 73.5% were iodized, and 56.5% had adequate iodine content (>15 ppm).
*79.3% of the deliveries were caesarean sections (C/S). Iodine-containing antiseptic was used before C/S and normal delivery. Iodine excess (UIC ≥200 µg/L) was 61%.
NA: not available, SAC: school-age children, UIC: urinary iodine concentration, w.: women

though their nursing mothers had ID (Table 4). In this study, the recall rate at screening was found to be 9.5% and three newborns required levothyroxine (L-T4) therapy (26). In conclusion, both maternal ID and perinatal iodine excess are ongoing problems in Türkiye and contribute to the high incidence of elevated neonatal TSH levels.

Unintended Consequence of CH Screening: Neonatal Hyperthyrotropinemia

Newborn screening for CH was first introduced in Canada and United States of America in the early 1970s (8,9,10). Before the introduction of NSPs, the incidence of CH based on clinical diagnosis ranged from 1/10,000 to 1/7000 live births. The establishment of screening programs has led to an increase in the incidence of CH to 1/3000 to 1/4000 live births (50). Screening strategies and T4-TSH cutoffs have changed over time and thus, the incidence of CH has doubled over the last two decades (27,51,52,53). Although it varies considerably by race and ethnicity, the current incidence of CH is nearly 1/2000 live births worldwide (50,54). The main reason for the increased incidence is mild cases of CH with normal/hyperplastic gland due to dyshormonogenesis (53). Therefore, the rate of dyshormonogenesis in the etiology of permanent CH has increased to 40% (53), as in our patient group from the Black Sea region (27). But, in the eastern region of Türkiye, where consanguineous marriage exceeds 50%, the frequency of dyshormonogenesis in the patients with permanent CH may be as high as 80% (55).

The initial aim of newborn screening was to prevent mental retardation due to severe CH. However, the detection of mostly mild cases of CH and NHT in the current NSPs has led to a management dilemma (56). A systematic review of 46 studies, nine of which investigated the NHT prevalence in a total of 2,715,031 infants, estimated the overall prevalence to be 1/1750 live births, and the calculated NHT:CH ratio was 1.2:1 (19). This meta-analysis showed that in 40% of the NHT cases, serum TSH levels returned to normal without treatment. Of those treated, 11% had to discontinue L-T4 therapy within the first year due to elevated T4 levels. In 30% of the remaining cases, L-T4 treatment was discontinued when TSH level remained normal after re-evaluation at 2-3 years of age (19). In summary, in two-thirds of the NHT cases, TSH elevation resolved in the newborn period or during treatment, but some cases were probably overtreated. Indeed, the Canadian experience reported by Oren et al. (23) showed that 78% (80/103) of infants with mild NHT (TSH 5-30 mU/L) were treated with L-T4, and 45% had evidence of overtreatment (high FT4 and/or low TSH) during follow-up. Moreover, Bongers-Schokking et al. (57) demonstrated that overtreatment of infants with CH during the first two years may be a greater threat to cognitive development than undertreatment. Therefore, overtreatment of NHT may pose a greater risk to later neurodevelopment of these children.

It is also necessary to draw attention to other problematic aspects of transient TSH elevation. Are we doing a good job of identifying mild cases of CH owing to low TSH cutoff at screening, or are we just increasing our clinical workload by detecting mostly false-positive and transient NHT cases? An increase in clinical workload also increases the economic burden by affecting the cost effectiveness of NSPs (58). Let us take the example of Türkiye. Despite a downward trend in recent years, an average of 1,300,000 babies are born in Türkiye each year. Out of 1,292,703 newborns screened with an NSP coverage of 98% in 2015, 13,556 (~1%) were referred for confirmatory testing, and 9950 of them (~73%) were false positives with normal serum TSH and FT4 levels. The remaining 3606 newborns were put in follow-up with suspected CH. Although data on the entire screening program are not available, 6-year follow-up results of 487 infants with elevated screening TSH in 2015 were recently reported by a multicenter study involving 17 pediatric endocrinology centers (29). Serum TSH and FT4 levels were found to be normal in one third of the study group. In addition, 14% had transient NHT that resolved in a median of 35 (21-49.5) days without any treatment. L-T4 treatment was applied to all babies with TSH >20 mU/L and to some babies with milder TSH elevation because the treatment decision was made in accordance with the European guideline (14). Of all treated babies, 54% had transient CH. As a result, only 23% (111/487) of referrals turned out to be permanent CH, 60% of which were due to dyshormonogenesis (29). Since the false-positive rate in this study (33%) was lower than the nationwide rate (73%), the true proportion of permanent CH in the entire screened population might be much lower. In this study, 21%, 42% and 37% of the cases with elevated serum TSH had transient NHT, transient CH and permanent CH, respectively. When this distribution is generalized to the 3606 newborns with elevated serum TSH across all centers, it becomes clear that probably only ~10% of all the 13,556 referrals (n=1334 equal to 37% of 3606) had a final diagnosis of permanent CH. From these figures, an estimated incidence of permanent CH for 2015 can be calculated as 1/969, representing about 2.5-3-fold increase compared to the rates of 1/2736-1/2354 detected with a whole blood TSH cutoff of 20 mU/L (32,37). Moreover, the incidence of transient NHT can be estimated as 1/1708 (for 757 cases, equal to 21% of 3606 infants with elevated serum TSH), which is consistent with meta-analysis data from nine studies (19).

Another issue is that a possible diagnosis of CH can cause great anxiety for family members and guardians. Long-term parental psychological reactions to false-positive screening tests for CH were documented years ago (59). Therefore, the follow-up and treatment of NHT cases with suspicion of CH may cause more concern for families. The data of the multicenter study (29) can also be evaluated from this perspective. The anxiety experienced by nearly 10,000 families due to a false positive result in 2015 is worth considering. Also, if the alternative approach suggested in this article had been applied, the outcome for at least some babies treated with a diagnosis of CH might have been different. Detection of transient NHT without treatment instead of transient CH could have significantly reduced parental stress.

The main problem here is that it is not known whether missing the babies with isolated TSH elevation or leaving them untreated will have adverse developmental effects at later ages. In addition, it is unknown whether L-T4 treatment improves neurodevelopmental outcomes, but overtreatment of NHT may have harmful effects (57). Many physicians choose to "play it safe" and treat babies with NHT (19), whereas available data on the effects of NHT on subsequent development are inconclusive and conflicting (60,61,62,63). For example, Cuestas et al. (60) found suspected developmental delay in 23 % (15/65) of the children with transient NHT at elemental school entry using a 10-question phone survey. Although this rate was higher than 11 % (21/185) in the control group, which implies developmental repercussions of NHT, the developmental assessment in this study was solely based on the subjective evaluations of parents. A population-based record-linkage study by Lain et al. (61) showed an association between poor educational or developmental outcomes and mildly increased neonatal TSH concentrations, which were below screening cutoff of 20 mU/L whole blood (particularly between 12 and 20 mU/L). This valuable study might justify lowering TSH cutoffs to detect milder forms of CH that may be detrimental to brain development. However, an important limitation of this anonymized study was the lack of data on definitive diagnosis, such as transient NHT or transient and permanent CH, which does not allow for a direct link between NHT and any neurodevelopmental outcome. In contrast, Trumpff et al. (62) found that neonatal TSH concentrations between 5 and 15 mU/L were not associated with impaired psychomotor development at preschool age. In this study, in which psychomotor development was assessed at home by a psychologist blinded to TSH values, psychomotor scores did not differ between children with neonatal TSH < 5 (n = 181) and > 5 mU/L (n = 103). A recent study by West et al. (63) also found that mild TSH elevation of 8-14 mU/L at newborn screening was largely transient, and that childhood neurocognitive performance of these children (n = 65) was similar to that of their siblings with normal neonatal TSH. Despite some shortcomings such as small sample size (especially for those with TSH levels close to 14 mU/L), and the absence of data regarding definitive diagnosis, follow-up, and treatment, this study suggests that mild neonatal TSH elevation has no clinically meaningful long-term negative effects. Finally, a systematic review of nine studies on NHT revealed no poor developmental outcome in any of the 94 subjects (19). Nevertheless, the exact neurodevelopmental risks posed by NHT remained unclear because 82 % of these infants received L-T4 treatment. Consequently, the optimal approach to NHT treatment is still a matter of debate, and whether to treat these infants is not a simple decision. A more comprehensive approach to newborns with elevated TSH levels is needed, which is the focus of this article.

An Alternative Approach to Infants with TSH Elevation on Screening

Treating every infant with mild to moderate TSH elevation would be overmedication, especially if other important determinants for the treatment decision were not taken into account, such as FT4 level (in the lower or upper half of the reference range) and TSH trend (increase or decrease by capillary measurement) (56). The possibility of unnecessary treatment is higher in Türkiye and similar countries where ID and excess problems that may cause transient NHT are relatively common (24-43,64,65). For this reason, we consider that in addition to serum FT4 level and TSH trend, the degree of TSH elevation should be evaluated more carefully during the newborn period. To avoid overtreatment in iodine-deficient countries, serum TSH level can be graded as mild (6-20 mU/L), moderate (20-30 mU/L) and severe (> 30 mU/L). In case of severe TSH elevation, L-T4 treatment is started immediately for compensated hypothyroidism, but mild to moderate TSH elevation, which we call isolated NHT, can be managed differently. Namely, mild NHT can be monitored without L-T4 treatment. In moderate NHT, the decision for treatment or follow-up can be made on an individual basis according to the age at confirmatory testing, the absolute FT4 level and TSH trend (Figure 1) (66). Indeed, the Indian Society of Pediatric and Adolescent Endocrinology has recently published its own guideline that recommends the use of higher TSH thresholds for confirmation and treatment of CH (67), compared to the American Academy of Pediatrics' CH guideline (16). In this publication, due to the lack of strong evidence for the treatment of mild CH (that can be thought of as the equivalent of isolated NHT), the authors stated that both guidelines can be followed in terms of the TSH threshold for L-T4 initiation.

The Thyroid Working Group of the Turkish Society for Pediatric Endocrinology and Diabetes recently conducted a survey among its members to question possible attitudes towards alternative approaches to the management of CH. This survey has shown that pediatric endocrinologists in Türkiye do not prefer to treat the infants with mild TSH elevation (< 20 mU/L), and when moderate TSH elevation (up to 40 mU/L) was offered as an option, the majority did not initiate treatment (68). As a result, management of neonatal TSH elevation may vary depending on local conditions. The flow diagram in Figure 1 illustrates such an algorithmic approach to the infants with elevated TSH on neonatal screening. The cornerstones of the approach are explained below, in accordance with the numbers indicated in Figure 1:

1. Capillary TSH screening: Initial part of the algorithm reflects the routine implementation of the current NSP. Please see the section of the national NSP for CH in Türkiye for details.

2. Venous TSH and FT4 measurement: For confirmation, serum TSH and FT4 levels should be measured. Most confirmatory tests are performed at weeks 2 to 3 of life, at which time the upper limit of normal range for serum TSH levels falls to anywhere between 6 and 10 mU/L. According to laboratory methods, the upper limit of TSH in newborns varies between 4.3 and 12.6 mU/L (69). Furthermore, the reference ranges for FT4 levels vary greatly depending on assay methods, with the lower limits ranging from 0.6 to 1.4 ng/dL in the newborn period (69). Therefore, TSH and FT4 levels must be evaluated according to the age- and assay-specific reference ranges.

3. False positive result: Although screening TSH is high, confirmatory test results may be normal. This very short-lasting hyperthyrotropinemia is classified as false positives at CH screening, and should not be considered transient NHT (19,56). Newborn screening before 24 to 48 hours of life causes an increase in false positive results because of the physiological TSH surge after birth. If confirmatory TSH and FT4 levels are normal, there is no need for additional testing and monitoring. Routine well newborn care is sufficient (16).

4. Normal TSH-low FT4: In central hypothyroidism, FT4 is low, and TSH is usually at normal or clearly low levels. However, sometimes there may be mild TSH elevation (5), not exceeding 20 mU/L in newborns (10 mU/L in children), and these cases may be captured in programs that use a low TSH threshold value as in our country (20). In cases of central CH, pituitary magnetic resonance imaging should be performed for etiologic evaluation. Genetic defects that may cause isolated or multiple pituitary hormone deficiencies may be investigated. In differential diagnosis, low T4 syndrome of prematurity and non-thyroidal illness (euthyroid sick) syndrome should be kept in mind. Both conditions mimic central hypothyroidism with low FT4 and TSH levels. Follow-up without treatment is generally recommended in such premature and/or sick babies (70). However, if treatment has been started, it should be stopped and thyroid tests should be repeated after the clinical condition improved.

5. High TSH-low FT4: This combination establishes a diagnosis of primary CH, which requires immediate initiation of L-T4 therapy. Nevertheless, if TSH levels are slightly high (< 20 mU/L), the possibility of central hypothyroidism should still be considered (20). Indeed, the patient may have multiple pituitary hormone deficiencies and coexisting central adrenal insufficiency. Initiation of L-T4 treatment with the thought of primary CH may trigger an adrenal crisis by accelerating cortisol metabolism and clearance (15). In babies with mildly elevated TSH, the adrenal axis should be checked before treatment. Another clue to central CH is that TSH levels fall below normal limits when FT4 levels return to normal with treatment.

Primary CH may occur due to thyroid dysgenesis or dyshormonogenesis (Table 1). After starting L-T4 treatment without delay, the etiology of CH should be determined to ensure a definitive diagnosis of underlying causes, such as ectopic thyroid or athyreosis that require lifelong treatment (15). Both scintigraphy and ultrasonography (US) are recommended for thyroid imaging because each method has some drawbacks in the diagnosis of thyroid dysgenesis (71). Scintigraphy is the best imaging tool to determine ectopic thyroid tissue, which is the most common cause of primary CH in iodine-replete populations (1). However, concerns about radiation exposure and increasing costs may limit the use of scintigraphy. The recent attitude survey revealed that 90% of pediatric endocrinologists in Türkiye prefer US alone as an imaging modality (68). This choice seems reasonable in order not to expose a large population to radioisotopes in an iodine-deficient country where transient CH and NHT are more common than permanent CH (29). Of note, US is an observer-dependent method, and require an experienced operator, a high-resolution device and special probe in newborns (20). A synchronous evaluation of urinary iodine levels of both infant and mother provides a more accurate assessment of iodine status (26). Serum thyroglobulin measurement may contribute to etiological evaluation; undetectable levels indicate true athyreosis and undetectable or low levels a synthesis defect. Finally,

genetic testing may provide a definitive diagnosis and alter long-term treatment decisions (72).

6. High TSH-normal FT4: This pattern is present in both compensated hypothyroidism and isolated NHT (12,13,17,18,19). In this group, our management approach can be summarized as follows:

• Mild NHT (TSH < 20 mU/L): Follow-up without treatment. Retest after 1-2 weeks.

• Moderate NHT (TSH 20-30 mU/L): Decide based on age, TSH trend and FT4 level.

- Start L-T4 treatment if age at confirmatory thyroid function testing is > 21 days.

- Start L-T4 treatment if serum TSH level shows no downward trend from screening TSH and FT4 level is in the lower half of the reference range in the first 21 days.

- Retest TSH and FT4 at weekly interval if serum TSH shows downward trend from screening TSH, and FT4 level is in the upper half of the reference range.

- Consider deciding based on thyroid imaging in in-between cases; for example, those with a downward trend in TSH but FT4 in the lower half, or *vice versa*.

- Start L-T4 treatment in any case if family is very concerned about high TSH.

• Compensated (subclinical) hypothyroidism (SCH) (TSH > 30 mU/L): Start L-T4 treatment.

• PHT or SCH (TSH > 10 mU/L after neonatal period): Start L-T4 treatment.

- Consider retesting if TSH level is between 6 and 10 mU/L, with a downward trend (TSH level maybe normal up to 10 mU/L depending on assay method).

The etiology of isolated hyperthyrotropinemia is complex. It may result from delayed maturation of the hypothalamic-pituitary-thyroid (HPT) axis, or several transient or permanent thyroid abnormalities. With increasing HPT maturation, molar TSH/FT4 ratio gradually decreases with age, from 15 in the midterm fetus, to 4.7 in term infants, and 0.97 in adults (73). The cold-stimulated TSH surge at birth causes a marked increase in T4 secretion, and HPT axis reaches a new equilibrium by 2-20 weeks (73). The markedly increased TSH concentration at birth (the TSH surge) returns to normal within 24-48 hours. Hence, TSH screening in the first 48 hours causes more false positives. However, in some babies, TSH levels normalize with a delay after confirmatory tests. This condition is characterized by high TSH and FT4 levels and does not require treatment. Indeed, transient NHT is mostly caused by maternal ID and/or perinatal iodine overload. A meta-analysis of six studies from Italy (n = 2), Türkiye (n = 2), Belgium (n = 1) and Japan (n = 1) showed that 46% of babies with NHT had iodine excess and 16% had ID (19). Two Turkish studies in the meta-analysis reflect the iodine problem in Türkiye (21,26). For that reason, a history of iodine overload during perinatal period should be questioned. In addition to iodine problems, maternal TSH receptor (TSHR) blocking antibodies and anti-thyroid drugs may cause transient NHT as well as transient CH (Table 1).

Thyroidal morphological abnormalities including large ectopic thyroid, hemiagenesis and hypoplasia may underlie persistent NHT or SCH (74,75,76). Therefore, thyroid imaging can be performed to decide on treatment or follow-up in babies with NHT. While the presence of thyroid dysgenesis requires initiation of L-T4 therapy, normal-sized gland *in situ* cases can be followed without treatment. However, since neonatal TSH elevation is a frequently encountered condition in our country, radiologic examinations performed in every case impose a huge financial burden on families and social security institutions (20). Therefore, we recommend performing thyroid US in infants with moderate NHT, especially in those with discrepancy between TSH trend and FT4 level as mentioned above. In addition, genetic variations in *TSHR*, thyroid peroxidase and dual oxidase 2 may be responsible for isolated NHT (19), which usually persists in later life in the picture of PHT or SCH. This condition will be discussed in the re-evaluation section.

7. Treatment: L-T4 treatment should be started immediately when the diagnosis of CH is confirmed, within the first two weeks of life if possible. The recommended starting doses of L-T4 is 10-15 µg/kg/day, but the dose should be meticulously adjusted to avoid overtreatment according to FT4 level. Indeed, CH can be classified as severe [FT4 < 0.4 ng/dL (< 5 pmol/L)], moderate [FT4 0.4-0.8 ng/dL (5-10 pmol/L)], and mild [FT4 > 0.8 ng/dL (> 10 pmol/L)] (14,15). In severe CH, most likely resulting from athyreosis or complete dyshormonogenesis, L-T4 dose should be the highest (15 µg/kg/day). In moderate CH, possibly caused by an ectopic or hypoplastic thyroid or partial dyshormonogenesis, a dose of ~10 µg/kg/day would be more appropriate. In mild CH and SCH, the dose should be reduced to 5-10 µg/kg/day. In daily practice, a full-term infant with a birthweight over 3 kg should be treated with L-T4 at a dose of 37.5 to 50 µg/day for moderate to severe CH, respectively. For SCH, L-T4 dose of 25 µg/day is usually adequate. Monitoring of treatment requires regular measurements of serum FT4 and TSH levels. If high dose L-T4 is started, thyroid tests should be checked in the first week to avoid overtreatment. Otherwise,

the L-T4 dose can be adjusted with measurements taken every 1 to 2 weeks until TSH levels return to normal limits. TSH level should be kept within the age-specific reference range and care should be taken not to suppress it. Serum FT4 level should be kept in the upper half of the age-specific reference range.

8. Re-evaluation: Re-evaluation of the HPT axis is indicated in CH with gland *in situ*. The guidelines of the European Society of Pediatric Endocrinology and the American Academy of Pediatrics recommend a trial off therapy after the age of 2-3 years (14,15,16). However, treatment may be discontinued earlier in the presence of conditions known to cause transient hypothyroidism, such as maternal blocking antibodies, and ID or overload. Despite low doses of L-T4, suppression of TSH necessitates earlier discontinuation of treatment (27). There is no need for re-evaluation in infants with thyroid ectopia or agenesis, or with TSH elevations that requires an increase in L-T4 doses during follow-up, as the definitive diagnosis is permanent CH (77).

A trial off therapy should be performed in children with normal, large, or small sized and normally located thyroid glands, or in children who have not had a thyroid imaging before starting treatment and whose L-T4 doses have not been increased during the follow-up period. Routinely, after L-T4 therapy is stopped for one month, a full evaluation is made with biochemical tests and imaging. If FT4 level becomes low, and/or TSH level rises over 10 mU/L at the end of this period, permanent CH is confirmed and treatment is restarted (16). It should be remembered that compensatory transient TSH elevation may occur after long-term L-T4 treatment in some overtreated children. Therefore, if FT4 level is within normal limits and TSH increases up to 15 mU/L in the first month of re-evaluation, monitoring is an option (78). If TSH level remains >10 mU/L in the third month of follow-up, treatment is reinstituted.

At re-evaluation, if FT4 and TSH levels are within normal limits in the first month of the trial off therapy, thyroid tests are repeated at the third and sixth months (77). If the values remain within the normal range, a diagnosis of transient CH is established. In these cases, TSH level should be checked during puberty and pregnancy periods when metabolic needs increase.

The third possibility, PHT, is characterized by normal FT4 and mild TSH elevation (5-10 mU/L), and occurs in about one-third of cases at re-evaluation (78). The management of PHT is another matter of debate, but most practitioners elect to treat cases of PHT, as in NHT (16). In fact, most of children with PHT have been already treated with a diagnosis of NHT/SCH since the neonatal period. Therefore, these children may have to receive lifelong treatment, even though there is no proven benefit. Leonardi et al. (74) showed that TSH levels returned to normal by age 9 years in 68 % of children with mild PHT detected at CH screening. In this study, the children with ongoing PHT had thyroid morphological and/or genetic abnormalities. Likewise, we observed that TSH levels normalized between the ages 5 and 9 years in some children with mild PHT who had no morphological or genetic abnormalities. However, the children whose PHT did not resolve had heterozygous variants in the *TSHR* gene (72). In summary, PHT may be a condition that resolves spontaneously in late childhood, possibly due to extremely delayed maturation of the HPT axis, or may be the result of an underlying structural or genetic defect. Therefore, treatment decision in PHT cases should be made on an individual basis.

Conclusion

Transient NHT is a common condition in Türkiye, and mostly occurs due to ID and overload problems in pregnant women and their offspring. Therefore, the recommendation to start treatment for every infant with a TSH level >20 mU/L may not be applicable. Monitoring of babies with mild to moderate TSH elevation will generally be an appropriate approach to avoid overtreatment. L-T4 treatment should be reserved for newborns with TSH >30 mU/L, and infants with PHT. However, all treated cases of NHT/PHT should be re-evaluated by a trial off therapy after two years of age. Nevertheless, it should be kept in mind that transient NHT or CH caused by ID or excess may resolve in a short time, which may require earlier discontinuation of treatment. This alternative approach will largely eliminate unnecessary treatment of infants with transient neonatal TSH elevation, and will reduce workload and costs by preventing unwarranted investigation and long-term follow-up.

Ethics

Footnotes

Authorship Contributions

Concept: Cengiz Kara, Hüseyin Anıl Korkmaz, Design: Cengiz Kara, Hüseyin Anıl Korkmaz, Data Collection or Processing: Cengiz Kara, Hüseyin Anıl Korkmaz, Analysis or Interpretation: Cengiz Kara, Hüseyin Anıl Korkmaz, Literature Search: Cengiz Kara, Hüseyin Anıl Korkmaz, Writing: Cengiz Kara, Hüseyin Anıl Korkmaz.

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Normative Values for Thyroid Volume and Tracheal Index in Healthy Turkish Newborns in an Iodine Sufficient Region

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What is already known on this topic?

Each community must determine its own normative values for accurate assessment of neonatal thyroid dimensions. In previous studies, local neonatal thyroid volume normative values for various regions of our country were given, but there is no data on tracheal index.

What this study adds?

Normative thyroid volume and tracheal index data of healthy newborns in Aydın city, which is iodine-sufficient, are presented. A handheld ultrasound device may be used to calculate the neonatal tracheal index.

Abstract

Objective: This study aimed to determine the normal values of thyroid volume and tracheal index in healthy, term newborns born in an iodine-sufficient population. Moreover, the usability of a handheld device for assessing tracheal index was assessed.

Methods: Thyroid imaging was performed at 0-2 days and 15-30 days using handheld and portable ultrasound (US) devices. Thyroid volume and tracheal index were calculated using standard formulae.

Results: A total of 144 healthy, term newborns with a mean birth weight 3230 g were enrolled. The normal thyroid volume for the entire population was 0.66 ± 0.25 mL at 0-2 days, which significantly increased to 1.12 ± 0.33 mL at 15-30 days ($p < 0.01$). There were no significant differences in thyroid volume between genders in either age group ($p = 0.246$ and $p = 0.879$). Thyroid volume correlated with birth weight, length, and head circumference, with the strongest correlation being with birth weight ($r = 0.404$, $p < 0.001$; $r = 0.252$, $p = 0.002$; $r = 0.223$, $p = 0.007$, respectively). The tracheal index at 0-2 days was 1.84 ± 0.30 in girls, 1.82 ± 0.27 in boys, and 1.83 ± 0.29 overall. At 15-30 days, it was 1.99 ± 0.23 in girls, 2.00 ± 0.28 in boys, and 1.99 ± 0.25 overall. Similar to thyroid volume, the tracheal index increased significantly with age ($p < 0.01$), with no significant gender differences in either age group ($p = 0.593$ and $p = 0.886$). Thyroid volume and tracheal index were moderately correlated in both measurements (rho = 0.538, $p < 0.01$). Measurements of the trachea, and thyroid lobe widths using portable and handheld US devices were positively correlated ($r = 0.449$, $p < 0.01$; $r = 0.638$, $p < 0.01$; $r = 0.497$, $p < 0.01$). There was also a correlation between tracheal index measurements using both devices at both the first and second measurements.

Conclusion: This study provides normative data for thyroid volumes and tracheal index in newborns from an iodine-sufficient population. The tracheal index may be used to estimate thyroid size when volume calculation is not feasible. Handheld US devices are effective for this assessment.

Keywords: Newborn thyroid volume, tracheal index, handheld ultrasonography

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Introduction

Congenital hypothyroidism (CH) is the most common endocrine disorder in the neonatal period, occurring in approximately 1:2000-1:3000 live births. The majority (85%) of cases are due to thyroid dysgenesis (aplasia, hypoplasia or ectopy) (1). Ultrasonography (US) is useful for evaluating the thyroid gland and may provide information on the structure, anatomical location, and size of the thyroid gland, thereby aiding in the etiological assessment of CH (2). However, US is operator dependent and may not be able to locate all instances of thyroid ectopia, even when using Doppler mode. In these cases, it is also helpful to use nuclear magnetic techniques, such as technetium scanning, which may identify small but usually very active ectopic thyroid tissue. There is evidence that using these modalities in combination will establish the etiology more successfully than using either modality in isolation. A large study from Glasgow demonstrated that the combined use of US and isotope scanning enabled accurate diagnosis in over 80% of newborns with elevated thyroid-stimulating hormone (TSH) levels (3).

US evaluation of the thyroid gland, when conducted by a trained sonographer, usually offers detailed information rapidly without the risks associated with radiation or contrast agents. Moreover, its widespread availability and ease of use present additional advantages (4).

The size of the thyroid gland in the neonatal period is influenced by factors such as gestational age, ethnic background, and iodine status. Consequently, it is recommended that each community establish its own normative thyroid volume data for accurate evaluation (5).

During thyroid US imaging, the US probe should be placed in the transverse plane, and the entire embryological path of the thyroid should be scanned from the tongue to the mediastinum (6). The conventional method for assessing thyroid size involves calculating thyroid volume by measuring the width, length, and height of the gland (4,7). However, in newborns with short necks and increased adiposity, accurately assessing the anatomical features and measurements of the thyroid gland can be challenging (8). Furthermore, in the absence of a dedicated probe for measuring the thyroid's longitudinal axis, a three-dimensional evaluation of the gland becomes impractical. In such cases, a simpler method known as the tracheal index can be used. The tracheal index is calculated by the ratio of the sum of the widths of both thyroid lobes to the width of the trachea (9).

The aim of this study was to determine the normal values of thyroid volumes and tracheal index in healthy newborns born in Aydın, a region with sufficient iodine levels (10). Additionally, the study evaluated the feasibility of using a handheld US device to assess thyroid size in newborns, a method that has garnered significant interest in recent years and has been found effective in assessing thyroid tissue in older children (11).

Methods

This prospective cohort study included healthy, term newborns, aged 0-2 days, born between January 1, 2023, and December 31, 2023, at Aydın Adnan Menderes University and Aydın Maternity and Children's Hospital, Türkiye. Exclusion criteria included congenital anomalies, low birth weight (< 2500 grams), prematurity (< 37 weeks), multiple pregnancies, refugees, and newborns of mothers with thyroid disease or other chronic conditions, such as diabetes mellitus or hypertension. Thyroid imaging was performed on newborns aged 0-2 days, with follow-up assessments conducted when they were between 15-30 days old.

Thyroid US imaging was conducted using a portable US device (Samsung HM70 EVO - POCUS) by an experienced radiologist, and a handheld US device (Sonostar C5PL) by a pediatric endocrinologist. The endocrinologist performing measurements with the handheld US device had previously received training in device usage and thyroid US imaging, with three years of experience, and was conducting these procedures as part of clinical practice (10). These two researchers, using both the handheld and portable US devices, performed independent, blinded measurements. Necessary adjustments - such as gain, depth, and focus - were made manually on the handheld US device in each case to ensure optimal image clarity during the thyroid measurements.

Babies were positioned supine with their necks extended. Measurements of each thyroid lobe, including the longitudinal length, were obtained in three planes using a portable US device. Thyroid volume for each lobe was calculated using the following formula: [anterior-posterior x mediolateral (ML) x longitudinal] x π/6 (6), and expressed in milliliters.

The tracheal index is calculated as the ratio of the sum of the maximum widths of the right and left lobes in the ML line on a transverse section of the thyroid gland to the tracheal width at the level of the thyroid.

Tracheal index = (right lobe width + left lobe width) / tracheal width

Since the measurement plane for tracheal index is the ML line, the difference in measurement during inspiration and expiration is not significant (Figure 1) (9).

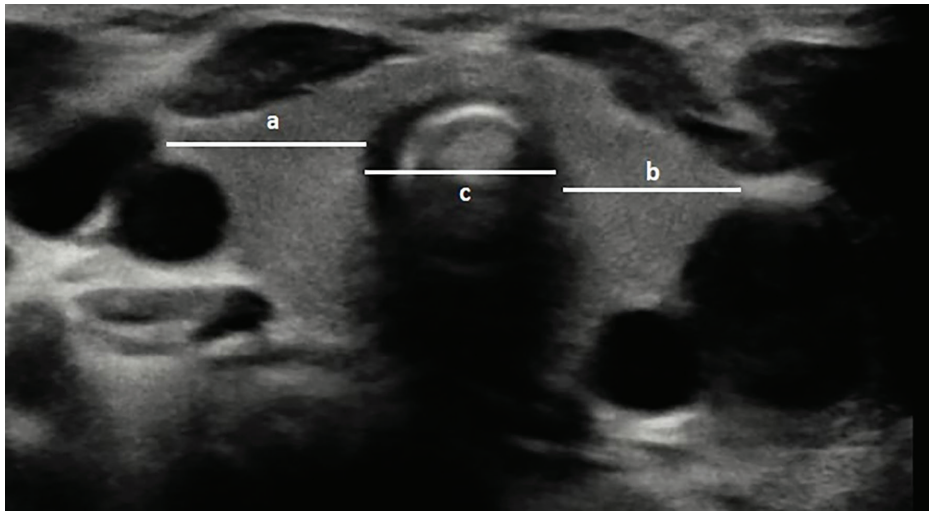

Figure 1. Calculation of the tracheal index on a transverse sonogram of the thyroid [the sum of the maximum width of each thyroid lobe (a + b) divided by the width of the trachea at the level of the thyroid (c) gives the transverse sonogram tracheal index]

The longitudinal measurements required to calculate thyroid volume could not be performed using the handheld US device, due to the probe length being unsuitable for the anatomy of the newborn's neck. Therefore, measurements from the handheld US device were used only for calculating the tracheal index, as volume data could not be provided. To assess the reliability of the handheld US device, the tracheal index data were compared between the results obtained from the two devices.

Statement of Ethics

All procedures involving human participants in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Non-interventional Ethics Committee of Aydın Adnan Menderes University (protocol no: 2022/213, date: 04.01.2023). Informed consent was obtained from all participants.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences, version 21 (IBM Corp., Armonk, NY, United States of America). Descriptive statistics are presented as mean and standard deviation (SD) for normally distributed data, and as median, minimum, and maximum values for non-normally distributed data. The normality of continuous variables was assessed using descriptive statistics, skewness and kurtosis coefficients, histogram, and the Shapiro-Wilk test. The chi-square test was used for categorical data. For comparing two independent groups, the t-test was used for normally distributed data, and the Mann-Whitney U test for non-normally distributed data. For variance analysis, ANOVA was used for normally distributed data (with Tukey post-hoc test if variances were homogeneous and Tamhane's T2 test if variances were not homogeneous); otherwise, the Kruskal-Wallis H test was used (with Dunn's test for post-hoc analysis). Bland-Altman analysis was used to assess the consistency of measurement data. Pearson's correlation was used for normally distributed data, and Spearman's correlation was used for non-normally distributed data. The type 1 error level was set at 0.05.

Results

The study included 144 healthy term newborns, of whom 49.3% were female. The gestational age of the subjects were 38.8 ± 1.30 weeks, birth weight was 3230 ± 426 grams, and the birth length was 48.5 ± 2.13 cm. All subjects had capillary TSH levels within the normal range (< 5.5 mU/L).

On days 0-2, the thyroid volume was 0.64 ± 0.26 mL in girls and 0.68 ± 0.23 mL in boys ($p > 0.05$). The mean thyroid volume for the entire population was 0.66 ± 0.25 mL. Between days 15-30, the thyroid volume was 1.12 ± 0.33 mL in girls, 1.13 ± 0.33 mL in boys, and 1.12 ± 0.33 mL for the entire population. Thyroid volume significantly increased in the second measurement as the infants grew ($p < 0.01$) (Table 1). No significant differences in thyroid volume were found between genders in either age group ($p = 0.246$ and $p = 0.879$, respectively).

There was a correlation between thyroid volume and birth weight, length, and head circumference, with the strongest correlation being with birth weight ($r = 0.404$, $p < 0.001$; $r = 0.252$, $p = 0.002$; $r = 0.223$, $p = 0.007$, respectively) (Figure 2). Thyroid volumes according to birth weight SD score are presented in Table 2.

Table 1. Normal thyroid volume by age and gender

	n	Thyroid volume (mL) 0.-2. day	Thyroid volume (mL) 15.-30. day	p
Girls	71	0.64 ± 0.26	1.12 ± 0.33	**< 0.01**
Boys	73	0.68 ± 0.23	1.13 ± 0.33	**< 0.01**
Total	144	0.66 ± 0.25	1.12 ± 0.33	**< 0.01**

mL: milliliters

Table 2. Thyroid volume normal values according to birth weight

	Boys Thyroid volume (mL)			Girls Thyroid volume (mL)		
Weight (SD)	**Mean ± SD (median)**	**-2 SD**	**+ 2 SD**	**Mean ± SD (median)**	**-2 SD**	**+ 2 SD**
-2-(-1) (n = 13)	0.50±0.16 (0.43)	0.18	0.82	0.45±0.17 (0.46)	0.11	0.78
-1-0 (n = 32)	0.71±0.23 (0.68)	0.25	1.17	0.62±0.18 (0.62)	0.26	0.98
0-1 (n = 23)	0.75±0.23 (0.76)	0.29	1.21	0.72±0.25 (0.73)	0.22	1.22
1-2 (n = 5)	0.71±0.19 (0.78)	0.33	1.09	1.19±0.48 (1.31)	0.23	2.15

SD: standard deviation, mL: milliliters

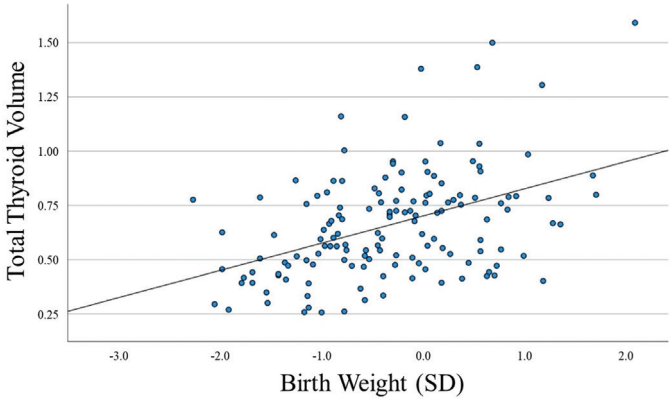

Figure 2. Correlation of thyroid volume with birth weight

SD: standard deviation

On days 0-2, the tracheal index was 1.84 ± 0.30 in girls, 1.82 ± 0.27 in boys, and 1.83 ± 0.29 in the entire population; median values were 1.85, 1.82, and 1.82, respectively. Between days 15-30, the tracheal index increased to 1.99 ± 0.23 in girls, 2.00 ± 0.28 in boys, and 1.99 ± 0.25 in the entire population, with median values of 1.99, 1.90, and 1.94, respectively. Similar to thyroid volume measurements, the tracheal index increased with age ($p < 0.01$), but no significant differences were found between genders in either age group ($p = 0.593$ and $p = 0.886$, respectively) (Table 3).

Thyroid volume and tracheal index were moderately correlated in both the first and second measurements (rho = 0.538, $p < 0.01$) (Figure 3).

Measurements of the trachea and the right and left thyroid lobe widths using both portable and handheld US devices were correlated ($r = 0.449$, $p < 0.01$; $r = 0.638$, $p < 0.01$; $r = 0.497$, $p < 0.01$, respectively). In both the first and second measurements, there was a correlation between tracheal index measurements using both portable and handheld US devices (Table 4).

Discussion

This study was designed to determine the normal thyroid volume values and tracheal index in healthy term newborns in an iodine-sufficient region (10), as well as to evaluate the feasibility of handheld US devices for these measurements. The study provided essential normative data for thyroid volume and tracheal index, stratified by gender and by early and late neonatal periods for the local population. However, these findings are not generalizable to the entire population of Türkiye, as not all regions are iodine-sufficient.

Thyroid Volume

Numerous studies from various regions of Türkiye and around the world have investigated thyroid volume. These studies have demonstrated that thyroid size varies based on ethnic background, geographical features, dietary habits, and particularly iodine status. Consequently, it is recommended to use community-specific normative data when assessing thyroid size (5).

In Türkiye, studies conducted in Bursa and Kayseri in 2008, and in Trabzon in 2012, reported larger thyroid sizes in newborns compared to our findings (12,13,14). This discrepancy may be attributed to the long-standing iodine sufficiency in our region, supported by the national iodized salt program initiated in 1998.

Table 3. Tracheal index by age and gender

	n	Tracheal index mean ± SD (median) day 0-2	Tracheal index mean ± SD (median) day 15-30	p
Girls	71	1.84±0.30 (1.85)	1.99±0.23 (1.99)	**< 0.01**
Boys	73	1.82±0.27 (1.82)	2.00±0.28 (1.90)	**< 0.01**
Total	144	1.83±0.29 (1.82)	1.99±0.25 (1.94)	**< 0.01**

The tracheal index is calculated as the ratio of the sum of the maximum widths of the right and left thyroid lobes in the transverse section to the width of the trachea at the thyroid level.
SD: standard deviation

Table 4. Correlation of tracheal index measure with handheld and portable ultrasound devices

		Portable device (first measurement)	Portable device (second measurement)
Handheld device (first measurement)	r	0.520	
	p	**< 0.001**	
Handheld device (second measurement)	r		0.421
	p		**0.001**

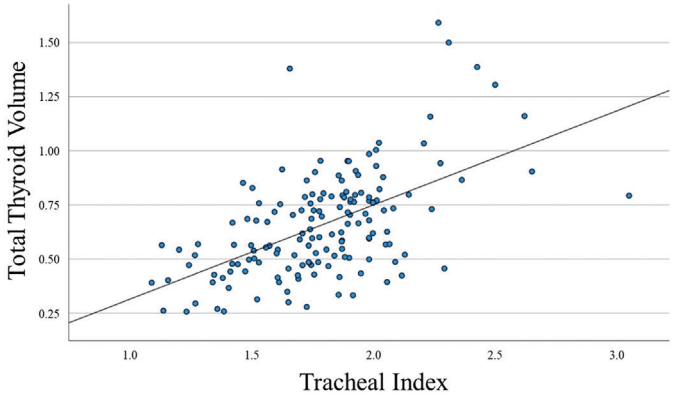

Figure 3. Correlation of tracheal index and thyroid volume

When compared with data from regions with mild to moderate iodine deficiency around the world, the thyroid volumes in our study were found to be lower (6,15,16). While we attribute this to residing in an iodine-sufficient community, we also recognize the potential influence of other confounding factors. In our study, thyroid volumes were observed to increase over time, from the initial measurements to those taken on days 15-30, consistent with the expected growth patterns in newborns. During this period, thyroid volume increased by 1.75-fold, while body weight increased by 1.22-fold, height by 1.08-fold, body mass index by 1.07-fold, and body surface area by 1.13-fold. Although thyroid volume was significantly larger on day 15-30 compared to baseline, this increase was not correlated with changes in anthropometric measurements. In addition, no significant differences were observed between genders in either age group, which is consistent with the existing literature (6,15,17).

When examining the relationship between thyroid volume and birth weight, length, and head circumference, the strongest correlation was with birth weight, although thyroid volume was correlated with all parameters. When assessing thyroid volume according to birth weight, it was observed that thyroid volume increased with each increase in weight SD in both genders. The only exception was seen in boys between +1 and +2 SD; however, the small sample size of this group precludes a definitive assessment. While the correlation between thyroid volume and auxological parameters is well-documented (17), larger-scale studies with a homogenous weight distribution are needed to recommend assessing thyroid size based on birth weight.

Tracheal Index

Measuring the long axis of the thyroid gland in neonates is technically challenging, which has led to the idea of evaluating thyroid size based solely on transverse plane imaging, a concept that has been considered for several years. While various techniques have been attempted, the calculation of the tracheal index, first introduced by Yasumoto et al. (9), has gained wider acceptance. However, it is ideal to have normative data for tracheal index, in a similar fashion to thyroid volume that is specific to each population. In this study the tracheal index norms for newborns in Aydın, an iodine-sufficient region of Türkiye was investigated.

The study found that the tracheal index increased with age, similar to thyroid volume, and did not differ between genders. Moreover, both thyroid volume and tracheal index showed a moderate correlation in both the first and second measurements. A study conducted in an iodine-sufficient population in Brazil, found a weak correlation between thyroid volume and tracheal index (15). We believe that our study supports this relationship and demonstrates the applicability of the tracheal index in neonates, where three-dimensional measurements may be challenging.

In the literature, cases with a tracheal index below 1.7 and low uptake on scintigraphy have been considered as thyroid hypoplasia (17). We propose that in our region, newborns with a tracheal index below 1.49 may be considered as having thyroid hypoplasia. However, larger series of studies are required to establish definitive thresholds.

The results of the present study demonstrated that measurements made using portable and hand-held US devices were correlated between the tracheal index and the widths of both the right and left thyroid lobes. The bedside handheld US device can be used in routine evaluations by trained clinicians due to its easy accessibility and practicality in estimating thyroid size.

Study Limitations

In our study, we were unable to perform longitudinal measurements with the handheld US device due to the incompatibility of the device's long axis with the anatomy of the newborn's neck. Instead, we were able to measure the widths of both lobes and the trachea in the transverse section and only compared these data. Including a comparison of thyroid volume would have increased the robustness of our study. Although previous studies have demonstrated that Aydın is an iodine-sufficient region, the urinary iodine levels of the mothers and newborns were not measured in this study, which is one of its potential limitations.

Conclusion

This study provided valuable normative data on thyroid volume and tracheal index for newborns in an iodine-sufficient region of Türkiye. The findings highlight the importance of region-specific references for thyroid measurements, given the differences found between Aydın and other Turkish regions. The findings also support the use of portable US devices as reliable tools for assessing tracheal index in newborns. Further research in diverse geographical and iodine status contexts will help to expand the understanding of normal thyroid size in newborns, and particularly the definitive relationship between thyroid volume and tracheal index which was moderately correlated in the present study.

Ethics

Ethics Committee Approval: The study was approved by the Non-interventional Ethics Committee of Aydın Adnan Menderes University (protocol no: 2022/213, date: 04.01.2023).

Informed Consent: Informed consent in this study was taken from all participants.

Footnotes

Authorship Contributions

Concept: Ahmet Anık, Design: Ahmet Anık, Data Collection or Processing: Göksel Tuzcu, Reyhan Deveci Sevim, Mustafa Gök, Ayşe Anık, Ahmet Anık, Analysis or Interpretation: Göksel Tuzcu, Reyhan Deveci Sevim, Ahmet Anık, Literature Search: Göksel Tuzcu, Reyhan Deveci Sevim, Mustafa Gök, Ahmet Anık, Writing: Göksel Tuzcu, Reyhan Deveci Sevim, Ahmet Anık.

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ORIGINAL ARTICLE

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Serum Neudesin Levels in Patients with Congenital Hypothyroidism

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What is already known on this topic?

Neudesin is a newly discovered protein; mainly secreted from adipose tissue and brain, which plays a role as a neurotrophic factor in the brain and as a negative regulator of energy expenditure. Neurodevelopmental delay and cognitive dysfunction are common features in cases with congenital hypothyroidism (CH) without treatment.

What this study adds?

This is the first study investigating the relationship of neudesin with CH. The infant group with CH had similar baseline neudesin levels to infants without CH. However, after one month of thyroxine replacement the levels of neudesin were significantly higher than at baseline in babies with CH.

Abstract

Objective: Neudesin is a newly discovered protein mainly secreted from adipose tissue and the brain. It plays a role as a neurotrophic factor in the brain and a negative regulator of energy expenditure. Neurodevelopmental delay and cognitive dysfunction are common features in cases with congenital hypothyroidism (CH) without treatment. Given the role of neudesin in brain development and its contribution to the survival of mature neurons, the relationship between neudesin and thyroid hormone was evaluated in babies diagnosed with CH.

Methods: Babies aged between 2-4 weeks and diagnosed with CH and healthy controls of similar age were included. All patients were evaluated for thyroid hormones and plasma neudesin levels. The basal neudesin levels between the patient and control groups and the patients' neudesin levels before and after l-thyroxine treatment were compared.

Results: Fifty-two babies [32 with CH, 14 (44%) female, aged 19 ± 7 days and 20 healthy controls, 7 (35%) female, aged 22 ± 8 days] were included. There was no significant difference in baseline neudesin between the CH and control groups (6.77 ± 6.41 vs. 7.93 ± 7.04 ng/mL, respectively; p = 0.552). However, neudesin levels increased significantly following one month of therapy in the CH group [median: 3.93 (minimum: 0.31, maximum: 30.06) vs. median: 6.15 (minimum: 2.17, maximum: 70.05) ng/mL, p = 0.019].

Conclusion: Although there was no difference in baseline neudesin levels between the patient and control groups, neudesin levels increased after short-term treatment. Larger prospective studies are needed to understand the pathophysiological role of neudesin in untreated and treated early CH.

Keywords: Congenital hypothyroidism, neudesin, levothyroxine sodium

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Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency at birth and occurs as a result of inadequate development or function of the thyroid gland (primary CH) or inadequate pituitary stimulation of the normal thyroid gland (central CH) (1). CH has an incidence of 1:2000 to 1:4000 worldwide (2,3,4). CH is one of the common preventable causes of intellectual impairment if left untreated, but the introduction of screening programs has assisted in the early detection and treatment of CH (5). The thyroid gland produces and secretes thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are necessary for growth, neurodevelopment, and normal energy metabolism. Thyroid hormones control the development of the central nervous system specifically by affecting myelination, synapsis development, and neuronal differentiation in the prenatal and neonatal periods but remain critical for brain development until around three years of age when this process is largely completed (6,7,8).

Neudesin [neuron-derived neurotrophic factor (NENF)] is a secreted neuronal protein of 21 kDa and 171 amino acids (9). The fundamental structure of neudesin exhibits a heme/steroid binding domain that resembles that of cytochrome b5, and it is categorized as a membrane-associated progesterone receptor (MAPR) (10). NENF is highly expressed in neurons at embryonic stages, particularly in the brain and spinal cord (9). Neudesin expression has been observed during embryonic brain cortical formation in the pre-plate region, in which post-mitotic neurons exist, but not in the regions of precursors that proliferate and migrate (11). Neudesin improves the survival of mature neurons and the proliferation and differentiation of neural precursors into a neuronal lineage (11). Moreover, it has also been shown that neudesin is a negative regulator of energy expenditure (12).

As neudesin and thyroid hormones have similar targets (brain development, energy expenditure), the primary focus of the present study was to examine the association between hypothyroidism and serum neudesin levels in mature newborns referred to the hospital with thyroid dysfunction or clinical suspicion and diagnosed with CH.

Methods

Patients

Newborns who were found to have elevated thyroid stimulating hormone (TSH) in the screening program for CH and who presented to our pediatric endocrinology outpatient clinic were included in the study. Venous blood samples of neonates were obtained at the first visit to confirm the CH diagnosis. In addition, blood samples were centrifuged at 2500 rpm for 10 minutes (Nüve NF 1200 was used as a cooled centrifuge), and obtained serum samples were stored at -80 °C for the study of neudesin levels. Neonates whose serum thyroid function tests (TFTs) were consistent with CH [TSH > 20 IU/mL with low free thyroxine (fT4) levels] were included in the patient group. In comparison, neonates with normal serum TFTs (TSH < 6 IU/mL andfree thyroxine (fT4) levels in the normal range) were included in the control group (1). Children with anatomical anomalies, small for gestational age, and premature children were excluded.

All patients‘ length standard deviation score (SDS), weight SDS, body mass index (BMI) SDS, head circumference SDS, gestational age, chronological age, gender, and mother‘s thyroid illness history were recorded in patient records. We also assessed the levels of anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin (anti-TG), thyroglobulin, and urinary iodine in the patient group.

Following the initial examination, levothyroxine (L-T4) treatment at 10-15 mcg/kg/day was started for CH patients immediately. Initial L-T4 dosage was adjusted on the fifteenth day of treatment based on clinical and biochemical status to preserve blood fT4 and TSH levels within the normal range. The etiology of CH was also investigated by thyroid ultrasonography. After the first month of the visit following L-T4 administration, fT4, and TSH levels were analyzed. In addition, second serum samples were collected from babies attending clinic and stored to assess the effect of L-T4 therapy on serum neudesin levels in CH patients.

Informed consent was obtained from the families of the participants, and the study protocol was approved by the Ethics Committee of Bezmialem Vakıf University (decision no: 17/7, date: 21.09.2022) and supported by the Scientific Research Project Department of Bezmialem Vakıf University (project number: 2021220).

Hormone Assays

Serum levels of TSH, free triiodothyronine (fT3), fT4, anti-TG, thyroglobulin (TG), and anti-TPO were determined at the Bezmialem University Hospital, İstanbul, Türkiye, by chemiluminescent enzyme immunometric assays using commercial kits (procured from Siemens Medical Atellica Solutions Diagnostics, United States of America (USA). The reference intervals for our study were 13.02 to 25.86 pmol/L (1.02-2.01 ng/dL) for fT4, 4.3 to 8 pmol/L for fT3, and 0.420 to 7.55 uIU/mL for TSH (13). Spot urinary iodine was detected by inductively coupled plasma mass spectrometry (ICP-MS) (ICP-MS; Agilent 770). Serum neudesin levels were measured with “Human Neudesin, NENF Elisa Kit (BT-LAB E4258hu)” (Shanghai Korain Biotech (Head office, Shanghai, China)

1008, 228 Ningguo Rd 200090, Yangpu Dist, Shanghai, China).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 23 (IBM Inc., Armonk, NY, USA). Variables were expressed as mean ± standard deviation, whereas especially neudesin which was non-normally distributed was also presented as median (minimum, maximum). The baseline data of the control and patient groups were evaluated with the Mann-Whitney U test. In contrast, the pre- and post-treatment data in the patient group were analyzed using the Wilcoxon, non-parametric test. Spearman's bivariate correlation analysis method was used to evaluate the relationship between BMI SDS and neudesin.

Results

In total 52 babies were recruited to the study. Of these 32 (61.5%) were diagnosed with CH based on initial serum TFT results while 20 (38.5%) had normal TFTs on formal venous testing. However, at the end of the first month of treatment, 6 of 32 patients with CH did not visit the clinic. Therefore, their control blood could not be obtained. Baseline anthropometric measurements, laboratory results, and comparison of the patient and control groups are shown in Table 1. Patients with CH who were treated with L-T4 and the control group were compared, and the two groups did not differ significantly concerning anthropometric measurements (height SDS, weight SDS, head circumference SDS). The statistical comparison of fT4, fT3, TSH, TG, urinary iodine levels, and neudesin levels of the CH and control groups at admission are summarized in Table 1. All patients in the control group had venous TSH levels below 6 mU/L while the patient group had elevated TSH (2.47 ± 0.74 mU/L vs. 280.99 ± 297.37 mU/L, respectively; $p < 0.001$). Similarly, the fT4 levels in patient and control groups were significantly different (6.31 ± 2.64 pmol/L vs. 14.99 ± 2.03 pmol/L, respectively; $p < 0.001$). Thyroid ultrasonography was performed in CH patients. Two patients had goiter, three had agenesis, and one had hemi-agenesis. The thyroid ultrasound of the remaining patients (26/32) was normal. In addition, iodine deficiency was found in 4 patients, iodine excess in 5 patients, and anti-thyroid peroxidase positivity in 2 patients. Baseline neudesin levels did not differ between the CH and control groups (6.77 ± 6.41 vs. 7.93 ± 7.04 ng/mL, respectively; $p = 0.552$).

At the end of one month of L-T4 treatment, neudesin levels were remeasured in babies diagnosed with CH (Table 2). Their neudesin levels increased significantly following one month of treatment [median: 3.93 (minimum: 0.31, maximum: 30.06) vs. median: 6.15 (minimum: 2.17, maximum: 70.05) ng/mL; $p = 0.019$] after 30 days of L-T4 treatment in the CH group, as expected, there was also an increase in fT4 and a decrease in TSH. The effect of L-T4 treatment on thyroid hormones and serum neudesin levels is shown in Table 2.

Table 1. Baseline data of 52 newborns (patients group vs. control group)

Variables	Patients (n = 32)	Control group (n = 20)	p value
Gender M/F	18/14	13/7	0.371
Age (day)	19 ± 7 (7-30)	22 ± 8 (14-30)	0.136
Length SDS	-0.34 ± 0.72	-0.51 ± 0.75	0.26
Weight SDS	-0.041 ± 0.77	-0.35 ± 1.1	0.24
Body mass index (kg/m^2)	14.18 ± 1.56	14.42 ± 1.90	0.418
Head circumference SDS	0.043 ± 0.80	-0.27 ± 0.77	0.16
Mother's thyroid disorder history	7/32 (21%)	1/20 (0.5%)	**< 0.001**
fT3 (pmol/L)	3.14 ± 2.01	6.06 ± 0.86	**< 0.001**
fT4 (pmol/L)	6.31 ± 2.64	14.99 ± 2.03	**< 0.001**
TSH (mU/L)	280.99 ± 297.37	2.47 ± 0.74	**< 0.001**
Thyroglobulin (ng/mL)	1482.68 ± 1351.97	67.74 ± 39.90	**0.002**
Urinary iodine (mcg/L)	400.83 ± 334.23	173.11 ± 96.73	**< 0.001**
Neudesin level* (ng/mL)	6.77 ± 6.41	7.93 ± 7.04	0.552
Thyroid USG	Agenesis: 3 Hemi-agenesis: 1 Goiter: 2 Normal: 26		

*Baseline neudesin levels.
M: male, F: female, fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone, Tg: thyroglobulin, USG: ultrasonography, SDS: standard deviation score

Table 2. Effect of levothyroxine sodium treatment on anthropometric measures, thyroid hormone, and neudesin levels

	Patients before treatment	Patients after treatment	p
Length SDS	-0.03 ± 0.72	-0.15 ± 0.66	0.41
Weight SDS	-0.42 ± 0.77	-0.01 ± 0.51	0.76
BMI	14.23 ± 1.49	15.76 ± 1.32	**< 0.001**
BMI SDS	-0.13 ± 0.91	0.41 ± 0.62	**< 0.001**
Head circumference SDS	-0.43 ± 0.80	-0.18 ± 0.75	0.15
fT4 (pmol/L)	6.31 ± 2.64	20.92 ± 3.97	**< 0.001**
TSH (mU/L)	280.99 ± 297.37 170.23 (32.93, 1100)	4.89 ± 16.07 1.52 (0.08, 24.12)	**< 0.001**
Neudesin level* (ng/mL)	6.46 ± 6.63 3.93 (0.31, 30.06)	12.85 ± 18.74 6.15 (2.17, 70.05)	**0.019**

*The second blood sample obtained only in 26 of 32 children.
Non-normally distributed parameters were also presented as median (minimum, maximum).
fT4: free thyroxine, TSH: thyroid stimulating hormone, BMI: body mass index, SDS: standard deviation score

No correlation was found between serum neudesin levels and BMI SDS in bivariate correlation analysis (r = 0.245, p = 0.172).

Discussion

Neudesin is a MAPR protein family member. It has been previously demonstrated that neudesin appears to be involved in energy metabolism, neural development and function, and tumorigenesis (12). Neudesin is primarily expressed in neurons. Moreover, neudesin exhibits significant neurotrophic activity in primary cultured neurons but not mitogenic activity in primary cultured astrocytes, indicating that it is a neurotrophic factor (9,12). Neudesin is also expressed in neural precursor cells before the appearance of neurons in mice, indicating its potential role in neural development (11). Neuronal differentiation may be promoted by neudesin, mediated through activation of the protein kinase A and PI3K pathways in cultured neural precursor cells. Neural cell proliferation may also be promoted by neudesin in the developmental process (11). It is well established that thyroid hormones are necessary for growth and for neurodevelopment (8). Moreover, although no molecular studies have demonstrated a relationship between thyroid hormones and neudesin, a few studies have demonstrated the relationship between thyroid hormones and other neurotrophic factors. Yajima et al. (14) reported that a lack of thyroid hormones induced a developmental delay in primary hippocampal neurons, likely caused by decreased brain-derived neurotrophic factor *(BDNF)* gene expression. Furthermore, *in vivo* experiments have shown that thyroid hormone administration increased BDNF expression in the brain tissue of young adult rats (15). In another study, Lasley and Gilbert (16) showed that BDNF expression decreased in adult rats with hypothyroidism, but this change was not detected in the neonatal period in the same study. As both thyroid hormones and neudesin affect neurodevelopment, we hypothesized that thyroid hormones might have a relationship with neudesin. Our results demonstrated no difference in levels of neudesin in babies with CH before replacement L-T4 was started and non-CH peers but there was a significant short-term increase in neudesin levels after L-T4 was started in patients with CH. However, this study was not designed or able to explain the pathophysiological mechanisms of this relationship.

Activating the parasympathetic system leads to energy expenditure in white adipose tissue and increased heat in brown adipose tissue. A study in neudesin knock-out mice has shown that the parasympathetic nervous system is over-activated in these animals. Based on this, it has been suggested that neudesin has a negative regulatory role in energy balance (17). Neudesin's role in different metabolic disorders, such as obesity, polycystic ovary syndrome, and type 2 diabetes mellitus have been investigated (18,19,20,21). Çelikkol et al. (21) reported a negative correlation between neudesin levels and BMI Z-score. Kratochvilova et al. (18) have also reported that neudesin levels change with chronic weight reduction or during prolonged fasting. Moreover, Polkowska et al. (20) reported that neudesin levels were higher in diabetic patients compared to the control group, again supporting a role in energy homeostasis for neudesin. In light of these data, neudesin levels are expected to decrease with increasing BMI. However, in our study, although there was a small increase in BMI SDS levels, neudesin levels also increased, and no correlation was detected between BMI SDS and neudesin. This conflicting finding is difficult to explain but may be due to differences in study populations. Previously, it has been shown that TRH/TSH is regulated by thyroid hormone feedback, and there is also central modulation by

nutritional signals, such as leptin, and peptides regulating appetite (22). The rapid recovery from slow metabolism with the normalization of thyroid hormones can result in increased energy consumption. One mechanism of adaptation to this rapid change in metabolism may be an increase in neudesin levels. Experimental studies are needed to evaluate the pathophysiological relationship and mechanisms between neudesin and thyroid hormones in terms of energy homeostasis.

Although there are a few studies into neudesin levels in metabolic disorders, to the best of our knowledge, there is no clinical study investigating neudesin levels in patients with CH or other neurodevelopmental diseases. Therefore, the levels of neudesin in children with or without neurological involvement in hypothyroidism are not yet known. The participants in our study were those with no neurological complaints, regular neurological examinations, and early hypothyroidism diagnoses as a result of the screening program. Our patient group was detected and treated relatively early. Investigating the relationship between neurological development and/or pathology and neudesin levels will require much more investigation.

Study Limitations

The most important limitation of our study was that, due to, second blood samples could not be taken from the group in which hypothyroidism was not detected because of ethical reasons. Therefore, we could not observe the change in the neudesin levels in the healthy control group or compare it with the CH group. The second limitation was the low number of patients.

Conclusion

In conclusion, although there was no difference in baseline neudesin levels between the CH patient and control groups, an increase in neudesin levels was observed in babies with CH after one month of replacement L-T4 treatment at 10-15 mcg/kg/day. However, more extensive clinical and/or experimental studies are needed to investigate the pathophysiological implications this finding in CH or the recovery process.

Ethics

Ethics Committee Approval: The study was approved by the Bezmialem Vakıf University of Ethics Committee (decision no: 17/7, date: 21.09.2022).

Informed Consent: Informed consent was obtained from the families of the participants.

Footnotes

Authorship Contributions

Concept: İlker Tolga Özgen, Design: İlker Tolga Özgen, Data Collection or Processing: Semra Bahar, İlker Tolga Özgen, Yaşar Cesur, Emel Hatun Aytaç Kaplan, Zümrüt Kocabey Sütçü, Analysis or Interpretation: İlker Tolga Özgen, Yaşar Cesur, Caner Yıldız, Ömer Faruk Özer, Literature Search: Semra Bahar, İlker Tolga Özgen, Writing: Semra Bahar, İlker Tolga Özgen.

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Current Practices in Hashimoto's Thyroiditis: Differences in Attitudes Between Pediatric and Adult Endocrinologists in Türkiye: A National Survey

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What is already known on this topic?

Hashimoto's thyroiditis (HT) is a common thyroid disease among adults, and its incidence in children increases over time. There are many published studies on diagnosis, follow-up, thyroid hormone replacement and supportive treatment methods, some with challenging results and findings. The lack of a consensus guideline on the diagnosis and management of HT may lead to different attitudes among endocrinologists. Differences in attitudes and tendencies between pediatric and adult endocrinologists (AEs) regarding the diagnosis and treatment of HT are unclear.

What this study adds?

This study reveals both similarities and differences in the attitudes of pediatric and AEs in Türkiye. Moreover, issues are highlighted that remain unclear to these specialists, which may lead to further investigations.

Abstract

Objective: This study aimed to assess the clinical practices and attitudes towards Hashimoto's thyroiditis (HT) among pediatric (PEs) and adult endocrinologists (AEs).

Methods: The members of Turkish Society for Pediatric Endocrinology and Diabetes (n = 502) and the Society of Endocrinology and Metabolism of Türkiye (n = 910) were invited to participate in an online survey.

Results: Of the respondents (n = 168), 72.6% (n = 122) were PEs and 27.3% (n = 46) were AEs. The response rate was 24% among PEs and only 5% among AEs. Respondents median age was 41 years. The use of "only thyroid peroxidase autoantibodies" was preferred more frequently by AEs (28.3%) than by PEs (4.1%) (p = 0.002). The rate of informing patient/parents at the time of diagnosis that HT

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lasts a lifetime was 91.3% for AEs and 62.3% for PEs (p = 0.001). The rate of beginning treatment in euthyroid cases with goiter was significantly higher in PEs (26.2%) compared to AEs (4.3%) (p = 0.017). Among AEs, 71.7% stated that they would never stop treatment, while among PEs, 33.6% did (p < 0.001). Moreover, 44% of PEs stated that they would attempt treatment discontinuation in euthyroid patients at the end of puberty. The rate of those who were undecided about selenium supplementation was higher amongst PEs (41%) than among AEs (21.7%) (p = 0.007). Although none of the PEs recommended gluten restriction, 6.5% of the AEs indicated that they would recommend gluten-free diet even without Celiac disease (p = 0.015).
Conclusion: There are significant differences between PEs and AEs encompassing aspects of diagnosis, treatment and nutritional supplementation in HT.
Keywords: Adult endocrinology, attitude in management, Hashimoto's thyroiditis, pediatric endocrinology, questionnaire

Introduction

Hashimoto's thyroiditis (HT), also known as autoimmune thyroiditis or chronic lymphocytic thyroiditis, remains the most common thyroid disease group in the general population. In recent years, the reported prevalence of HT in childhood is 1.2%, the prevalence in adults has been reported as 7.5% (1,2). While it is the most common thyroid gland disease in both children and adults, there are no published treatment guidelines on the management of patients with HT. There is no consensus among clinicians on which autoantibodies should be evaluated for diagnosis, whether subclinical hypothyroidism (SH) cases need levothyroxine (LT4) treatment, and how long the treatment period should be in cases where treatment is initiated.

While serum thyroid peroxidase antibodies (TPO-ab) are present in approximately 95% of patients, thyroglobulin antibodies (Tg-ab) are present in 60-80%, therefore the opinion is that the measurement of Tg-ab alone may be less reliable for diagnosis, is getting accepted more commonly (3,4). However, as far as we know, there is no published data on the extent to which clinicians request these antibodies. There are differing opinions on both the diagnosis and treatment of hypothyroidism. While it has been suggested that treatment should be lifelong, long-term follow-up of pediatric cases has shown that 30-50% of individuals with hypothyroidism become euthyroid during follow-up, indicating that lifelong LT4 treatment may not be necessary (5,6,7,8). There is no clear answer regarding when to discontinue the treatment. The presence of goiter is an important factor in starting and continuing treatment for patients with HT. The debate about hormone replacement in HT cases with SH is ongoing. However, LT4 replacement is generally not recommended in euthyroid HT cases.

There are also different opinions about nutrition, supplements, and additional treatment methods for adult and pediatric cases of HT. Recently, certain nutritional recommendations have gained popularity for preventing HT in individuals predisposed to autoimmunity and treating individuals with HT. Some studies, which form the basis of these recommendations, have shown that the frequency of HT increases in regions where iodine prophylaxis is performed (9,10). Indeed, the role of iodine in triggering thyroid autoimmunity is strongly supported by animal models (11). As a result of these studies, the need for iodine restriction in HT patients has become a topic of discussion, and some experts have even raised concerns about the potential harms of iodine prophylaxis in HT patients and individuals at risk for HT (12).

Another recent and debatable recommendation for individuals with HT is a gluten-free diet. Some experts advocate this based on the close relationship between celiac disease and autoimmune thyroid diseases and numerous studies that have suggested that people with HT may benefit from a gluten-free diet, even in the absence of celiac disease (13). Similarly, selenium supplementation in HT has recently become a hot topic and the subject of numerous studies. Seleno-proteins play a crucial role in thyroid hormone deiodination, and selenium deficiency may be considered a predisposing factor for HT as a dietary environmental element (14). However, the results of studies investigating the effect of selenium supplementation in HT cases are contradictory, and there is no compelling evidence supporting selenium supplementation in individuals without selenium deficiency (13).

Many studies on the attitudes of clinicians in the management of HT have focused on adults, yet there is still a lack of consensus among adult endocrinologists (AEs). There have been very few studies involving pediatricians. The absence of a unified guideline for diagnosing and managing HT may result in differing approaches among endocrinologists. The aim of this study was to assess the clinical practices and attitudes towards the diagnosis, treatment, and follow-up of HT among pediatric endocrinologists (PEs) and compare them with those of AEs.

Methods

The questionnaire was developed by six PEs from the TSPED Thyroid Working Group, and its content validity was

ensured through expert review. A pilot study was conducted with a small group of specialists, and revisions were made based on their feedback. Due to the descriptive nature of the survey, advanced statistical validation methods were not applied. A web-based survey was constructed with Google Forms (Google, Mountain View, CA, USA). The questionnaire was e-mailed to 502 members of the TSPED and 910 members of the Society of Endocrinology and Metabolism of Türkiye. An initial e-mail including an electronic link to the questionnaire was sent, followed by two reminders. The inclusion criteria were: (i) having practiced in Türkiye; (ii) being a pediatric or adult endocrinology fellow or attending physician; and (iii) voluntarily filling out the survey. The study protocol was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Health Practices and Research Centre Local Ethics Committee (protocol no: 4449, date: 25.06.2024). The questionnaire consisted of a total of 41 questions. These included eight questions evaluating the demographic characteristics and 33 multiple-choice questions about the attitude on diagnosis, follow-up, treatment, nutrition and nutritional supplements. The entire survey is available as an online supplement (Supplementary Survey 1).

Statistical Analysis

The resulting data were analyzed using IBM Statistical Package for the Social Sciences, version 28.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used for evaluating the distribution of data. Descriptive statistics are presented as mean ± standard deviation for normally distributed variables, and as median (minimum-maximum) for non-normally distributed variables. The Mann-Whitney U test was used to compare differences between continuous variables with non-normal distribution. The chi-square test was used to compare categorical variables. The Bonferroni correction was used for post-hoc analysis. A p value less than 0.05 was considered statistically significant.

Results

Survey Respondents

A total of 168 participants completed the questionnaire. Of the respondents 72.6% (n = 122) were PEs, and 27.3% (n = 46) were AEs. The response rate to the survey was 24% among PEs (n = 502) and 5% among AEs (n = 910). Of the participants, 72% (n = 121) were female. The median age was 41 years. The median duration of clinical experience was longer amongst AE than for PE (overall median = 8 years; for AEs 10.5 vs. 7 for PEs, p = 0.005). There was a significant difference between AEs and PEs regarding their titles, the proportion of professors was higher among AEs than PEs. The main clinical practice centers were the Ministry of Health Training and Research Hospitals (45.9%) in the PEs group and state university hospitals (32.6%) in the AEs group (p < 0.001). The characteristics of the respondents are summarized in Table 1.

Attitude Regarding the Diagnosis, Follow-up and Treatment

As a diagnostic tool, the most preferred thyroid autoantibody test option in both PEs (86.1%) and AEs groups (58.7%) was "the combination of TPO-ab and Tg-ab". However, the use of "only TPO-ab" was preferred more frequently in AEs

Table 1. The characteristics of the respondents

	All the participants (n = 168)	PEs (n = 122)	AEs (n = 46)	p value
Median age (year)	41 (8)	41 (8)	42 (10.5)	0.441
Gender				
Female (%)	121 (72%)	91 (74.6%)	30 (65.2%)	0.25
Median duration of speciality practice (year)	8 (10)	7 (10)	10.5 (15)	**0.005**
Having > 5 years of experience (%)	62	57	73	0.067
Title				**0.03**
Fellow	37 (22%)	31 (25.4%)	6 (13%)	
Consultant	68 (40.5%)	52 (42.6%)	16 (34.8%)	
Assistant professor	8 (4.8%)	7 (5.7%)	1 (2.2%)	
Associated professor	21 (12.5%)	14 (11.5%)	7 (15.2%)	
Professor*	34 (20.2%)	18 (14.8%)	16 (34.8%)	
Clinical practice center				**< 0.001**
Ministry of health training and research hospital	63 (37.5%)	56 (45.9%)	7 (15.2%)	
State university hospital	56 (41.1%)	41 (33.6%)	15 (32.6%)	
State hospital	16 (9.5%)	12 (9.8%)	4 (8.7%)	
Private university hospital	10 (6%)	7 (5.7%)	3 (6.5%)	
Private hospital†	15 (8.9%)	3 (2.5%)	12 (26%)	
Private center	8 (4.8%)	3 (2.5%)	5 (11%)	

*Significant in relation to "Professor", †Significant in relation to "Private Hospital".
PEs: pediatric endocrinologists, AEs: adult endocrinologists

(28.3%) than in PEs (4.1%) (p = 0.002). The rate of request for thyroid ultrasound (US) at the time of diagnosis was not significantly different between PEs (94.2%) and AEs (82.6%) (p = 0.061). However, the frequency of the respondents who request thyroid US at the follow-up was higher amongst PEs than AEs (95.9% vs. 76.1%, p < 0.001). There was no significant difference between PEs and AEs in terms of the frequency of outpatient visits (p = 0.051), the use of fT3 levels alongside thyroid stimulating hormone (TSH) and fT4 levels (p = 0.35), or the ranges at which autoantibody levels are regarded as positive (p = 0.08). Among AEs, 91.3% informed the patient/parents at the time of diagnosis that HT lasts a lifetime, which was significantly more frequent than PEs (62.3%) (p = 0.001). There was no significant difference between PEs and AEs in providing information about the possibility of changes in thyroid function status (p = 0.562).

In cases of SH without goiter, both PEs and AEs mostly stated they would start LT4 treatment when TSH levels were above 10 IU/L (p = 0.287). However, the rate of beginning treatment in euthyroid cases with goiter was significantly higher in PEs (26.2%) compared to AEs (4.3%) (p = 0.017). There were no significant differences in terms of experience period, age and title between the PEs (n = 32) who indicated that they would start treatment in this condition and those who would not (n = 85) (p = 0.11, p = 0.406, and p = 0.393, respectively). Among AEs, 71.7% stated that they would never stop treatment, which was significantly higher than the rate among PEs (33.6%) (p < 0.001). In the whole-group analysis, there was no significant difference in the propensity to discontinue treatment between participants who recommended initiating treatment at lower TSH levels and those who favored a higher threshold (TSH > 10 IU/L). Among the participants, 38% of who recommended treatment for TSH > 10 IU/L, 48% of who recommended treatment for TSH > 5 IU/L, and 57% of who recommended treatment for TSH above the reference range indicated that they would never discontinue treatment (p = 0.461). Among the PEs, no significant difference was noted between those who stated that they would never stop the treatment (n = 41) and those who stated that they would stop the treatment at a certain time (n = 81) in terms of experience period, age, and title (p = 0.326, p = 0.358, and p = 0.242, respectively). Additionally, 44% of PEs stated that they would try to discontinue treatment in euthyroid cases when puberty was completed. The attitudes of PEs and AEs regarding the diagnosis, follow-up and treatment are summarized in Table 2.

Attitude Regarding Nutritional Modifications and Supplements

The attitudes regarding nutritional modifications and supplements are given in Table 3. There were no significant differences between PEs and AEs in terms of indications for performing urinary iodine analysis (p = 0.29), recommending or eliminating iodized salt in the diet (p = 0.434). The rate of those who were undecided about selenium supplementation was higher among PEs (41%) than among AEs (21.7%) (p = 0.007). Although none of the PEs recommended gluten restriction, 6.5% of the AEs indicated that they would recommend gluten-free diet, even for patients without celiac disease (p = 0.015).

Discussion

The findings of this study reveal that there was no consensus among clinicians regarding the management of HT in Türkiye. Furthermore, there were significant differences in HT management between PEs and AEs. These differences encompass aspects of diagnosis, treatment initiation and continuation, and nutritional supplementation, reflecting variations in clinical practices.

A notable difference in the diagnostic approach was the preference for thyroid autoantibody testing. PEs overwhelmingly prefered a combination of TPO-ab and Tg-ab, whereas a significant proportion of AEs were content with TPO-ab alone. This might suggest a more cautious approach among PEs, who perhaps seek a comprehensive antibody profile for better diagnostic accuracy. Although both antibodies have been shown to be positive at rates up to 20-25% in the normal population, there is a known relationship between TPO-ab positivity and TSH levels (15). Despite differing recommendations in various sources regarding the testing for TPO-ab and/or Tg-ab antibodies, there are no definite recommendations for measuring thyrotropin receptor antibodies (TRAb or TSHR-Ab) levels (15,16,17). The prevalence and functional significance of TSHR-blocking autoantibodies (TBAb) in autoimmune hypothyroidism have been investigated less than TSHR-stimulating antibodies, but it is known that there is a low rate of TBAb positivity in HT cases (18). Interestingly, in our study, the rate of those who requested TRAb in addition to the other two antibodies for the diagnosis of HT was approximately 10% among PE and 13% among AEs, which was not significantly different. The increasing evidence showing that TBAb is important in the diagnosis and management of autoimmune thyroiditis cases, facilitated by recently developed laboratory techniques (19), may be the reason behind this approach.

Table 2. Attitude regarding the diagnosis, follow-up and treatment

Responses	All of the participants (n = 168)	Pediatric endocrinologists (n = 122)	Adult endocrinologists (n = 46)	p value
'As a diagnostic test, I use the following thyroid autoantibodies'				**0.002**
TPO-ab + Tg-ab	132 (78.6%)	105 (86.1%)	27 (58.7%)	
TPO-ab + Tg-ab + TRAB-	18 (10.7%)	12 (9.8%)	6 (13%)	
Only TPO-ab*	18 (10.7%)	5 (4.1%)	13 (28.3%)	
Thyroid autoantibody positivity				0.08
'I would consider any value above the reference range as positive.'	79 (47%)	50 (41%)	29 (63%)	
'I would consider as positive if it is at least twice the upper limit or higher.'	48 (28.6%)	40 (32.8%)	8 (17.4%)	
'I would consider as positive if it is at least 3 times the upper limit or higher.'	26 (15.5%)	19 (15.6%)	7 (15.2%)	
Other	15 (8.9%)	13 (10.6%)	2 (4.3%)	
Request for T3 and, or free T3 test				0.350
Yes	33 (19.6%)	22 (18%)	11 (23.9%)	
No	130 (77.4%)	95 (77.9%)	35 (76.1%)	
Undecided	5 (3%)	5 (4.1%)	0	
Request of thyroid ultrasound at the time of diagnosis				0.061
Yes	153 (91.1%)	115 (94.2%)	38 (82.6%)	
No	1 (0.6%)	0	1 (2.2%)	
Only in case of suspicious nodule on physical examination	14 (8.3%)	7 (5.8%)	7 (15.2%)	
Request of thyroid ultrasound at the follow-up period#				**< 0.001**
Yes	152 (90.5%)	117 (95.9%)	35 (76.1%)	
No	16 (9.5%)	5 (4.1%)	11 (23.9%)	
'When I give information about the diagnosis of HT, I also inform that it lasts a lifetime'				**0.001**
Agree†	118 (70.2%)	76 (62.3%)	42 (91.3%)	
Disagree	28 (16.7%)	25 (20.5%)	3 (6.5%)	
Undecided	22 (13.1%)	21 (17.2%)	1 (2.2%)	
'When I give information about the diagnosis of HT to the patients and/ or their relatives, I also inform that their thyroid functions may change over time.'				0.562
Agree	165 (98.2%)	119 (97.5%)	46 (100%)	
Disagree	2 (1.2%)	2 (1.6%)	0	
Undecided	1 (0.6%)	1 (0.8%)	0	
The frequency of outpatient visits for HT cases who do not require LT4 treatment				0.051
Every 3 months	16 (9.5%)	14 (11.5%)	2 (4.3%)	
Every 6 months	106 (63.1%)	84 (68.9%)	22 (47.8%)	
Annually	33 (19.7%)	16 (13.1%)	17 (37%)	
Other	13 (7.7%)	8 (6.5%)	5 (10.9%)	
'I start LT4 treatment in a patient with subclinical hypothyroidism without goiter if':				0.287
TSH > 10 IU/L	103 (61.3%)	83 (68%)	20 (43.5%)	
TSH > 5 IU/L	31 (18.5%)	21 (17%)	10 (21%)	
TSH is above the reference ranges.	34 (20.2%)	18 (15%)	16 (34.8%)	
'I start LT4 treatment in a case of HT with Goiter':				**0.017**
Even if the patient is euthyroid‡	34 (20.2%)	32 (26.2%)	2 (4.3%)	
If TSH > 10 IU/L	23 (13.7%)	16 (13.1%)	7 (15.2%)	
If TSH > 5 IU/L	74 (44%)	50 (41%)	24 (52.2%)	
If TSH is above the reference ranges	31 (18.5%)	20 (16.4%)	11 (24%)	
Other	6 (3.6%)	4 (3.3%)	2 (4.3%)	
General approach to discontinue thyroid hormone treatment in a patient who is diagnosed with HT and started treatment#				**< 0.001**
'I do not recommend discontinuing treatment'	74 (44%)	41 (33.6%)	33(71.7%)	
'I try to discontinue treatment if the patient is euthyroid in the follow-up at any time'	94 (56%)	81 (66.4%)	13 (28.3%)	

*Significant in relation to "Only TPO-ab", #Fisher test was used. †Significant in relation to "Agree", ‡Significant in relation to "Even if the patient is euthyroid".
Tg-ab: thyroglobulin antibody, TPO-ab: thyroid peroxidase antibody, TRAB: thyroid stimulating hormone receptor antibody, LT4: levothyroxine, HT: Hashimoto's thyroiditis, TSH: thyroid stimulating hormone

Table 3. Attitude regarding nutritional modifications and supplements

Responses	All of the participants (n = 168)	Pediatric endocrinologists (n = 122)	Adult endocrinologists (n = 46)	p value
Selenium supplementation				**0.007**
It may be given after measuring blood/urinary level and if necessary and,or if the patient has overt/subclinical hypothyroidism.	53 (31.6%)	31 (25.4%)	22 (47.8%)	
I'm undecided*	60 (35.7%)	50 (41%)	10 (21.7%)	
It is completely unnecessary	55 (32.7%)	41 (33.6%)	14 (30.4%)	
Gluten-free diet†				**0.015**
I state that no restrictions are required	83 (49.4%)	65 (53.3%)	18 (39.1%)	
I don't make suggestions unless asked.	73 (43.5%)	54 (44.3%)	19 (41.3%)	
I recommend.	3 (1.8%)	0	3 (6.5%)	
Other	9 (5.4%)	3 (2.4%)	6 (13.1%)	
Iodine restriction				0.434
I state that no restrictions are required	98 (58.3%)	74 (60.7%)	24 (52.2%)	
I don't make suggestions unless asked.	36 (21.5%)	28 (23%)	8 (17.4%)	
I recommend.	14 (8.3%)	6 (4.9%)	8 (17.4%)	
I decide based on urine iodide level	20 (11.9%)	14 (11.5%)	6 (13%)	

*Significant in relation with 'undecided'. †For the statistical analysis only 2 groups included ('I recommend' and the others)

The information provided about the prognosis at the time of diagnosis also differed significantly between the groups. Almost all AEs (91.3%) informed their patients that the disease would last for life, compared to 62.3% of PEs. Similarly, when LT4 treatment was initiated, a significant proportion of AEs (approximately 72%) stated that they would never attempt to discontinue treatment, whereas this rate was approximately 34% amongst PEs. There is no consensus in the literature regarding the duration of LT4 treatment in HT patients. However, some studies have shown that hypothyroid pediatric patients with HT can become euthyroid in 30-50% of cases during follow-up, indicating that lifelong treatment may not be necessary for these patients (5,6,7,8). Raddetti et al. (8) even suggested that discontinuation of treatment should be attempted in pediatric patients with TSH levels < 10 U/L at diagnosis. Despite these studies in pediatric patients, to the best of our knowledge, there are no similar studies in adults. Thus, the discrepancy could stem from differing perspectives on the natural history of HT in children versus adults, with AEs possibly anticipating a more chronic course based on their patient population.

When it comes to initiating treatment, both groups showed a consensus in starting LT4 therapy in cases of SH when TSH levels exceeded 10 IU/L. However, surprisingly, the proportion of those who recommended LT4 therapy to patients with goiter, even if they were euthyroid, was significantly higher among PEs than among AEs. In two surveys conducted among adult thyroid specialists in the United Kingdom and Australia, only 9% and 11% of the respondents, respectively, would consider using thyroid hormone treatment in euthyroid patients with an enlarging goiter (20,21). Although some studies have shown that LT4 treatment reduces thyroid volume in both pediatric and adult HT patients with goiter, even if they are euthyroid (22,23), a more recent randomized controlled trial demonstrated that this reduction in thyroid volume was not permanent (24). No significant difference was found at the end of 36 months when comparing pediatric patients who were euthyroid at baseline and started on LT4 with those who were not. However, in our study, PEs were more likely to initiate treatment in cases of euthyroid goiter, highlighting a more aggressive approach to goiter in children, which may be driven by concerns about further gland enlargement and the development of thyroid nodules during childhood.

The attitudes of respondents to nutritional modifications in HT management were similar regarding iodine restriction. Only 5% of PEs and 17% of AEs recommended iodine restriction. Although some data suggest that iodine can trigger thyroid-related autoimmunity and that the prevalence of HT increases in areas where iodine prophylaxis is used (9,10,11), studies which report the effect of iodine restriction for the treatment of HT are extremely scarce. To the best of our knowledge, there is no such study in children. Yoon et al. (25) demonstrated that iodine restriction normalized thyroid function in adults with HT. However, it should be taken into consideration that the region where the study was conducted was a region with excessive iodine intake. Given that mild to moderate iodine deficiency is still a problem in Türkiye (26,27), it is not surprising that very few of the participants, especially PEs, recommended iodine restriction in HT.

The attitudes towards gluten restriction showed variability between the two groups. For instance, while none of the PEs recommends gluten restriction without diagnosed celiac disease, a small percentage of AEs do. This may reflect an emerging, albeit controversial, belief among some AEs that gluten could play a role in thyroid autoimmunity even in the absence of celiac disease. Indeed, Pobłocki et al. (28) found that a gluten-free diet decreased TSH levels in patients receiving LT4 treatment. However, studies demonstrating a positive effect of a gluten-free diet on thyroid status are extremely limited. Two systematic reviews, which included three and six studies respectively, showed that a gluten-free diet decreased anti-TPO levels but did not affect TSH levels (29,30). Notably, all of these studies were conducted in adults (28,29,30). To the best of our knowledge, there are no studies examining the effects of a gluten-free diet on HT in children, which may be related to the fact that none of the PEs recommended this dietary modification.

The present study also showed a lack of consensus between PEs and AEs regarding selenium supplementation, a popular recommendation in HT management in recent years. Notably, a higher proportion of PEs remained undecided compared to AEs (41% vs. 21.7%). In a 2018 survey, only 20% of European Thyroid Association members believed that selenium supplementation has evidence-based benefits, yet a significant proportion (67%) reported recommending selenium supplementation to their patients (31). Systematic reviews have shown that selenium supplementation, like iodine restriction and gluten-free diet recommendations, has no favorable effect on thyroid functions, although it does decrease the level of thyroid autoantibodies in HT cases (32,33). In addition, the possible side effects of selenium, such as gastric irritation, hair loss, or skin rash should be considered. There are no evidence-based guidelines that highlight cases that warrant selenium supplementation, or whether selenium levels should be evaluated beforehand, and even the appropriate doses if supplementation is performed (34). Moreover, it is controversial whether the decrease in antibody levels resulting from these nutritional modifications is clinically significant, and it is clear that more evidence is needed for these recommendations to become widely applicable.

Study Limitations

This study is not without limitations. The main limitation is the low response rate for the survey, particularly among AEs. This low response rate may limit the generalizability of the findings to the broader population of endocrinologists in Türkiye. In addition, the attitudes and practices of non-responders might differ significantly from those who chose to participate, which could skew the study results. Nevertheless, we think that the results of our study are important in terms of showing the current problems and contradictions among clinicians in Türkiye in HT management.

Conclusion

In conclusion, while the management of HT shows significant variation between PEs and AEs in Türkiye, these differences highlight the need for continued research and the development of comprehensive, evidence-based guidelines to harmonize practices and optimize patient outcomes in HT. As nutritional and supplementation practices evolve, robust clinical trials are needed to establish the efficacy and safety of interventions, including iodine restriction and selenium supplementation, in HT patients. This will help standardize care and ensure all patients receive the most effective and evidence-based treatments.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Health Practices and Research Centre Local Ethics Committee (protocol no: 4449, date: 25.06.2024).

Informed Consent: It is a survey study filled out voluntarily by participants.

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Presented in: The study has been presented as an oral presentation at National Pediatric Endocrinology and Diabetes Congress in 03.04.2024.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Gül Yeşiltepe Mutlu, Bahar Özcabı, Elif Sağsak, Aydilek Dağdeviren Çakır, Yavuz Özer, Cengiz Kara, Concept: Gül Yeşiltepe Mutlu, Design: Gül Yeşiltepe Mutlu, Bahar Özcabı, Elif Sağsak, Aydilek Dağdeviren Çakır, Yavuz Özer, Cengiz Kara, Data Collection or Processing: Gül Yeşiltepe Mutlu, Bahar Özcabı, Aydilek Dağdeviren Çakır, Analysis or Interpretation: Gül Yeşiltepe Mutlu, Bahar Özcabı, Cengiz Kara, Literature Search: Gül Yeşiltepe Mutlu, Bahar Özcabı, Cengiz Kara, Writing: Gül Yeşiltepe Mutlu, Bahar Özcabı, Cengiz Kara.

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ORIGINAL ARTICLE

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Machine Learning-driven Identification of the Honeymoon Phase in Pediatric Type 1 Diabetes and Optimizing Insulin Management

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What is already known on this topic?

The honeymoon phase in type 1 diabetes (T1D) is characterized by a temporary period of reduced insulin needs and better glucose control. Current methods for identifying this phase rely on clinical observations, but they lack precision and often result in delayed or suboptimal insulin management.

What this study adds?

This study introduces advanced machine learning models, such as long short-term memory networks and transformer models, to accurately detect the honeymoon phase in T1D patients. By analyzing continuous glucose monitoring data, these models enhance the precision of honeymoon phase identification, leading to more personalized insulin management and improved overall glycemic control.

Abstract

Objective: The honeymoon phase in type 1 diabetes (T1D) represents a temporary improvement in glycemic control but may complicate insulin management. The aim was to develop and validate a machine learning (ML)-driven method for accurately detecting this phase to optimize insulin therapy and prevent adverse outcomes.

Methods: Data from pediatric T1D patients aged 6-17 years, including continuous glucose monitoring data, glucose management indicator (GMI) reports, hemoglobin A1c (HbA1c) values, and patient medical history, were used to train ML models including long short-term memory (LSTM) networks, transformer models, random forest, and gradient boosting machines (GBMs). These were designed to analyze glucose trends and identify the honeymoon phase in T1D patients.

Results: The transformer model achieved the highest accuracy at 91%, followed by GBMs at 89%, LSTM at 88%, and random forest at 87%. Key features, such as glucose variability, insulin adjustments, GMI values, and HbA1c levels were critical to model performance. Accurate identification of the honeymoon phase enabled optimized insulin adjustments, enhancing glucose control and reducing hypoglycemia risk.

Conclusion: The ML-driven approach provides a robust method for detecting the honeymoon phase in T1D patients, demonstrating potential for improved personalized insulin management. The findings suggest significant benefits in patient outcomes, with future research focused on further validation and clinical integration.

Keywords: Honeymoon phase, insulin management, machine learning, type 1 diabetes

Introduction

Type 1 diabetes (T1D) is a chronic autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreas, leading to lifelong dependence on exogenous insulin therapy (1,2). The honeymoon phase is a well-recognized but transient period following the initial diagnosis of T1D, where patients experience a

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temporary remission of symptoms and improved glycemic control (3,4,5). During this phase, the body retains some residual insulin secretion, reducing the exogenous insulin requirements and stabilizing blood glucose levels. This phase can last from a few months to over a year and varies significantly between patients (6).

However, the honeymoon phase also presents a clinical challenge, as fluctuating insulin needs complicate management strategies, leading to a higher risk of both hypoglycemia and hyperglycemia if not accurately detected and managed (Figure 1) (7). The honeymoon phase is quantified based on significant reductions in insulin requirements, typically defined as a 20-30% decrease in the insulin dose over a 3-6-month period, along with a stable or improving trend in blood glucose levels. Moreover, glucose variability is measured by analyzing the standard deviation of continuous glucose monitoring (CGM) readings during this period (8).

Accurate detection of the honeymoon phase is important for optimizing insulin therapy. Early identification enables healthcare providers to adjust dosages precisely, potentially prolonging the phase and improving patient outcomes (9). Traditional detection methods, such as clinical judgment and periodic hemoglobin A1c (HbA1c) monitoring (Figure 2), often lack the precision required to capture nuanced fluctuations in glucose levels, leaving a gap in timely and effective management (10,11,12).

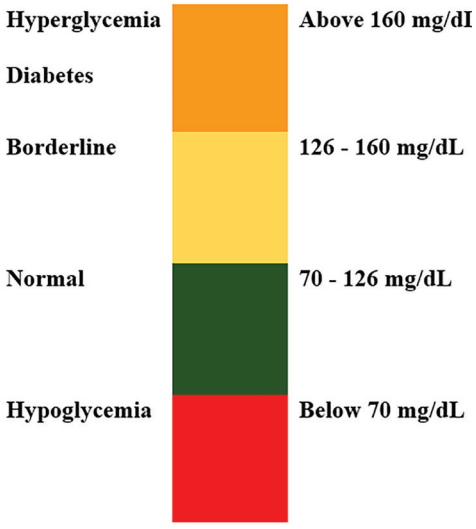

Figure 1. Glucose levels classification

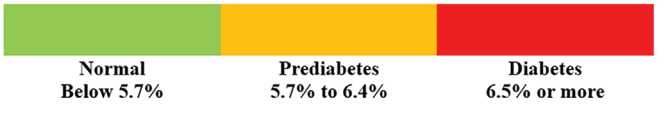

Figure 2. A1c levels for diagnosing diabetes

Recent advances in machine learning (ML) techniques offer a promising alternative by leveraging large datasets to uncover patterns not apparent through conventional methods (13,14,15). ML has already demonstrated significant potential in diabetes management, including predicting glucose trends, optimizing insulin delivery, and personalizing treatment strategies (16,17,18,19,20). For instance, transformer models and long short-term memory (LSTMs) networks have been employed to predict glucose variability, while reinforcement learning approaches have facilitated personalized insulin dosing strategies using CGM data (21,22). ML applications are also being explored for predicting hypoglycemic events and enhancing artificial pancreas systems (23,24).

This study focused on applying ML modeling to identify the honeymoon phase in T1D patients, an area that remains largely unexplored in prior research. By employing algorithms such as LSTM networks, transformer models, random forest, and gradient boosting machines (GBMs), the proposed approach aims to overcome the limitations of traditional techniques (25,26,27). The analysis relied on a comprehensive dataset comprising CGM data, glucose management indicator (GMI) reports, HbA1c values, and patient medical history, which add credibility and robustness to the study (28,29).

Building on previous work, this study uniquely addresses the honeymoon phase using a data-driven framework. Early and accurate detection has the potential to personalize insulin therapy, reduce glycemic variability, and extend the duration of partial remission, ultimately improving long-term outcomes for T1D patients.

Methods

The dataset for this study was sourced from multiple clinical sites, encompassing a diverse range of T1D patient profiles. Each site contributed de-identified data to ensure patient confidentiality and adherence to ethical standards. By aggregating data from various clinical settings, the study captured a comprehensive array of patient experiences and glucose management scenarios, facilitating a robust analysis of the honeymoon phase in T1D (30). This approach not only enhanced the generalizability of the findings but also upheld rigorous ethical practices by anonymizing patient information throughout the data collection and analysis processes (31). The dataset, which included information from the Kaggle platform, further supports this by providing a rich resource for developing and validating ML models aimed at optimizing insulin management and identifying the honeymoon phase in T1D pediatric patients (32,33).

Data Collection

CGM devices were calibrated against a standard glucose meter to ensure accuracy before data collection. Patients wore the devices continuously, typically on the upper arm or abdomen, providing real-time glucose monitoring. Data was transmitted securely to a server, with encryption and backups ensuring data integrity and patient confidentiality. High-resolution glucose measurements were recorded every 5 minutes, with monthly GMI reports summarizing long-term control. Patient medical history, including demographics, insulin regimens, and historical glucose data, was comprehensively documented to support detailed analysis (34).

In addition to clinical data, a publicly available, anonymized diabetic dataset from Kaggle was used to validate ML models. This supplemental dataset provided additional diversity in glucose trends and patient characteristics, aimed at enhancing the robustness of the analysis. The combined dataset included 150 pediatric T1D patients, with an age range of 6 to 17 years.

The CGM system recorded glucose levels in the interstitial fluid at regular intervals, providing a comprehensive view of glucose fluctuations over time. Each 24-hour period yielded between 96 and 288 data points, critical for analyzing short- and long-term glycemic control (35). Day-wise GMI reports monitored glucose levels and identified hypoglycemic events, focusing on readings below 70 mg/dL, as shown in Figure 3. This data enabled accurate adjustments to insulin management strategies.

Insulin doses were adjusted based on real-time CGM data and day-wise GMI reports to optimize glucose control. The adjustment protocol involved reducing doses when glucose levels fell below 70 mg/dL to prevent severe hypoglycemia. Conversely, doses were increased when glucose levels exceeded the target range or insulin needs changed due to meal times or physical activity (36).

To optimize glucose control during the study, insulin doses were adjusted using a structured approach based on real-time CGM data and the automated bolus suggestion (ABS) formula. The ABS formula, applied to each patient, accounts for current blood glucose levels, target glucose goals, insulin sensitivity, and carbohydrate intake.

HbA1c levels were monitored to reflect long-term glucose control by averaging blood glucose over the past two to three months. Comparing HbA1c trends with CGM data evaluated whether short-term insulin modifications improved long-term glycemic control. Regular HbA1c monitoring provided insights into the success of treatment strategies, with lower levels indicating better control and reduced risk of complications (37). Key features extracted included glucose levels, insulin doses, glucose variability, and hypoglycemic events, focusing on episodes where glucose fell below 70 mg/dL. GMI reports were also incorporated, offering monthly summaries that reflected long-term glucose control and trends. HbA1c values (38), reflecting the average blood glucose levels over the past two to three months (Figure 4), were used to validate the effectiveness of insulin adjustments and the overall glucose management strategy.

Ethical Considerations

Patient data were anonymized to protect confidentiality and comply with data protection regulations. Institutional Review Board approval was obtained for the use of patient

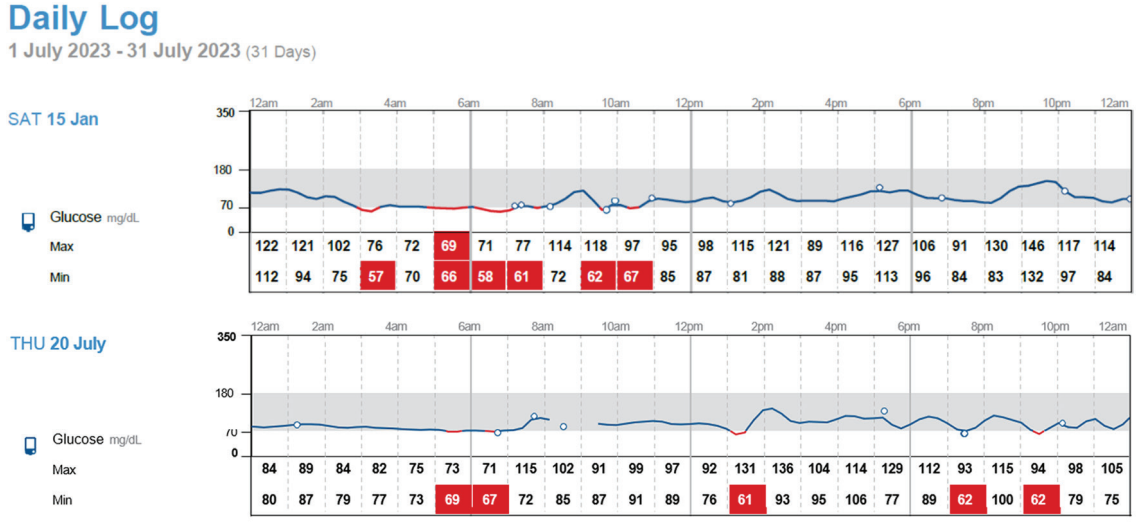

Figure 3. Day-wise glucose management indicator reports

Max.: maximum, Min.:minimum

data, and informed consent was acquired from the patient for the use of their data in this study. The dataset from Kaggle was used to supplement the analysis, which contains anonymized data from multiple patients with diabetes, and was used in compliance with ethical standards for secondary data analysis. The study was approved by the Narasaraopeta Engineering College: Narasaraopeta of Institutional Review Board (IEC ref. no: 01/2024, date: 28.08.2024).

Statistical Analysis

The statistical analysis for this study was conducted to evaluate the effectiveness of insulin dose adjustments and glucose management in identifying the honeymoon phase in pediatric T1D patients. Descriptive statistics, including mean, median, standard deviation, and coefficient of variation, were calculated to summarize glucose levels and insulin doses over the study period. Temporal metrics, such as time-in-range, time-below-range, and time-above-range, were computed to assess glycemic control. Correlation analysis and linear regression were employed to examine the relationship between insulin doses and glucose levels, with statistical significance set at $p < 0.05$.

All statistical analyses were performed using R, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Additional data processing and visualization were conducted using Python (version 3.11.5) with the pandas and matplotlib libraries (Python Software Foundation, Wilmington, Delaware, USA).

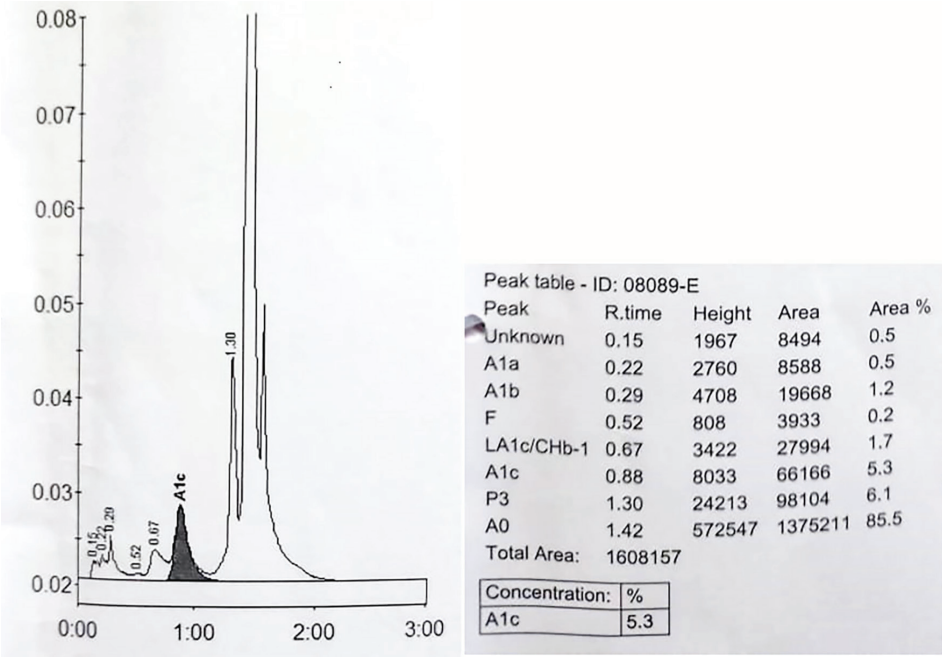

Figure 4. Longitudinal A1c report

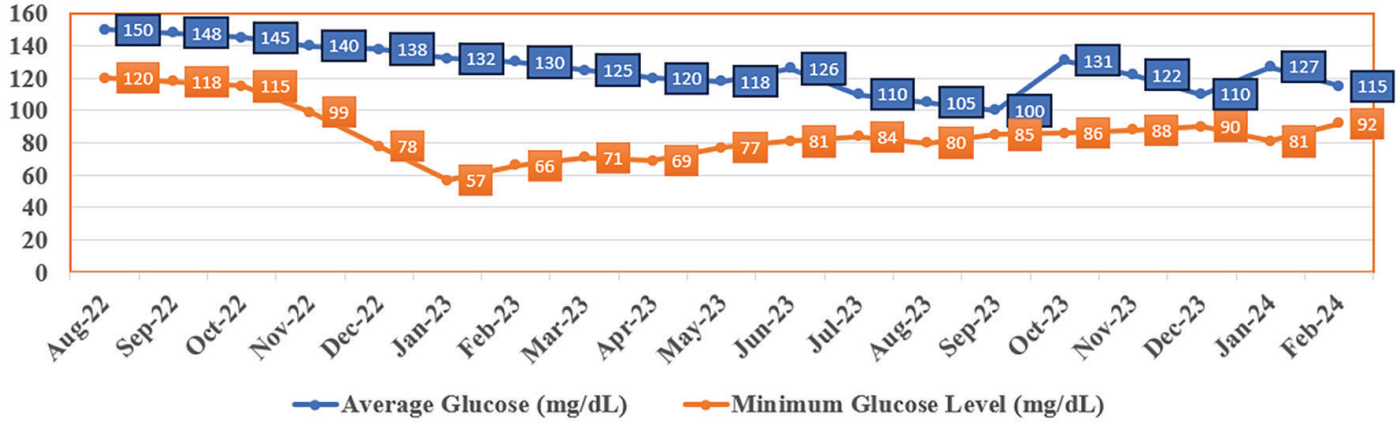

Figure 5. Glucose management indicator trends over time

Machine Learning Models

ML models were employed to enhance the identification of the honeymoon phase in T1D pediatric patients by analyzing data from CGM devices, insulin dosages, glucose variability, and hypoglycemic events. These models used advanced algorithms to detect patterns and trends indicative of the honeymoon phase, characterized by a temporary improvement in glycemic control and reduced insulin requirements (39,40).

Rationale for Model Selection

The selection of ML models in this study was based on the unique characteristics of the dataset and the challenges of detecting the honeymoon phase. LSTM networks were chosen for their ability to capture temporal patterns in sequential CGM data. Transformers, with their self-attention mechanisms, offer precision in identifying complex relationships between glucose data and insulin adjustments. Random forest classifiers were used for their robustness in handling noisy and diverse datasets, while GBMs were selected for their ability to iteratively improve prediction accuracy by identifying subtle patterns in glucose data. This combination of models ensures a comprehensive approach, taking advantage of each model's strengths to address the dataset's temporal, variable, and noisy nature (41).

LSTM networks were used for their ability to analyze time-series CGM data effectively, interpreting temporal patterns to identify significant glucose trends. LSTM memory cells and gating mechanisms allows a focus on relevant patterns while filtering out noise, optimizing insulin adjustments based on real-time glucose trends (21,42).

Transformers were applied to capture intricate patterns in glucose fluctuations and insulin adjustments using self-attention mechanisms. These models excel in preserving sequence order through positional encoding, enabling precise long-term trend interpretation and supporting personalized insulin management (25,43).

Random forest classifiers handled the diversity and noise in glucose data by constructing multiple decision trees and aggregating their predictions. This ensemble technique reduces overfitting and accommodates variations in glucose measurements and insulin regimens, enhancing classification robustness (26,44).

GBMs were employed for their ability to model complex relationships and sequentially refine predictions. By capturing subtle patterns in CGM data, GBMs improve accuracy and reliability in identifying the honeymoon phase, contributing to more personalized and effective treatment strategies (27-45).

The performance of these models was evaluated using metrics including accuracy, precision, recall, and F1-score, ensuring reliable detection of the honeymoon phase while minimizing false positives and negatives. These models collectively enhanced the classification of complex glucose patterns, supporting tailored insulin management for T1D patients (46).

Results

The honeymoon phase in T1D was identified through a comprehensive analysis of the patient's longitudinal glucose data, insulin dose adjustments, and ABS reports. This section details the process of identifying the honeymoon phase.

Glycemic Control and Insulin Adjustments

The GMI trends provided essential insights into glycemic control throughout the study. GMI estimates average glucose levels over time, helping assess the effectiveness of insulin therapy. As shown in Figure 5, GMI values initially indicated higher glucose levels (150 mg/dL in August 2022) due to the recent T1D diagnosis and insulin initiation. Over time, GMI values decreased consistently, reaching 125 mg/dL by May 2023, reflecting improved glycemic control and the onset of the honeymoon phase.

The most significant reduction in GMI occurred between May 2023 and August 2023, with values dropping to 112 mg/dL. This decline coincided with the identification of the honeymoon phase, marked by partial remission and decreased insulin needs. From August 2023 to February 2024, GMI values stabilized between 112-114 mg/dL, confirming the phase and enabling precise insulin dose adjustments based on CGM data. These results suggest that regular GMI monitoring supports effective identification and management of the honeymoon phase in T1D.

As detailed in Table 1, insulin dose adjustments reflected the fluctuations in insulin needs during the honeymoon phase, which is crucial for optimal management of T1D in this phase. In the early phase (August 2022 to February 2023), both average and minimum glucose levels gradually decreased, prompting reductions in insulin doses. This trend aligned with the onset of the honeymoon phase, where partial endogenous insulin production reduced the need for exogenous insulin. During the mid-phase (March 2023 to July 2023), further insulin reductions were made to address occasional hypoglycemic events, marking the peak of the honeymoon phase with the lowest insulin requirements. In the late phase (August 2023 to February 2024), glucose levels and insulin need stabilized, indicating the end of the honeymoon phase. These adjustments highlight the

importance of real-time monitoring to optimize insulin therapy and manage glucose levels effectively, minimizing the risks of hypoglycemia and hyperglycemia.

HbA1c Trends and Long-term Glycemic Control

Regular monitoring of HbA1c values provided critical insights into long-term glycemic control and its relationship with the honeymoon phase. As shown in Table 2, initial HbA1c levels of 6.9% in August 2022 decreased steadily to 5.8% by May 2023, marking the onset of the honeymoon phase. The most significant drop occurred by August 2023, with HbA1c reaching 5.3%, representing the peak of the honeymoon phase. From November 2023 to February 2024, HbA1c values stabilized between 5.6% and 5.9%, reflecting sustained glycemic control and successful management during this period. These findings demonstrate the honeymoon phase's potential to improve long-term glycemic control, which is essential for reducing the risk of diabetes-related complications.

By August 2023, HbA1c had dropped to 5.3%, aligning with the identification of the honeymoon phase-a period of partial remission and reduced insulin needs. This phase persisted, as reflected in HbA1c values of 5.9% in November 2023 and 5.6% in February 2024. These trends demonstrate the honeymoon phase's impact on improved glycemic control, and highlights the potential for optimizing diabetes management in the long term. Regular HbA1c monitoring provided essential insights for tailoring treatment strategies, ensuring better long-term outcomes.

The ML models were trained and validated using the collected datasets to identify the honeymoon phase, focusing on features such as glucose levels, insulin doses, glucose variability, hypoglycemic events, and HbA1c values. Their performance in detecting the honeymoon phase was evaluated based on predictive accuracy, sensitivity, specificity, and overall effectiveness, as summarized in Table 3.

Table 1. Insulin dose adjustments based on CGM

Patient ID	Date	Day average glucose (mg/dL)	Minimum glucose level (mg/dL)	Insulin dose adjustment	Notes
1	01.08.2022	150	120	Reduced	Slight decrease in insulin
1	01.11.2023	145	115	Reduced	Further decrease in insulin
1	01.02.2023	132	94	Reduced	Hypoglycemia detected
1	15.07.2023	92	57	Reduced	Hypoglycemia detected
1	20.07.2023	96	61	Reduced	Frequent hypoglycemia
1	25.07.2023	123	82	None	Normal glucose levels
1	01.08.2023	127	89	None	Normal glucose levels

Table 2. A1c trends and honeymoon phase correlation

Patient ID	Date	A1c (%)	Notes
1	01.08.2022	6.9	Initial report
1	01.11.2022	6.5	Slight decrease
1	01.02.2023	6.2	Continued improvement
1	01.05.2023	5.8	Stable control
1	01.08.2023	5.3	Honeymoon phase noted
1	01.11.2023	5.9	Honeymoon phase continued
1	01.02.2024	5.6	Honeymoon phase continued

Table 3. Performance metrics of machine learning models for identifying the honeymoon phase in type 1 diabetes

Model	Accuracy	Sensitivity	Specificity	Precision	Recall	F1 score
LSTM	88%	85%	90%	86%	85%	85%
Transformer	91%	89%	92%	90%	89%	89%
Random forest	87%	84%	89%	85%	84%	84%
Gradient boosting	89%	86%	91%	88%	86%	87%

LSTM: long short-term memory

In this study, the LSTM model, trained on daily glucose readings, insulin dosages, glucose variability, and hypoglycemic events, achieved an accuracy of 88%. It identified the honeymoon phase in 88% of test cases, with a sensitivity of 85% and specificity of 90%, demonstrating its effectiveness in detecting periods of insulin sensitivity associated with the honeymoon phase while minimizing false positives.

The transformer model, known for its ability to handle complex sequential data through self-attention mechanisms, achieved the highest accuracy of 91%. It had a sensitivity of 89% and a specificity of 92%, excelling in detecting subtle glucose fluctuations and transitions in insulin needs indicative of the honeymoon phase. Its capacity to process long-range dependencies contributed to its superior performance.

The random forest model achieved an accuracy of 87%, with a sensitivity of 84% and specificity of 89%. It effectively managed variability and noise in glucose data, distinguishing between different phases of diabetes management, making it a reliable tool for identifying the honeymoon phase.

The GBM model achieved an accuracy of 89%, with a sensitivity of 86% and a specificity of 91%. It excelled at capturing complex, non-linear relationships in CGM data, balancing sensitivity and specificity for accurate identification of the honeymoon phase.

The comparative analysis of the ML models revealed varying strengths in identifying the honeymoon phase in T1D, as shown in Figure 6. The transformer model led in performance highlighting its superior ability to capture complex patterns and long-range dependencies in glucose data. It outperformed the LSTM model, which achieved an accuracy of 88%, with a sensitivity of 85% and specificity of 90%. While the LSTM model effectively identified temporal dependencies, its slightly lower sensitivity suggests it may miss some true honeymoon phase cases, potentially leading to delayed insulin adjustments. The random forest achieved the next best performance and was strong when managing data variability but with slightly reduced sensitivity and accuracy compared to the transformer and LSTM models. These performance variations underscore the importance of model selection based on specific clinical needs, such as the need for high sensitivity in early honeymoon phase detection.

The GBM model was also effective and excelled in capturing non-linear relationships and subtle glucose trends. Overall, the transformer model's ability to handle complex data and long-range dependencies provided the most accurate and reliable identification of the honeymoon phase, while the other models offered valuable insights and robustness in different aspects of the analysis.

Discussion

This study demonstrated the potential of ML models, particularly the transformer and GBM, to accurately detect the honeymoon phase in T1D patients. The models achieved high accuracy, with the transformer model reaching 91%, suggesting that ML can effectively identify periods of reduced insulin requirements and improved glycemic control.

Our findings align with previous research highlighting the utility of ML in diabetes management, particularly in predicting glucose trends and optimizing insulin therapy. However, our study uniquely focused on the honeymoon phase, a critical transitional period that has been underexplored in prior ML studies (21,22,23,24,25,26,27,28,29). While other studies have

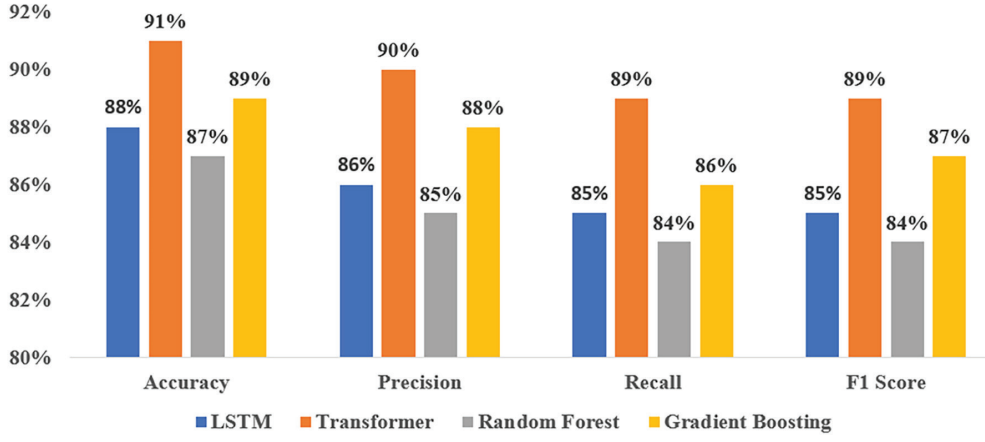

Figure 6. Performance metrics of machine learning models

LSTM: long short-term memory

explored glucose prediction and long-term management, our study is the first to investigate the dynamic insulin needs during the honeymoon phase and how ML can facilitate its early detection (42,43,44,45).

While the models' overall performance was promising, discrepancies were observed when applied to pediatric patients. These discrepancies may be attributed to age-related variations in insulin sensitivity, growth patterns, and puberty, which were not fully accounted for in the models. This underlines the need for further research to refine the models by incorporating pediatric-specific factors.

Clinical Implications

The high accuracy of these ML models suggests their potential for integration into clinical decision support systems. Early identification of the honeymoon phase allows clinicians to adjust insulin therapy more effectively, optimizing glycemic control and reducing the risk of hypoglycemia and hyperglycemia. By incorporating real-time data from CGM, the models can offer personalized recommendations for insulin dose adjustments, improving overall diabetes management.

Limitations and Future Directions

Despite the promising results, the generalizability of the models to pediatric populations remains a limitation. The current models were trained on adult data, and further studies should focus on validating these models in pediatric populations, incorporating factors such as age, pubertal insulin resistance, and growth patterns. Future research should also explore the integration of genetic factors, lifestyle variables, and more granular patient-specific data to improve the models' predictive accuracy.

Recommendations

The insights gained from the ML models offer valuable guidance for personalizing insulin management during the honeymoon phase of T1D. By accurately identifying this phase, clinicians can tailor insulin therapy to better align with the patient's changing insulin needs, optimizing glycemic control and reducing the risk of hypoglycemia and hyperglycemia.

This study highlights the importance of CGM and other key metrics in recognizing the honeymoon phase. Implementing a structured monitoring protocol that leverages these findings can lead to more effective tracking of glucose levels, insulin dosages, and fluctuations, ensuring timely adjustments to treatment plans during this transitional period.

It is important to note that pediatric patients may exhibit different insulin sensitivity and glucose patterns than adults. Therefore, further research is needed to validate the applicability of these models in pediatric diabetology. Age-related insulin sensitivity, growth, and pubertal changes may affect the performance of the models in children.

Validation across larger and more diverse patient cohorts is essential to ensure the robustness and generalizability of the findings. Expanding the dataset will provide clearer insights into how well the models perform in varied clinical settings and demographics. In addition, refining the ML models by incorporating patient-specific factors, genetic information, and lifestyle variables will enhance their ability to handle complex data patterns. Continuous improvements in these models will contribute to more accurate predictions, further personalizing care, and ultimately leading to better management of T1D during the honeymoon phase.

Conclusion

This study presents a robust ML-driven approach for identifying the honeymoon phase in T1D, using a comprehensive dataset that included CGM data, GMI reports, HbA1c values, and patient medical history. The implementation of LSTM networks, transformer models, random forest, and GBM has shown potential for accurately detecting this critical phase, with model accuracies ranging from 87% to 91%. The ML models effectively identified the honeymoon phase, enabling more precise insulin management and improved glucose control. This approach may enhance the optimization of insulin therapy and reduce the risk of adverse glycemic events, such as hypoglycemia. The successful application of these models underscores their potential for integration into clinical practice, offering a valuable tool for personalized diabetes management.

Future research should focus on evaluating the long-term impact of these ML-driven insulin management strategies on patient outcomes. Specifically, exploring how such models influence the duration of the honeymoon phase, overall glycemic control, and the prevention of diabetes-related complications could provide valuable insights into optimizing care for T1D patients. Moreover, studies exploring the real-time adaptation of these models to changing patient conditions would be key to enhancing clinical decision-making. Finally, future work could aim to integrate these models into digital health platforms, enabling seamless use in clinical settings and expanding access to personalized care for a wider patient population.

Ethics

Ethics Committee Approval: The study was approved by the Narasaraopeta Engineering College: Narasaraopeta of Institutional Review Board (IEC ref. no: 01/2024, date: 28.08.2024).

Informed Consent: Informed consent was acquired from the patient for the use of their data in this study.

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ORIGINAL ARTICLE

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The Impact of the 2023 Türkiye Earthquakes on Glycemic Control and Stress Levels in Children with Type 1 Diabetes: Single-center Experience

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What is already known on this topic?

Major natural disasters, such as earthquakes, can significantly disrupt the management of chronic conditions like type 1 diabetes mellitus (T1DM). In children with T1DM, stress and trauma from such events can impair glycemic control and lead to heightened psychological distress.

What this study adds?

This study is one of the first to evaluate the impact of the 2023 Türkiye earthquakes on glycemic control and psychological well-being in children with T1DM. It highlights the influence of parental stress, particularly maternal stress, on children's HbA1c levels and underscores the need for tailored interventions to support diabetes management during natural disasters.

Abstract

Objective: The 2023 earthquakes in southeastern Türkiye significantly impacted physical and emotional well-being in the region. This study evaluated the effect of the earthquakes on glycemic control, diabetes management, and stress levels in children with type 1 diabetes mellitus (T1DM).

Methods: Pediatric T1DM patients were assessed before and after the earthquake. Key parameters included glycated hemoglobin (HbA1c), insulin dosage, and psychological assessments using the Problem Areas in Diabetes Scale-Teen (PAID-T) version and the Post-Traumatic Stress Reaction Scale (PTSRS). Mixed-effects models were used to compare data across time points.

Results: Of the 79 participants, 45.6% were male, with a mean age of 143.5 ± 45.0 months. The earthquake disrupted insulin therapy in 36.7% of patients and caused glycemic control issues in 77.2%. HbA1c levels dropped from 9.7 ± 2.7% pre-earthquake to 8.8 ± 2.2% in the first three months, rose to 10.6 ± 1.9% in the following three months, and stabilized at 9.7 ± 1.9% by the fourth period. A positive correlation was observed between parental stress and children's HbA1c ($r = 0.423$, $p = 0.031$). Psychological effects were notable, with 43% reporting distress, and 63.3% experiencing loss of close family or friends. The mean PAID-T scores were 42.0 ± 14.5 for children and 53.7 ± 12.8 for parents, indicating a moderate to high level of diabetes-related distress in both groups. Although no validated cut-off score exists for the PAID-T, higher values reflect a greater perceived burden. The mean PTSRS score was 35.1 ± 17.4, which corresponds to a moderate level of post-traumatic stress reaction based on established cut-off values 35.1 ± 17.4.

Conclusion: The earthquake significantly affected glycemic control and psychological well-being in children with T1DM. Fluctuations in HbA1c levels and the link between parental stress and glycemic outcomes suggest a need for tailored interventions during crises.

Keywords: Earthquake, type 1 diabetes, children, disaster

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Introduction

On February 6, 2023, two devastating earthquakes, with magnitudes of 7.8 and 7.6, struck Kahramanmaraş, severely impacting southeastern Türkiye. These earthquakes caused widespread destruction, displaced millions, and resulted in tens of thousands of casualties (1,2,3). Following the initial quake, aftershocks continued to affect the region, with a significant earthquake of magnitude 6.4 occurring in Hatay on February 20, 2023 (4). Beyond the physical devastation, the emotional and psychological toll on affected populations was immense, particularly among vulnerable groups, such as children with chronic diseases (5).

These aftershocks exacerbated the destruction, intensifying the physical and psychological impacts on affected communities. Large-scale disasters not only cause significant physical destruction but also impose immense stress on individuals' mental health. Such events severely disrupt community infrastructure and healthcare services, complicating chronic disease management (6). In Antakya, Hatay, Mustafa Kemal University Hospital was the only facility providing medical care after the initial earthquake. However, it sustained damage during the February 20 earthquake, necessitating the relocation of patient care to a field hospital.

Type 1 diabetes mellitus (T1DM) is one of the most common chronic conditions among children and adolescents, requiring continuous monitoring and careful management. In individuals with T1DM, stress and traumatic events can directly affect glycemic control (7). Major disasters, like these earthquakes,often make managing glycemic levels more difficult, leading to both short-term and long-term health consequences. Disruptions in diabetes management can result in erratic blood glucose levels and severe health complications. In addition, earthquakes may trigger psychological problems, such as post-traumatic stress disorder (PTSD), anxiety, and depression, particularly in children and adolescents (8). Children and adolescents with T1DM face a dual health burden: managing their chronic illness while coping with the psychological effects of the trauma they have experienced. This combination can significantly impair their quality of life. The uncertainty and loss caused by the earthquake can further deteriorate their emotional and psychological well-being (9).

In the present study, the immediate and long-term effects of these catastrophic earthquakes on the glycemic control and stress levels of children with T1DM were examined. The emotional stress levels of their parents were also assessed, particularly mothers, who bear the primary responsibility for managing their children's diabetes in the aftermath of the disaster. Although previous studies have investigated the impact of natural disasters on glycemic control and psychological well-being in adults with T1DM, to the best of our knowledge, no similar studies have been conducted in pediatric populations. This gap in the literature underscores the novelty and importance of the present study, as children with T1DM may face unique challenges in managing their condition during and after large-scale disasters.

Methods

Study Population

Participants were selected from a pool of pediatric patients, aged 11 to 18, diagnosed with T1DM, along with their parents, who were receiving regular care at the Hatay Mustafa Kemal University Pediatric Endocrinology Department. Patients with additional comorbidities or those on medications affecting glucose metabolism were excluded. Further exclusion criteria encompassed pre-existing psychiatric disorders (such as depression, anxiety, or PTSD), developmental disorders, and conditions that could independently impact glycemic control (e.g., Cushing's syndrome or untreated thyroid disorders). Patients with a history of substance abuse or severe cognitive impairment that could hinder adherence to diabetes management protocols were also excluded. In addition, participants with a diabetes duration of less than six months and those residing outside the affected region during the earthquake were not eligible for inclusion.

The study was approved by the Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine (protocol no.: 2023/37, date: 14.12.2023) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from both the patients and their parents prior to participation.

Study Design

This study was designed as a prospective observational analysis. Data were collected at two time points: baseline (one month before the earthquake) and follow-up (post-earthquake). Patients who were unable to attend regular follow-up visits due to the earthquake were included from their first available post-event visit. Follow-up evaluations were conducted at 3-month intervals for up to one year. The primary outcomes of interest included changes in glycated hemoglobin (HbA1c) levels, continuous glucose monitor (CGM) readings, insulin dosages, and the frequency of hypoglycemic episodes. Psychological assessments of children were performed using the validated Problem Areas

in Diabetes-teen Scale (PAID-T) and the Post-traumatic Stress Reaction Scale (PTSRS). Mothers' diabetes-related stress was evaluated using the Problem Areas in Diabetes-parents of Teens (P-PAID-T) Scale (see below).

Patients were assessed during clinical visits both before and after the earthquake. At each time point, they underwent physical examinations, blood glucose testing, and completed questionnaires measuring diabetes-related issues and post-traumatic stress levels.

Scales Used in the Study

1. Data Collection Form: This form was developed by the researchers and includes questions about the demographic information of both the children and their parents, living conditions after the earthquake, experiences during the earthquake, and diabetes management following the event.

2. Problem Areas in Diabetes-parents of Teens Scale (P-PAID-T): Originally developed by Weissberg-Benchell and Antisdel-Lomaglio (10) in 2014 to identify problem areas faced by parents of adolescents with diabetes, the scale was later revised by Shapiro et al. (11) in 2017 reducing the number of items to 15. It is a 6-point Likert scale with scores divided into three main categories: "not a problem (1-2)", "moderate problem (3-4)", and "serious problem (5-6)". The total score ranges from 15 to 90, with higher scores indicating more significant stress perceived by parents in managing their child's diabetes. The Turkish validity and reliability study of the scale was conducted by Sari et al. (12).

3. Problem Areas in Diabetes-teen Scale (PAID-T): This 14-item scale follows the same 6-point Likert structure as the parent version, with categories for "not a problem (1-2)", "moderate problem (3-4)", and "serious problem (5-6)". Originally developed by Weissberg-Benchell and Antisdel-Lomaglio (10) in 2011 to identify problem areas for adolescents with diabetes, it was revised in 2017 to its current form (11). Scores range from 14 to 84, with higher scores reflecting more significant stress perceived by adolescents in relation to their diabetes management. The Turkish validity and reliability study of the scale was conducted by Sarı et al. (13).

4. Post-traumatic Stress Reaction Scale (PTSRS) for Children: Developed by Pynoos et al. (14) this 20-item scale assesses specific stress reactions following a traumatic event. It uses a 5-point Likert scale (0: never, 1: very rarely, 2: rarely, 3: often, 4: very often), with higher scores indicating a greater severity of trauma impact. A total score of 12-24 indicates a mild level of post-traumatic stress reaction, 25-39 a moderate level, 40-59 a severe level, and ≥60 a very severe reaction. The scale was adapted into Turkish by Erden et al. (15) and validity and reliability studies were performed.

Laboratory and Clinical Assessments

The physical and laboratory assessments included the following:

Glycemic Control Measures: HbA1c, random blood glucose levels, CGM data, insulin dosage, and the frequency of hypoglycemia.

Biochemical Parameters: Total cholesterol, triglycerides, liver function tests, kidney function (creatinine and estimated glomerular filtration rate), and complete blood count.

Psychological Assessments: PAID-T and PTSRS scores were used to evaluate the emotional and stress-related impact of the earthquake on diabetes management. These scales provided insights into how patients perceived their diabetes management and the emotional burden associated with the traumatic event.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentages. The normality of continuous data was assessed using the Shapiro-Wilk test. Since HbA1c values and questionnaire scores were found to be approximately normally distributed, paired t-tests were used to compare pre-and post-earthquake HbA1c levels. Mixed-effects models were applied to repeated measures across time points. Mixed-effects models were used to analyze repeated measures across the two-time points. Associations between psychological stress scores and glycemic control were evaluated using Pearson correlation. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 29.0 (IBM Corp., Armonk, NY, USA).

Results

From an initial recruitment of 100 patients, 21 were excluded based on study criteria, leaving a final cohort of 79 patients and their parents were enrolled in the study. Table 1 presents the socio-demographic characteristics of the children and their families.

All patients were receiving insulin injections, with 53.2% using continuous CGM sensors. The intensive care unit (ICU) admission rate for T1DM was 29.1%. Regarding comorbidities, 5.1% (4/79) of patients had celiac disease, 5.1% (4/79) had hypothyroidism, and 13.9% (11/79) had other medical conditions. In addition, 25.3% of patients had

Table 1. Demographic characteristics of the study participants

Characteristic	Percentage (%) (n/79)
Gender, % (n)	
Male	45.6% (36/79)
Female	54.4% (43/79)
Age (years, mean ± SD)	12.0 ± 3.8
Duration of diabetes (years, mean ± SD)	4.3 ± 2.9
Puberty duration (years, mean ± SD)	3.2 ± 1.9
Residence, % (n)	
Urban	60.8% (48/79)
Suburban	27.8% (22/79)
Rural	11.4% (9/79)
Mother's educational level, % (n)	
Primary	43.0% (34/79)
Secondary	25.3% (20/79)
High school	15.2% (12/79)
Father's educational level, % (n)	
Primary	40.5% (32/79)
Secondary	25.3% (20/79)
High school	16.5% (13/79)
Family type, % (n)	
Nuclear	86.1% (68/79)
Divorced/separated	5.1% (4/79)
Economic status, % (n)	
Below minimum wage	35.4% (28/79)

SD: standard deviation

sought psychiatric consultation, with 2.5% using psychiatric medications. Following the earthquake, 77.2% (61/79) of patients experienced glycemic control issues.

During the earthquake, 89.9% of patients reported feeling the tremor strongly, while 3.8% felt mild shaking. After the earthquake, 24.1% of patients stayed in their family cars. During the post-earthquake period, 46.9% lived in tents, 45.6% in homes, and 3.8% in containers. Two patients (2.5%) were trapped under rubble, one for 1 hour and the other for 2 hours. Although there were no permanent physical injuries or immediate family losses, 63.3% of patients reported losing close friends or relatives.

Regarding living conditions after the earthquake, 34.2% reported no significant challenges, while 29.1% experienced difficulties accessing food and water. Furthermore, 15.2% had trouble obtaining food, 5.1% struggled to access water, and 5.1% faced difficulty acquiring insulin. Only 2.5% of patients stated they were unaffected by the earthquake. In contrast, 43% reported psychological and economic impacts, 40.5% reported primarily psychological impacts (fear, anxiety), and 3.8% reported economic impacts. Of note, 83.5% of participants had no earthquake emergency preparedness kit (Table 2).

Table 2. Impact of the earthquake on participants' lives

Characteristic	Percentage (%) (n/79)
Strong perception of earthquake, % (n)	89.9% (71/79)
Lived in a tent post-earthquake, % (n)	46.9% (37/79)
Patients trapped under debris, % (n)	2.5% (2/79)
Hospitalization post-earthquake, % (n)	13.9% (11/79)
House damage, % (n)	
Minor	30.4% (24/79)
Severe	12.7% (10/79)
Destroyed	13.9% (11/79)
Main adverse effect psychological, % (n)	40.5% (32/79)
Economic impact, % (n)	3.8% (3/79)
Lack of emergency kit, % (n)	83.5% (66/79)

In terms of housing damage, 30.4% of patients' homes were classified as "lightly damaged", 22.8% as "undamaged", 13.9% as "destroyed", 12.7% as "severely damaged", and 6.3% as "moderately damaged". When asked about the time it took to return to everyday life, 8.9% of patients recovered within one week, 3.8% within one to two weeks, 5.1% within two to four weeks, 17.7% after more than four weeks, 8.9% within one to three months, and 17.7% within one to six months. However, 3.8% reported that they had not yet returned to everyday life.

Physical activity habits also changed post-earthquake, with 38.0% of patients reporting no physical activity, 30.4% engaging in activities such as walking, and 17.8% engaging in exercise. Regarding sleep, 8.9% of patients reported insomnia, 6.3% experienced inadequate sleep, and 30.4% reported reduced sleep quality, resulting in 45.6% of patients experiencing sleep disturbances.

Medical information was unavailable for 19.0% of patients. Earthquake-related stressors were identified in 57% of patients. Post-earthquake, 8.9% sought psychiatric support, with 1.3% receiving medication. Interestingly, none of the patients had prepared an emergency earthquake kit following the disaster.

After the earthquake, 36.7% of patients experienced disruptions in their insulin therapy, with 21.5% reusing needles and 27.8% encountering shortages of test strips. Post-earthquake diabetes-related hospital admissions occurred in 13.9% of patients, with 1.3% requiring ICU care. Moreover, 77.2% of patients recognized and reported difficulties in maintaining glycemic control.

The results of the patients' glycemic control, evaluated at three-month intervals before and after the earthquake, are shown in Table 3.

Table 3. Glycemic control before and after the earthquake

Timepoint	HbA1c % (mean ± SD)
Pre-earthquake	9.7 ± 2.7
Post-earthquake	9.5 ± 2.3
Post-earthquake (first three months)	8.8 ± 2.2
Post-earthquake (second three months)	8.7 ± 1.9
Post-earthquake (third three months)	10.6 ± 1.9
Post-earthquake (fourth three months)	9.7 ± 1.9

SD: standard deviation, HbA1c: glycated hemoglobin

When examining the timing of hospital visits post-earthquake, 11.4% occurred within the first month, 11.4% within two months, 15.2% within three months, 6.3% within four months, 8.9% within five months, and 3.8% within six months, with 53.2% seeking care within the first six months.

The mean scores for the assessments were as follows: the PAID-T child scale score was 42.0 ± 14.5 (with a possible score of 14-84), the PAID-T parent score was 53.7 ± 12.8 (with a possible score of 15-90), and the PTSRS average score was 35.1 ± 17.4 with a possible score of 0-80).

The mean PAID-T child scale score was 42.0 ± 14.5, the PAID-T parent score was 53.7 ± 12.8, and the PTSRS average was 35.1 ± 17.4.

Table 4 presents the correlation analysis between psychological scales and diabetic measurements, revealing variable relationships across different time points. While the PAID-T for children showed a positive correlation with HbA1c levels after the earthquake, the significance was not strong, indicating that higher reported stress levels may not directly correspond to glycemic control. The PAID-T for parents exhibited a notable positive correlation with HbA1c during the third three months post-earthquake ($r = 0.423$, $p = 0.031$), suggesting that parental stress could have some influence on the glycemic outcomes of their children during this period. Conversely, the PTSRS scores for children did not show significant correlations with glycemic control at any time point. This may suggest that post-traumatic stress reactions did not have a direct impact on diabetes management - or that the severity of PTSD symptoms in children was not strong enough to influence glycemic outcomes. Notably, the mean PTSRS score of 35.1 ± 17.4 falls within the moderate range but with considerable variability; thus, only a subset of children may have experienced clinically significant PTSD. Overall, these findings highlight the complex interplay between psychological stressors and diabetes control in the aftermath of traumatic events, suggesting that further investigation into these relationships may be warranted.

Table 4. Correlation analysis between scales and diabetic measurements

		PAID-T for children	PAID-T for parents	PTSRS for children
Age	Correlation coefficient (r)	0.056	0.225	-0.119
	Significance (*p*)	0.688	0.061	0.436
	Number of patients (n)	53	70	45
HbA1c (%) before earthquake	Correlation coefficient (r)	0.36	0.225	-0.376
	Significance (*p*)	0.109	0.201	0.113
	Number of patients (n)	21	34	19
HbA1c (%) after earthquake first 3 months	Correlation coefficient (r)	-0.167	0.364	-0.309
	Significance (*p*)	0.553	0.087	0.304
	Number of patients (n)	15	23	13
HbA1c (%) after earthquake second 3 months	Correlation coefficient (r)	0.506	0.224	-0.18
	Significance (*p*)	0.200	0.562	0.669
	Number of patients (n)	8	9	8
HbA1c (%) after earthquake third 3 months	Correlation coefficient (r)	0.296	**0.423**	0.059
	Significance (*p*)	0.219	**0.031***	0.857
	Number of patients (n)	19	**26**	12
HbA1c (%) after earthquake fourth 3 months	Correlation coefficient (r)	0.254	-0.147	0.257
	Significance (*p*)	0.426	0.633	0.420
	Number of patients (n)	12	13	12

*Pearson correlation analysis was used.
PAID-T: Problem Areas in Diabetes-Teen Scale, PTSRS: Post-Traumatic Stress Reaction Scale for Children, HbA1c: glycated hemoglobin

Discussion

The 2023 earthquakes in southeast Türkiye not only disrupted the daily lives of children with T1DM but also had a profound and lasting impact on their glycemic control and psychological well-being. This underscores the critical need for tailored disaster preparedness and mental health support in managing chronic conditions during crises (5,7).

The findings of this study suggest that the earthquake may have contributed to disruption of glycemic control and elevated stress levels in children with T1DM. The aftermath of the earthquakes appears to have posed immediate challenges to diabetes management. It may have led to long-term effects on both physical and mental health outcomes, as indicated by the observed fluctuations in HbA1c levels and the psychological distress reported within our cohort. In contrast to previous studies, we observed a transient improvement in HbA1c levels during the first three months following the earthquake (9). This initial decline may be attributed to the heightened attention families devoted to diabetes management in response to the trauma, as well as the increased efforts made by healthcare providers to maintain contact with patients. During the acute post-earthquake period, we established a support group for families of children with diabetes through phone communication, facilitating frequent interaction and guidance. Furthermore, after the 6.4 magnitude aftershock, when healthcare services were relocated to a field hospital and it became evident that hospital-based services would not be available for emergencies, families may have intensified their efforts to regulate glycemic control, knowing that immediate care could be inaccessible (16). However, the sharp rise in HbA1c levels during the third three-month period underscores the limitations of these short-term coping mechanisms in the face of prolonged disaster-related stress and healthcare disruptions. The subsequent deterioration in glycemic control suggests that as the emotional and logistical burdens of the earthquakes persisted, cumulative stress negatively affected the children's diabetes management routines (17).

The return of HbA1c levels to pre-earthquake values in the final phase of the study suggests a stabilization of diabetes management practices. However, this recovery in glycemic control does not mitigate the negative impacts experienced during the intermediate period, indicating the prolonged stress and difficulties families encountered (17). Our data highlight the importance of providing long-term support following natural disasters, as the challenges of managing a chronic condition are significantly amplified when healthcare systems, social support networks, and daily routines are so disrupted.

Another critical factor influencing diabetes management in our cohort was the prolonged disruption of daily living conditions. Only 17.8% of patients could return to their pre-earthquake routines within the first month, while 17.7% managed to re-establish daily normality after six months. Alarmingly, 3.8% of participants had not regained their routines even one year post-disaster. For these families, the immediate priority shifted to securing necessities-shelter, food, and water-while disease management understandably took a backseat. The psychological and logistical strain of living in temporary housing for an extended period undoubtedly contributed to the fluctuations in glycemic control. The continued displacement and uncertainty surrounding the resumption of everyday life likely exacerbated stress for both children and their caregivers, complicating their ability to effectively manage T1DM (9). That some families remained unable to return to regular routines underscores the profound and lasting impact that such immense disasters can have on chronic disease management.

Psychological assessments further revealed considerable emotional strain on both children and their parents. The elevated scores on the PAID-T and PTSRS indicate that a significant portion of our cohort experienced substantial psychological distress (12). This finding aligns with existing literature showing that children with chronic diseases are particularly vulnerable to the psychological impacts of natural disasters, as they must navigate the dual burden of managing both their physical health and the emotional trauma of the event (9,17). Notably, the relatively low rate of psychiatric support uptake (8.9%) despite the widespread prevalence of stress-related symptoms (57%) highlights a critical gap in mental health services post-disaster, emphasizing the urgent need for targeted interventions.

In the present study, a positive correlation was observed between the PAID-T scores for parents and children's HbA1c levels during the third three-month period post-earthquake-the time point at which mean HbA1c peaked at 10.6%. This finding suggests that parental stress may play a role in diabetes management during prolonged post-disaster adversity. However, it is also possible that worsening glycemic control during this period may have contributed to elevated parental stress rather than being caused by it. Given the observational nature of this study, causality cannot be established, and the directionality of this association remains uncertain. Further longitudinal or interventional research is needed to understand the dynamics of this relationship better. Conversely, the lack of significant correlations between the PTSRS for children and glycemic control suggests that the psychological effects

of trauma may not directly impact diabetes management routines. This complexity highlights the necessity for further research to explore the nuanced relationships between various dimensions of psychological distress and diabetes outcomes, ultimately guiding targeted interventions for families affected by traumatic events.

In the study conducted by Şengül et al. (9) on adults with T1DM after the Marmara earthquake, an improvement in HbA1c levels was observed one year post-earthquake. However, the present study found that HbA1c levels in children increased one year after the earthquake but compared to the first three months following the event. This difference may be attributed to the long-term effects of diabetes on glycemic regulation in pediatric patients.

In terms of healthcare access, disruption to insulin therapy and diabetes management were reported by a significant portion of participants (36.7%), with nearly 28% experiencing difficulties with glucose monitoring supplies. These disruptions, alongside the high prevalence of living in temporary housing (such as tents and containers), further exacerbated the challenges of maintaining stable glycemic control (18). The physical stressors associated with displacement, combined with the emotional toll of loss and trauma, with 63.3% of participants reporting the loss of friends or family, indicates the necessity of integrating disaster preparedness into chronic disease management frameworks, especially in regions prone to natural disasters (9). This holistic approach will ensure that vulnerable populations, like children with T1DM, receive the comprehensive support they need during crises.

Clinical and Public Health Implications

Our findings suggest an urgent need for robust disaster preparedness plans tailored specifically for vulnerable populations, including children with T1DM. These plans must ensure continuous access to essential medications, glucose monitoring supplies, and healthcare services during natural disasters. Moreover, there is a need to integrate mental health support into diabetes care, especially in times of crisis, as psychological distress has been shown to directly impact glycemic control and overall health outcomes (16,18).

Efforts should also focus on raising awareness among healthcare providers, patients, and their families regarding the potential effects of disasters on diabetes management. Health systems should prioritize the development of emergency protocols that specifically address the unique needs of children with chronic diseases, ensuring that they are not overlooked during large-scale crises (16,18,19).

Study Limitations

A literature review revealed a paucity of studies investigating the impact of natural disasters on children with T1DM, particularly as most existing research on the health impacts of earthquakes has primarily involved adult populations. Despite the limited number of children included in our study because of challenges such as casualties, relocation, and restricted access to healthcare services, we believe our findings are significant as they represent the first investigation of this age group in this context. Moreover, this study uniquely explored diabetes-related stress levels in both children and their mothers, offering valuable insights into the pivotal role parents play in managing their child's diabetes care under extraordinary circumstances.

However, several limitations of the study should be acknowledged. One key limitation is the focus on HbA1c levels without examining other potential contributing factors, such as body mass index, SD score (SDS), or changes in physical activity levels. Including these variables in future analyses could provide a more comprehensive understanding of the observed HbA1c fluctuations and offer a deeper interpretation of the data.

Another limitation is that participants completed the psychological scales at varying time points after the earthquake. This variability in timing may have influenced the standardization of results, potentially affecting the reliability of comparisons across the study population. Moreover, the psychological scales were administered at different time points following the earthquake, depending on when patients were able to attend follow-up visits at our center. Some completed the scales during their first post-earthquake visit, while others did so later during subsequent visits, potentially up to six months after the event. This variability likely influenced stress levels, which may have shifted from acute trauma to chronic distress. This heterogeneity limits the comparability of psychological scores across patients.

While correlation analyses were conducted to explore relationships between variables, they cannot fully address the variability introduced by differing assessment times. Future studies could improve data consistency and reliability by standardizing the timing of psychological evaluations.

A further limitation lies in the study's reliance solely on self-report scales for assessing psychological distress in both children and their mothers. The absence of semi-structured psychiatric evaluations by child psychiatrists limited the ability to diagnose specific psychiatric disorders, such as depression, anxiety disorders, or PTSD, which may have emerged following the earthquake. Incorporating such

clinical assessments in future research would provide a more robust understanding of the psychological impact of natural disasters on this population.

Lastly, the study did not document the duration participants spent in temporary housing, such as tents or shelters. Prolonged exposure to such conditions likely exacerbated psychological stress and increased vulnerability to illnesses, such as upper respiratory infections, which could have indirectly influenced blood glucose levels. Further investigation into these environmental factors would enhance the contextual interpretation of our findings.

Despite these limitations, this study illustrated the profound impact of natural disasters on the physical and psychological well-being of children with T1DM and their families, especially their mothers. We believe that these findings highlight critical areas for future research and intervention development.

Conclusion

In summary, the 2023 earthquakes in the southeast of Türkiye had a profound impact on the glycemic control and psychological well-being of children with T1DM. Our findings illustrated significant fluctuations in HbA1c levels and heightened psychological distress among this vulnerable population, emphasizing the need for tailored interventions in disaster preparedness and mental health support. The study reinforced the complex interplay between emotional stressors and diabetes management, revealing that immediate responses to crises may lead to temporary improvements, but prolonged disruptions can result in deteriorating health outcomes. Importantly, our results suggest a real need for enhanced awareness and proactive strategies among healthcare providers, families, and policymakers to ensure that the unique needs of children with chronic conditions are addressed in the wake of natural disasters. By implementing comprehensive support systems, healthcare providers can better equip families to navigate the challenges posed by such events, ultimately improving health outcomes and quality of life for children with chronic diseases, including T1DM.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine (protocol no.: 2023/37, date: 14.12.2023) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from both the patients and their parents prior to participation.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Gül Trabzon, Seda Aybüke Sarı, Concept: Gül Trabzon, Seda Aybüke Sarı, Simge Bilaloğlu, Şeyma Demiray Güllü, Design: Gül Trabzon, Seda Aybüke Sarı, Data Collection or Processing: Gül Trabzon, Seda Aybüke Sarı, Simge Bilaloğlu, Şeyma Demiray Güllü, Analysis or Interpretation: Servet Yüce, Literature Search: Servet Yüce, Simge Bilaloğlu, Şeyma Demiray Güllü, Writing: Gül Trabzon, Seda Aybüke Sarı, Servet Yüce.

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Diagnostic Challenge of Phenotypic Variability in *COL2A1*-related Disorders: Four Novel Variants That Expand the Clinical Spectrum

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What is already known on this topic?

Type 2 collagenopathies are caused by heterozygous mutations in the *COL2A1* gene, leading to a broad spectrum of clinical phenotypes ranging from mild to severe skeletal dysplasias. These disorders are characterized by diverse clinical presentation, including short-trunk dwarfism, joint pain, ocular complications, and hearing loss. Despite the variability in clinical manifestations, accurate diagnosis and classification of these disorders are essential for effective genetic counseling and management.

What this study adds?

This study expands the clinical and molecular spectrum of *COL2A1*-related disorders by identifying four novel variants (c.1023 + 2T > C, p.Gly465Asp, p.Gly855Asp, p.Gly669Ala) in patients with kniest dysplasia, spondyloepiphyseal dysplasia congenita, and spondyloepimetaphyseal dysplasia Strudwick type. The findings highlight the phenotypic variability and diagnostic challenges associated with type 2 collagenopathies, highlighting the need for comprehensive genetic and radiological assessments for accurate diagnosis.

Abstract

Objective: Heterozygous *COL2A1* gene mutations are associated with type 2 collagenopathies, characterized by a wide, diverse, and overlapping clinical spectrum in related diseases. Our goal is to describe the clinical, radiological, and molecular findings of patients with *COL2A1*-related dysplasia and investigate the phenotype-genotype correlation. We also highlight the challenge of categorizing *COL2A1*-related diseases with similar clinical and radiological phenotypes.

Methods: Six patients from five unrelated families presented with disproportionate short stature.delayed motor milestones, waddling gait, normal intelligence, and similar radiological features, including delayed epiphyseal ossification, epimetaphyseal changes, scoliosis, lordosis, and platyspondyly. All underwent whole exome sequencing. Demographic, clinical, laboratory, and radiological data were retrospectively obtained from hospital records. Segregation analysis was conducted using Sanger sequencing in all patients.

Results: Based on clinical, radiological, and molecular results, the six patients were categorized into kniest dysplasia, spondyloepiphyseal dysplasia congenita, and spondyloepimetaphyseal dysplasia Strudwick type. Four novel variants (c.1023 + 2T > C, p.Gly465Asp, p.Gly855Asp, p.Gly669Ala) were identified in the *COL2A1* gene.

Conclusion: Accurate classification of type 2 collagenopathies is vital to provide appropriate genetic counseling. Predicting extraskeletal manifestations and reducing morbidity through early diagnosis and treatment will significantly improve the quality of life for patients.

Keywords: *COL2A1* gene, *COL2A1*-related disorders, short-trunk dwarfism, type 2 collagenopathies, whole exome sequencing

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Introduction

The most prevalent proteins in the human body, collagens, are involved in the structure and mechanical qualities of tissues (1). One of the fibrillar collagens, type 2 collagen, is mainly present in cartilage, and partially in the vitreous humor, inner ear, and nucleus pulposus (2). It is the main protein of endochondral bone development and growth. The collagen type 2 alpha-1 gene (*COL2A1*, MIM *120140) is located on the long arm of chromosome 12 at band 13.11 and is 31.5 kb in size. According to the common transcript (NM_001844.4), it is a gene with 54 exons that encodes the type 2 pro-collagen alpha 1 protein. This protein forms a triple helical structure and assembles into a pro-collagen homotrimer structure consisting of approximately 300 Glycine-X-Y amino acid repeats. The type 2 pro-collagen molecule has non-helical N- and C-terminal propeptides that do not contain Gly-X-Y repeats. After being secreted into the extracellular matrix, type 2 pro-collagen undergoes cleavage of N- and C-terminal propeptides to form mature collagen (3).

Heterozygous *COL2A1* gene mutations are referred to as type 2 collagenopathies, and the associated diseases exhibit a broad, heterogeneous, and overlapping clinical spectrum (Table 1). The disease spectrum ranges from only osteoarthritis with normal stature or ocular complications and hearing loss to severe micromelia, dwarfism, and perinatal lethality. Achondrogenesis type 2 (ACG2) or hypochondrogenesis (HCG) and platyspondylic skeletal dysplasia Torrance type are perinatal lethal forms; kniest dysplasia (KD), spondyloepiphyseal dysplasia congenita (SEDC), spondyloepimetaphyseal dysplasia (SEMD) Strudwick type, spondyloepiphyseal dysplasia Stanescu type and spondyloperipheral dysplasia are moderate forms; epiphyseal dysplasia multiple with myopia and deafness, vitreoretinopathy with phalangeal epiphyseal dysplasia, avascular necrosis of the femoral head, Czech dysplasia, Legg-Calve-Perthes disease, osteoarthritis with mild chondrodysplasia, Stickler syndrome type 1 (STL1), and non-syndromic ocular STL1 are mild forms (4). While the overall prevalence remains unknown, the estimated incidence worldwide ranges from 20.4 to 35.9/100,000 across various locations and populations (5). Due to *COL2A1* mutations leading to different phenotypes, even within the same family, clinical variability is observed.

Table 1. Diseases associated with *COL2A1* mutation

Phenotype	MIM number
Epiphyseal dysplasia, multiple, with myopia and deafness	132450
Vitreoretinopathy with phalangeal epiphyseal dysplasia	619248
Achondrogenesis, type 2 or hypochondrogenesis	200610
Avascular necrosis of the femoral head	608805
Czech dysplasia	609162
Kniest dysplasia	156550
Legg-Calve-Perthes disease	150600
Osteoarthritis with mild chondrodysplasia	604864
Platyspondylic skeletal dysplasia, Torrance type	151210
Spondyloepiphyseal dysplasia congenita	183900
Spondyloepimetaphyseal dysplasia, Strudwick type	184250
Spondyloepiphyseal dysplasia, Stanescu type	616583
Spondyloperipheral dysplasia	271700
Stickler syndrome, type 1	108300
Stickler syndrome, type 1, non-syndromic ocular	609508

MIM: Mendelian inheritance in man

In general, when type 2 collagenopathies are mentioned, the first things that come to mind are short trunk dwarfism, eye involvement (myopia and vitreoretinal detachment), hearing loss, and joint pain. Cleft palate, midface hypoplasia, and micrognathia may also be considered dysmorphic facial features. Radiographic manifestations include platyspondyly, irregular vertebral endplates, kyphosis, lordosis, delayed epiphyseal ossification, and epimetaphyseal changes.

Short stature is one of the problems that pediatric endocrinologists and geneticists spend a significant amount of time on. A considerable proportion of these patients are composed of skeletal dysplasias, and genetic counseling is important in this respect. Here, we report the clinical, radiological, and molecular genetic features of six patients from five different families and report four novel variants in the *COL2A1* gene, expanding the molecular spectrum of the diseases with a clinical diagnostic challenge.

Methods

Five of the six patients were of Turkish descent, with one being an Uzbek refugee. All six exhibited short-trunk dwarfism, a waddling gait, normal intelligence, and similar radiological findings. They underwent whole exome sequencing, and an expert clinical geneticist examined all patients. Demographic, clinical, laboratory, and radiological data were retrospectively collected from hospital records.

Genomic DNA was extracted from peripheral blood using instruments and a DNA blood 520 µL kit (Xiamen Zeesan Biotech, Fujian, China) following standard protocols. Whole exome capture and sequencing were performed using the Twist Human Core Exome V2 Kit (South San Francisco,

CA, USA). Libraries were sequenced on a NovaSeq 6000 system (Illumina Inc., San Diego, CA, USA) according to the manufacturer's instructions. Variant calls from FASTQ files were generated with the Sophia DDM version 5.10.50.1 (Lausanne, Switzerland) bioinformatics platform, which was also used for variant annotation and analysis.

Initially, variants with a minor allele frequency greater than 0.01 were excluded using data from the 1000 Genomes Project and gnomAD databases. Genes associated with the patients' phenotype, especially those related to skeletal dysplasia, were prioritized. Candidate variants were assessed using the ClinVar, LOVD, and HGMD databases along with relevant publications. The pathogenicity of identified variants was evaluated using several *in silico* prediction tools, including DANN, DEOGEN2, EIGEN, MutationTaster, Polyphen-2, and SIFT. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines (6). Segregation analysis of all variants in the families was conducted using Sanger sequencing.

Written informed consent for genetic testing and publication of clinical findings, patient photographs, and molecular results was obtained from each patient or their parents. The study adhered to the Declaration of Helsinki and was approved by the Ethical Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, (approval number: B.10.1.TKH.4.34.H.GP.0.01/293, date: 05.09.2024).

Statistical Analysis

Descriptive statistics of the clinical and laboratory findings are expressed as mean ± standard deviation, numbers, or percentages. Comparative statistics were not performed because the number of patients was limited and not homogeneously distributed.

Results

Clinical Features

Patient 1: A boy was referred at four months of age due to dysmorphic facial features. He was born to non-consanguineous parents at 40 weeks of gestation. His birth weight was 3500 g (58th percentile), length was 51 cm (67th percentile), and head circumference was 38.5 cm [+2.5 standard deviation score (SDS)]. His neuromotor development was normal except for delayed walking, which occurred at 18 months. At his last physical examination at three years of age, his weight was 13.5 kg (23rd percentile), height was 90 cm (4th percentile), and head circumference was 52.5 cm (94th percentile). Notable dysmorphic features included relative macrocephaly, midface hypoplasia, hypertelorism, a depressed nasal bridge, a fleshy and upturned nose with anteverted nares, a bifid uvula, and micrognathia. In addition, he exhibited short trunk dwarfism and lordosis. He had a waddling gait. Ophthalmological and hearing examinations were normal, and other system examinations revealed no abnormalities.

Patient 2: A 3-year-old girl with short stature was referred for evaluation of possible skeletal dysplasia. She is the third child of a consanguineous, healthy Uzbek couple with no notable family history. She was born full-term with a birth weight of 3200 g (40th percentile) and a length of 43 cm (-3 SDS) with an unknown head circumference. Short-trunk dwarfism was noted at birth. She required a 20-day stay in the neonatal intensive care unit for respiratory distress. There was a delay in all motor milestones, with walking achieved at 2.5 years. At six years old, her weight was 14 kg (-2.9 SDS), height 88 cm (-5.9 SDS), and head circumference 52 cm (72nd percentile). Her facial features were normal except for a depressed nasal bridge and hypertelorism. She had limited and painful extension in her knee and elbow joints, genu valgum, and a waddling gait. She experienced hearing loss and myopia. Spinal magnetic resonance imaging showed odontoid hypoplasia, but her neurological examination was normal.

Patient 3: The boy, the fourth child of healthy unrelated parents, was noted to have short limbs on prenatal ultrasound. Postnatal history included a three-month stay in the neonatal intensive care unit for respiratory distress and surgeries for inguinal hernia and cleft palate. Motor milestones were delayed. At 12 years old, his weight was 27 kg (-2.4 SDS), height 90 cm (-8.3 SDS), and head circumference 55 cm (0.2 SDS). He had no facial dysmorphism but exhibited pectus carinatum, kyphosis, and lordosis. He had hearing loss but his eye examination was normal. Cervical computed tomography revealed atlantoaxial dislocation and cord compression.

Patient 4: The girl, the second child of healthy unrelated parents, was born at 38 weeks of gestation. Short limbs were noted on prenatal ultrasound. Her birth weight was 3800 g (87th percentile), height 46 cm (5th percentile), and head circumference 35 cm (64th percentile). Postnatally, she spent 10 days in the neonatal intensive care unit for respiratory distress and had congenital hypotonia and hip dysplasia. Motor development was delayed, with head control at one year, sitting without support at 14 months, and walking at two years. At 4.5 years old, her weight was 10.5 kg (-4.5 SDS), height 75 cm (-7.8 SDS), and head circumference 52.5 cm (86th percentile). Facial features were normal except for a prominent forehead and micrognathia. Short-trunk

dwarfism, pectus excavatum, and genu valgum were noted. She complained of pain in large joints with no hearing or visual impairments.

Patient 5: The boy, noted to have short limbs on prenatal follow-up, was born at 33 weeks of gestation. His birth weight was 2080 g (50-90th percentile), height 38 cm (< 3rd percentile), with an unknown head circumference. He spent three months in the neonatal intensive care unit for respiratory distress. Neuromotor development was normal except for walking at 18 months. At 5 years and 10 months, his weight was 16.4 kg (-2 SDS), height 90 cm (-5.3 SDS), and head circumference 50.5 cm (18th percentile). Facial features were normal. Physical examination revealed short-trunk dwarfism and a barrel chest. He exhibited a waddling gait after excessive walking. Eye and hearing examinations were normal. His mother also had marked short stature.

Patient 6: The affected mother of patient 5. Prenatal and natal history are unclear, and her birth measurements are unknown. She had surgery for hip dysplasia in childhood. On physical examination, her weight was 43 kg (-2.8 SDS), height 123 cm (-6.6 SDS), and head circumference 54 cm (-2 SDS). Facial features were normal. She had short-trunk dwarfism and scoliosis. Ophthalmological and hearing examinations were normal.

Common Findings

In all six patients, metabolic screening (calcium, phosphorus, alkaline phosphatase, parathyroid hormone, 25-hydroxy vitamin D, and thyroid hormone) and biochemical tests for liver and kidney functions were normal. Abdominal ultrasonography and echocardiography were normal. All patients had normal intelligence. Clinical and radiological characteristics of the patients are provided in Table 2, with photographs in Figure 1.

Radiological Findings

All of the patients' radiographic findings exhibit a remarkable degree of resemblance. Short long bones and the absence of ossification of capital femoral epiphyses were observed in all patients. All patients had insufficient pubic ossification except for patient 5 and patient 6. Platyspondyly with irregular vertebral end-plates were detected in patients 1, 3, 4, and 6. Irregular and mildly flared metaphyses were seen in patients 1, 2, 3, and 4. Various degrees of lordosis were present in all patients except for patient 4. The radiological images of the patients are described in detail in Figure 2.

COL2A1 Variants

Whole exome sequencing was performed, and five different heterozygous *COL2A1* variants were detected in the six patients from five families (Table 2). These variants were classified according to ACMG criteria. Two of the patients were a mother and her son. Four variants were not previously reported in the literature. One of the patients had a splicing variant, while the others had missense variants. The splicing variant was c.1023+2T>C (PVS1, PM2) in patient 1. In patient 2, molecular analysis identified the c.905C>T (p.Ala302Val) (PM2, PP5) variant in exon 14. This missense variant has been previously reported. The c.1394G>A (p.Gly465Asp) (PM2, PM5, PP3) variant in exon 22 was a novel variant and was detected in patient 3. The other novel variant was c.2564G>A (p.Gly855Asp) (PM2, PM5, PP3) in exon 39 in patient 4. patient 5 and her mother, patient 6, were found to have the c.2006G>C (p.Gly669Ala) (PM2, PP3) missense variant in exon 31, which has not been reported in public databases or literature. Segregation analysis revealed that patients 1-4 and 6 inherited the variants *de novo*, while patient 5 had maternal inheritance from patient 6, his mother. All variants are shown in Figure 3. The pedigrees of the patients with novel *COL2A1* variant are shown in Figure 4. In addition, biomolecular modellings of the *COL2A1* novel missense variants are shown in Figure 5.

Discussion

The disorders associated with *COL2A1* exhibit a broad range of phenotypes. Radiological signs and clinical findings of type 2 collagenopathies are very similar, making it quite difficult to diagnose. Phenotypic variability is most likely a result of environmental influences and variations in disease-altering genes and/or regulatory components. In the present case series, six patients were classified into KD (n=3; P1, P2, P4), SEDC (n=2; P5 and P6), and SEMD Strudwick type (n=1; P3) based on clinical, radiological, and genetic results. Five variants were identified, four of which were novel. We believe that our clinical, radiological, and genetic findings may be helpful in evaluating diseases associated with *COL2A1*.

According to the Human Gene Mutation Database (HGMD Professional 2024.1; HGMD June 2024), there are 759 pathogenic and likely pathogenic *COL2A1* variants. Among these, 423 are missense/nonsense, 137 are small deletions, 129 are splicing, 40 are small insertions, 16 are small indels, 10 are large deletions, and the others are large insertions and complex rearrangements. The majority of *COL2A1* gene variations are missense variants, and the substitution in glycine residues is the most prevalent form (7). Moreover, most of the variations are located in the triple helix domain of the protein. One of the patients in our study had a splicing variant, while the remaining patients had missense

Table 2. Clinical summary of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
***COL2A1* heterozygous mutation (NM_001844.4)**	c.1023 + 2T > C	c.905C > T:p. Ala302Val	c.1394G > A:p. Gly465Asp	c.2564G > A:p. Gly855Asp	c.2006G > C:p. Gly669Ala	c.2006G > C:p. Gly669Ala
Mutation type	Splicing	Missense	Missense	Missense	Missense	Missense
Inheritance	*De novo*	*De novo*	*De novo*	*De novo*	Maternal	*De novo*
Novel variant	+	-	+	+	+	+
Gender	Male	Female	Male	Female	Male	Female
Age of diagnosis (years)	0.42	3	7.5	1.5	1 y	28
Age at last admission (years)	3	6	12	4.5	5 y 10 mo 5.83	32
Short-trunk dwarfism, identifiable at birth	-	+	+	+	+	?
Height SDS	-2	-5.9	-8.3	-7.8	-5.3	-6.8
Weight SDS	-0.9	-2.9	-2.4	-4.5	-2	-2.8
Head circumference SDS	1.5	0.5	0.2	1.4	-0.9	-2
Congenital hypotonia	-	+	+	+	-	+
Flat midface	+	+	-	-	-	-
Round face	+	+	-	-	-	-
Malar hypolasia	-	-	-	-	-	-
Short neck	+	+	+	+	+	+
Cleft palate	-	-	+	-	-	-
Hearing loss	-	+	+	-	-	-
Myopia	-	+	-	-	-	-
Retinal detachment	-	-	-	-	-	-
Pectus excavatum	-	-	-	+	-	-
Pectus carinatum	-	-	+	-	-	-
Barrel chest	-	-	-	-	+	-
Inguinal hernias	-	-	+	-	-	-
Atlanto-axial instability	-	+	+	-	-	-
Odontoid hypoplasia	-	+	+	-	-	-
Platyspondyly	+	-	+	+	-	+
Irregular vertebral endplates	+	+	+	+	-	+
Coronal vertebral clefts	-	-	+	-	-	-
Kyphosis	-	-	+	-	-	-
Scoliosis	-	+	+	-	-	+
Lordosis	+	+	+	+	+	+
Dislocation of hip, congenital	-	?	-	+	-	+
Coxa vara	-	-	-	-	-	-
Coxa valga	+	-	-	-	-	-
Flexion contractures, especially at hip and knee	-	+	-	-	-	+
Absent pubic ossification, infancy	+	+	+	+	+	?
Delayed epiphyseal ossification, childhood	+	+	+	+	+	+
Enlarged epiphyses	+	-	-	-	-	-
Irregular epiphyses	+	+	+	+	-	+
Metaphyseal irregularity	+	+	+	+	-	-
Osteosclerosis/osteopenia zones	-	-	+	-	-	-
Short, dumbbell appearance of long bones	+	-	-	+	-	-
Limited joint mobility	-	+	-	-	-	+
Painful joints	-	+	+	+	-	-
Enlarged joints	+	+	-	-	-	-
Delayed motor milestones	+	+	+	+	+	+
Abnormal gait	+	+	+	+	+	-
Normal intelligence	+	+	+	+	+	+

SDS: standard deviation score

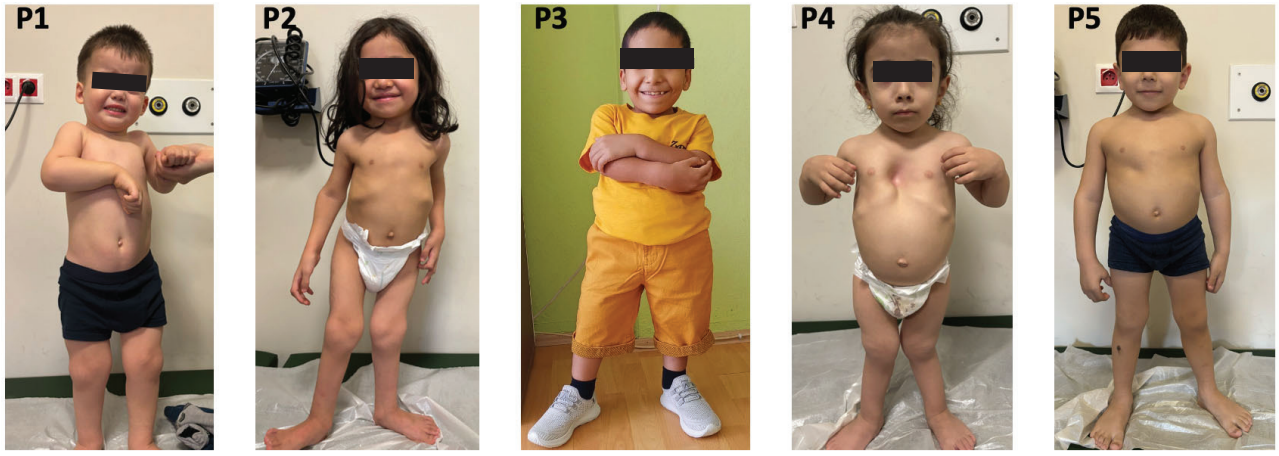

Figure 1. Photographs of the patients 1-5. All patients have short trunk dwarfism. **P1** (3 years old): Round face, midface hypoplasia, depressed nasal bridge, micrognathia, enlarged knee and elbow joints. **P2** (6 years old): Round face, depressed nasal bridge, enlarged knee and elbow joints, genu valgum deformity. **P3** (12 years old): Enlarged wrists. **P4** (4,5 years old): Micro/retrognathia, pectus excavatum and genu valgum deformity. **P5** (5 years 10 months old): Barrel chest

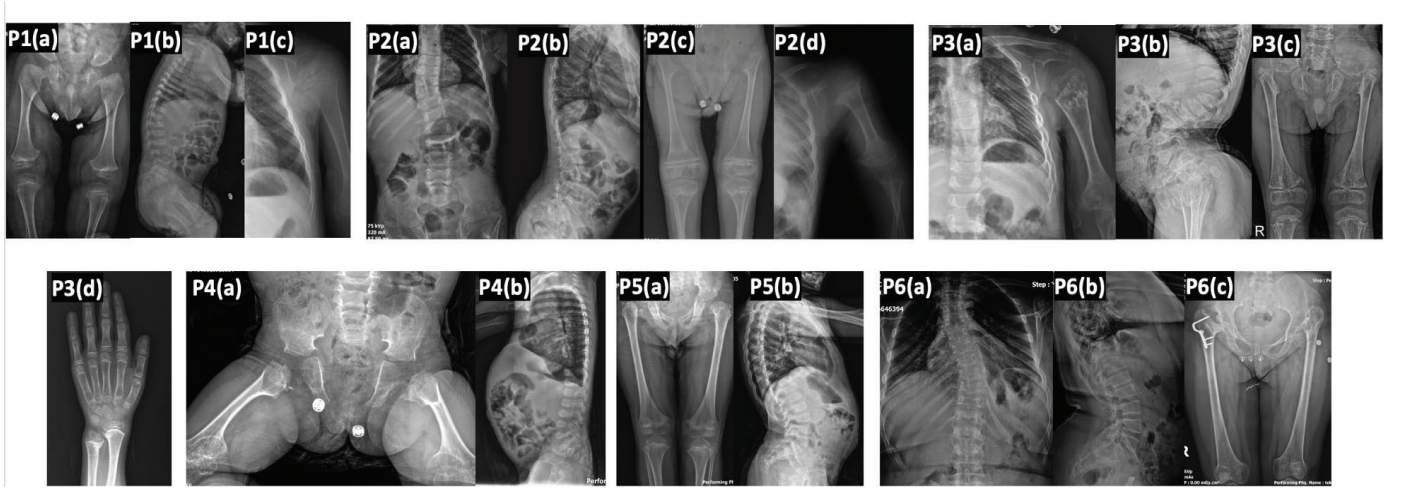

Figure 2. X-rays of all the patients. All tubular long bones are short. **P1(a)** (14 months old**):** Insufficient pubic ossification, absence of ossification of capital femoral epiphyses, very broad femoral necks, irregular femur distal metaphyses and epiphyses, large proximal tibiae epiphyses, short-dumbbell shaped femur, coxa valga. **P1(b)** (2 months): Platyspondyly with irregular vertebral endplates, mild lordosis. **P1(c)** (3 years old): Expanded and irregular epiphysis with mildly broad diaphysis. **P2(a)** (5 years old): Thoracolombar scoliosis. **P2(b):** Irregular vertebral endplates, lordosis. **P2(c):** Small with horizontal inferior margins of the ilia, insufficient pubic ossification, absence of capital femoral epiphyses, short and broad femoral necks, coxa valga, irregular and mild flared metaphyses, irregular epiphyseal margins especially on the left side. **P2(d)** (2 years old): Dumbbell shaped humerus. **P3(a)** (10 years old): Thoracal scoliosis and enchondroma-like appearance in the proximal metaphysis of the humerus. **P3(b):** Platyspondyly with irregular vertebral endplates, posterior wedging of lower lomber vertebra, kyphosis, severe lordosis. **P3(c):** Short ilium, horizontal acetabula, narrow and shallow sciatic notch, lack of ossification of the os pubis, absence of capital femoral epiphyses and necks, irregular metaphyses and epiphyses. **P3(d):** Epiphyseal and metaphyseal irregularity. Osteosclerosis and osteopenia zones at distal radius and ulna metaphyses. Carpal bone ossification is delayed. **P4(a)** (4 years old): Horizontal acetabula, absence of pubic ossification, absence of capital femoral epiphysis on the left side, very small capital femoral epiphysis on the right side, short-dumbbell shaped femur, irregular and enlarged metaphyses. **P4(b)** (1 year old): Platyspondyly with irregular vertebral endplates (pear-shaped appearance). **P5(a)** (5 years 10 months old): Absence of capital femoral epiphyses, multicentric ossification of right femoral neck, small and irregular femoral necks, coxa valga, small proximal tibia epiphyses. **P5(b):** Flattaned with pear-shaped vertebrae and lordosis. **P6(a)** (mother of Patient 5): Thoracal scoliosis. **P6(b):** Platyspondyly with irregular vertebral endplates, posterior wedging of lower lomber vertebra, lordosis. **P6(c):** Irregular margins of ilia, shallow acetabular fossa, irregular ossified (deformed) femoral necks, absence of femoral heads

variants. Among the patients with missense variants, only one exhibited an alanine-valine substitution, while all others had glycine substitutions.

There are two main mechanisms through which pathogenic molecular variants in the *COL2A1* gene might cause diseases: haploinsufficiency and dominant-negative effects (4). Missense variations resulting in the substitution of the glycine residue within the Gly-X-Y triplet exhibit a dominant-negative effect, causing the disturbance of the helical structure and function of type 2 collagen (8).

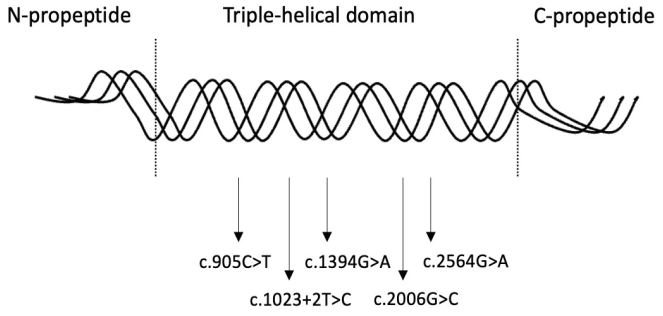

Figure 3. Schematic representation of the variants in our study based on domains of the type 2 pro-collagen trimer

Haploinsufficiency is caused by pathogenic mutations that result in the premature termination of protein synthesis. The dominant-negative effect causes more severe type 2 collagenopathies, whereas haploinsufficiency leads to a mild phenotype. Furthermore, substituting amino acids other than glycine through missense mutations typically results in a less severe phenotype due to the destabilization of the protein (9).

There is a lack of data regarding the genotype-phenotype correlation in type 2 collagenopathies. However, Zhang et al. (10) reported some potential genotype-phenotype correlations, based on the location of variants. Variants in the N-propeptide region, particularly in exon 2, result in mild symptoms, such as in STL1. In contrast, variants in the C-propeptide region give rise to severe and often lethal phenotypes. Replacing glycine with serine results in phenotypes that range in severity from mild to severe. Conversely, substituting glycine with a non-serine amino acid leads to more severe phenotypes, such as HCG or SEDC, often accompanied by severe coxa vara (11). The non-glycine missense mutations primarily involve the substitution of arginine with cysteine, resulting in mild phenotypes characterized by either normal or short stature (12). Small deletion variants, excluding frameshift variants caused by nucleotide deletions, result in severe or fatal diseases.

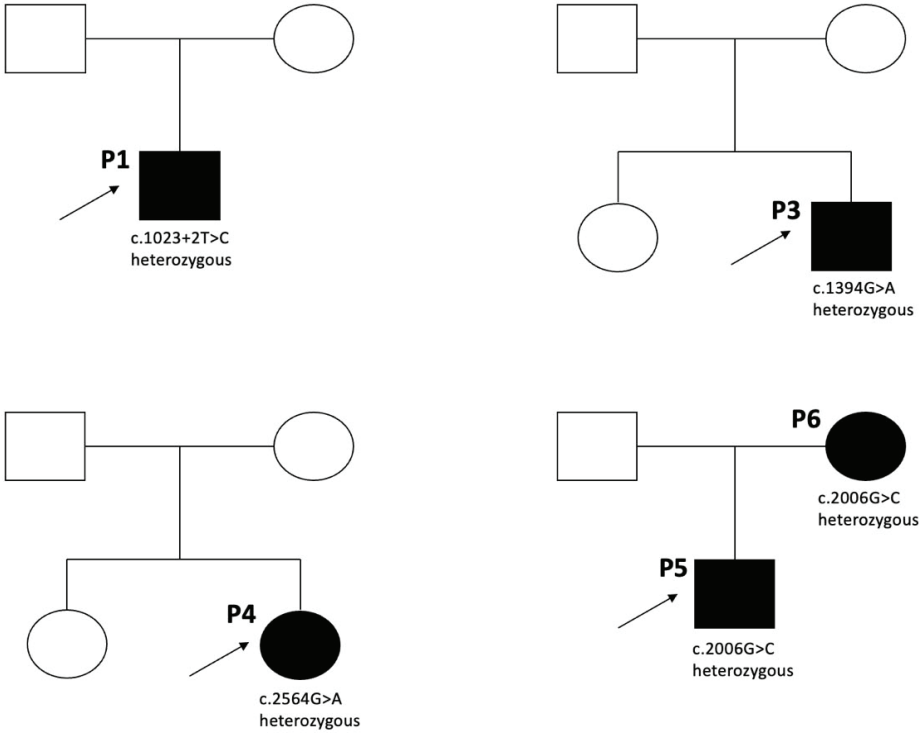

Figure 4. Pedigrees of the patients with novel *COL2A1* variants

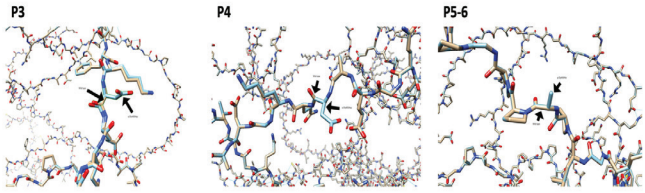

Figure 5. Biomolecular modeling of the collagen alpha-1(2) chain (AF-P02458-F1-v4) with three novel variants: p.(Gly465Asp), p(Gly669Ala), and p.(Gly885Asp)

KD is characterized by short-trunk dwarfism, flat midface, prominent eyes, cleft palate, myopia, retinal detachment, cataract, hearing loss, umbilical/inguinal hernia, enlarged painful joints, and limited joint mobility. Radiological findings of KD are kyphoscoliosis, odontoid hypoplasia, atlanto-axial instability, coronal vertebral clefts, platyspondyly, short and broad ilia, delayed epiphyseal ossification, epimetaphyseal irregularity, and short-dumbbell shaped long bones. The ossification of the proximal femoral epiphyses is significantly delayed and may not occur until puberty in severe involvement (13). Since the dominant features in patients 1, 2, and 4 were delayed epiphyseal ossification, metaphyseal and epiphyseal changes, and dumbbell-like long bones, a diagnosis of KD was made. The features of SEDC are very similar to KD. However, micro/retrognathia, pear-shaped vertebral bodies, almost unaffected metaphyses, and the absence of dumbbell-like long bones may distinguish it from KD. Patients 5 and 6 were diagnosed with SEDC because they exhibited epiphyseal involvement and preserved metaphyses in X-rays. In patient 3, in addition to epiphyseal delay and metaphyseal changes, the presence of metaphyseal sclerosis in the distal radius and ulna and an enchondroma-like appearance in the proximal metaphysis of the humerus led to the diagnosis of SEMD Strudwick type. SEMD Strudwick type can be considered a form of SEDC because the radiological appearance is very similar to SEDC in the neonatal period. However, metaphyseal changes begin to occur during childhood. In addition to enlarged, irregular, and mottled metaphyses, an enchondroma-like appearance and zones of osteosclerosis and osteopenia at the metaphyses are also notable (13). As mentioned before, it may be difficult to conclusively determine diagnoses because clinical and radiological findings are closely intertwined.

In the present study, one splicing variant (c.1023 + 2T > C) and two missense variants (c.905C > T p.Ala302Val; c.2564G > A p.Gly855Asp) were associated with KD. Zhang et al. (10) identified a hotspot variant c.905C > T in KD. Chen et al. (14) previously conducted a functional analysis on this variant, demonstrating its impact on the splicing process by causing the skipping of 21 nucleotides. The splicing variant c.1023 + 2T > C has not been reported previously. The c.1023 + 2T > C variant was analyzed using the SpliceAI tool. This variant is located in the canonical splice donor site region of exon 16 of this 54-exon gene. The variant is predicted to affect mRNA splicing and lead to out-frame intron retension. However, this mechanism must be supported by functional studies. It is worth mentioning that splicing variants in other genes have precise explanations, such as alterations in the length of exons or the skipping of exons resulting in premature stop codons. The distinctive architecture of collagen proteins (including type 1 collagen) results in the possibility of splicing causing diverse functional consequences. Hence, functional analysis plays a vital role in the interpretation of splicing variants and comprehension of their molecular impacts on protein structure and function. Splice variants are responsible for approximately 65% of the pathology in KD (4). The patient with the c.1023 + 2T > C splice variant had mild short stature, unlike the other KD patients. If a genotype-phenotype correlation for this variant is made, it may be associated with mild short stature, although this is speculative at present. More patient series are needed to make a clear assessment. The Gly855Asp variant was a novel variant. The substitution of glycine to aspartate has not been widely observed in the literature and is more commonly associated with ACG2/HCG and STL1. Severe short stature and pectus excavatum were remarkable in our patient.

The c.1394G > A (p.Gly465Asp) variant was associated with SEMD Strudwick type in the present study. This missense variant was also novel. In the literature, the substitution of glycine with alanine at position 465 has been classified as SEDC (15). The substitution of glycine with serine at the same position has also been demonstrated in the literature and was also associated with SEDC. It has been proposed that this replacement does not lead to severe short stature (8). The glycine to aspartate substitution reported here may result in more severe skeletal features, including severe short stature, pectus carinatum, marked lordosis, and atlanto-axial instability. In addition, cleft palate, hearing loss, and inguinal hernia were present as extra-skeletal findings. Another novel variant c.2006G > C (p.Gly669Ala) has been associated with SEDC. Markova et al. (16) reported a patient with a glycine to serine conversion at the same position. This patient had severe short stature (-9.7 SDS) and myopia and was diagnosed with SEDC. Our patients were also diagnosed with SEDC. They had severe short stature but did not have extra-skeletal manifestations, such as visual or hearing impairments. In studies involving patients diagnosed with

SEDC and glycine to alanine conversions, none of them exhibited extra-skeletal manifestations, contrast to the patients presented herein (17,18,19). Furthermore, glycine to alanine conversions has been described as extremely rare, and to the best of our knowledge, it is most commonly associated with SEDC. It may be that SEDC patients with a glycine to alanine conversion may not exhibit extra-skeletal manifestations. However, additional studies are needed to confirm this. Mild manifestations of SED are frequently (mis) diagnosed as "rheumatoid-like" arthritis or "degenerative conditions" affecting the hip joints (16). Therefore, early-onset joint pain and a family history of joint prostheses should raise suspicion for type 2 collagenopathies.

As is the case with other collagenopathies, patients with the *COL2A1* variant should be monitored with a multidisciplinary approach. Atlantoaxial dislocation, odontoid hypoplasia, and retinopathy may be life-threatening or result in significant morbidity. From the perspective of pediatric endocrinology, these patients may present with short stature of varying clinical severity, which may be classified as idiopathic short stature or skeletal dysplasia and monitored accordingly. From the perspective of pediatric endocrinology, as the patients will be monitored by endocrinologists until they reach adulthood, it is important to enhance awareness and understanding of potential comorbidities, multidisciplinary management strategies, and future treatment options. Patients with skeletal dysplasia tend to be referred to pediatric endocrinology for short stature and pediatric rheumatology for joint problems. The phenotypic features in this small patient group showed that the severity of short stature was variable and increased with age. Mild cases presenting at a young age, like patient 1, may present with mild short stature and be considered idiopathic short stature. However, the presence of dysmorphic findings, such as short neck, lordosis, and absence of pubic ossification, which were observed in all patients in our cohort, may assist in the targeted planning of molecular studies by suggesting the possibility of chondrodysplasia due to *COL2A1*.

These patients represent a group for whom there is limited experience with growth hormone (rhGH) therapy. Concerns have been raised about the potential for skeletal disproportion, scoliosis, and retinal complications, in addition to the limited benefit in terms of height gain with rhGH. A recent study from China published in 2022 investigated the efficacy of rhGH treatment in nine collagenopathy patients, two of whom had treatment combined with GnRHa. The results indicated an improved growth rate and height SDS; however, it was concluded that close monitoring of adverse reactions such as scoliosis is required. Among the five patients with a confirmed *COL2A1* mutation who received growth hormone therapy, there was a mean improvement of approximately +0.61 in height SDS over the course of one year (20). Future studies in collagenopathy patients, whose numbers are increasing with the increase in molecular diagnostic possibilities, will focus on the long-term morbidity and response to rhGH and alternative treatment options. Another potential concern is the possibility of early-onset osteoporosis. Type 2 collagen alpha 1, encoded by *COL2A1*, is the primary collagen found in articular cartilage and is synthesized by chondrocytes. *COL2A1* variants have been linked to an impairment of bone microstructure, which can lead to early onset osteoporosis, skeletal dysplasia, and osteoarthritis. In some cases, the dysplasia component may be so mild that only the pseudorheumatoid joint problems come to clinical attention. Therefore, a skeletal assessment is essential to accurately identify the condition and develop an optimal therapeutic strategy. Early diagnosis may prevent a progressive decline in bone mass, as antiresorptive treatment represents a valuable treatment option (21).

We report four novel variants in the *COL2A1* gene, expanding the molecular spectrum of type 2 collagenopathies. Analyzing the clinical and genetic aspects of different types of type 2 collagenopathies can enhance our comprehension of the underlying mechanisms and enable more precise prediction of their progression in the early stages. This, in turn, can lead to improved medical treatment and quality of life for affected individuals. In contrast to the past, the possibility of diagnosing rare genetic diseases has increased as genetic tests have become cheaper and more accessible. Furthermore, precise identification of type 2 collagenopathies is important to provide accurate genetic counseling. Patients should be offered pre-implantation genetic testing because of the notable risk of recurrence.

Study Limitations

This study was conducted with a limited number of cases. Furthermore, functional studies are required to confirm the pathogenicity of the identified variants.

Conclusion

Short stature is one of the most common conditions encountered in clinical practice. In skeletal dysplasias, *COL2A1*-related diseases are relatively common. We described six patients with type 2 collagenopathies, four of whom had novel variants, including three with KD, two with SEDC, and one with SEDC Strudwick type. Identification of novel variants is key to expanding the range of genetic variations in diseases and in gaining a clearer understanding of the relationship between genotype and phenotype in larger patient cohorts. The similarity of clinical and radiological findings and the variability of phenotype in

COL2A1-related diseases make it challenging to categorize patients.

Ethics

Ethics Committee Approval: The study adhered to the Declaration of Helsinki and was approved by the Ethical Committee of ***University of Health Sciences Türkiye, Ümraniye Training and Research Hospital*** (approval number: B.10.1.TKH.4.34.H.GP.0.01/293, date: 05.09.2024).

Informed Consent: Written informed consent for genetic testing and publication of clinical findings, patient photographs, and molecular results was obtained from each patient or their parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Burcu Yeter, Concept: Burcu Yeter, Yasemin Kendir Demirkol, Ahmet Hamdi Akgülle, Design: Burcu Yeter, Ahmet Hamdi Akgülle, Data Collection or Processing: Metin Eser, Yasemin Kendir Demirkol, Betül Sözeri, Analysis or Interpretation: Burcu Yeter, Yasemin Kendir Demirkol, Literature Search: Burcu Yeter, Yasemin Kendir Demirkol, Heves Kırmızıbekmez, Writing: Burcu Yeter, Yasemin Kendir Demirkol, Heves Kırmızıbekmez.

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ORIGINAL ARTICLE

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ACTION Teens Global Survey–Türkiye Report: More Worry and Less Motivation for Adolescents Living with Obesity

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What is already known on this topic?

Childhood/adolescent obesity rates have been rising in Türkiye so there is a need to identify local barriers to effective obesity care. The global ACTION Teens survey found that adolescents living with obesity (ALwO), caregivers, and healthcare professionals (HCPs) have different perceptions of obesity, and identified a need for greater education and enhanced communication.

What this study adds?

This subanalysis of ACTION Teens data from Türkiye found that, compared with the global analysis, a greater proportion of ALwO in Türkiye worried about weight impacting future health, although similar proportions had made a recent weight-loss attempt. Results suggest Turkish ALwO require greater weight-management support from HCPs.

Abstract

Objective: ACTION Teens (NCT05013359) surveyed adolescents living with obesity (ALwO), their caregivers, and healthcare professionals (HCPs) in 10 countries to identify attitudes, perceptions, behaviors, and barriers preventing effective obesity care. This subanalysis identified key findings from Türkiye.

Methods: In Türkiye, 700 ALwO (aged 12 <18 years), 700 caregivers, and 324 HCPs completed a cross-sectional survey (September-November 2021).

Results: ALwO had poor mean World Health Organization-5 Well-Being Index (36.7) and Rosenberg Self-Esteem Scale (14.6) scores. Most ALwO (85%) were worried about their weight, and many ALwO (92%) and caregivers (96%) worried about weight affecting their/their child's future health. Furthermore, many respondents agreed weight loss is completely the ALwO's responsibility (ALwO: 70%; caregivers: 47%; HCPs: 42%). Despite this, only 24% of ALwO reported being highly motivated to lose weight, although 59% reported a weight-loss attempt in the past year. Their most common weight-loss barrier was being unable to control hunger, according to ALwO (76%) and caregivers (73%). HCPs reported discussing weight with 42% of ALwO, on average, with 34% indicating insufficient time during appointments prevents them from discussing weight.

Conclusion: Compared with the global ACTION Teens analysis, a greater proportion of ALwO in Türkiye worried about weight impacting future health (92% vs. 85%), yet a similar proportion had made a recent weight-loss attempt (59% vs. 58%), perhaps due to lower

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motivation (24% vs. 45%). These results suggest ALwO in Türkiye require greater weight-management support, particularly support with controlling hunger and so, measures should be taken to reduce HCPs' time constraints.
Keywords: Adolescents, clinical care, family practice, obesity treatment, physician attitudes

Introduction

Childhood and adolescent obesity rates have been rising worldwide, including in Türkiye (1,2,3). This is concerning given the considerable mental health challenges experienced by children and adolescents living with obesity (ALwO) (4). In addition, early-onset obesity typically continues into adulthood, with severe health implications in later life (5,6,7). Furthermore, weight struggles at an early age are associated with more severe obesity class and feelings of hopelessness in adulthood, suggesting the enduring impact of early-onset obesity is more severe, relative to adult-onset obesity (8). Early intervention for obesity in children and adolescents is important as it is associated with improved long-term weight-loss outcomes (9).

An international survey evaluating attitudes, perceptions, and behavior among adults living with obesity and healthcare professionals (HCPs) found that initial weight-management conversations with HCPs were typically delayed by several years after the person first began struggling with their weight, and were often triggered by the presence of complications related to obesity (10). However, it is important to initiate weight-management conversations at an earlier stage before complications arise.

To improve obesity care for ALwO, there is a need to better understand the lived experience of, and challenges faced by, ALwO, plus their caregivers and HCPs. The global ACTION Teens study, which was performed in 10 countries, including Türkiye, identified differences between ALwO, caregivers, and HCPs in terms of their perceptions of obesity. General findings included caregivers under-appreciating the burden of obesity on ALwO, and HCPs misconceiving the major motivators and barriers for weight loss (11). The results indicated a need for greater education and enhanced communication between these groups. However, there is also a need to evaluate country-specific data to identify local barriers to effective obesity care.

Here, we present key findings from an ACTION Teens subanalysis that evaluated data from Türkiye, and highlight important differences from the global data set.

Methods

Study Design and Participants

Methods for the global, cross-sectional, survey-based ACTION Teens study (NCT05013359) have previously been reported (11). In Türkiye, participants completed the survey between September 24, 2021, and November 8, 2021.

Eligible participants were: (i) adolescents (aged 12 to <18 years) in Türkiye living with obesity, that is, those with a current body mass index (BMI; determined using self-reported weight, height, sex, and age) ≥95th percentile for sex and age according to charts appropriate for Türkiye (12); (ii) caregivers aged ≥25 years who resided (at least half of the time) with an ALwO in Türkiye and were involved in making decisions related to their ALwO's healthcare; and (iii) HCPs practicing in Türkiye with ≥2 years' clinical practice experience, who typically saw or treated ≥10 ALwO on a monthly basis, and spent at least half of their time caring for patients directly. ALwO who had (or caregivers whose ALwO had) experienced a significant change in weight resulting from illness or major injury in the previous six months were excluded from the study, as were ALwO who perceived themselves (or caregivers who perceived their ALwO) to be extremely muscular. Each respondent provided informed consent to participate in the study; informed consent was also obtained from the parent or legal guardian of each ALwO.

The study – which was approved by an independent ethics committee in Türkiye (Marmara University Ethics Committee, İstanbul, Türkiye; approval number: 09.2021.1080, date: 03.09.2021) – was conducted in line with the EphMRA Code of Conduct, the Declaration of Helsinki, and all relevant regulations for managing personal data.

Procedures

Three separate surveys (for ALwO, caregivers, and HCPs) with overlapping questions were developed and have been previously published (11). An international steering committee comprising HCPs and subject matter experts co-developed and approved the surveys.

Participants were recruited via online databases and panels. ALwO and caregivers were recruited from panels handled by Eksen. HCPs were recruited from panels handled by Dynata and databases handled by M-Motions. Caregivers of ALwO were identified by targeting and screening a stratified adult general population sample, with ALwO subsequently recruited via their caregivers. All caregivers were asked if their ALwO could participate to ensure the recruitment of as many matched pairs of caregivers and ALwO as possible. When enrollment of matched pairs had been maximized,

recruitment of caregivers and ALwO continued until the target sample size was achieved.

Data collection was carried out by KJT Group Inc. (Rochester, NY, USA), with data obtained via online surveys that were programmed using Decipher Survey Software (Forsta, Stamford, CT, USA). In Türkiye, the surveys were provided in Turkish and could be completed either online or via computer-assisted telephone or in-person interviews. All survey questions were mandatory to prevent missing data.

Outcomes

The primary objective of the ACTION Teens study was to identify attitudes, perceptions, behaviors, and barriers preventing effective obesity care.

Primary outcome measures across several categories were assessed: attitudes about obesity (including people living with obesity and the impact of living with obesity); weight loss (attempts to lose weight in the past year, motivating factors, barriers, definition of successful weight loss); weight-related conversations between ALwO/caregivers and HCPs (history, frequency, the initiator, responsibility for initiating conversations); interactions between HCPs and ALwO/caregivers (reasons for not discussing obesity, frequency of diagnosing obesity, frequency of scheduling obesity-related follow-up appointments); and sources for obtaining information on obesity, weight loss, weight management, and healthy lifestyles. These outcomes were evaluated through use of single or multiple item selection, Likert scales, or numeric responses.

Exploratory outcome measures included ALwO well-being and self-esteem, which were assessed using the World Health Organization-5 Well-Being Index (WHO-5) and Rosenberg Self-Esteem Scale (RSES), respectively (13,14,15,16). The Turkish versions of the WHO-5 and the RSES have previously been validated (17,18).

Statistical Analysis

The sample size targeted for Türkiye was 700 ALwO, 700 caregivers, and 300 HCPs with completed surveys; this considered the need to balance recruitment feasibility with statistical power.

De-identified data from all completed surveys were analyzed by KJT Group using Statistical Package for the Social Sciences (IBM, version 23.0), Stata (StataCorp LLC, version IC 14.2), and Excel (Microsoft 365), and data were reported using descriptive statistics. For continuous variables, outliers were removed from the data set where appropriate.

Data from surveys completed by caregivers were weighted to reflect demographic targets based on government and other public data (sex, age, region, education, and household income (19,20,21,22) that were representative of Türkiye, in order to reduce selection bias and enhance generalizability. ALwO data were not weighted because ALwO demographics were not publicly available for all countries included in ACTION Teens.

Results

Participant Characteristics

There were 700 ALwO, 700 caregivers, and 324 HCPs surveyed from Türkiye (Supplementary Figure 1). Half (52%) of the ALwO were female and most ALwO were aged 16-17 years (59%). The proportions of ALwO with obesity class 1 (BMI >95th percentile for age and sex), 2 (BMI >120th

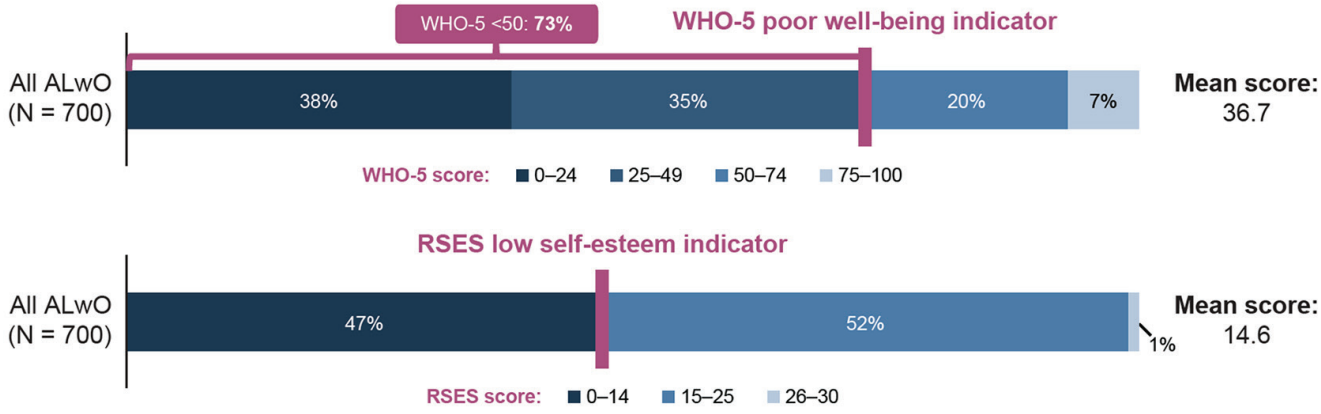

Figure 1. WHO-5 and RSES scores. Proportion of respondents with each score category and mean scores. The WHO-5 (ALwO Q102) ranges from 0 to 100; a score <50 indicates poor well-being (14). The RSES (ALwO Q103) ranges from 0 to 30; a score <15 suggests low self-esteem (16)

ALwO: adolescents living with obesity, RSES: Rosenberg Self-Esteem Scale, WHO-5: World Health Organization-5 Well-Being Index

percentile), and 3 (BMI >140th percentile) were 38%, 50%, and 12%, respectively (Table 1). Most HCPs (69%) were family physicians, 11% were general pediatricians, and the remaining 20% were specialists, including pediatric endocrinologists and nutrition specialists.

The proportion of HCPs who self-reported completing advanced weight management or obesity training after medical school was 18%, and only 6% of HCPs reported receiving training with evaluation/certification that lasted for >1 day. Furthermore, only 43% of HCPs were aware of any clinical guidelines for treating ALwO and of these, 92% considered the guidelines to be somewhat/very effective.

Information Sources

Only 26%, 23%, and 13% of ALwO reported using YouTube, search engines, and social media (such as Facebook, Instagram, X, TikTok), respectively, as an information source for weight management; they most commonly obtained information from doctors (53% of all ALwO). Information from doctors was also their most important source (selected by 45% of ALwO who had used information sources). Similarly, doctors were caregivers' most frequently used information source (56% of all caregivers) and most important source (selected by 59% of caregivers who had used information sources). The most frequently used sources of information on obesity for HCPs were journal articles, medical education or continuing medical education programs, and conferences (56%, 52%, and 52%, respectively).

Perceptions of Obesity

The proportions of ALwO who thought excess weight would make it somewhat/much harder to get a job, make friends, and do well in school were 78%, 64%, and 48%, respectively; similar proportions of caregivers felt the same (74%, 67%, and 51%, respectively). Overall, 93% of HCPs, 82% of caregivers, and 81% of ALwO thought that obesity has a strong impact on people's well-being and health. Furthermore, obesity was considered to be at least as serious as cancer by 70% of HCPs, 68% of caregivers, and 69% of ALwO.

Impact of Obesity

Scores on the WHO-5 (mean score: 36.7) and RSES (mean score: 14.6) indicated that poor well-being and low self-esteem were common among ALwO (Figure 1). Most ALwO indicated that they often/always feel unhappy because of their weight (70%) and feel insecure because of their body (63%). Similarly, most caregivers indicated that their child often/always feels unhappy (68%) and insecure (58%) because of their weight or body image, respectively. Few ALwO (6%) and caregivers (9%) reported that they/their child often/always feels comfortable with their body. Notably, nearly one-third of ALwO (32%) reported that they are often/always bullied because of their weight.

Almost all ALwO (95%) and caregivers (99%) felt their/their child's weight was slightly/a lot/extremely above normal, and approximately half (47% and 50%, respectively) rated their/their child's health as poor/fair. The majority of ALwO

Table 1. Demographics and characteristics of respondents from Türkiye

	ALwO (n = 700)	Caregivers (n = 700)	HCPs (n = 324)
Age in years, mean (SD)	15.3 (1.7)	40.3 (5.8)	44.9 (10.5)*
Sex			
Female, n (%)	363 (52)	432 (62)	121 (37)
Male, n (%)	337 (48)	268 (38)	203 (63)
ALwO obesity class†			
Obesity class 1 (BMI ≥95th percentile for age and sex)	38% (n = 264)	30% (n = 213)	57% (SD: 22)
Obesity class 2 (BMI ≥120% of 95th percentile for age and sex)	50% (n = 350)	50% (n = 347)	27% (SD: 13)
Obesity class 3 (BMI ≥140% of 95th percentile for age and sex)	12% (n = 86)	20% (n = 140)	17% (SD: 12)
BMI classification of caregivers and HCPs, n (%)‡			
Underweight (< 18.5 kg/m^2)	N/A	3 (< 1)	3 (1)
Healthy weight (18.5-24.9 kg/m^2)	N/A	280 (40)	104 (48)
Overweight (25.0-29.9 kg/m^2)	N/A	341 (49)	85 (40)
Obesity class 1-3 (≥30.0 kg/m^2)	N/A	76 (11)	23 (11)

Percentages may not sum to 100% due to rounding.
*Calculated for all HCPs, excluding one outlier (i.e., n = 323).
†Obesity class of ALwO respondents, the ALwO of caregiver respondents, and the ALwO patients of HCP respondents. Data are the percentage (number) of ALwO (for ALwO and caregivers) or the mean percentage (SD) of ALwO patients (for HCPs).
‡BMI classification of all caregiver respondents (n = 700) and the subset of HCP respondents who provided height and weight data (excluding one outlier: n = 215).
Table 1 adapted from reference 11.
ALwO: adolescents living with obesity, BMI: body mass index, HCP: healthcare professional, N/A: not applicable, SD: standard deviation

were somewhat/very/extremely worried about their weight (85%) and at least a little worried about weight impacting their health in future (92%) (Figure 2). Similarly, most caregivers thought their child was somewhat/very/extremely worried about weight (73%) and were personally at least a little worried about weight impacting their child's future health (96%) (Figure 2). Among HCPs, 68% agreed that obesity in adolescence has an impact on life expectancy.

Weight Loss

Two-thirds of ALwO (67%) and caregivers (66%) agreed that weight loss would be possible if they/their child really set their mind to it, but only 24% of ALwO and 27% of caregivers thought they/their child was highly motivated to lose weight (Figure 3). In addition, 30% of caregivers thought their child would slim down naturally over time (Figure 3). Notably, more ALwO (70%) than caregivers (47%) and HCPs (42%) agreed that weight loss was completely their/their child/their ALwO patients' responsibility.

Although 59% of ALwO reported making a weight-loss attempt in the past year, only 40% of caregivers reported an attempt by their child; however, most ALwO (74%) and caregivers (67%) indicated a weight-loss attempt over the next six months was at least somewhat likely.

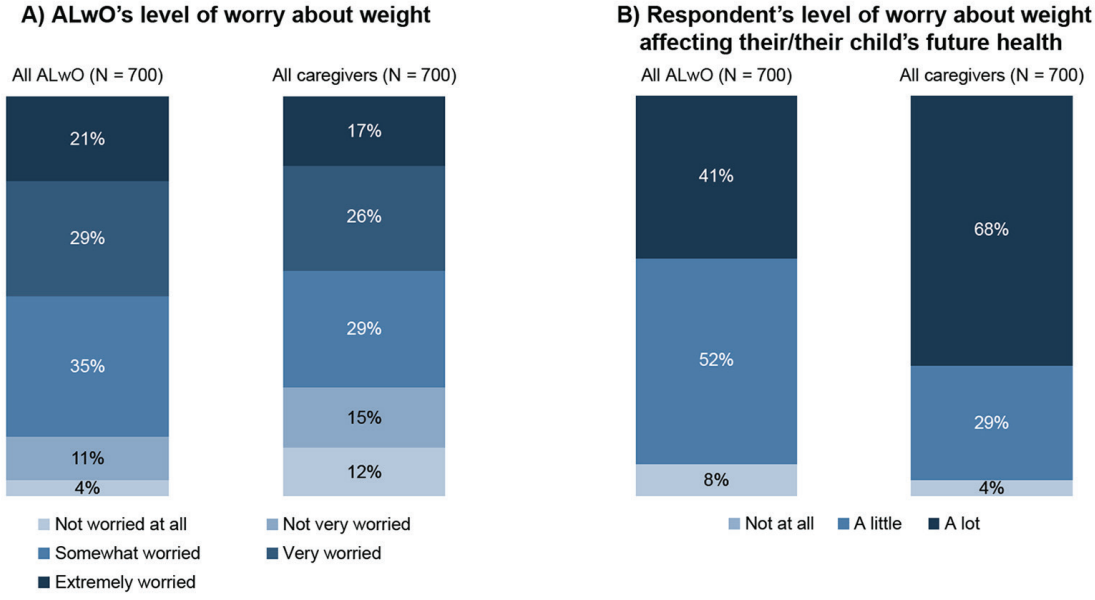

Figure 2. Level of worry about weight and its impact on future health. Proportion of respondents who selected each option (panel A: ALwO Q108 and caregiver Q112; panel B: ALwO Q512 and caregiver Q515). Percentages may not sum to 100% due to rounding. Figure 2 adapted from reference 11

ALwO: adolescents living with obesity

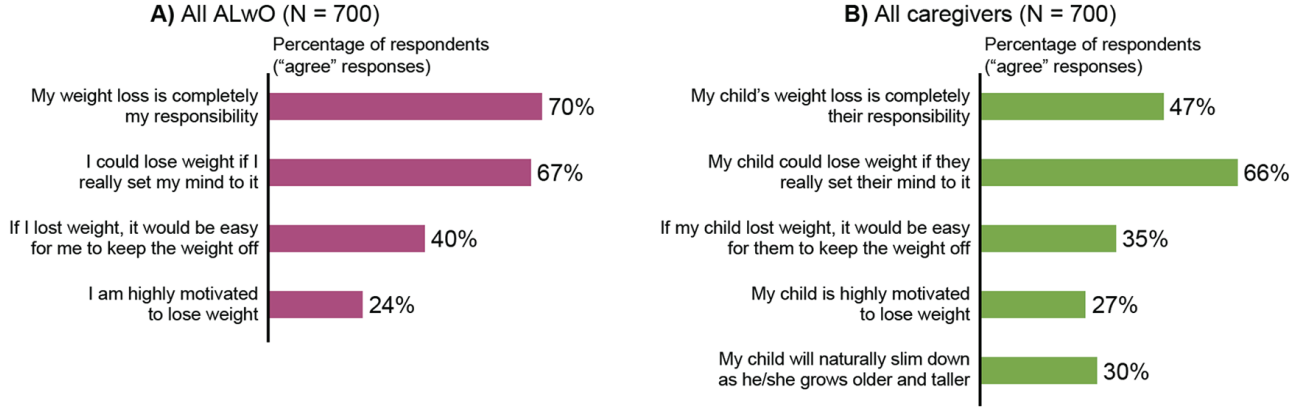

Figure 3. Attitudes toward ALwO weight loss. Proportion of respondents who selected either "somewhat agree" or "strongly agree" in response to each statement (panel A: ALwO Q113; panel B: caregiver Q113). Figure 3 adapted from reference 11

ALwO: adolescents living with obesity

ALwO and caregivers reported that the top four motivators for ALwO to lose weight were not being happy with their weight, wanting to look like their peers, a doctor's recommendation, and the desire to be in better shape/more fit (Figure 4). The top four motivators selected by HCPs were wanting to look like peers (73%), be in better shape/more fit (64%), be more confident (63%), and improve their social life/popularity (56%).

The top weight-loss barrier was ALwO being unable to control their hunger, according to ALwO and caregivers; other top barriers included lack of motivation and not liking exercise (Figure 5). By comparison, HCPs most often identified lack of exercise, unhealthy eating habits, and a preference for unhealthy food as weight-loss barriers for ALwO (93%, 93%, and 92% of HCPs agreed, respectively). Of note, although most ALwO reported typically having dinner with family (73%) and having fruit/vegetables available at home (61%), half reported sugary snacks (51%) and beverages (51%) were typically available at home.

Successful weight loss was most frequently defined as not gaining weight (ALwO: 70%; caregivers: 61%) or maintaining target weight for ≥6 months (HCPs: 61%) and having a better diet (ALwO: 60%; caregivers: 64%; HCPs: 66%). Many HCPs defined successful weight loss as improved psychological health (57%); this definition (improved mental health) was less common among ALwO (18%) and caregivers (14%).

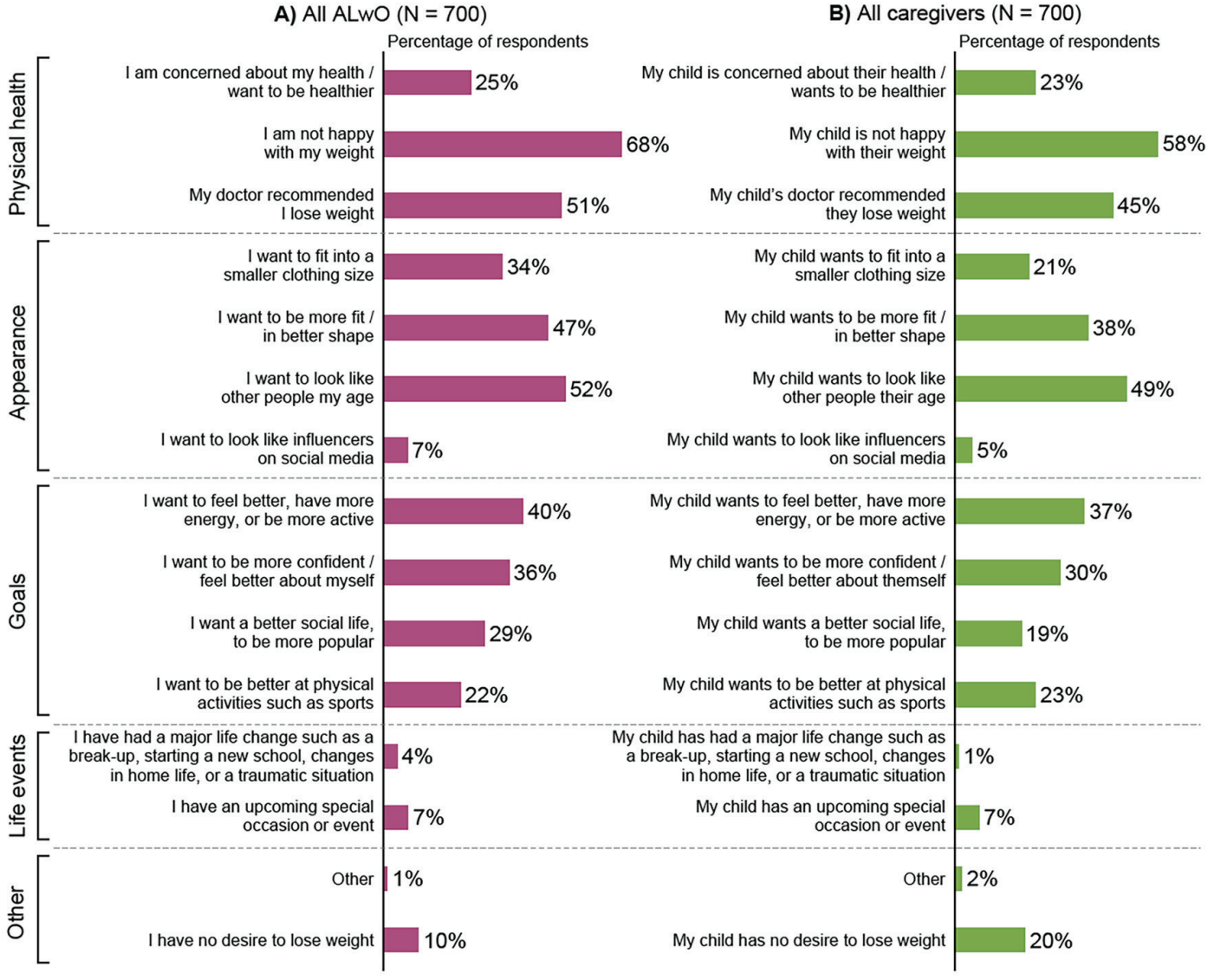

Figure 4. Motivators for ALwO to lose weight, according to ALwO (A) and caregivers (B). Proportion of respondents who selected each option (panel A: ALwO Q208; panel B: caregiver Q208). Figure 4 adapted from reference 11

ALwO: adolescents living with obesity

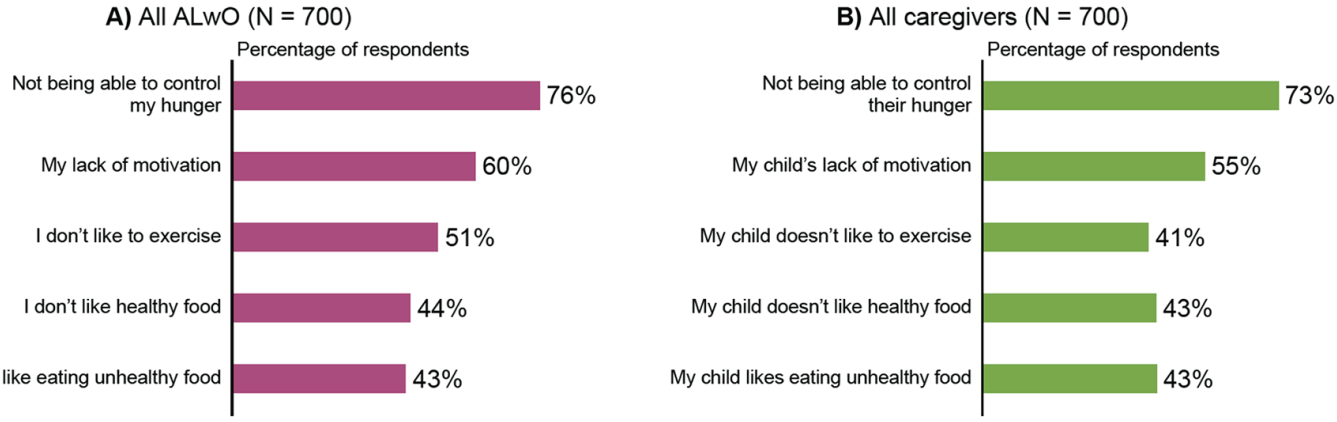

Figure 5. Top barriers to ALwO losing weight, according to ALwO (A) and caregivers (B). Proportion of respondents who selected each option (panel A: ALwO Q210; panel B: caregiver Q210); only the five most commonly selected barriers are shown. Figure 5 adapted from reference 11

ALwO: adolescents living with obesity

Conversations About Weight

Two-thirds of ALwO (69%) reported being able to talk honestly about their weight with either their mother or father. Most ALwO (70%) and caregivers (61%) reported talking to an HCP about their/their child's weight in the past year, but HCPs indicated they discuss weight with only 42% of their ALwO patients, on average. Among the subset of ALwO (n = 492) and caregivers (n = 481) who had discussed weight with an HCP in the past year, 26% of ALwO and 47% of caregivers reported they themselves usually initiated the discussions, while HCPs reported that they start discussions 48% of the time, on average.

Overall, 47% of ALwO, 20% of caregivers, and 26% of HCPs believed they themselves were responsible for raising the topic of weight during appointments. However, ALwO reported many barriers that prevented them from discussing weight with HCPs, most commonly not believing they were able to lose weight (39%) and not being comfortable raising the topic (27%). By comparison, most HCPs reported being at least somewhat comfortable having weight discussions with ALwO (85%) and caregivers (79%). However, like ALwO, HCPs identified many reasons why they might not initiate weight discussions, most commonly insufficient time, having more important health issues to discuss, and the patient's perceived lack of motivation (Supplementary Figure 2). Of note, the most common factors HCPs considered when contemplating raising the topic of weight with ALwO/caregivers were the ALwO's BMI-for-age-and-sex (63% of HCPs), weight (57%), obesity-related comorbidities (56%), and vital signs (56%).

Regarding the diagnosis of obesity, 68% of ALwO and 61% of caregivers had been informed by an HCP that they/their child has obesity, whereas HCPs indicated they informed 82% of ALwO/caregivers (on average) about the diagnosis.

Among those who had discussed their/their child's weight with an HCP in the previous year, 79% of ALwO and 83% of caregivers reported having ≥1 positive feeling after the most recent discussion (whereas 56% and 37% reported ≥1 negative feeling), and 76% of ALwO and 62% of caregivers agreed they felt comfortable discussing weight with the HCP.

Weight Management

Most HCPs considered obesity to be a chronic disease (75% agreed) and thought 5-10% body weight loss would be extremely beneficial for the health of ALwO (89% agreed).

The weight-management methods HCPs most often recommended to their ALwO patients were improving eating habits, increasing physical activity, following a specific diet, and reducing screen time; on average, HCPs recommended these to 54%, 53%, 41%, and 41% of their ALwO patients, respectively. HCPs also frequently indicated these were the weight-management methods that were most effective (selected by 84%, 77%, 57%, and 61% of HCPs, respectively).

The most common weight-management methods used by ALwO in the past year were improving eating habits (59%), following a specific diet (35%), seeing an obesity doctor (35%), increasing physical activity (31%), recording the foods they ate (25%), and seeing a nutritionist or dietitian (23%). The proportions of caregivers reporting their child had used these methods were 43%, 18%, 31%, 32%, 18%, and 16%, respectively. ALwO and caregiver responses suggest few ALwO started a formal exercise program (ALwO: 2%; caregivers: 3%) and reduced their screen time in the past year (ALwO: 11%; caregivers: 14%).

Discussion

The global ACTION Teens study contributed important data on the needs of ALwO, caregivers of ALwO, and HCPs involved in obesity management/treatment, and has provided valuable insights regarding their attitudes, perceptions, and behaviors, as well as barriers to the effective management of adolescent obesity (11). Here, we report findings from a subanalysis of the Turkish data and highlight important differences versus the global data set.

Regarding perceptions of obesity and its impact, relative to the global data set, a greater proportion of ALwO and caregivers in Türkiye recognized that obesity has a strong impact on well-being and health (81% and 82% in Türkiye vs. 72% and 67% globally) and reported that they/their child often/always feels unhappy because of their weight (70% and 68% vs. 44% and 37%) and insecure because of their body (63% and 58% vs. 37% and 27%). Moreover, a greater proportion of ALwO in Türkiye indicated they are often/always bullied because of their weight (32% vs. 24% globally), and a much lower proportion of caregivers in Türkiye reported that their child often/always feels comfortable with their body (9% vs. 42% globally). Furthermore, a greater proportion of adolescents and caregivers in Türkiye were worried about the impact of weight on their/their child's future health (92% and 96% vs. 85% and 80% globally). Taken together, these findings suggest that adolescents and caregivers in Türkiye are more cognizant of the negative impact of obesity than their global counterparts. This may be related to the higher obesity class of the ALwO surveyed in Türkiye versus globally; fewer ALwO in Türkiye had obesity class 1 (38% vs. 65% globally). Alternatively, it may be a natural consequence of ALwO and caregivers in Türkiye being more aware that their/their child's weight is above normal (95% and 99% vs. 76% and 66% globally).

Although ALwO and caregivers in Türkiye appeared to be more aware of their/their child's weight status and concerned about the impact of obesity than their global counterparts, this did not translate to a greater proportion reporting recent ALwO weight-loss attempts (59% and 40% in Türkiye vs. 58% and 41% globally) or likelihood of future ALwO weight-loss attempts (74% and 67% in Türkiye vs. 75% and 63% globally); there were no notable differences between Türkiye and the global data set in this regard. This suggests a relative lack of motivation among ALwO in Türkiye; indeed, ALwO and caregivers' responses indicate a lower proportion of ALwO in Türkiye were highly motivated to lose weight (24% and 27% vs. 45% and 38% globally). This could partially be due to ineffective communication with HCPs, as positive interactions with HCPs – in addition to having weight-loss goals and self-efficacy (i.e., confidence in one's own ability to achieve a goal) – are associated with increased weight-loss motivation among adults living with obesity (23). It has also been shown that adults living with overweight or obesity who increase their eating or physical activity self-efficacy during behavioral intervention programs experience greater weight loss (24). As such, ALwO who are ready to engage in weight management may benefit from HCP support (23).

Despite the apparent lack of weight-loss motivation among ALwO in Türkiye, more ALwO and caregivers in Türkiye believed that weight loss was entirely their/their child's responsibility (70% and 47% vs. 65% and 37% globally). More caregivers in Türkiye also recognized that weight loss is an active process; only 30% believed their child would slim down with age, versus 45% globally.

Encouragingly, although some ALwO in Türkiye reported using YouTube (26% vs. 34% globally) and social media (13% vs. 28% globally) to obtain weight-management information, their primary information source was doctors (53% vs. only 24% globally), and they considered doctors to be their most important information source (45% vs. only 14% globally). HCPs in Türkiye should therefore view weight-management discussions as opportunities to share trustworthy weight-management information with ALwO patients. Moreover, when discussing weight management with ALwO, HCPs in Türkiye should be mindful of the factors that motivate ALwO and those that act as weight-loss barriers. Relative to their global counterparts, a greater proportion of ALwO in Türkiye identified being unhappy with their weight (68% vs. 37%) and wanting to look like peers (52% vs. 28%) as motivators. This could be linked to surveying a slightly higher proportion of female ALwO in Türkiye (52%) versus globally (44%), as a study of adolescents in the USA found that obesity was associated with a significant decrease in self-esteem among White and Hispanic female adolescents, but only a mild decrease in self-esteem among male adolescents (25). Similarly, a survey of Turkish adolescents demonstrated that female gender was predictive of perceived overweight and body dissatisfaction, and these factors were associated with low self-esteem (26). In terms of weight-loss barriers, the top responses from ALwO in Türkiye were not being able to control hunger (76% vs. 38% globally), lack of motivation (60% vs. 34% globally), not liking exercise (51% vs. 28% globally), not liking healthy food (44% vs. 21% globally), and liking unhealthy food (43% vs. 32% globally). Caregivers in Türkiye were aligned regarding the top weight-loss barriers for ALwO. This suggests that strategies for managing adolescent obesity in Türkiye should prioritize increasing

opportunities to exercise and limiting access to unhealthy food. However, given that ALwO's top weight-loss barrier was their inability to control hunger, it appears that ALwO in Türkiye could benefit from greater weight-management support from HCPs, particularly support with controlling hunger.

Regarding the recent weight-management methods used by ALwO, a greater proportion of ALwO in Türkiye than in the global data set had improved their eating habits (59% vs. 41%) and followed a specific diet (35% vs. 17%), but a similar proportion had increased their physical activity (31% vs. 34%), and a lower proportion had started a formal exercise program (2% vs. 14%) and reduced their screen time (11% vs. 18%). HCPs in Türkiye should therefore emphasize the importance of increasing physical activity and reducing screen time when discussing weight management with ALwO patients.

Responses from HCPs in Türkiye also provided valuable insights. Compared with HCPs from the global data set, fewer HCPs in Türkiye had received advanced obesity training (18% vs. 43%) and were aware of clinical treatment guidelines for ALwO (43% vs. 67%), and a greater proportion believed their ALwO patients were entirely responsible for weight loss (42% vs. 27%). This suggests a need to offer additional obesity training to HCPs in Türkiye.

In terms of HCP–ALwO weight discussions, HCPs in Türkiye and the global data set indicated they typically initiate weight discussions half of the time (Türkiye: 48%; global: 54%) and inform approximately 80% of ALwO patients/their caregivers about the obesity diagnosis (Türkiye: 82%; global: 78%). They also concurred that the top three barriers preventing them from initiating weight discussions with ALwO were insufficient time during appointments, having more important health issues to discuss, and the ALwO not being motivated to lose weight. Aligned with this, time constraints have previously been highlighted as the main barrier to managing childhood obesity for family physicians in Türkiye (27). As such, measures should be taken to reduce HCPs' time constraints so that they can provide more weight-management support during appointments with ALwO. For example, the primary care setting may benefit from recruitment of additional HCPs who are trained exclusively in obesity management.

Study Limitations

Despite the robust design of the ACTION Teens surveys, potential limitations include the use of self-reported weight and height data, which can underestimate BMI, and the lack of data on body composition (11). The use of recruitment quotas (i.e., the non-probability sampling approach) may have introduced selection bias. However, the broad eligibility criteria enabled recruitment of respondents who were representative of ALwO, caregivers, and HCPs who see/treat ALwO across Türkiye. In addition, ALwO and caregivers were recruited via a stratified general population sample and caregiver responses were weighted on local demographic targets to reduce selection bias and enhance generalizability.

Further research is required to assess the impact of implementing strategies to overcome the identified barriers to effective adolescent obesity care in Türkiye.

Conclusion

This ACTION Teens subanalysis provides important insights into the attitudes and experiences of ALwO, caregivers and HCPs in Türkiye. Based on these insights, we propose the following strategies to improve adolescent obesity management in Türkiye: first, given that (relative to their global counterparts) fewer ALwO in Türkiye were motivated to lose weight despite being more worried about their future health, caregivers and HCPs should aim to encourage and support ALwO, with a view to increasing motivation and thus promoting engagement in weight-management programs. Second, based on ALwO's reported weight-loss barriers and recent weight-management methods, we recommend that weight-management programs place greater focus on increasing exercise, limiting access to unhealthy food, and reducing screen time; however, as hunger control was ALwO's top weight-loss barrier, it may also be beneficial for HCPs to offer medical assistance with controlling hunger. Third, HCPs' top barrier to initiating weight-management conversations with ALwO was insufficient time during appointments, suggesting that measures should be taken to reduce HCPs' time constraints so that they can provide more weight-management support. Finally, less than one-fifth of HCPs had received advanced obesity training indicating a gap in HCP training. Given the prevalence of adolescent and childhood obesity, additional obesity training should be offered to existing HCPs in Türkiye.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Ethics Committee, İstanbul, Türkiye (approval number: 09.2021.1080, date: 03.09.2021).

Informed Consent: Each respondent provided informed consent to participate in the study; informed consent was also obtained from the parent or legal guardian of each ALwO.

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Footnotes

Authorship Contributions

Design: Abdullah Bereket is a member of the ACTION Teens Steering Committee and thus contributed to the design of the study. Analysis or Interpretation: Abdullah Bereket, Neşe Perdahlı Fiş, Batu Gürser, Şükrü Hatun, Sibel Sakarya, Volkan Yumuk, Belma Haliloğlu, Writing: Abdullah Bereket, Neşe Perdahlı Fiş, Batu Gürser, Şükrü Hatun, Sibel Sakarya, Volkan Yumuk, Belma Haliloğlu.

Conflict of Interest: Abdullah Bereket received consultancy fees from Novo Nordisk for his role as member of the ACTION Teens Steering Committee during the conduct of the study. One author of this article, Abdullah Bereket, is member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, he was not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. Neşe Perdahlı Fiş reports no conflicts of interest in relation to this manuscript. Batu Gürser was employed by Novo Nordisk during development of this manuscript, however, at time of manuscript submission, he was employed by Lilly Gulf. Şükrü Hatun reports no conflicts of interest in relation to this manuscript. Sibel Sakarya reports no conflicts of interest in relation to this manuscript. Volkan Yumuk reports honoraria from Eli Lilly for providing a single advisory activity and from Novo Nordisk for providing educational sessions and attending advisory boards. Belma Haliloğlu is a consultant for Rhythm Pharmaceuticals and a member of the Rhythm Pharmaceuticals Scientific Committee.

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ORIGINAL ARTICLE

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Frequency of Polycystic Ovary Syndrome and "Being at Risk for Polycystic Ovary Syndrome" in Obese Adolescent Girls in Light of Current Definitions

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What is already known on this topic?

Polycystic ovary syndrome (PCOS) has become an important comorbidity in obese adolescent girls. Obesity and insulin resistance are associated with an increased risk of PCOS. The diagnosis of PCOS can be challenging in adolescent girls due to the physiological transition period following menarche until they reach full biological maturity. The sensitivity and specificity of diagnostic tests are sub-optimal and none of the tests used in diagnosis are perfect markers.

What this study adds?

Previous studies examining the prevalence and characteristics of PCOS in obese adolescents have predominantly used the diagnostic criteria for PCOS that were primarily validated for adult women. This study indicated that the prevalence of PCOS according to the "current recommendations for adolescents" was 8.3% in obese Turkish girls. The prevalence of individuals classified as "at risk for PCOS" was 46%. Among the diagnostic tests for PCOS, free androgen index (FAI) was found to be the most useful marker. For the optimum sensitivity and specificity, a cut-off value of 0.44 ng/mL for total testosterone and 11 for the FAI was identified.

Abstract

Objective: Obesity is associated with an increased risk of polycystic ovary syndrome (PCOS). It can be difficult to differentiate between PCOS and physiological oligomenorrhoea/anovulation in adolescent girls. To date, studies of the prevalence of PCOS in adolescents have predominantly used diagnostic criteria validated primarily in adult women. The aim of this study was to investigate the prevalence of PCOS in obese girls using the current diagnostic criteria for adolescents.

Methods: The diagnosis of PCOS was based on the presence of menstrual irregularity, clinical hyperandrogenism and hyperandrogenemia and the exclusion of other causes. Patients with one or two of these conditions were classified as "at risk for PCOS". The control group consisted of patients with obesity alone but no other comorbidity.

Results: A total of 421 patients were included in the study. The number of patients meeting the definition of PCOS was 35, representing a prevalence of 8.3%, while 200 patients (46%) were defined as "at risk for PCOS". The diagnostic value of the free androgen index (FAI) was found to be adequate, while other tests were poor. The cut-off values were 11 for FAI and 0.44 ng/mL for total testosterone, with optimal sensitivity and specificity.

Conclusion: Despite the increasing number of studies, the diagnosis and management of PCOS in adolescents remains challenging. While efforts should be made to avoid overdiagnosis, it is also important to recognize that many more patients may be at risk of developing PCOS.

Keywords: Adolescent, obesity, polycystic ovary syndrome, total testosterone, free androgen index

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Introduction

Polycystic ovary syndrome (PCOS) is characterized by androgen excess, ovulatory dysfunction and dysfunction of the hypothalamic-pituitary-ovarian axis, resulting in a self-perpetuating vicious cycle of neuroendocrine and metabolic dysfunction. The disease is complex and multigenic, with environmental factors playing a role (1). Obesity and insulin resistance are associated with an increased risk of PCOS and, when present in PCOS, more severe clinical manifestations (2). During puberty, insulin resistance increases due to activation of the growth hormone axis. This leads to compensatory hyperinsulinemia, which increases ovarian and adrenal androgen production, decreases hepatic sex hormone binding globulin (SHBG) production and impairs ovarian follicular dynamics and function (3). PCOS has become an important comorbidity in obese adolescent girls because of the presence of these physiological changes, environmental factors affecting metabolic health and epigenetic factors may also be involved.

In 1990, the National Institutes of Health criteria for PCOS were defined as "hyperandrogenism and/or hyperandrogenemia and oligo-anovulation, and exclusion of other diseases" (4). In 2003, the Rotterdam criteria were established, in which the diagnosis of PCOS requires the presence of two or more of the following criteria: oligo-ovulation/anovulation, clinical or laboratory androgen excess, the presence of multiple ovarian cysts, and the exclusion of other diseases (5). According to the criteria established by the Androgen Excess Society in 2006, PCOS should be diagnosed when ovarian dysfunction and/or polycystic ovarian morphology (PCOM) and clinical and/or biochemical findings of hyperandrogenism were present and other causes were excluded (6).

Due to the physiological transition from menarche to full biological maturity in adolescent girls, it can be difficult to differentiate true cases of PCOS from those who are normal. To date, studies investigating the prevalence and characteristics of PCOS in obese adolescents have predominantly used the diagnostic criteria described earlier, which have been validated primarily in adult women. In 2020, Peña et al. (7) published an international evidence-based guideline for adolescents. This latest guideline gives specific recommendations for diagnosing PCOS in adolescents, thus aiming to avoid misdiagnosis or delayed and under- or over-diagnosis. Further aims were to avoid unnecessary testing and to identify adolescents 'at risk' of PCOS. In this guideline, the definition of PCOS in adolescent girls is met by the criteria of "clinical and/or biochemical hyperandrogenism" in the presence of "irregular menstrual cycle" and exclusion of other possible causes. It was also noted that ultrasound findings should not be used for diagnostic purposes and that biochemical hyperandrogenism should be determined using appropriate high-quality assays. An international consortium update by Ibáñez et al. (8) has previously recommended that confirmation of biochemical hyperandrogenism in adolescents is important before a definitive diagnosis of PCOS is made, due to ethnic and racial differences in the clinical signs of androgen excess.

The aim of the present study was to investigate the prevalence of PCOS and the prevalence of being at risk of PCOS in obese adolescent girls in the context of the adolescent-specific diagnostic criteria described by Peña et al. (7). In addition, the study aimed to investigate the clinical and biochemical characteristics of these girls, thereby contributing updated information to the existing literature on this topic.

Methods

The present study was conducted with female patients who presented to the Pediatric Endocrinology outpatient clinic because of excessive weight gain between January 1, 2019, and March 1, 2023. Of the 1,000 patients aged 15-18 years who presented with excessive weight gain, 421 girls with a body mass index (BMI) above the 95th percentile, who had reached final height and pubertal stage (Tanner-5) and had menarche at least one year prior were included in the study. The study population consisted of individuals who completed the study forms in full and consented to undergo examination of all body parts for hirsutism. Informed consent forms were obtained from the patients themselves. Individuals with a medical history of congenital or acquired systemic diseases, or drug use that could lead to menstrual irregularities and abnormal body hair, were excluded from the study.

A questionnaire was administered to patients inquiring about their age at the onset of menstruation, the frequency of their menstrual cycles, the number of days and amount of bleeding, the presence of acne, and the presence of abnormal hair growth outside the genital and axillary regions.

Obesity was defined as BMI > 95th percentile according to age and gender or > 30 kg/m^2 (whichever was lower) in adolescents who had reached their final height (9). The World Health Organization defines obesity as "mild" if the BMI is between 30 and 35 or greater than 100 and 120% of the 95th percentile, "moderate" if the BMI is between 35 and 40 or greater than 120 and less than 140% of the 95th percentile, and "severe" if the BMI is greater than 40 or

greater than 140% of the 95th percentile. In this study, the BMI reference values for Turkish children were employed (10,11).

The diagnosis of PCOS was made based on the presence of menstrual irregularity, clinical hyperandrogenism (confirmed through biochemical hyperandrogenemia), and the exclusion of other potential causes. In instances where patients exhibited one or two of these conditions but did not fully meet the diagnostic criteria for PCOS, they were classified as "at risk for PCOS."

Menstrual Irregularity

The patients who had experienced menstrual cycles for at least one year were included in the study. The definition of irregularity used the Peña et al. (7) guideline recommendations:

1. 1-3 years after menarche: inter-cycle interval < 21 or > 45 days,
2. > 3 years after menarche: inter-cycle interval < 21 or > 35 days or < 8 cycles per year,
3. > 90 days for any cycle > 1 year after menarche,
4. No menstruation at age 15 or 3 years after thelarche (primary amenorrhea).

Clinical Hyperandrogenism

On physical examination, male-type terminal hair in hormone-sensitive areas (Ferriman-Gallwey score > 5-6) was considered "hirsutism" (12), and moderate and/or severe inflammatory-nodular acne on the face, back, and extensor faces with more than 10 lesions on the face was considered "severe acne" (13). Hirsutism and/or severe acne were accepted as clinical hyperandrogenism.

Hyperandrogenemia

The total testosterone and free androgen index (FAI) [total testosterone (nmol/L) / SHBG (nmol/L) x100] parameters were used. Blood samples were collected within the first week of the follicular phase. In our laboratory, total testosterone is quantified by means of an electrochemiluminescence immunoassay method, employing the Roche E801 autoanalyzer and Roche branded test kits. SHBG concentration was also determined by an electrochemiluminescence immunoassay method, using Elecsys SHBG kits on a Cobas e immunoassay analyzer. A value of > 0.48 ng/mL for total testosterone, which is the upper limit of the adult female reference value provided by our test kit, and a value of > 5 for FAI according to the recent literature were accepted as biochemical hyperandrogenemia (14). In the presence of clinical hyperandrogenism, total testosterone > 0.48 ng/mL and/or FAI > 5 was considered hyperandrogenism.

Polycystic Ovarian Morphology

In patients in whom ultrasound was required to support the diagnosis, the appearance characterized by multiple peripheral cysts with any ovarian volume above 12 mL was considered "PCOM". Ultrasonography findings were not used for diagnostic purposes because they were not appropriate for the gynecologic age of our patient group.

Insulin Resistance

A baseline homeostatic model assessment of insulin resistance (HOMA-IR) value of > 3.8 in girls or elevated serum insulin levels (> 300 µU/mL) on oral glucose tolerance test, with/without impaired glucose metabolism, was considered "insulin resistance" in the presence of clinical findings, such as truncal obesity, keratosis pilaris and acanthosis nigricans (15).

Exclusion of Other Causes

Among patients with 17-hydroxyprogesterone (17-OHP) levels > 2 ng/mL, those who demonstrated normalization on repeated measurements or normal results on the adrenocorticotropin hormone stimulation test were included in the study group. Patients with dehydroepiandrosterone sulfate (DHEAS) levels > 600 µg/dL underwent ultrasonography, and those with no adrenal mass were included in the study. Among patients with prolactin levels > 25 ng/mL, a clinical evaluation was conducted, and those whose prolactin levels normalized on repeated measurements in the follow-up were included in the study group. Those whose prolactin levels continued to increase were excluded. Patients with abnormal thyroid hormones at the time of diagnosis and for three months prior were excluded. Patients receiving thyroid hormone replacement therapy and euthyroid within the last three months were included in the study group. Patients receiving corticosteroids, antipsychotics, or antidepressant drugs were excluded from the study.

The control group consisted of patients with obesity alone, without menstrual irregularities, clinical or biochemical primary hyperandrogenism, or any other comorbidity. Patients with insulin resistance and metformin users were also excluded from the control group.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences, version 25.0 (IBM Inc., Armonk, NY, USA).

The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Descriptive statistical methods were employed to evaluate the study data. Data that conformed to a normal distribution are expressed as the mean and standard deviation, while those that did not conform are expressed as the median and interquartile range. The independent samples t-test was employed for the comparison of normally distributed data between two groups, while the one-way ANOVA test was used for the comparison of more than two groups. The Mann-Whitney U test was used for comparison of non-normally distributed data between two groups, and the Kruskal-Wallis test was used for comparison of more than two non-parametric groups. If the results were found to be significantly different in more than two group comparisons, the *post-hoc* Bonferroni test was applied. Pearson correlation analysis was employed for data that exhibited a normal distribution, whereas Spearman correlation analysis was used for data that did not. The objective was to ascertain the relationship between the study parameters. The chi-square test was used to evaluate categorical data. The significance level was set at $p < 0.05$ for all tests.

Receiver operating characteristic (ROC) curve analysis was employed to determine the sensitivity and specificity ratios, the area under the curve (AUC), the value of the diagnostic test, and the optimal cut-off values for diagnostic and supportive biochemical markers. Tests with an AUC value greater than 0.6 were considered "usable but inadequate," while those with an AUC value greater than 0.7 were considered "satisfactory".

Results

The mean age of the 421 adolescent female patients included in the study was 16.29 ± 0.94 years. The gynecologic age (post-menarche period) was between 1 and 8 years, with a mean of 4.01 ± 1.41 years. The age at which menstruation first occurred ranged from 8 to 17.5 years, with a mean of 12.27 ± 1.24 years. Twenty-four patients (5.7%) had menstruated at the age of 10 years or younger, while 14 patients (3.3%) had started menstruating at the age of 15 years or older.

In our cohort of obese adolescent girls, 126 (29.9%) patients exhibited menstrual irregularities, 139 (33.0%) demonstrated clinical hyperandrogenism, and 120 of 157 (76.4%) patients with laboratory tests exhibited biochemical hyperandrogenism. Of the 139 patients with clinical hyperandrogenism, 83 (59.7%) exhibited hirsutism alone, 21 (15.1%) exhibited severe acne, and 35 (25.2%) exhibited both hirsutism and severe acne. Of the 112 patients who underwent pelvic ultrasound examination, 57 (50.9%) were found to have PCOM. Acanthosis nigricans was identified in 144 (34.2%), and 81 (56.25%) of them were diagnosed with insulin resistance supported by laboratory findings, and metformin treatment was initiated in addition to lifestyle change recommendations.

The number of patients meeting the definition of PCOS was 35, representing an 8.3% prevalence. Moreover, 200 patients (46%) were defined as "at risk for PCOS" based on the presence of one or two of the following criteria: menstrual irregularities, clinical hyperandrogenism, or biochemical hyperandrogenism. Among the 35 patients diagnosed with PCOS, 14 (40%) had been prescribed metformin due to insulin resistance, while five (14.3%) had a family history of type 2 diabetes mellitus. Among the 200 patients considered to be at risk of PCOS, 45 (22.5%) had been prescribed metformin due to insulin resistance, while 47 (23.5%) had a family history of type 2 diabetes mellitus.

There were no statistically significant differences in age, age at menarche, gynecological age, or anthropometric measurements between the PCOS, PCOS at risk, and control groups. Fasting insulin, HOMA-IR, and low-density lipoprotein (LDL) were higher in those at risk for PCOS compared to the control group ($p = 0.009$, $p = 0.010$, and $p = 0.043$, respectively). In addition, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were higher in PCOS group than in control group ($p = 0.026$ and $p = 0.006$, respectively).

The levels and comparison of hormone tests of patients in the "PCOS" and "at risk" groups are shown in Table 1. The results indicated that, except for biochemical hyperandrogenism and insulin resistance, there were no significant differences in clinical presentations according to the severity of obesity (Table 2).

In correlational analyses, a positive correlation was observed between total testosterone and luteinising hormone/follicle stimulating hormone (LH/FSH) ratio, as well as 1,4-androstenedione ($r = 0.274$; $p < 0.01$; $r = 0.493$; $p < 0.001$, respectively). The FAI demonstrated a positive correlation with total testosterone, 1,4-androstenedione, and LH/FSH ratio ($r = 0.609$; $p < 0.001$, $r = 0.534$; $p < 0.001$, and $r = 0.292$; $p < 0.001$, respectively). Furthermore, the LH/FSH ratio demonstrated a positive correlation with the inter-cycle interval ($r = 0.364$; $p = 0.003$).

Data were analyzed from 167 patients (35 with PCOS and 132 at risk for PCOS) in whom the parameters total testosterone, FAI, 1,4-androstenedione and LH/FSH ratio were measured as diagnostic markers. The AUC values in the ROC curve were significant and fell into the "usable"

Table 1. A comparative analysis of diagnostic tests between patients with PCOS and patients at risk for PCOS

	PCOS (n = 35)	At risk (n = 200)	p
LH (IU/L)	9.58 ± 4.20	9.34 ± 6.6	0.839
FSH (IU/L)	4.31 ± 1.15	4.94 ± 1.44	**0.033***
Estradiol (pg/mL)	45.9 (27)	39.1 (22.6)	0.358
Total testosterone (ng/mL)	0.56 ± 0.20	0.46 ± 0.25	**0.043***
SHBG (nmol/L)	15.5 (8.18)	20.0 (12.5)	**0.002***
Free androgen index	11.6 (6.8)	8.0 (7.0)	**< 0.001***
17-hydroxyprogesterone (ng/mL)	1.36 (1.04)	1.07 (0.97)	**0.020***
1,4-androstenedione (ng/mL)	4.36 (1.28)	3.33 (1.61)	**0.003***
DHEAS (mcg/dL)	289 (202)	313 (164)	0.598
LH/FSH ratio	2.24 ± 0.89	1.92 ± 1.29	0.182

*p < 0.05. Normally distributed data were compared by independent-samples t-test and results were expressed as mean ± standard deviation; non-normally distributed data were compared by Mann-Whitney U test and results were expressed as median and IQR.
SHBG: sex hormone binding globulin, DHEAS: dehydroepiandrostenedione sulfate, PCOS: polycystic ovary syndrome, IQR: interquartile range, LH/FSH: luteinising hormone/follicle stimulating hormone

Table 2. A comparison of the distribution of patients' clinical features and diagnostic definitions according to the severity of obesity

	Mild (n = 124)	Moderate (n = 192)	Severe (n = 105)	p
PCOS	9 (7.2%)	19 (9.9%)	7 (6.6%)	0.553
At risk for PCOS	59 (47.5%)	93 (48.4%)	48 (45.7%)	0.904
Menstrual irregularity	39 (31.4%)	60 (31.2%)	27 (25.7%)	0.553
Clinical hyperandrogenism	47 (37.9%)	60 (31.2%)	27 (25.7%)	0.384
Biochemical hyperandrogenemia	27 (21.7%)[a]	59 (30.7%)[b]	34 (32.3%)[b]	**0.014***
Polycystic ovary morphology	16 (12.9%)	28 (14.5%)	13 (12.3%)	0.926
Insulin resistance	10 (8.0%)[a]	37 (19.2%)[b]	34 (32.3%)[c]	**< 0.001***

*p < 0.05. Chi-square test was used for categorical data comparison. Bonferroni test was applied in *post-hoc* analyses. Statistically significant differences and similarities are shown by superscripts ([a, b, c]).
PCOS: polycystic ovary syndrome

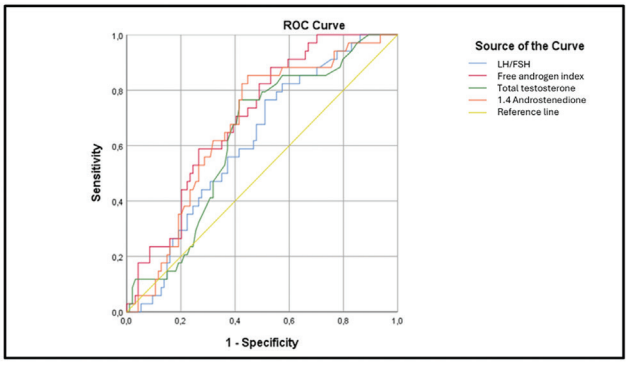
category for all tests, but their diagnostic values were low. Among the diagnostic tests, FAI was classified as adequate (AUC = 0.703, p < 0.001), while the AUC values of the other tests were poor (Figure 1).

Furthermore, the cut-off value for the FAI was 11, with an optimal sensitivity and specificity of 59% and 72%, respectively. The cut-off value for total testosterone was 0.44 ng/mL, with an optimal sensitivity and specificity of 76% and 60%, respectively.

Although not used for diagnostis but as a supporting and follow-up parameter, the cut-off value for 1,4-androstenedione was 3.5 ng/mL with an optimal sensitivity of 82% and specificity of 56%. The cut-off for the early follicular phase LH/FSH ratio, a parameter known to increase in chronic anovulation but not used for diagnostic purposes, was found to be > 2 with an optimal sensitivity of 59% and specificity of 60%.

Discussion

The prevalence of obesity and, in parallel, the frequency of PCOS, one of the most important comorbidities of obesity in adolescent girls, is increasing. Environmental and epigenetic changes may also increase the propensity for PCOS independently of obesity. The present study was conducted to provide updated information on the prevalence of PCOS in accordance with current diagnostic criteria, clinical features, and predisposing factors in Turkish adolescent girls with obesity. The results indicated that the prevalence of PCOS, defined as clinical hyperandrogenism (hirsutism and/or severe acne) that has been biochemically confirmed (early follicular phase total testosterone > 0.48 ng/mL and/or FAI > 5) in the presence of irregular menstrual cycles, was 8.3% in obese Turkish girls aged 15-18 years. The prevalence of individuals classified as "at risk for PCOS," defined as having one or two of these conditions but not meeting the criteria for PCOS, was 46%.



Diagnostic test	Area under curve (AUC)	Standard error	p	Lower limit	Upper limit
LH/FSH ratio	0.615	0.052	0.047	0.514	0.717
Free androgen index	0.703	0.047	0.000	0.611	0.796
Total testosterone	0.630	0.052	0.025	0.528	0.732
1.4 Androstenedione	0.673	0.050	0.003	0.574	0.772

Figure 1. The diagnostic value, sensitivity and specificity of the diagnostic tests for polycystic ovary syndrome

LH/FSH: luteinising hormone/follicle stimulating hormone, AUC: area under the curve, ROC: receiver operating characteristic

The diagnosis of PCOS during adolescence may be challenging due to the complex nature of the physiological transition period, individual variability, and ethnic and environmental factors among populations, and the frequent overlap between normal and pathological conditions. Treatment approaches also vary in this age group. This study considered the current recommendations for the diagnosis of PCOS, including irregular menses and a rational evaluation of hyperandrogenism due to the features of the population.

For many years the Rotterdam criteria were used to diagnose PCOS in adolescents, prior to the publication of a consensus document by Ibáñez et al. (8) in 2017. However, more recent data suggest that the presence of PCOM in an adolescent who does not have hyperandrogenism and oligo-anovulation does not indicate a diagnosis of PCOS. In 2020, Peña et al. (7) published a guideline that built upon the evidence-based international guidelines on adolescent PCOS by Teede et al. (16) in 2018. This guideline offers further recommendations to enhance diagnostic accuracy and prevent overdiagnosis. The Peña et al. (7) guideline defined irregular menstrual cycles according to the gynecologic age. Irregular menstrual cycles ≤1 year post-menarche represent a normal pubertal transition. The definition of hyperandrogenism required the presence of hirsutism and/or severe acne, while the definition of biochemical hyperandrogenism required measurements using validated, high-quality assays. Pelvic ultrasound was not recommended for the diagnosis of PCOS within 8 years post menarche, and anti-Müllerian hormone levels were not recommended for PCOS diagnosis. Peña et al. (17) also published a literature review on the diagnostic criteria in 2022 defining PCOS as irregular menstrual cycles and hyperandrogenism (clinical and/or biochemical) after excluding other conditions that mimic PCOS. In the present study, irregular menstruation was defined as described in the guideline by Peña et al. (7) and clinical hyperandrogenism was defined as severe acne resistant to topical therapy and/or a Ferriman Gallwey score of >6. In adult guidelines and current adolescent criteria, androgen excess is defined using clinical findings and/or biochemical tests. However, since there are no ultra-sensitive methods for androgen measurements and again considering the genetic characteristics of our population, we considered the recommendation that clinical hyperandrogenism findings should be confirmed with laboratory tests (8). Following these recommendations, the diagnosis of PCOS in the present study was made in cases of irregular menstruation and clinical hyperandrogenism, together with a total testosterone level of >0.48 ng/mL (the upper limit for adult woman given by our laboratory) and/or FAI of >5.

The results of our study once again showed that the sensitivity and specificity of diagnostic tests are not high and that none of the tests used in diagnosis are perfect markers.

In a study conducted in Turkiye, clinical hyperandrogenism was detected in 44 (84.6%) while biochemical hyperandrogenism was detected in 40 (76.9%) of 52 adolescents with PCOS (18). Another study by Yüce et al. (19) showed clinical hyperandrogenism in 76 (67.9%) of 112 PCOS adolescent patients, while biochemical hyperandrogenism was detected in 30 (30.9%). It is thought that the variability between clinical hyperandrogenism rates and biochemical hyperandrogenism rates in different studies may be related to differences in measurement methods and accepted cut-off values. In addition, since hirsutism is determined clinically by observational scoring, it is a highly subjective assessment. There may also be differences in the evaluation of acne as androgen excess.

Despite the control group comprising obese adolescents, fasting insulin, HOMA-IR, and LDL parameters, biomarkers of possible insulin resistance or metabolic syndrome, were higher in those deemed at risk for PCOS than in the control group. Moreover, ALT and AST, which are the markers used to screen for fatty liver, were higher in PCOS patients than in controls. Our findings are consistent with the evidence that insulin resistance and metabolic syndrome in obese adolescents are more strongly associated

with chronic anovulation and hyperandrogenism, and that hyperinsulinism plays an important role in the pathogenesis of PCOS (20,21,22,23). Obesity-associated hyperandrogenemia also occurs, due to expanded adipose tissue and potential effects of abnormal adipokine/cytokine levels (24). An increased risk of cardiovascular disease has been reported in women with PCOS, regardless of the severity of obesity. Due to differences in body composition and genetics, individuals with similar BMIs have different levels of systemic inflammation, insulin resistance and metabolic dysfunction. Studies have shown that PCOS is more common in obese women who have an unhealthy metabolic profile (25).

Correlation analyses indicated a positive correlation between total testosterone, 1,4-androstenedione, and the LH/FSH ratio, which supports the hypothesis of chronic anovulation. The elevated androstenedione and 17-OHP levels observed in the PCOS group, in the absence of a difference in DHEAS levels, suggest that the increased androgens are of gonadal origin. However, none of the diagnostic tests was found to be highly predictive, with the FAI being the most reliable among them.

Study Limitations

As our study did not include a healthy control group in which diagnostic tests were performed, the cut-off values we determined were those that differentiate between individuals "at risk of PCOS" and individuals diagnosed with "PCOS." Since hyperandrogenism alone or menstrual irregularity alone is not diagnostic, in our clinical practice, biochemical tests are usually ordered if both are present, or the signs of clinical androgenism is significant. The majority of patients with only irregular menses did not undergo hormone tests, so only 132 of 200 patients who were defined as "at risk" were involved in the analyses for cut-off values. In addition, the subjective evaluation of the clinical findings required for the diagnosis, which constitutes a limitation in almost all PCOS studies in adolescents, was also a limitation of our study.

Conclusion

The diagnostic value of laboratory tests usually depends on the presence of clinical criteria. It is therefore suggested that clinical findings not supported by laboratory tests should not be considered diagnostic of PCOS. Despite the increasing number of scientific studies and the constant updating of guidelines, the diagnosis and management of PCOS in adolescents remains a puzzle. While efforts should be made to avoid overdiagnosis, it is also important to recognize that many more patients may be 'at risk' of developing PCOS. It is recommended that obese girls at risk should be closely monitored for progressive findings. The most recent publication on diagnostic criteria by Ibáñez and de Zegher (12) in 2023 proposed a diagnostic approach by combining criteria from a consortium rooted in pediatric endocrinology and criteria from a consortium rooted in adult endocrinology and gynecology. These recent combined criteria and the cut-offs for diagnostic tests identified in the present study may be incorporated into the methodology of future studies in Turkish adolescent girls with obesity.

Ethics

Informed Consent: Informed consent forms were obtained from the patients themselves.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Fatma Güliz Atmaca, Fatma Dursun, Gülcan Seymen, Pınar Atla, Esma Ebru Altun, Ayşe Yaşar, Heves Kırmızıbekmez, Concept: Özlem Yüksel, Fatma Güliz Atmaca, Heves Kırmızıbekmez, Design: Özlem Yüksel, Heves Kırmızıbekmez, Data Collection or Processing: Özlem Yüksel, Fatma Güliz Atmaca, Pınar Atla, Heves Kırmızıbekmez, Analysis or Interpretation: Özlem Yüksel, Heves Kırmızıbekmez, Literature Search: Özlem Yüksel, Fatma Güliz Atmaca, Heves Kırmızıbekmez, Writing: Özlem Yüksel, Fatma Dursun, Esma Ebru Altun, Ayşe Yaşar, Heves Kırmızıbekmez.

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CASE REPORT

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Novel Variant of *SLC34A3* in a Compound Heterozygous Brazilian Girl with Hereditary Hypophosphatemic Rickets with Hypercalciuria

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What is already known on this topic?

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is caused by loss-of-function variants of the sodium-phosphate co-transporter NPT2c and is an fibroblast growth factor-23-independent disorder that causes rickets. Phosphate supplementation alone is the standard of care. As $1,25(OH)_2D$ is already elevated, active vitamin D analogs are not indicated. The best approach for managing hypercalciuria has not yet been established.

What this study adds?

We report a novel variant of the *SLC34A3* gene that was present in compound heterozygosity in a Brazilian girl with HHRH. We discuss treatment strategies and observed that thiazide diuretics may be useful as adjunctive therapy to lower urinary calcium excretion.

Abstract

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare fibroblast growth factor-23-independent disorder caused by biallelic variants in the *SLC34A3* gene. The disease severity varies, and patients have an increased risk of developing renal complications. Phosphate supplementation is the standard of care and active vitamin D analogs are not indicated as they could worsen the hypercalciuria. We report a Brazilian girl with HHRH who presented with knee pain and progressive genu valgum deformity that became apparent from the age of eight years onwards. Nephrocalcinosis was also identified at age 13 years. Targeted next-generation sequencing for hereditary forms of rickets detected compound heterozygous pathogenic variants in *SLC34A3*, including a novel missense variant c.1217G>T (p.Gly406Val). Compliance to oral phosphorus therapy was suboptimal and adjunctive chlorthalidone therapy improved hypercalciuria. This report highlights the phenotypic variability and also expands the list of *SLC34A3* variants associated with HHRH. An accurate diagnosis is key for optimal treatment. Of note, thiazide diuretics may be useful as adjunctive therapy for controlling hypercalciuria.
Keywords: Hereditary hypophosphatemic rickets with hypercalciuria, *SCL34A3* pathogenic variants, hypercalciuria

Introduction

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare disorder caused by biallelic mutations in *SLC34A3*, the gene encoding the sodium-phosphate co-transporter type 2c (NPT2c) (1). NPT2c is expressed in the renal proximal tubule cells and mediates renal phosphate resorption. HHRH is a fibroblast growth factor-23 (FGF-23)-independent disorder, and pathogenic variants of *SLC34A3* lead to hypophosphatemia due to excessive urinary phosphate wasting. Circulating levels of 1,25

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di-hydroxyvitamin D [1,25$(OH)_2$D] are appropriately elevated, leading to increased intestinal calcium resorption, hypercalciuria, and parathyroid hormone (PTH) suppression (1,2).

The clinical spectrum of skeletal disease varies, while renal complications including nephrolithiasis and nephrocalcinosis, may occur in approximately half of the affected subjects (2). Correct diagnosis is important as patients should receive only oral phosphate treatment. Active vitamin D analogs should not be used, as they may exacerbate hypercalciuria and increase the risk of renal complications (2).

We describe a Brazilian girl with HHRH who presented with progressive genu valgum deformity that became apparent after the age of eight years. Genetic analysis detected compound heterozygous pathogenic variants in *SLC34A3*, including a novel pathogenic variant. Here, we discuss the clinical spectrum of the disease and its treatment strategies.

This study was approved by the Ethics Committee of the SARAH Network of Rehabilitation Hospitals (Certificate of Presentation for Ethical Appreciation number: 36961620.9.0000.0022) and performed in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient and her parents.

Case Report

A 16-year-old Brazilian girl was initially admitted for orthopedic evaluation at the age of 10 years because of knee pain and genu valgum deformity that became apparent after she reached the age of eight years.

She was born healthy to non-consanguineous parents. No dental or hearing problems or other signs of rickets, such as muscle weakness, widening of knees or wrists, rachitic rosary or cranial abnormalities (dolichocephaly, craniosynostosis), were observed. Pubertal development was normal, and menarche occurred at 12 years of age. At age 16 years, Tanner stage was 4 for both breast development and pubic hair. However, her height (144.5 cm; standard deviation score -2.8) was below her parental target height (father was 170 cm, and mother was 159 cm tall) and near the final height prediction (145.4 ± 0.8). She had no family history of bone disease but her father reported a history of nephrolithiasis.

Laboratory data at the first orthopedic evaluation at age 10 years showed elevated alkaline phosphatase (ALP), low-normal serum PTH, normal calcium and phosphorous levels, a 25-hydroxyvitamin D value of 29.54 ng/mL, and elevated urinary calcium excretion (calcium/creatinine ratio of spot urine: 407 mg/g) (Table 1). Blood gas analysis did not indicate acidosis, and the urinalysis results were negative

Table 1. Laboratory data of the patient and her parents

Biochemical parameters	10-year-old (age at presentation)	13-year-old	16-year-old	Mother	Father	Reference range
Serum						
Calcium (mg/dL)	9.22	9.15	8.68	8.99	8.86	8.5-10.1
Phosphorous (mg/dL)	3.41 (3.2-5.7)	2.61 (2.9-5.1)	2.53 (2.7-4.9)	3.01 (2.5-5.1)	2.87 (2.5-5.1)	[a]
25(OH)D (ng/mL)	29.54	27.0	21.84	24.51	19.3	> 20
PTH (pg/mL)	16.1	12.92	20.1	52.62	49.35	15-65
ALP (U/L)	486 (51-332)	249 (50-162)	157 (47-119)	56 (42-98)	64 (53-128)	[a]
CTX (ng/mL)	-	2.61 (0.144 1.202)	1.07 (0.048-0.579)	0.429 (0.025-0.573)	0.868 (0.016-0.584)	[a]
Creatinine (mg/dL)	0.76	0.62	0.68	0.71	0.96	0.46-0.81 > 18 y: 0.70-1.30
eGFR	120	136	129	122	104	> 90
Urine						
Calcium/creatinine (mg/mg)	0.407	0.333	-	0.108	0.102	< 0.200
Urine calcium excretion	-	8.2 mg/kg/d	3.4 mg/kg/d	115 mg/d	118 mg/d	Child < 4 mg/kg/d Adult Female < 250 mg/d Male < 300 mg/d
TRP (%)	-	84	82	-	-	> 85
TmP/GFR (mg/dL)	-	2.19 (2.9-6.5)	2.07 (2.9-6.5)	-	-	[a]

Laboratory data were obtained after fasting overnight.

[a]Reference ranges according to age and sex are given in parenthesis following the results; Urinary calcium/creatinine: analyzed in spot urine.

TRP: tubular resorption of phosphate, TmP/GFR: ratio of the maximal renal phosphate reabsorption to glomerular filtration rate, 25(OH)D: 25 hydroxyvitamin D, PTH: parathyroid hormone, ALP: alkaline phosphatase, CTX: C-telopeptide of type 1 collagen, eGFR: estimation of glomerular filtration rate according to the CKD-EPI equation, Dashes: data not available, y: year

for aminoaciduria and glycosuria. Skeletal radiographs showed marked genu valgum deformity (Figure 1), and she underwent bilateral distal femoral epiphysiodesis at age 11 years.

Biochemical analysis when she was 13 years revealed an elevated ALP and C-telopeptide of type 1 collagen, hypophosphatemia with a reduced maximum rate of renal tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR) indicating urinary phosphate wasting, and elevated 24-h urinary calcium excretion of up to 8 mg/kg/day, with normal serum calcium and low PTH levels, raising suspicion of HHRH (Table 1). Renal ultrasonography revealed discrete bilateral increases in the renal medullary echogenicity, suggesting nephrocalcinosis. Bone mineral density (BMD) obtained by dual-energy X-ray absorptiometry showed decreased BMD in the lumbar spine (Z-score -2.7) and total body (Z-score total body less head -3.3).

A targeted next-generation sequencing (NGS) panel for 13 genes associated with inherited forms of rickets (*ALPL*, *CLCN5*, *CYP27B1*, *CYP2R1*, *DMP1*, *ENPP1*, *FAH*, *FGF23*, *KL*, *PHEX*, *SLC34A1*, *SLC34A3*, and *VDR*) was performed using genomic DNA extracted from oral mucosa. A compound heterozygous mutation in *SLC34A3* was detected (Refseq NM_080877.3). The novel missense variant c.1217G>T (p.Gly406Val) was identified in the paternal allele, and classified as a variant of uncertain significance. Glycine at position 406 of the protein is highly conserved among different species (Figure 2), and this variant was predicted to be deleterious or disease-causing by *in silico* analysis (PolyPhen and Mutation Taster). The second variant c.1058G>T (p.Arg353Leu), inherited from the mother, was previously described in patients with HHRH and classified as likely pathogenic (1).

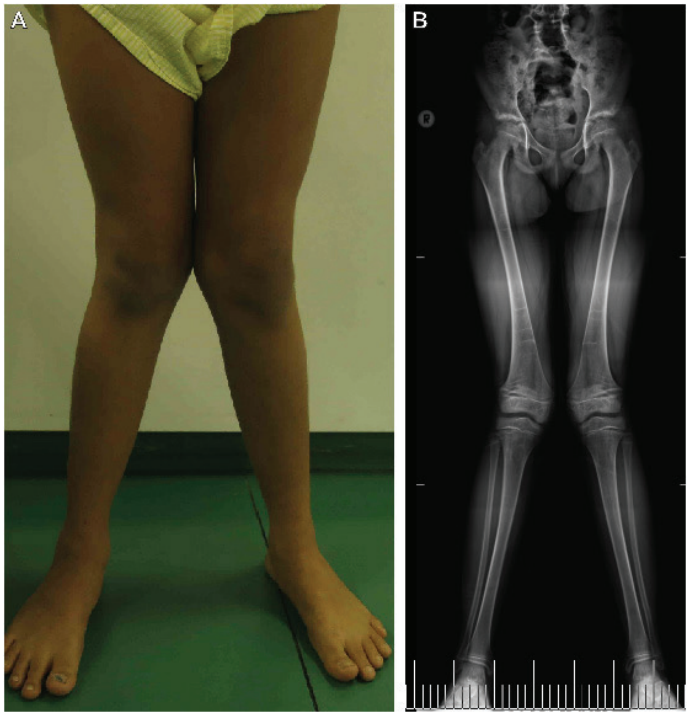

Figure 1. (A) Clinical photographs of lower limbs at age 10 years showing marked genu valgum. B) Panoramic radiograph of lower limbs showing diffuse bone demineralization, marked valgus deviation of the knees, coxa valga, and sclerotic and irregular contour of the acetabulum.

Phosphate therapy (20 mg/kg of elemental phosphorous per day) was initiated after genetic diagnosis, with poor tolerance due to gastrointestinal symptoms and suboptimal compliance. A thiazide diuretic (chlorthalidone 25 mg/day) was initiated as an adjunctive treatment for hypercalciuria when she was 15 years of age. Bone turnover markers decreased, and urinary calcium excretion improved following treatment (Table 1). No adverse effects of thiazide diuretic, such as hypercalcemia or electrolytic abnormalities, were reported during the follow-up period. She required right femoral osteotomy at age 15 years and left femoral osteotomy at age 16 years to correct lower limb deformities.

Serum calcium, phosphorous, ALP, and PTH levels of her parents were normal. The 24-h urinary calcium excretion of the father was normal, but he exhibited concurrent vitamin D deficiency (Table 1).

Discussion

This report describes the clinical and biochemical features of a Brazilian girl with HHRH caused by compound heterozygous variants in *SLC34A3*, one of which was novel.

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HUMAN LGWLGGYLAVLAGAGLTFALQSSSVFTAAVVPLMGVGVISLDRAYP
RAT FGWLSGYLAILVGAGLTFLLQSSSVFTAAIVPLMGVGVINLERAYP
MOUSE FGWLSGYLAILVGAGLTFLLQSSSVFTAAIVPLMGVGVIDLERAYP
CATTLE FGWLSGYLAMLVGAGLTFALQSSSVFTAATVPLIGVGVISLERAYP
DOG FSWLSGYLAILVGAGLTFVLQSSSVFTAAIVPLMGVGVISLERAYP
RHESUS MONKEY LGWLGGYLALLAGAGLTFALQSSSVFTAAIVPLMGVGVISLDRAYP
CHIMPANZEE LGWLGGYLAVLAGAGLTFALQSSSVFTAAVVPLMGVGVISLDRAYP
:.**.****:*.****** ********** ***:*****.*:****
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Figure 2. Multiple amino acid alignment of human NPTC2 protein (sodium-dependent phosphate transport protein 2C) with other mammalian SLC34A3 proteins. p.406G is shown in red and is highly conserved among different species. Sequence alignment was performed with BLAST/UniProt (www.uniprot.org). Human (*Homo sapiens*, Q8N130|). Rat (*Rattus norvegicus*, G3V7E1); Mouse (*Mus musculus,* Q80SU6|); Cattle *(Bos taurus*, G3MXY5), Dog (*Canis lupus familiaris*, A0A8I3PKB4), Rhesus monkey (*Macaca mulatta,* A0A5F8AJ48), Chimpanzee (*Pan troglodytes*, A0A2J8N9J5). Alignment data (*) identical and conserved; (:) strongly similar; (.) weakly similar

This expands the knowledge of the phenotype and genetic variants associated with HHRH, a rare metabolic disorder.

HHRH has an estimated prevalence of 1:250.000, which is approximately 10-fold less frequent than X-linked hypophosphatemia (XLH), the most common form of inherited hypophosphatemic rickets (2). Pathogenic variants in *SLC34A3* result in hypophosphatemia due to urinary phosphate wasting from NPT2c dysfunction. FGF-23 is downregulated in response to hypophosphatemia, leading to the compensatory up-regulation of renal 1-alfa hydroxylase. Thus, patients present with hypophosphatemic rickets/osteomalacia, increased $1,25(OH)_2D$ levels, and hypercalciuria (2,3). These biochemical findings differentiate HHRH from FGF-23-mediated disorders (4).

Skeletal abnormalities typically occur in childhood, but some patients may exhibit late-onset clinical features, such as early-onset osteoporosis, recurrent fractures, and renal stones (5,6,7). The patient described herein presented with knee pain and progressive lower-limb deformity that only became apparent after eight years of age. This contrasts with the XLH phenotype, in which bone involvement is usually present in the first years of life.

In the present case, the laboratory findings were not entirely consistent with hypophosphatemic rickets at first evaluation, with normal phosphorus levels. Subsequent biochemical evaluation revealed hypophosphatemia with a low TmP/GFR, indicating renal phosphate wasting. Although serum $1,25(OH)_2D$ and FGF-23 levels could not be measured, concurrent findings of hypercalciuria and low serum PTH are not expected in FGF-23-mediated disorders, raising the suspicion of HHRH. Kremke et al. (8) also reported a case in which hypophosphatemia was absent at the first evaluation, suggesting that serum phosphorous levels may fluctuate in this condition, and repeated biochemical evaluation may be necessary to establish the diagnosis.

Individuals with HHRH carry homozygous or compound heterozygous pathogenic variants in *SCLA34A3* (1,2). A single heterozygous pathogenic variant has been associated with isolated hypercalciuria, which increases the risk of nephrocalcinosis and nephrolithiasis without apparent bone disease (2,3). However, skeletal abnormalities, including osteomalacia, predominant cortical loss, and osteoporosis, have been observed in subjects with monoallelic *SCLA34A3* variants (9).

Rickets is more prevalent in homozygous patients than in those with compound heterozygous pathogenic variants in *SCLA34A3* (10). The milder phenotypes of subjects carrying heterozygous variants are probably related to a lower degree of urine phosphate loss, possibly because of increased residual NPT2c activity and higher serum phosphate levels (11). The variability in the age of onset may be related to the incomplete penetrance of variants and complex interactions with environmental and nutritional factors.

Accurate diagnosis of HHRH is important for correct treatment, as a presumptive diagnosis of XLH or another FGF-23-mediated disorder may lead to inappropriate therapy with calcitriol, which would worsen the hypercalciuria and increase the risk of renal complications (2,4). Target genetic panels directed to inherited forms of rickets are relevant for accurate diagnosis and facilitate correct treatment.

In the presented patient, a targeted NGS panel identified a previously reported pathogenic heterozygous variant in the maternal allele of *SLC34A3* (p.Arg353Leu) and a novel heterozygous mutation in the paternal allele (p.Gly406Vl). Although we did not perform *in vitro* functional tests, the glycine at position 406 of the protein is highly conserved among different species and the p.Gly406Val variant was predicted to be deleterious or disease-causing by *in silico* analysis. A rare variant at the same codon (c.1217G>A, p.G406E, rs139408872*)* is described in dbSNP and, like the p.G406V, is predicted to be pathogenic (12). In addition, the heterozygous father reported a history of nephrolithiasis, which reinforced the probable pathogenicity of this *SLC34A3* variant. Although hypercalciuria was not detected in the father, the increased level of urinary calcium excretion may have been concealed by his vitamin D deficiency (8).

The standard treatment of HHRH consists of monotherapy with oral inorganic phosphate (Pi), which improves skeletal bone disease and hypercalciuria, presumably by reducing $1,25(OH)_2D$ (2,4,11). However, Pi therapy can cause several adverse events, including gastrointestinal symptoms and, with chronic treatment, secondary or tertiary hyperparathyroidism, and nephrocalcinosis (13). Long-term patient compliance to oral Pi can be challenging. In addition, data regarding the long-term safety of Pi therapy for renal calcification are unknown, and the best approach for managing hypercalciuria has not been established.

It is also unclear whether a biochemical parameter or genetic factor (variant type) could be associated with an increased risk of renal complications in HHRH. Dasgupta et al. (14) found that serum $1,25(OH)_2D$, low serum phosphate and decreased tubular resorption of phosphate (TRP) may be positive predictors of renal calcifications. Recently, Stürznickel et al. (9) reported that urinary calcium excretion and $1,25(OH)_2D$ levels, but not TRP levels, were associated with nephrocalcinosis, and urinary calcium excretion was suggested as a therapeutic target.

In patients with idiopathic hypercalciuria, thiazide is used to decrease urinary calcium excretion and may prevent or delay the progression of renal complications (15). Thiazide diuretics can be used to reduce calciuria in patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis, a rare disorder characterized by renal magnesium wasting, hypercalciuria, nephrocalcinosis and kidney failure (16). Hydrochlorothiazide also decreases calciuria and may prevent the sonographic progression of nephrocalcinosis in patients with XLH (17). Therefore, it is plausible that thiazide diuretics may be useful in other metabolic disorders with hypercalciuria, such as HHRH.

In the presented patient, compliance with Pi therapy was suboptimal, and so it was not possible to evaluate if higher doses of Pi alone would have led to resolution of her hypercalciuria. However, considering the risk of nephrocalcinosis progression and deterioration of renal function with persistent hypercalciuria, adjunctive thiazide diuretic was initiated. We observed that oral Pi therapy with a thiazide diuretic led to improved serum markers of rickets and adequate control of hypercalciuria. Longitudinal follow-up and additional studies are required to evaluate whether this treatment strategy protects against or slows the progression of nephrocalcinosis (9).

Conclusion

In summary, we described a Brazilian girl with HHRH whose skeletal abnormalities only became apparent later in childhood. Genetic analysis revealed compound heterozygous variants in *SLC34A3*, including a novel variant. Accurate diagnosis of HHRH is crucial for proper treatment as calcitriol is contraindicated in this condition. Furthermore, thiazide diuretics may be useful as adjunctive therapy for controlling hypercalciuria but more data is required.

Ethics

Informed Consent: Informed consent was obtained from the patient and her parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Concept: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Design: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Data Collection or Processing: Luciana Pinto Valadares, Analysis or Interpretation: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Literature Search: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Writing: Luciana Pinto Valadares, Daniel Rocha de Carvalho.

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CASE REPORT

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Diagnosis of Lymphocytic Infundibuloneurohypophysitis After Positive Anti-rabphilin-3A Antibody Test in an 8-year-old Boy with Early-onset Central Diabetes Insipidus

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What is already known on this topic?

Recently, anti-rabphilin-3A antibodies (RPH3A-Ab) have emerged as a promising diagnostic marker for lymphocytic infundibuloneurohypophysitis (LINH) in adults. However, few reports of this association exist for the pediatric population.

What this study adds?

We report the case of an 8-year-old boy with central diabetes insipidus diagnosed with LINH based on a positive test for RPH3A-Ab. This case study illustrates the potential of RPH3A-Ab as an early diagnostic marker for pediatric-onset LINH.

Abstract

Childhood-onset lymphocytic infundibuloneurohypophysitis (LINH) has rarely been reported. Pathological evaluation via pituitary biopsy is necessary for a definitive diagnosis of LINH. However, pituitary biopsy is a highly invasive procedure. Recently, anti-rabphilin-3A antibody (RPH3A-Ab) has been reported as a promising diagnostic marker for LINH in adults but.there are few reports of this association in the pediatric population. We report the case of an 8-year-old boy with central diabetes insipidus (CDI) who was diagnosed clinically with LINH, based on RPH3A-Ab positivity. He was initially diagnosed with CDI using a water deprivation test combined with desmopressin administration. Serum and cerebrospinal fluid tumor markers were negative, and T1-weighted magnetic resonance imaging (MRI) revealed the absence of high signal intensity in the posterior pituitary gland and an enlarged pituitary stalk. Anterior pituitary function tests revealed no abnormalities. No pituitary biopsy was performed because of its invasive nature, and desmopressin treatment was initiated. Three months after the diagnosis of CDI, the patient tested positive for RPH3A-Ab. MRI performed nine months after CDI diagnosis revealed amelioration of the pituitary stalk enlargement, and this clinical course corroborated our diagnosis of LINH. RPH3A-Ab may be useful as an early diagnostic tool for LINH in the pediatric population.

Keywords: Central diabetes insipidus, lymphocytic infundibuloneurohypophysitis, rabphilin-3A antibody, lymphocytic hypophysitis, pituitary

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Introduction

Central diabetes insipidus (CDI) may occur in children and adolescents in the absence of a known underlying disease (idiopathic), or associated with inflammatory/autoimmune conditions, such as lymphocytic hypophysitis or immunoglobulin G4 (IgG4)-related diseases, Langerhans cell histiocytosis (LCH), intracranial germ cell tumors (GCTs), infectious and vascular diseases, trauma resulting from surgery or an accident and, rarely, metastasis (1). Lymphocytic hypophysitis is classified into lymphocytic adenohypophysitis, lymphocytic infundibuloneurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH), based on the site of involvement and clinical symptoms (2).

Magnetic resonance imaging (MRI) of a patient with CDI often reveals an absence of high signal intensity of the posterior pituitary gland and an enlarged pituitary stalk. The most common causes of an enlarged pituitary stalk in children are GCTs, LCH, and LINH (3).

Serum measurement of alpha-fetoprotein (AFP), human chorionic gonadotropin-beta (HCG-β), and placental alkaline phosphatase (PLAP) have been shown to be useful in the diagnosis of GCTs (4). Imaging studies, including cranial MRI and computed tomography (CT), should be performed when LCH is suspected. These tests are important for the differential diagnosis of children with CDI, whereas pituitary biopsy plays an important role in the definitive and histopathological diagnosis of these conditions.

Serum rabphilin-3A antibody (RPH3A-Ab) testing has been reported as a useful noninvasive method for the diagnosis of LINH (5). However, to the best of our knowledge, there are few reports on the use of RPH3A-Ab in the pediatric population (6,7,8). Here, we report a case in which a patient with CDI was clinically diagnosed with LINH using RPH3A-Ab testing shortly after diagnosis of CDI.

Case Report

The patient was an 8-year-old boy who presented with a 2-month history of polyuria and polydipsia. Two years before admission, his urine specific gravity was >1.030, and his frequency of urination was 3-4 times a day. However, two months prior to admission, he experienced polydipsia (2-4 L/day) and frequent urination at night. He was referred to our hospital for further investigation and treatment of persistent polyuria.

Upon initial examination, no headaches or visual field defects were observed. The patient had no history of head injury. His mother and maternal grandmother had a history of aldosteronism.

The patient's height and weight were 121.5 cm [standard deviation score (SDS) -1.5] and 22 kg (-0.8 SDS), respectively. His complete blood count and serum chemistry profile were normal: serum sodium concentration, 140 mEq/L and plasma arginine vasopressin (AVP) concentration, 0.5 pg/mL. His plasma osmolality, urinary osmolality, and urine relative density were 282 mOsm/kg, 47 mOsm/L, and 1.002, respectively. Urine test results were negative for glucosuria and pyuria.

A water deprivation test resulted in a maximum urine osmolality of 128 mOsm/kg, with a low AVP concentration, even though the plasma osmolality increased to 290 mOsm/kg. Two hours after administration of subcutaneous desmopressin, his urine osmolality increased to 499 mOsm/kg, and a diagnosis of CDI was made.

T1-weighted MRI revealed the absence of high signal intensity of the neurohypophysis and diffuse enlargement of the pituitary stalk (Figure 1). Contrast-enhanced MRI revealed a uniform contrast effect in the pituitary gland.

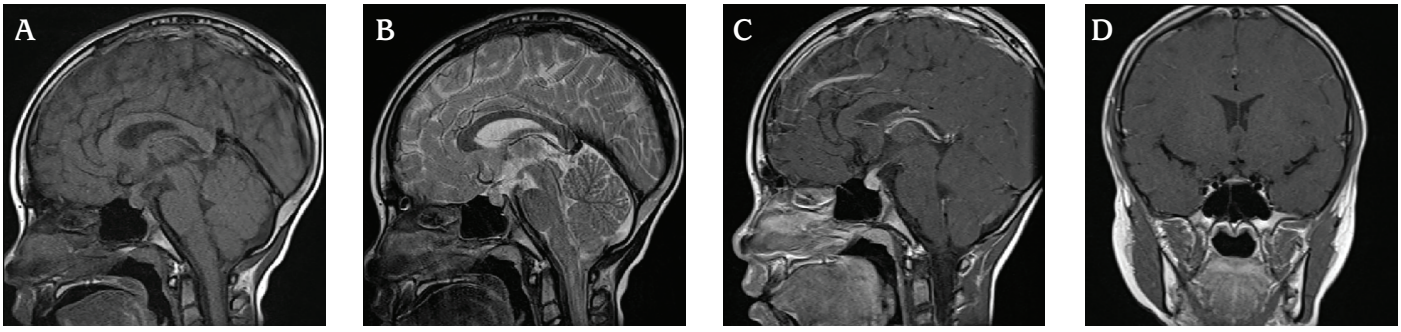

Figure 1. Pretreatment magnetic resonance images of the 8-year-old boy. A) Sagittal T1-weighted MRI at the time of diagnosis of CDI. B) Sagittal T2-weighted MRI at the time of diagnosis of CDI revealing loss of high signal intensity in the posterior lobe and enlargement of the pituitary stalk. C, D) Sagittal and coronal sections of T1-weighted contrast-enhanced MRIs at the time of diagnosis of CDI revealing a uniformly enhanced pituitary gland

MRI: magnetic resonance image, CDI: central diabetes insipidus

Anterior pituitary function tests revealed no abnormalities. Tumor markers associated with GCTs were not elevated: the patient's serum AFP concentration was 2 ng/mL (normal range: 0-7 ng/mL); his serum carcinoembryonic antigen concentration was 2 ng/mL (normal range: 0-5 ng/mL) and both HCG-β and PLAP antibody tests in cerebrospinal fluid were negative. IgG4 concentrations were not elevated. The myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA), proteinase 3-ANCA, and T-SPOT test results were negative. Technetium-99m scintigraphy revealed no abnormal accumulations suggestive of LCH. Three months after the diagnosis of CDI, the patient tested positive for RPH3A-Ab, a potential marker for the diagnosis of LINH (Figure 2).

Based on the above results, the patient was diagnosed with LINH. We did not perform a pituitary biopsy because of its highly invasive nature; rather, we planned to closely observe the patient. He was treated with desmopressin, and his polyuria and polydipsia improved. Considering the possibility of a tumor, no steroid therapy was administered. Nine months after CDI diagnosis, brain MRI revealed shrinking of the enlarged pituitary stalk (Figure 3) and no elevation in tumor markers was found. The patient was not exposed to radiation, including CT scans, during the course of the disease. His symptoms of CDI persisted after shrinking of the enlarged pituitary stalk.

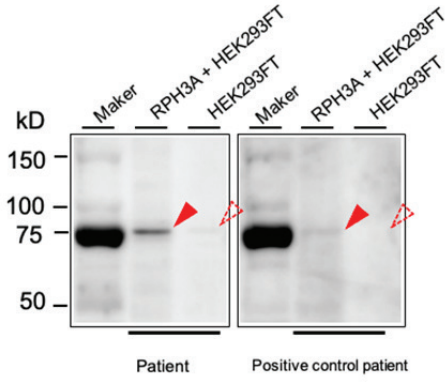

Figure 2. Detection of anti-rabphilin-3A antibodies by Western blotting

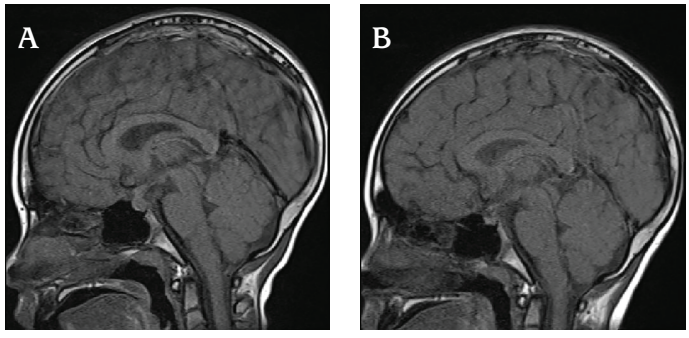

Figure 3. (A, B) Pre- and posttreatment magnetic resonance images of the 8-year-old boy

Discussion

This report describes a case of a pediatric patient with CDI who tested positive for RPH3A-Ab three months after diagnosis of CDI. His anterior pituitary hormonal function and tumor markers were normal. Follow-up pituitary MRI revealed amelioration of the earlier pituitary enlargement, and RPH3A-Ab positivity suggested a diagnosis of LINH.

Pituitary biopsy is required for the definitive diagnosis of LINH but its is highly invasive and thus problematic, especially in children. Recently, RPH3A-Ab was reported as a noninvasive diagnostic marker of LINH in adults. However, its use in the diagnosis of LINH early in the condition has not been clarified.

RPH3A is expressed in the posterior pituitary gland and supraoptic nucleus of the hypothalamus, where AVP-expressing neuronal cell bodies are located, but rarely in the anterior pituitary gland. RPH3A-Ag has been reported as a pathogenic autoantigen in which T cells specific for RPH3A are involved in the pathogenesis of neurohypophysis (5).

Measurement of RPH3A-Ab in serum was performed at the Fujita Health University. Briefly, a vector containing the full-length human rabphilin-3A gene was transfected into HEK293FT cells to produce a recombinant human rabphilin-3A protein. As a control, the same vector but without the rabphilin-3A gene was transfected into HEK293FT cells. RPH3A-Ab in the serum was detected by Western blotting using the recombinant human rabphilin-3A protein lysate as the antigen and patient serum as the primary antibody. A protein band of 76 kDa appeared in the lysate of cells transfected with rabphilin-3A protein but not in that of control cells, which was considered to be positive for RPH3A-Ab, as reported previously (9).

Murai et al. (10) reported the sensitivity and specificity of RPH3A-Ab in pituitary diseases. Sensitivity was 100%, 11.1%, and 80.0% for LINH, LAH, and LPH, respectively. The overall specificity of the sellar/suprasellar mass was 97.4%. Moreover, Iwama et al. (9) reported that RPH3A-Ab was detected in 5 of 41 samples from healthy control subjects (sensitivity, 88%). Therefore, RPH3A-Ab may be useful to diagnose LINH.

We are aware of only three case reports of RPH3A-Ab positivity in pediatric patients with CDI (6,7,8). The patients tested positive for RPH3A-Ab at six and eight months, and nine years after CDI onset. All had growth hormone deficiency, which is suggestive of LPH. In the presented case, the patient tested positive for RPH3A-Ab three months after diagnosis of CDI.

To the best of our knowledge, this is the first report of a pediatric patient with LINH who tested positive for RPH3A-Ab so soon after CDI onset. In our case, RPH3A-Ab testing during the early stages of CDI led to a diagnosis of LINH. However, we cannot rule out other causes of CDI as pituitary biopsy was not performed.

There is no strong evidence to support the utility of glucocorticoids as first line LINH treatment, however, the use of glucocorticoids has been associated with complete disease regression in some cases (11). Early diagnosis of LINH should result in fewer invasive investigations and also early treatment, which may improve prognosis.

The cause of the shrinking of the enlarged pituitary stalk in the presented patient is unclear. The inflammatory process in LINH may be self-limiting, and radiological follow-up may show regression. CDI in patients with LINH may be permanent, likely due to neuronal destruction (12). The management and follow-up of LINH requires repetitive MRI scans every six months (11). A previous study reported a patient who was diagnosed with LINH by pituitary biopsy, however, the pituitary stalk swelled, tumor marker levels increased, and the patient was ultimately diagnosed with GCT (13). Pituitary biopsy should be considered if tumor markers are elevated and pituitary stalk swelling does not improve. In addition, as there is a possibility that hypopituitarism may occur, we intend to perform monitoring hormonal assessments.

Conclusion

This report describes an 8-year-old boy diagnosed with LINH because of the presence of serum RPH3A-Ab, first detected three months post-CDI diagnosis. His clinical course was consistent with such a diagnosis. This case study illustrates the potential of RPH3A-Ab as an early diagnostic marker for pediatric-onset LINH. However, the utility of these antibodies as a diagnostic marker needs to be validated with more cases in the future.

Ethics

Informed Consent: Informed consent form was obtained from the patient's family.

Presented in: Previous presentation of the content of the manuscript: The 55th Annual Scientific Meeting of the Japanese Society for Pediatric Endocrinology on 02.11.2022 in Kanagawa, Japan.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Yukino Shoji, Yuki Naruse, Concept: Yukino Shoji, Yuki Naruse, Masato Mori, Ryugo Hiramoto, Design: Yukino Shoji, Yuki Naruse, Data Collection or Processing: Yukino Shoji, Yuki Naruse, Naoko Iwata, Haruki Fujisawa, Atsushi Suzuki, Yoshihisa Sugimura, Analysis or Interpretation: Yukino Shoji, Yuki Naruse, Naoko Iwata, Haruki Fujisawa, Atsushi Suzuki, Yoshihisa Sugimura, Literature Search: Yukino Shoji, Writing: Yukino Shoji.

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CASE REPORT

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A Rare Case of Monogenic Obesity Due to a Novel Variant in the *ADCY3* Gene: Challenges in Follow-up and Treatment

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What is already known on this topic?

Adenylate cyclase 3 (*ADCY3*) gene alterations have been previously found to be associated with obesity. However, only a small number of cases with homozygous mutations have been reported. Besides early-onset severe obesity, hyperphagia, insulin resistance, hyperlipidemia, anosmia/hypo-osmia and intellectual disability may occur. The follow up and treatment options, especially in affected young children, are still unclear.

What this study adds?

In patients with homozygous *ADCY3* mutations, severe obesity and insulin resistance may occur from infancy. These cases should be followed and supported in term of neuromotor developmental delay. Moreover, serious complications of obesity may be exhibited at very young ages. The treatment is challenging, especially in young children, and so more data is needed.

Abstract

Adenylate cyclase 3 (*ADCY3*) gene alterations have been reported to be associated with obesity. However, few patients with homozygous mutations have been described to date and the follow-up procedure and treatment options are unclear. A 10-month-old female presented with increased appetite and weight gain. She was born from a consanguineous marriage. Weight, height, and head circumference measurements and standard deviation scores (SDS) were 19 kg (+6.98 SDS), 82 cm (+3.53 SDS), and 49 cm (+3.07 SDS), respectively. Laboratory tests revealed a fasting glucose level of 103 mg/dL (5.7 mmol/L), insulin level of 25.39 µIU/mL, and homeostatic model assessment for insulin resistance value of 6.43. Whole-exome sequencing revealed a novel, homozygous c.1102G>A (p.Asp368Asn) variant in *ADCY3*. Her parents and healthy sister were heterozygous for the variant. At the age of 2.5 years, neurodevelopmental delay was observed. At the age of 3.5 years, the patient's weight, height, and body mass index values were 49.5 kg (+8.16 SDS), 111 cm (+2.59 SDS), and 40.18 kg/m^2 (+6.48 SDS), respectively. Signs of Blount disease and acanthosis nigricans were evident, and she had hyperphagia. She was undergoing speech therapy. Homozygous *ADCY3* variants may present with early onset, severe obesity, insulin resistance, and neurodevelopmental delay in children. Severe complications may occur, even at young ages. More data in terms of the optimal treatment and follow-up process of these patients are needed.

Keywords: *ADCY3* gene, hyperphagia, insulin resistance, monogenic obesity

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Introduction

Monogenic obesity (MO) is a severe, early onset form of obesity caused by a single gene mutation that leads to dysfunction in the leptin-melanocortin pathway controlling energy balance (1). During the past 30 years, more than a dozen genes have been identified in the leptin-melanocortin pathway and the tyrosine kinase receptor B-brain-derived neurotrophic factor signalling system. However, alterations in previously defined genes account for only 5% to 30% of cases of MO, and melanocortin 4 receptor (MC4R) deficiency is the most common cause of MO (1,2).

ADCY3 gene alterations were recently found to be associated with severe obesity (1,3-14). The *ADCY3* gene (OMIM*600291) is located on the short arm of chromosome 2 (2p23.3) and encodes the adenylate cyclase 3 enzyme (ADCY3) (13). This protein has a pseudosymmetric structure of two transmembrane and two cytoplasmic domains. Nine isoforms of *ADCY3* are expressed in various human tissues, such as adipose tissue and the hypothalamus. *ADCY3* catalyses the synthesis of cyclic adenosine monophosphate (cAMP), which plays a role in intracellular signal transduction. In the paraventricular nucleus of hypothalamus, *ADCY3* co-localizes with MC4R and inhibition of signaling at the primary cilia of these neurons results in increased body weight (1,13). *ADCY3*-cAMP signaling also controls the metabolic processes of carbohydrates and lipids; and appears to regulate the proliferation and differentiation of adipocytes (10). Some anorexigenic peptides, such as glucagon-like peptide-1 (GLP-1), act centrally to control appetite by upregulating cAMP formation (1,13,15,16,17). Apart from its effects on appetite and body weight, *ADCY3* seems to be linked to olfactory signal transduction based on the finding that disruption of *ADCY3* causes peripheral and behavioral anosmia (15). To date, only 12 patients with homozygous *ADCY3* alterations have been reported in large cohorts, and severe obesity, anosmia or hypo-osmia, hyperlipidemia, and insulin resistance were common features in these individuals (Table 1) (7,10).

Nevertheless, data on long-term follow-up and treatment strategies in these patients remain limited, despite the well-established link between *ADCY3* deficiency and obesity. Here, we report a child with early-onset and severe obesity caused by a novel homozygous *ADCY3* mutation. We present follow-up data and discuss potential treatment approaches, with a particular focus on management in young children.

Case Report

A 10-month-old female infant presented with increased appetite and weight gain. She had been born from a consanguineous marriage at 38 weeks of gestation, and her birth weight was 3050 g with a standard deviation score (SDS) of -0.08. Her mother had been diagnosed with insulin resistance and required dietary intervention during pregnancy. The infant's medical records revealed that her weight at the age of two months and seven months were 6.5 kg (+2.03 SDS) and 14 kg (+5.06 SDS), respectively. She was still breastfeeding and had not yet been successfully transitioned to complementary feeding. No steroids or other medications were being used. Physical examination at the age of 10 months showed a weight, height, and head circumference of 19 kg (+6.98 SDS), 82 cm (+3.53 SDS), and 49 cm (+3.07 SDS), respectively. Her weight age was 5.3 years, weight-for-height centile was 213%, and body mass index (BMI) was 28.26 kg/m^2 (+4.81 SDS) (18). Her target height was 155 cm (-1.38 SDS). She was at Tanner stage 1. She was able to sit up without support. The patient's appearance, together with height, weight, and BMI measurements on a growth chart are shown in Figure 1a, 1b. Laboratory testing found a fasting glucose level of 103 mg/dL (5.7 mmol/L), insulin concentration of 25.39 µIU/mL, and homeostatic model assessment for insulin resistance (HOMA-IR) value of 6.43 (>2.22) (calculated as fasting blood glucose × fasting insulin / 22.5) (19). Thyroid function test results were within the reference ranges. The insulin-like growth factor-1 level was 44 ng/mL (reference range: 40.8-93.6 ng/mL) (20). The basal cortisol level was 5.9 µg/dL, and the peak level stimulated by a low-dose adrenocorticotrophic hormone (ACTH) stimulation test with 1 µg/kg intravenous cosyntropin was 18.4 µg/dL, with an ACTH level of 20.1 pg/mL. A leptin level test could not be performed. The ophthalmologic examination and echocardiography findings were normal.

The patient was diagnosed with MO based on the presence of early onset and severe obesity, hyperphagia, normal height without dysmorphic/syndromic features, birth from a consanguineous marriage, and a family history of insulin resistance and obesity. After an MO panel for known common obesity-related genes was reported as normal, whole-exome sequencing analysis was performed and a novel homozygous c.1102G>A (p.Asp368Asn) variant in *ADCY3* was found (Figure 2). This variant had not been previously reported and was classified as a variant of unknown significance with a high pathogenicity score according to the American College of Medical Genetics classification (21).

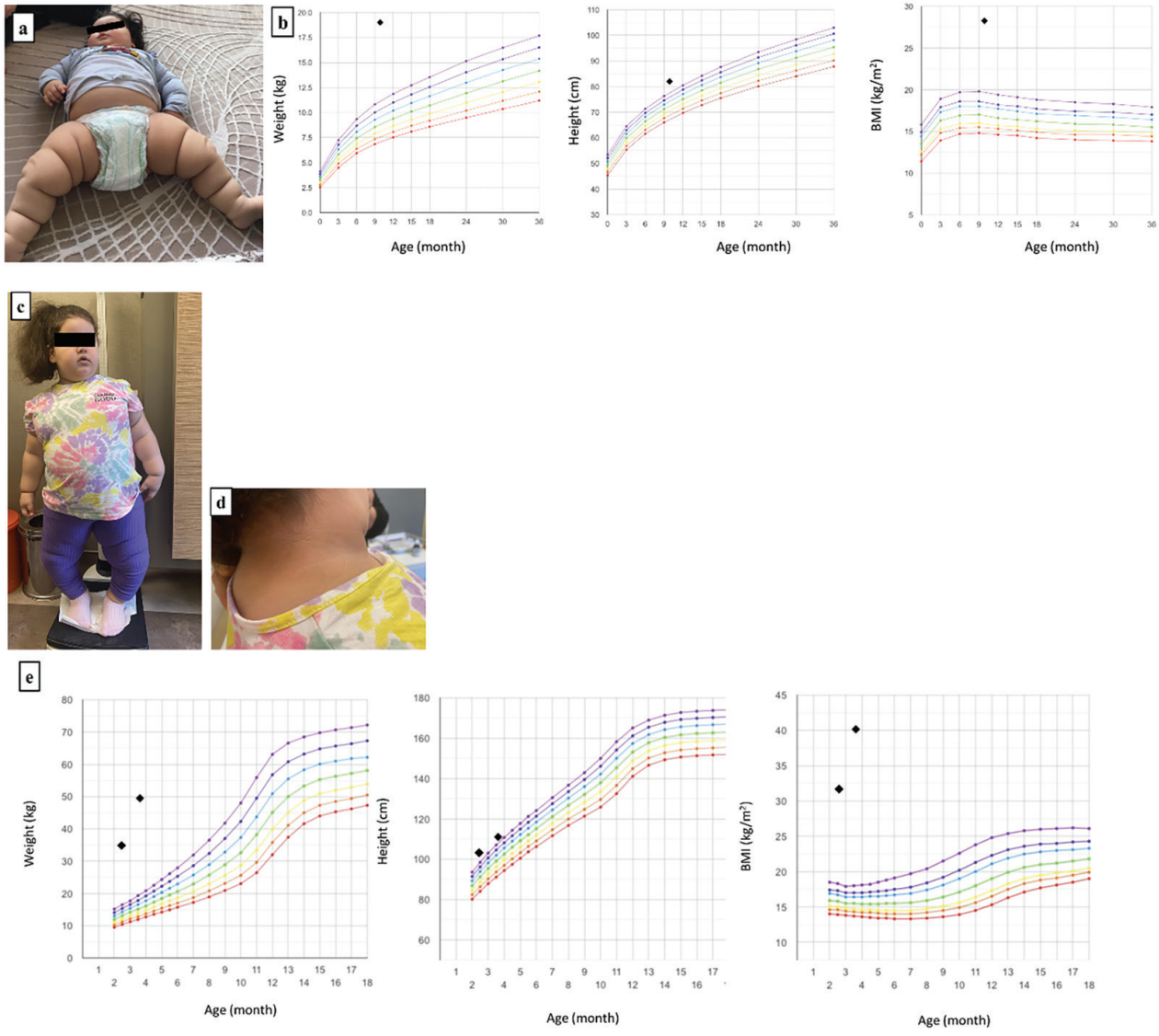

Figure 1. (a) Appearance of the patient at the age of 10 months; b) height, weight and body mass index measurements plotted on a growth chart at the age of 10 months; c) appearence of the patient at the age of 3.5 years; d) acanthosis nigricans; e) height, weight and body mass index plotted on a growth chart at the age of 3.5 year

DM: diabetes mellitus, IR: insulin resistance

The patient's pedigree is shown in Figure 2. Her mother was heterozygous for the same variant c.1102G>A (p.Asp368Asn) and had obesity and insulin resistance. Her father was also a heterozygous carrier of the mutation but was of normal weight. The patient's brother and sister had been diagnosed with ulcerative colitis, but only the sister was a heterozygous carrier of this variant (Figure 2).

At the age of 2.5 years, the patient's weight, height, and BMI were 34 kg (+8.42 SDS), 103 cm (+3.06 SDS), and 32.05 kg/m^2 (+6 SDS), respectively. Her weight age was 10.3 years (18). She had hyperphagia. She was unable to say two consecutive words. The Denver II Developmental Screening Test revealed that she was delayed in two domains: personal-social (13.5 months) and language (8.5 months). Her audiometry results were within the normal range. She was referred for speech therapy.

One year later at the age of 3.5 years, the patient's weight, height, and BMI were 49.5 kg (+8.16 SDS), 111 cm (+2.59 SDS), and 40.18 kg/m^2 (+6.48 SDS), respectively. Her weight age was 12.9 years (18). Signs of Blount disease

and acanthosis nigricans were evident. She continued to be hyperphagic. The patient's clinical features and height, weight, and BMI measurements are also shown on the growth chart shown in Figure 1. Laboratory testing showed that her fasting glucose level was 86 mg/dL (4.8 mmol/L), fasting insulin level was 20.9 µIU/mL, c-peptide level was 3.27 ng/mL, and HOMA-IR value was 4.44 (19). Thyroid function test results, uric acid and alanine aminotransferase levels, and a lipid profile were within normal ranges. Metformin was initiated at a dose of 250 mg/day, but was promptly discontinued as it had no significant effect on insulin levels or insulin resistance. An operation for Blount disease was planned. Her parents reported that she was able to smell and react to pleasant and unpleasant odors. An odor identification test was planned, to rule out hypo-osmia but was postponed because of speech delay.

The patient's parents provided written informed consent for publication.

Discussion

ADCY3 catalyses the formation of cAMP and mediates G_s signalling from G protein-coupled receptors. It co-localises in the primary cilia of the paraventricular nucleus neurons with MC4R (a type of G protein-coupled receptor), which transduces anorexigenic signals. In addition, cAMP seems to be involved in intracellular signaling of anorexigenic peptides such as GLP-1, and GLP-1 upregulates *ADCY3* (1,3-14).

Specific inhibition of *ADCY3* activity in MC4R-expressing neurons was found to be associated with obesity in mice (22). Wang et al. (22) showed that *ADCY3*-knockout mice may exhibit both severe obesity and hyperphagia, low locomotor activity, and hypogonadism. Several studies in different populations have also supported the association between *ADCY3* and severe obesity in humans (3,4,5,7,8,9,11,12,13). Three population-based genetic studies have demonstrated

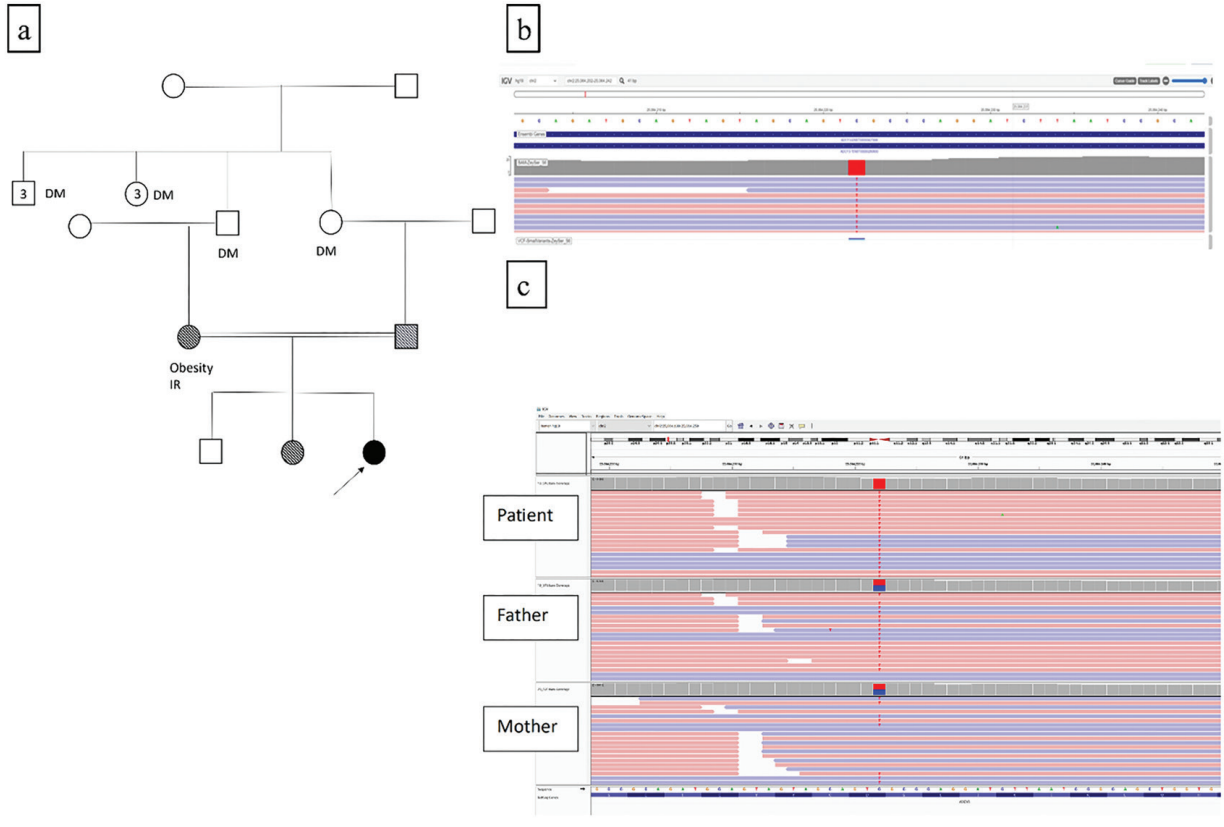

Figure 2. (a) The pedigree of the patient; b) homozygous *ADCY3* c.1102G > A(p.Asp368Asn) variant detected in the case; c) Sanger sequencing confirmation of the patient and segregation analysis of the variant in parents

DM: diabetes mellitus, IR: insulin resistance

Table 1. The mutations in the *ADCY3* gene and the phenotypes of the previously reported cases and our patient

Patients	Age (year)	Sex	Genetic evaluation	Clinical evaluation
1-7 (7)	NA	NA	Homozygous c.2433-1G > A	3 cases: type 2 DM 1 case: impaired glucose tolerance 1 case: impaired fasting glucose 2 cases: normal
8 (10)	15	F	Homozygous c.3315del (frameshift mutation) (p.Ile1106Serfs*3)	87 kg/150 cm (BMI: 38.7) (BMI SDS: +3.5 SDS) Hyperphagia Anosmia Slight to moderate intellectual disability Secondary amenorrhea (menarche: 14 y) Dyslipidemia, IR
9 (10)	6	M	Homozygous c.2578-1G > A (splicing mutation)	52 kg/137 cm (BMI: 28) (BMI SDS: +6.5) Hyperphagia Anosmia Obesity in parents
10 (10)	6	M	Homozygous c.191A > T (a nonsynonymous missense mutation) (p.Asn64Ile)	49 kg/132 cm (BMI: 28.1) (BMI SDS: +6.5) Hyperphagia Hypoosmia Slight to moderate intellectual disability
11 (10)	NA	F	Homozygous c.191A > T (a nonsynonymous missense mutation)	BMI: 32.8 kg/m^2 Hyperphagia Hypoosmia
12 (10)	11	M	Compound heterozygous c.1268del (frameshift mutation) (p.Gly423Alafs*19) c.3354_3356del (an amino acid deletion mutation) (p.Phe1118del)	89 kg/154 cm (BMI: 37.8) (BMI SDS: +4.6) Hyperphagia Anosmia
13 (the current case)	0.9	F	Homozygous c.1102G > A(p.Asp368Asn)	Early onset severe obesity Hyperphagia Insulin resistance Neuromotor developmental delay Blount disorder

NA: not available, M: male, F: female, y: year, BMI: body mass index, DM: diabetes mellitus, IR: insulin resistance, SDS: standard deviation score

that *ADCY3* variants are also associated with type 2 diabetes (3,7,11). In 2018, patients with homozygous variants in the *ADCY3* gene were first reported. Grarup et al. (7) identified seven patients with homozygous c.2433-1G > A variant in a large cohort of the Greenland population (n = 4,217). The affected individuals had a 7.3-kg/m^2 higher BMI, an 8.1% higher body fat mass, a 17-cm larger waist circumference, and higher fasting glucose and 2-hour plasma glucose concentrations than the rest of the study group. Saeed et al. (10) reported three homozygous mutations in four patients with severe obesity from three unrelated Pakistani families, as well as a compound heterozygous mutation in a Euro-American child. The mutations and phenotypes of previously reported patients and the presented case are summarized in Table 1. The girl presented here had more severe obesity with a higher BMI than previously described patients. Moreover, she had prominent insulin resistance defined at a younger age than two patients reported by Saeed et al. (10) (6 and 15 years of age). Hyperphagia was present in all previously reported patients, as in the current patient. Anosmia was reported in three patients and two others had hypo-osmia (10). The patient described in this report was able to smell but hypo-osmia could not be ruled out because the patient's age and speech delay prevented the performance of an odor identification test. While neurodevelopmental delay is relatively common in monogenic forms of obesity (MO) (1), it has not been previously documented in association with *ADCY3* gene variants. Intellectual disability was reported in two earlier cases; however, detailed information regarding their neurodevelopmental progress was not provided. The association between neurological development and *ADCY3* gene alterations is not well defined but an animal model showed that loss of type 3 adenylyl cyclase in mice led to decreased neuronal activity, altered sleep pattern, and depression-like behavior (23). Of note, although the currently presented patient exhibited complications of obesity, including Blount disease at a young age, such findings have not been described in the previously reported cases (10).

No clear follow-up procedure for patients with homozygous *ADCY3* mutations has been established. Insulin resistance and complications of obesity, including Blount deformity, were exhibited early in our patient. Furthermore, speech delay was marked and neuromotor developmental delay was a major problem for the patient and her family. Another important feature reported in an animal study was hypogonadism (22). Saeed et al. (10) reported secondary

amenorrhoea in the adolescent proband with a normal profile of serum gonadotropins and oestradiol. We suggest close follow-up of these children in terms of obesity and its complications, neurological development, puberty, and other additional features not previously detected.

The mother, father, and sister of the index case were heterozygous carriers of the c.1102G>A (p.Asp368Asn) mutation in *ADCY3*. The mother had obesity and insulin resistance, but the father and the sister were of normal weight. Some heterozygous carriers of *ADCY3* gene variants have previously been reported to not exhibit obesity or insulin resistance (10). Interestingly, the brother and sister of our patient had been diagnosed with ulcerative colitis. Inflammatory bowel diseases have been associated with *ADCY3* variants (24). However, only the sister was a carrier. Therefore, we plan to perform further genetic analyses for ulcerative colitis in the brother and sister of our patient.

Although there are previously reported treatments for children with MO, the treatment in patients with *ADCY3* variants are not established. Setmelanotide is an MC4R agonist that is 20 times more potent than endogenous melanocortin-stimulating hormone. It was approved in 2020 for the treatment of MO syndromes affecting the proximal leptin signal pathway in adults and children aged ≥6 years (25). The ADCY3 protein plays a role in correct function of MC4R. As ADCY3 does not function correctly in patients with MO due to variants in *ADCY3*, whether setmelanotide would be effective in this condition remains questionable. However, setmelanotide increases MC4R activity. The MC4R pathway appears to be a modifiable system, and another question is therefore whether it can be effectively used for overcoming and improving *ADCY3* dysfunction by regulating food intake and preference. Liraglutide is a GLP-1 analogue approved in children aged >12 years with type 2 diabetes and obesity and is also the subject of ongoing clinical trials in children aged 7-12 years (26). Liraglutide was found to be effective in increasing hepatic AC3 mRNA and protein levels, and serum AC3 levels, in mice, as well as upregulating *ADCY3* (17). Liraglutide has also been useful for regulating appetite in diabetic patients with hypothalamic hyperphagia and obesity (16). In one study of adolescents with obesity, the use of liraglutide with lifestyle therapy reportedly led to a significantly greater reduction in the BMI SDS. However, this drug has also been found to be associated with some serious complications, such as pancreatitis (26). Unfortunately, the treatment options for MO are limited and the presented patient was younger than other children treated with these agents. *ADCY3* has recently been proposed as a target for anti-obesity agents (27). The main safety concern regarding such agents is the risk of malignancy because the upregulation of *ADCY3* may lead to an increase in the tumorigenic potential of cells via activation of the cAMP-response element binding protein pathway (28).

Conclusion

Homozygous *ADCY3* variants may lead to very early onset severe obesity, insulin resistance, and neurodevelopmental delay in children. Severe complications may occur in the early stages. More evidence is needed to determine optimal management of these patients beginning at young ages.

Ethics

Informed Consent: The written informed consent was obtained from the parents of the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Bahar Özcabı, Concept: Bahar Özcabı, Samim Özen, Design: Bahar Özcabı, Samim Özen, Data Collection or Processing: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Hasan Önal, Samim Özen, Analysis or Interpretation: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Hasan Önal, Samim Özen, Literature Search: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Hasan Önal, Samim Özen, Writing: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Samim Özen.

Conflict of Interest: One author of this article, Samim Özen, is member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, he was not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions.

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CASE REPORT

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Familial Clinical Heterogeneity of Medullary Thyroid Cancer with Germline *RET* S891A Protooncogene Mutation: 7-year Follow-up with Successful Sorafenib Treatment

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What is already known on this topic?

Different mutations in the rearranged during transfection *(RET)* gene are associated with varying age-dependent penetrance and disease manifestations in medullary thyroid carcinoma (MTC). The American Thyroid Association has classified hereditary MTC into three risk categories ("moderate", "high", and "highest") based on the type of *RET* mutation. The S891A mutation in *RET* is a rare germline mutation associated with a moderate risk of MTC. The use of sorafenib and other RET-targeting tyrosine kinase inhibitors in childhood thyroid cancers MTC and disseminated thyroid cancer have rarely been reported.

What this study adds?

Despite the well-defined genotype-phenotype correlation of moderate risk *RET* p.S891A germline mutation, we report an early-onset, inoperable case of medullary thyroid carcinoma (MTC). We also found an additional *SDHA* somatic mutation, p.S408L, in the same patient, which may have triggered the severity of the presentation. This co-occurrence has not been reported before. *RET* p.S891A may cause mixed MTC and papillary thyroid carcinoma. The patient experienced growth retardation possibly due to the side effects of sorafenib.

Abstract

Hereditary forms of medullary thyroid carcinoma (MTC) are rare. Different phenotypes with the same mutation may be due to differences in the timing of rearranged during transfection *(RET)* activation steps, additional mutations in other regions of the gene, or the co-occurrence of germline and somatic mutations, which is an infrequent possibility. Here, we present the different features and challenges during the follow-up of three family members with the same germline mutation. A 4-year-old male patient with respiratory distress was diagnosed with MTC and found to have a heterozygous germline mutation C.2671T > G(S891A) in the *RET* gene (classified as intermediate risk by the American Thyroid Association. As the tumor was inoperable, treatment with a tyrosine kinase inhibitor (sorafenib) was initiated. This treatment with sorafenib prevented tumor progression for seven years. Whole exome sequencing did not identify additional mutations. Segregation analysis showed the same mutation in the asymptomatic mother and sister. In the proband, thyroid tissues were examined for somatic mutations, and *SDHA* c.1223C > T (p.S408L) was found. The clinical presentation of rare mutations such as *RET* p.S891A differed among family members carrying the same germline mutation. Our index case's more severe clinical presentation may be due to an additional somatic mutation. Sorafenib treatment can be an option for advanced MTC and may prevent disease progression.

Keywords: Medullary thyroid carcinoma, *RET,* sorafenib

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Introduction

Medullary thyroid carcinoma (MTC) is a rare tumor that develops from parafollicular C cells of the thyroid gland, accounting for 1-5% of thyroid malignancies (1,2). It can occur sporadically or as part of a genetic syndrome, such as multiple endocrine neoplasia type 2 (MEN2). The pathogenesis of MTC involves activation of the "*Rearranged during Transfection*" (*RET*) protooncogene through germline mutations, somatic mutations, or gene fusions (2). *RET* encodes a receptor tyrosine kinase that plays a significant role in developing the enteric nervous system and the thyroid gland. Germline mutations in *RET* are important in the clinical progression and prognosis of hereditary MTC (MEN2A, MEN2B, and familial MTC), which are autosomal dominant disorders. Different mutations in *RET* are associated with varying age-dependent penetrance and disease manifestations. The American Thyroid Association (ATA) has classified hereditary MTC into three risk categories, "moderate", "high", and "highest", based on the type of *RET* mutation (2,3).

Genetic testing is therefore crucial in identifying patients at risk of familial MTC, as early diagnosis and prophylactic surgery may improve patient outcomes. Treatment of MTC typically involves surgical resection of the tumor (2). Systemic chemotherapy, such as cis-platinum, doxorubicin, vincristine, and 5-fluorouracil, has demonstrated limited effectiveness for metastatic MTCs (4). Fortunately, new targeted therapies with tyrosine kinase inhibitors (TKIs), such as vandetanib, cabozantinib, and sorafenib, provide hope for metastatic MTC treatment (4). The Food and Drug Administration recently approved Sorafenib for radioactive iodine-refractory thyroid cancer in adults, which inhibits RET and vascular endothelial growth factor (VEGF) receptor. It is approved for use in children aged 12 and above. For the patient we are sharing, the treatment was initiated after an international request was made under humanitarian aid provisions, and the medication was brought in based on expert committee reports (5). A meta-analysis by Vuong et al. (4) assessed data from eight trials involving 101 metastatic MTC cases. The results showed that sorafenib was a therapeutic option for patients with metastatic MTCs, particularly in cases where other treatment regimens have proven ineffective.

The S891A mutation in *RET* is a rare germline mutation associated with a moderate risk of MTC (2). Despite a well-defined correlation between genotype and phenotype, we present an inoperable case of a 4.2-year-old boy with a germline S891A mutation. To the best of our knowledge, there are no reported cases of individuals who carry both RET p.S891A germline mutation and a succinate dehydrogenase subunit A (*SDHA)* somatic mutation [p.S408L (c.1223C > T), which this patient was also found to harbor. This report also describes our experience with the treatment success and potential side effects of sorafenib.

Case Report

A 4.2-year-old male patient was admitted to the outpatient clinic due to difficulty in breathing, stridor, loss of appetite, and weight loss. His medical history was that he was born to non-consanguineous parents. Before his current hospitalization, he had been hospitalized three times and was misdiagnosed with bronchiolitis. On physical examination, he was 104 cm in length [-0.28 standard deviation (SD)] with a body mass index (BMI) of 13.87 kg/m^2 (-1.48 SD) and had a goiter. Chest X-ray showed an apple core lesion around the trachea (Figure 1A). Further radiologic examination with a thorax computed tomography scan revealed a hypoechoic lesion with punctate calcifications measuring 32x25x34 mm involving the right anterior cervical region, invading the thyroid parenchyma and encompassing the right internal carotid artery and the trachea. The scan also showed the presence of several lymph nodes with metastatic involvement (Figure 1B).

Laboratory evaluation reported normal thyroid function. Although the levels of thyroid stimulating hormone (TSH) at 3.24 mIU/mL [normal range (NR) 0.38-5.33 mIU/mL] and fT4 at 17.95 pmol/L (NR 11-22 pmol/L) were within the NR, the levels of human thyroglobulin (hTg), calcitonin, and carcinoembryonic antigen (CEA) were significantly elevated [54.2 ng/dL for hTg, 1093 pg/mL for calcitonin (NR 0-10 ng/mL), and 22.74 ng/mL for CEA (NR < 0.3 ng/mL)]. Following the biopsy of the lesions, histopathological examination reported MTC. Molecular analysis revealed a heterogeneous pathogenic *RET* mutation [p.S891A (c.2671T > G) (rs75234356)]. According to ATA, this specific variant was in the moderate risk category (2). Due to the inoperable nature of the tumor, sorafenib was started at a daily dose of 200 mg and dosage titrated during close follow-up. He underwent annual thyroid and thorax magnetic resonance imaging (MRI). Although the tumor did not exhibit complete regression, there was a gradual reduction. In the second month of treatment, the tumor decreased to 24x16 mm. Furthermore, following sorafenib treatment, there was a decrease in calcitonin and CEA levels (Table 1).

Segregation analysis showed that the patient's asymptomatic mother and sister had the same *RET* mutation. The family received genetic counseling. Although they had normal thyroid glands on imaging, the sister

had a slightly elevated calcitonin level at 1.5 years of age (calcitonin 26.2 pg/mL, CEA 0.54 ng/mL), while the mother's serum calcitonin and CEA levels were normal. The younger sister and mother underwent prophylactic thyroidectomy at the age of 2 and 35 years, respectively. Pathological examination of thyroidectomy materials showed that the younger sister had C cell hyperplasia, while the mother had papillary thyroid cancer and accompanying medullary microcarcinoma (Figure 2). Whole exome sequencing (WES) was conducted on all family members to identify additional mutations, but none were found. The index case, who had the same *RET* mutation as the mother and sister in the moderate-risk category, had presented with a more severe clinical picture compared to them. When the pathological materials were molecularly evaluated for the possibility of a somatic mutation, *SDHA* somatic mutation [p.S408L (c.1223C > T)] was found in the index case's material, and no somatic mutation was found in the mother's. However, sister's pathological material was unsuitable for somatic mutation analysis.

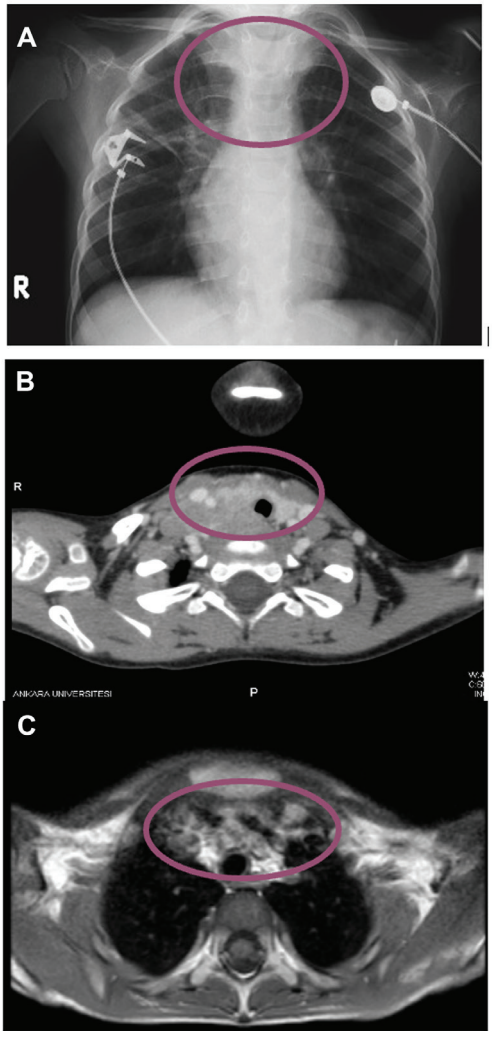

Figure 1. (A) An apple core lesion around the trachea. B) A heterogeneous hypoechoic lesion with punctate calcifications measuring 32x25x34 mm in size involving the right anterior cervical region adjacent to the thyroid gland, invading the thyroid parenchyma and encompassing the right internal carotid artery, causing circumferential stenosis, and displacing and compressing the trachea to the left of the midline. This lesion extended into the anterior mediastinum and was similar in contrast to the left lobe of the thyroid. The existence of several lymph nodes with metastatic involvement was shown (C)

Based on ATA guidelines, the index patient and his sister were evaluated for MEN2A. Calcitonin, CEA, and serum calcium levels were monitored (Table 1). On follow-up, he had no symptoms of hyperparathyroidism (HPTH) or pheochromocytoma (PHEO). At the age of 11 years, we began to screen 24-hour urine for metanephrines and catecholamines for PHEO. All were normal.

A notable slowing of growth velocity was observed under sorafenib treatment during follow-up (Figure 2). Hemogram and biochemical parameters were normal, including liver and kidney function, blood glucose, tissue transglutaminase autoantibody immunoglobulin A (IgA), and serum total IgA level. In addition, his urine analysis was normal. This phenomenon was considered a side effect of sorafenib. Somatamedin-C was 53.6 ng/mL (NR 76-499 ng/mL). At the age of 11 years a slight elevation of TSH (11 mIU/mL) with normal fT4 (14 pmol/L) was observed and thyroglobulin (69 pg/mL) was elevated. Thyroid peroxidase antibody and thyroglobulin antibody (TgAb) were negative, and urine iodine level was normal. He was on no other medication that could cause an elevation in TSH. It was concluded that this mild elevation of TSH was associated with tyrosine kinase inhibition, and L-thyroxine (L-T4) treatment was initiated at

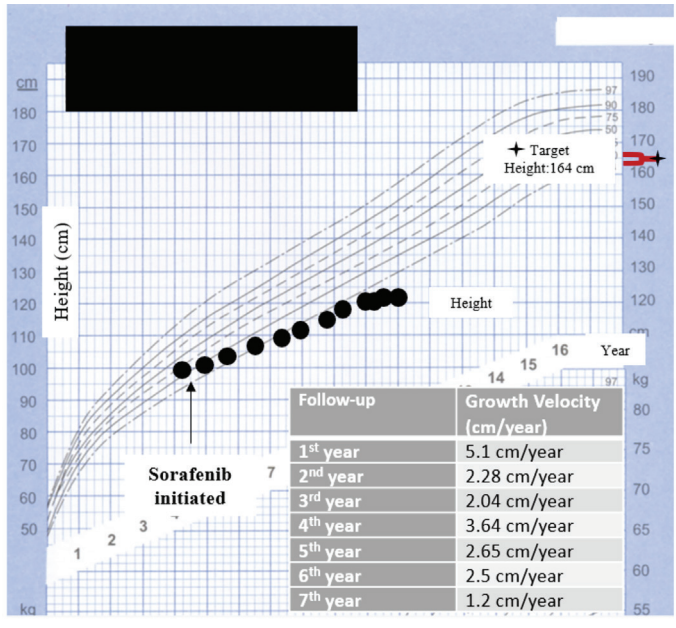

Figure 2. Height curves and the growth velocity of the patient

Table 1. Biochemical monitoring of the patient

Age	Calcitonin (pg/mL)	CEA (ng/mL)	Ca (mg/dL)	P (mg/dL)	ALP (U/L)	PTH (pg/mL)	TSH µIU/mL	FT4 pmol/L	Sorafenib (mg/day)
4.2	**1093**	**22.74**	9.7	4.3	219	14	3.24	17.95	100
4.9	**216**	**6.1**	10.4	4.6	236	15	3.64	21.5	100 + 100
5.6	**119**	**4.91**	9.6	3.17	135	43.5	6.2	21.6	200 + 100
5.9	**41.1**	**5.99**	9.8	3.43	155	32	5.31	10.57*	200 + 100
6.6	**67.6**	**3.76**	10	3.6	151	8.5	7.33	13.2*	200 + 100
6.9	**47**	**4.33**	10	5.4	165	92	5.74	14.04*	200 + 100
7.2	**39**	**3.5**	9.2	3.8	137	33.5	6.1	11.06*	200 + 100
8.8	11	2.9	9.4	3.8	152	62.4	6.12	13.61*	200 + 200
9.6	6.9	2.6	8.9	4.9	167	43	5.18	18.8	200 + 200
10.1	10	3.14	9	3.9	122	80	3.31	14	200 + 200
10.5	10.7	1.99	9.4	3.6	175	35	3.62	18	200 + 200
11.2	9.1	2.54	9.1	3.17	102	19	**11****	14	200 + 200

Normal range for calcitonin: 5.2-11.7 pg/mL, FT4: 11-22 pmol/L, FT4*: 7-15.96 pmol/L, CEA: < 0.3 ng/mL.
**1.2 mcg/kg/day L-thyroxine treatment initiated.
CEA: carcinoembryonic antigen, Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathyroid hormone, TSH: thyroid stimulating hormone, FT4: free thyroxine

a dose of 1.2 mcg/kg/day.

The patient is now 11 years of age and on 400 mg of sorafenib treatment. His height is 124 cm (-3.21 SD); his BMI is 14.5 kg/m^2 (-1.9 SD). Bone age is 6 years and 10 months. Throughout the follow-up period, it is important to note that the patient remained in a prepubertal state (follicle stimulating hormone 0.8 mIU/mL, LH < 0.3 mIU/mL, total testosteron 2.5 ng/dL). He has retarded growth and normal development (normal language, cognitive abilities, social skills, and fine motor development). He is on L-T4 1.2 µg/kg/day. Tumor markers are negative. He has no symptoms and signs of HPTH or PHEO. He is under close follow-up by physical examination every three months, with laboratory evaluation every six months and periodic MRI annually. The mass size remained stable, and no metastases were observed (Figure 1C).

Discussion

The varying clinical presentation in individuals with the same *RET* germline mutation is likely due to incomplete penetrance, allelic/chromosomal imbalance, a second hit mutation, and/or differences in the timing, location, and severity of somatic mutations during tumor development. It is also important to note that environmental factors and epigenetic modifications, such as DNA methylation, histone modification, and microRNA dysregulation, can influence gene expression and tumor development and contribute to differences in clinical presentation (6,7). Although the case presented herein had a well-defined classification of moderate risk with heterogeneous *RET* p.S891A, he had a rapid and severe onset tumor, contrary to expectations. The patient's sister and mother also had the same mutation with different clinical presentations. This variability in clinical presentation among family members highlights the importance of genetic testing and surveillance in families with a history of MTC. Genetic testing for *RET* mutations is recommended for individuals with a first-degree relative history of MTC or other related cancers (*HRAS, NRAS, KRAS*) and individuals with clinical features suggestive of MTC to enable earlier detection and intervention (2).

Additional somatic mutations, such as in the *KRAS, NRAS*, *CCND1, FGF3, FGF19* and *CDKN2A* genes, may be associated with more aggressive forms of MTC and poorer outcomes (8). Somatic mutations may influence the clinical course of MTC. In the case of this boy, it might be speculated that additional somatic mutations occurred early in tumor development, leading to a more aggressive and advanced form of MTC. In contrast, the healthy adult mother may have experienced fewer deleterious somatic mutations, resulting in a less severe form of MTC or a slower disease progression. Surprisingly, we identified a somatic mutation in *SDHA*. This has commonly been associated with paragangliomas and PHEOs. Both papillary and follicular thyroid tumors showed a significant reduction in *SDHC* and SDHD mRNA expression compared to normal thyroid tissues. Thyroid tumors with low *SDH* expression were associated with earlier age at diagnosis and higher pathological TNM stage (9). It has been suggested that the variant may lead to increased succinate levels, which can activate HIF-1α and VEGF expression and promote tumor growth (10). However, the mutation was graded as tier 3, corresponding to "variants with unknown

clinical significance" (11) and the exact mechanism by which this *SDHA* c.1223C>T mutation may have contributed to MTC pathogenesis is not clear. Since we excluded other germline mutations by WES, we hypothesized that this somatic mutation might have led to the more aggressive tumor. In the study of Schulte et al. (12), the youngest age at which MTC was observed to manifest in a cohort in which a large number of cases with S891A mutation were included was 17 years and the median (range) age was 46 (17-80) years. Within the literature, the clinical presentation of the index case and the laboratory and pathological findings (onset of high calcitonin levels and C-cell hyperplasia) of the sister manifested at a significantly younger age, suggesting a more aggressive clinical course. No somatic mutation was found in the mother's pathological samples. The mother's enduring clinical silence led to the investigation of additional mutations that might have caused the differences in the same family. The missing puzzle piece, in this case, might be the confirmation of the same *SDHA* somatic mutation in the sister's pathological material. The onset of MTC in the sister occurred earlier than expected. However, this important step was not taken because the pathological material was unsuitable for somatic mutation analysis. Currently, there is limited evidence or data in existing databases to support the association of SDHA somatic mutations with the condition. Functional studies are needed to establish the exact relationship. Even in the absence of conclusive evidence, cases with atypical clinical presentations should also be investigated for other potential pathogenic factors. Environmental factors and epigenetic modifications are other options that should be considered.

The other remarkable point about this case is that the mother carrying the *RET* p.S891A had papillary thyroid cancer and accompanying medullary microcarcinoma with no symptoms. There are two hypotheses on histogenesis. The first is two types of tumor cells derived from the same transformed stem cells. The second is that triggering oncogenesis may pathogenetically affect the normal thyroid tissue (13). It can be speculated that *RET* p.S891A mutation may have triggered the simultaneous formation of two tumors. The detection of a differentiated thyroid cancer during follow-up of the index case would support this speculation. In this respect, long-term follow-up will be instructive.

The treatment of advanced MTC is challenging. Systemic therapy with TKIs, such as cabozantinib and vandetanib, has been approved for treating advanced MTC but is not widely available in all countries (2). Studies showed that sorafenib could be considered a first-line medical treatment for advanced cases (14). Sorafenib controlled the progression and metastases of the disease and resulted in a reduction in tumor size and a decrease in calcitonin and CEA levels in the index case. However, as with any therapy, there are potential side effects and risks associated with TKI treatment. Studies have shown a deceleration in growth velocity in pediatric patients who have been administered TKIs for at least six months (15,16,17).

Neovascularization is essential in the normal physiological growth of a developing skeleton. The administration of TKIs, such as sorafenib, has been associated with cartilage abnormalities and growth plate alterations, which was related to the anti-VEGF effect. A typical progression involved the gradual narrowing of normal growth plates; however, it has been reported that a distinct widening is observed during therapy. Due to the limited number of patients in studies, any correlation between growth plate toxicity and factors such as "treatment dose, age, gender, or tumor type" could not be reported (18). Thus far, we have not observed this effect in our patient, although radiological evidence may emerge in the future. The growth retardation impact of TKIs is also attributed to deficiencies in growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) (19). Our patient had IGF-1 deficiency. Recombinant GH therapy was not considered appropriate due to an underlying malignancy and associated metastases. It suggests the potential involvement of as-yet-unexplained mechanisms contributing to this growth inhibition. Further research is warranted to elucidate the intricate interplay between TKIs, cancer treatment, and growth dynamics in pediatric patients.

It is well-documented that sorafenib can lead to hypothyroidism. The mechanism of inducing hypothyroidism involves the upregulation of T4 and T3 metabolism through deiodinase type 3 (18,20). Treatment was initiated at the age of 11.2 years when TSH levels reached 11 IU/mL, while T4 levels remained within normal limits. Although closer patient monitoring without treatment could be a management option, the family's inability to comply with more frequent follow-up appointments made it clear that closer monitoring would not be feasible. Typically, hypothyroidism develops sooner with sorafenib treatment (18). Our evaluation did not reveal non-pharmacological factors, such as iodine deficiency or autoimmune factors, that could explain the observed mildly elevated TSH. Surprisingly, TSH elevation presented in the seventh year of sorafenib treatment. A long-term follow-up of the patient's thyroid function will likely provide a more definitive etiological explanation.

Conclusion

In conclusion, the varying clinical presentation of closely related individuals with the same *RET* p.S891A may be due to somatic mutations, epigenetic modifications, and environmental factors. Additional somatic mutations, like *SDHA* present in the index case, may worsen the disease. The presence of additional somatic mutations in patients with MTC may also be important for treatment and monitoring purposes. TKIs, such as sorafenib, have shown promise in the treatment of advanced MTC although growth abnormalities have been reported in pediatric patients, including in the present case. Genetic testing and surveillance are important and long-term follow-up is necessary for understanding disease progression and treatment efficacy.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Ayşegül Ceran, Koray Ceyhan, Ayça Kırmızı, Zehra Aycan, Handan Dinçaslan, Emel Ünal, Merih Berberoğlu, Concept: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Zehra Aycan, Merih Berberoğlu, Design: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Zehra Aycan, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Ayşegül Ceran, Koray Ceyhan, Ayça Kırmızı, Handan Dinçaslan, Emel Ünal, Analysis or Interpretation: Sirmen Kızılcan Çetin, Ayşegül Ceran, Koray Ceyhan, Ayça Kırmızı, Handan Dinçaslan, Emel Ünal, Literature Search: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Ayşegül Ceran, Merih Berberoğlu, Writing: Sirmen Kızılcan Çetin, Zeynep Şıklar, Elif Özsu, Merih Berberoğlu.

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CASE REPORT

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A Challenging Case of Ectopic Adrenocorticotropin Hormone Syndrome with Bronchial Carcinoid and Literature Review

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What is already known on this topic?

Ectopic adrenocorticotropin hormone (ACTH) syndrome is very rare in children. Diagnosis may be delayed because of its rarity. However, early diagnosis is important to prevent comorbidities and improve the patients quality of life.

What this study adds?

Ectopic ACTH cases are mostly reported as individual cases. The case presented here is an example of ectopic ACTH syndrome with bronchial carcinoid. This combination is exceedingly rare in children so all pediatric cases of bronchial carcinoid ectopic ACTH were reviewed. Since this article describes all these cases and the diagnostic process is described in detail, it is hoped this report will be a guide for other colleagues.

Abstract

We report an adolescent boy diagnosed with ectopic adrenocorticotropin hormone syndrome (EAS) due to an atypical bronchial carcinoid. The patient was managed by a multidisciplinary team. He underwent surgery and subsequent chemotherapy and radiotherapy treatments. The patient is still under our follow-up. At the time of writing, eighteen pediatric and adolescent patients with EAS because of bronchial carcinoid tumors have been reported. EAS due to bronchial carcinoids is very rare in children and adolescents. Careful diagnostic evaluation and rapid treatment should be started immediately. Although complete remission is possible, atypical carcinoids have a more aggressive nature. A multidisciplinary approach and follow-up is recommended in terms of quality of life and survival.
Keywords: Ectopic adrenocorticotropin hormone syndrome, carcinoid, Cushing

Introduction

Endogenous Cushing syndrome (CS) is very rare in the pediatric and adolescent periods, resulting from the overproduction of glucocorticoids with an annual incidence rate of 0.7-2.4 cases per million persons (1). CS may be adrenocorticotropin hormone (ACTH) dependent or ACTH independent. Around 80 to 85% of endogenous CS is ACTH-dependent, and of these, 75-80% is caused by ACTH-producing pituitary adenoma, when it is known as Cushing disease. Ectopic ACTH syndrome (EAS), accounts for almost 15% of all CS cases and occurs when there is production of ACTH from an ectopic source in the body, usually mostly neuroendocrine tumors (NETS) (1,2). ACTH-secreting NETS are usually located in the thymus, lungs, pancreas, or gastrointestinal system, but may also present as Ewing sarcoma, pheochromocytoma, or medullary thyroid carcinoma (3).

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Bronchial carcinoids that arise from bronchial mucosal neuroendocrine cells are the most frequently seen primary malignant lung tumors and also the most common cause of EAS in children (4). These NETS are well differentiated, and the word "carcinoid" distinguishes them from poorly differentiated ones, which include small-cell lung cancer and large-cell neuroendocrine carcinomas. They are subdivided into two groups based on malignancy potential, as typical carcinoids (TC) and atypical carcinoids (AC), and the majority of pediatric patients present with the typical type. The median age of presentation of EAS cases is 9.5 years, with a female predominance (5).

The initial diagnosis does not usually consider CS based on anamnesis and physical examination of pediatric cases. Furthermore, EAS constitutes a very small part of the etiology of CS so the diagnosis and treatment process may be delayed. We discuss a case of an ectopic ACTH-secreting bronchial carcinoid who had been in seen in various centers. However, none of these centers had considered CS, despite presenting because of gynecomastia and even having a scheduled gynecomastia procedure planned. In addition, the current literature currently describing pediatric cases of EAS due to bronchial carcinoid is reviewed.

Case Report

A 13.7-year-old boy complained of gynecomastia and excessive weight gain. In his anamnesis, it was learned that he had been examined in different centers for gynecomastia for around one year, and an operation was even planned. There was no prior physical sickness or steroid use. On physical examination, weight was 61 kg [0.55 standard deviation score (SDS)], height was 157 cm (-0.81 SDS), and body mass index (BMI) was 24.7 kg/m^2 (0.9 SDS). His blood pressure was 95/65 mmHg (75-90th centile). He had moon facies, truncal adiposity, a buffalo hump, purple striae over the abdomen and breast, hypertrichosis, and gynecomastia (Figure 1). He had pubic hair stage 3 with a stretched penile length of 7 cm and bilateral testicular volume of 10 mL each. The other systemic examination was unremarkable. Biochemical evaluation for liver and renal function tests and lipid profiles were normal. On hormonal evaluation, serum ACTH level was 60.2 pg/mL (NR 7.2-30 pg/mL) and basal cortisol was 20.4 mcg/dL. His midnight and evening serum cortisol concentrations were 19.9 μg/dL and 25.1 μg/dL. CS was confirmed using a low-dose (1 mg) dexamethasone suppression test (LDDST), which revealed non-suppressed blood cortisol (1988 g/dL). Twenty-four-hour urinary free cortisol levels (UFC) were elevated (2760 nmol/24-hour and 3800 nmol/24-hour). A high-dose dexamethasone suppression test (HDDST) also showed no suppression (baseline serum cortisol = 19.2 μg/dL; cortisol after test = 22.1 μg/dL). The serum level of chromogranin-A was elevated (191 ng/mL, NR < 100 ng/mL). Dynamic contrast magnetic resonance imaging (MRI) of the pituitary was normal.

Contrast-enhanced computed tomography (CT) of the thorax and abdomen was performed to identify the peripheral ACTH-secreting tumor. This identified a 21x12 mm hypodense homogeneous solid lesion in the left hilus and a 7 mm nodule in the lingula of the left lung with micro mediastinal lymph node enlargements. To further investigate this lesion, ^{68}Ga-DOTATATE positron emission tomography (PET)/CT was performed, which revealed pathological activity on the hilus and lingula of the left

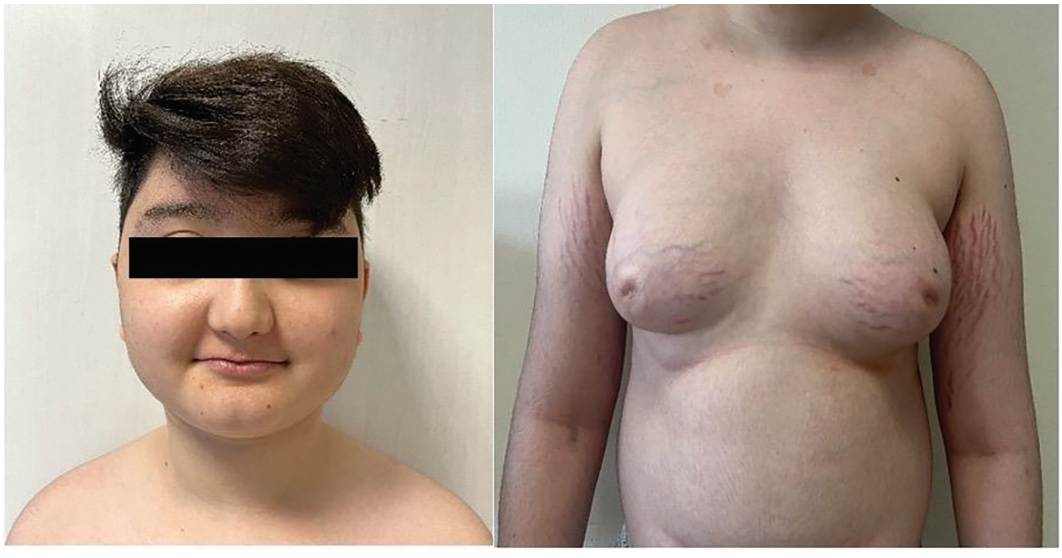

Figure 1. Preoperative physical examination findings: moon facies, gynecomastia, purple striae

lung (Figure 2). This finding strengthened the possibility of the lesion being the source of EAS. A biopsy performed on the lesion under endobronchial US revealed findings consistent with a carcinoid tumor (strongly positive ACTH antibody). The patient underwent surgery. The lesion in the hilus was dissected as completely as possible although it was in close proximity to the main bronchus and vascular structures) and removed *en bloc*, and wedge resection was done for the lesion in the left lung. In the histopathological examination of the lung, proliferation consisting of cells with spindle-oval-shaped chromatin in the form of a salt and pepper appearance, showing solid and insular organization, was observed. On immunohistochemistry, tumor cells were positive for chromogranin-A, synaptophysin, CD56, thyroid transcription factor-1, and ACTH, suggesting a NETS. The Ki67 proliferation index was 2-3%. Up to 5 mitoses were counted under x10 magnification with pHH3 (phosphohistone H3).

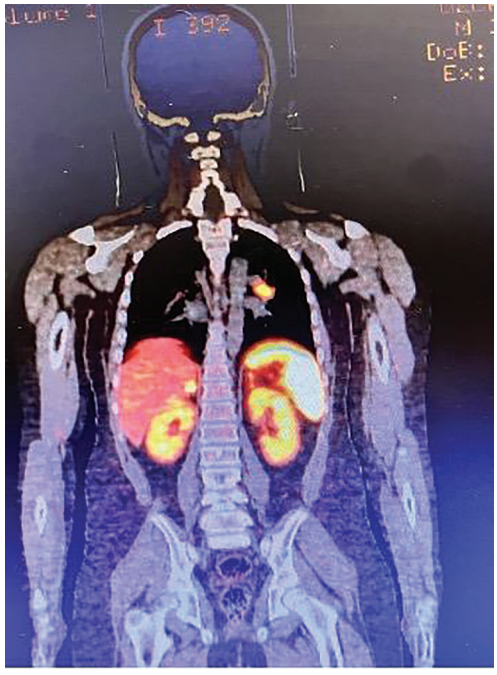

Figure 2. Positron emission tomography/computed tomography images: lesion in the left lung

The postoperative first-day ACTH level of the patient decreased to 14.6 pg/mL. The patient was initiated on hydrocortisone replacement (10 mg/m^2/day) and monitored every month with morning serum cortisol and ACTH and hydrocortisone was tapered over three months. However, due to incomplete resection of the lesion, radiotherapy and six cycles of chemotherapy (carboplatin and etoposide) treatment were given. In the first year of follow-up, his midnight and evening serum cortisol concentrations were 1.4 μg/dL and 0.55 μg/dL, respectively. A LDDST showed suppressed serum cortisol (0.5 μg/dL). Twenty-four-hour UFC was 41 nmol/24-hours. The pathological activity involvement was reduced in the monitoring ^{68}Ga-DOTATATE PET/CT. He had no new metastasis. At his last follow-up (fifteen months postoperatively), he was 15.2 years old, his weight was 47 kg (-1.8 SDS), his height was 171 cm (-0.01 SDS), and his BMI was 16 kg/m^2 (-2 SDS). He had pubic hair stage 4 with a stretched penile length of 8.5 cm and bilateral testicular volume of 15 mL each. Laboratory examination showed no endocrine abnormalities (growth hormone deficiency, thyroid dysfunction, gonadal suppression, or hyperglycemia). The physical examination findings related to CS, especially gynecomastia, had regressed (Figure 3). Pediatric endocrinology, pediatric oncology, radiation oncology, thoracic surgery, nuclear medicine, and radiology departments continue multidisciplinary follow-up. The endocrinology department performs anthropometric and hormonal (glucose metabolism, ACTH, cortisol,

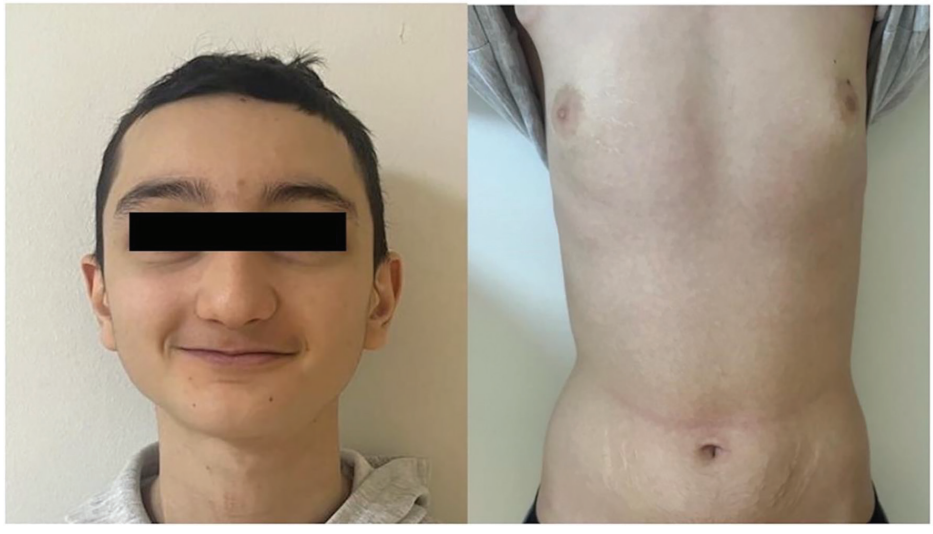

Figure 3. Postoperative regression in gynecomastia, striae, and cushingoid face appearance

lipid metabolism, bone metabolism, puberty evaluation, and other endocrinpathies that may accompany EAS) evaluations every three months. Oncology and radiation oncology departments use laboratory and imaging methods for monitoring remission or metastasis after chemotherapy and radiotherapy treatments. Nuclear medicine and radiology departments interpret tomography and PET/CT images and jointly decide on the frequency of the tests to be performed.

Literature Search

At the time of writing eighteen pediatric and adolescent patients with EAS because of bronchial carcinoid tumors have been reported in 13 case reports and literature reviews (4,6,7,8,9,10,11,12,13,14,15,16,17). The mean age of the reported patients was 14.1 ± 2.7 years. There were 11 females (61%) and 6 males (39%). In one case sex was not disclosed. Two cases were defined as AC. Lymph node metastasis was reported in seven (38.9%) patients. All of the patients had thoracic surgery, while three had bilateral adrenalectomy operations (Table 1).

There were two more major series of EAS. In the first one, the ages ranged between 8-72 years, and there were 35 patients with bronchial carcinoid tumors. Three deaths and four relapses were reported (18). In the second series, the ages ranged between 12-74 years. There were 81 patients with bronchial carcinoid tumors, and 26 deaths were reported (19). However, the number and outcome of the treatment follow-up of the pediatric cases in these case series were not reported separately from the adult data.

Discussion

CS is very rare in children. The more silent and progressive course of the syndrome in children and the difficulty of the testing often result in a long delay in CS diagnosis. Clinical suspicion based on anamnesis and physical examination is the initial stage in the diagnostic process. Screening and diagnostic procedures for CS evaluate the level of cortisol secretion. These procedures include the late-night salivary/serum cortisol test, the overnight 1-mg LDDST, the 24-hour UFC, and the HDDST (2). The gold standard for identifying hypercortisolemia is to measure cortisol at midnight with an intravenous catheter inserted; a cortisol level exceeding 4.4 mg/dL at that time ensures a high sensitivity and specificity for CS (2). Diurnal testing, however, necessitates an overnight hospital stay and has a limited role in standard screening tests. A serum cortisol < 1.8 µg/dL at 0800 h in the morning after LDDST is considered a normal response. The 24-hour UFC threshold value is 90 mcg/24 hours by radioimmunoassay or 50 mcg/24 hours by high performance liquid chromatography/immunochemiluminescence. Anorexia, chronic and severe obesity, pregnancy, chronic activity, depression, poor diabetes control, anxiety, malnourishment, and too much water consumption are all pseudo-Cushing states that may result in false-positive elevations during 24-hour UFC measurements. All of these tests have limits, and additional tests are typically required to confirm the diagnosis because none of them has 100% diagnostic accuracy (2). In the presented case, firstly, the diagnosis of CS was confirmed by demonstrating elevated midnight cortisol, indicating a lack of diurnal rhythm, poor suppression in the LDDST, and elevated 24-h UFC. Once the CS diagnosis was confirmed, serum ACTH level should be evaluated to distinguish ACTH-dependent (Cushing disease or ectopic ACTH) and ACTH-independent CS. Children with an ACTH-dependent type of the syndrome can be identified with a sensitivity of 70% using a spot morning plasma ACTH level of at least 29 pg/mL (2). The patient had a high serum ACTH level and thus had ACTH-dependent CS.

EAS in children is much less common than in adults (4). Diagnosis may be challenging. In both children and adults, the diagnostic procedure to distinguish EAS from a pituitary adenoma is the same (2,5). Cushing disease and EAS can be distinguished using the desmopressin or corticotropin-releasing hormone stimulation test, the HDDST, and bilateral inferior petrosal sinus sampling (BIPSS). Combining the blood tests with MRI is a non-invasive strategy (2,5). Hypophyseal and cerebral MRIs were performed because pituitary adenoma in children is the main cause of ACTH production. In ACTH-dependent CS, whole-body CT should be performed after hypopituitary imaging to seek an ectopic cause (2,5). In the present case, CT of the thorax and abdomen showed a solid lesion in the left lung after normal hypopituitary MRI results. It may be challenging to pinpoint the location of the ACTH-secreting tumor, and a single positive imaging study may be a falsely positive result. An octreotide scan may be used to validate the diagnosis of EAS (2,4). According to a recent meta-analysis, both ^{68}Ga-DOTA-peptide and ^{18}F-fluorodeoxyglucose (FDG) are very sensitive for identifying pulmonary carcinoids, but ^{68}Ga-DOTA-peptide is more sensitive than ^{18}F-FDG (90.0% vs. 71.0%) (20). In our case, ^{68}Ga-DOTATATE PET/CT revealed pathological activity at the hilus and lingula of the left lung. Despite having the highest sensitivity and specificity, BIPSS was not necessary for our patient since we were able to make the correct diagnosis using precise, concordant biochemical and radiological investigations.

Biopsy confirmed a carcinoid tumor, and the pathologic examination showed it to be an AC tumor. The most frequent primary malignant lung tumor in children is

Table 1. Review of literature on bronchial carcinoid tumors causing ectopic adrenocorticotropin hormone syndrome

Reference	Year	Age	Sex	Type	LN metastasis	Treatment	RT	Outcome	Recurrence
Ward et al. (7)	1983	15	F	BC		Metyrapone + surgery		6th month control normal	
Magiokou et al. (8)	1994	11	F	BC		Bilateral adrenalectomy + surgical resection			
Weber et al. (9)	1995	17	F	BC	+	Metyrapone + surgery	+	Well after 5 years follow-up	
Ilias et al. (18)	2005	8-72 years	35 patients BC		+ in 18 patients	Preoperative treatment? + surgery + CT in 6 patients	6 patients	Death in 3 patients	In 4 patients
More et al. (10)	1988	18	M	Atypical BC	-	Ketoconazole + mitotane + bilateral adrenalectomy + surgery		Well after 16 years follow-up	-
	1995	15	M	Typical BC	+	Surgery		Well after 4 years follow-up	
	1995	17	F	Typical BC	+	Ketoconazole + mitotane + surgery		Well after 16 years follow-up	4 times
	2005	16	M	Typical BC	+	Ketoconazole + surgery		Well after 3 years follow-up	-
Dias et al. (11)	2006	NR	NR	BC					
Bhansali et al. (12)	2009	NR	M	BC		Surgery + recurrence: bilateral adrenalectomy + CT	+	Alive	1 times
		10	M	BC		Surgery - ARDS		Death	
Kakade et al. (13)	2013	9	F	BC					
		14	F	BC	-	Surgery		Alive	
Goldberg et al. (14)	2014	15	F	Atypical BC	+	Surgery		Well after 1 year follow-up	-
Karageorgiadis et al. (15)	2015	13,5	F	BC	+	Surgery (2 times)			1 times
Banerjee et al. (16)	2015	14	F	BC	+	RT + CT + temezolomide + mifepristone		Death	
Potter et al. (5)	2019	13	F	BC		Surgery			
Saxena et al. (4)	2019	12	F	Typical BC	-	Surgery		Well after 1 year follow-up	
Golounina et al. (19)	2021	12-74 years	81 patients BC			Surgery		Death in 26 patients	
Attri et al. (17)	2023	17	M	BC		Surgery		Structural remission	

LN: lymph node, RT: radiotherapy, F: female, M: male, BC: bronchial carcinoid, CT: chemotherapy, NR: not reported, ARDS: acute respiratory distress syndrome

bronchial carcinoid, and 4% of these tumors are associated with CS. Histopathological analysis supports the diagnosis. Depending on the presence or absence of necrosis and an increased mitotic index (>2 mitoses/HPF), they are categorized as atypical (19%) and typical (90%) (4,6). Biomarkers such as synaptophysin and chromogranin A may be positive in either kind. All bronchial carcinoids are best treated surgically, and when feasible, lung-sparing resections (such as wedge, segment, or sleeve resections) are advised for children and adolescents (6,21). Lymph node resection is recommended in both types, but is important especially in AC because of their malignant potential (4). Somatostatin-based treatment, cytotoxic chemotherapy, and/or radiation should all be considered in cases with unresectable tumors (4,22). In the present case, complete resection was not possible, but lymph node resection was done, as recommended in the literature. Inhibitors of steroidogenesis, such as metyrapone and ketoconazole, as well as anti-glucocorticoid medications (mifepristone), can be used to treat hypercortisolemia when contraindication of surgery is present or when the patient has not recovered from surgical resection after surgery (4,23). The tumor's size, lymph node status, and histology all affect the prognosis. AC tumors have a worse 5-year survival rate of 60-75% in pediatric series, while this is 88-92% for TC tumors (4,6,21). In a study by Degnan et al. (22), aggressive characteristics of ACs were shown in the pediatric cohort, and two of the five bronchial carcinoids were shown to have a higher prevalence of metastatic illness. Bronchial carcinoid tumor recurrence was reported in 10% of cases in an investigation of the National Cancer Database (n=3335) (3% in TC and 25% in AC) (24). Lou et al. (25) reported that post-resection recurrence rates were 5% for TC and 20% for AC.

The hypothalamic-pituitary-adrenal axis may be inhibited for up to a year following surgery for Cushing disease. After removal of tumors causing CS, including EAS, glucocorticoid replacement treatment is thus for up to a year, and occasionally even longer (23,26). The duration of tertiary adrenal insufficiency may vary depending on the origin of the condition: it was shortest in cases of ectopic CS, intermediate in cases of Cushing disease, and longest in cases of adrenal CS brought on by cortisol-producing adenoma (27). In the present case, we were able to taper and later cut the hydrocortisone treatment within 3 months.

Patients being treated for AC or TC with positive lymph node involvement should have CT surveillance (24). The sensitivity of ^{68}Ga-DOTATATE for ectopic CS location in diagnosis is high for both occult primary tumors and metastatic lesions (28). However, there is an ongoing debate over the use of PET/CT for assessing tumor response to therapy. This is because lower uptake on PET/CT may suggest a decrease in tumor volume, but this is only true for well-differentiated NETs that are positive for the somatostatin receptor (SSR). Poorly differentiated SSR-poor tumors are challenging to visualize on ^{68}Ga-DOTATATE PET/CT, but are typically well seen on FDG PET/CT due to their strong glycolytic metabolism (29).

Although a change in tumor size is a good indicator of true response, no decrease in size does not necessarily indicate that there has been no response to treatment. Some lesions may enlarge as a result of cystic or liquefied necrosis that develops following successful therapy. If imaging is carried out a few weeks or months following therapy, such structural alterations are more frequent and may deceive the decision-maker. Radiologists should also be aware that increased cellular expression of SSR in a variety of physiological and other pathologic processes, such as the activity of the pancreatic unsinate process, epiphyseal growth plates, reactive nodes, degenerative bone disease, and changes following radiation therapy, can cause interpretation errors (29,30). Combined with anatomical imaging (CT or MRI), it is the gold standard functional imaging modality for evaluating well-differentiated NETs (28,29).

Conclusion

EAS caused by bronchial carcinoids is very rare in children and adolescents. Careful diagnostic evaluation is important and treatment should be started immediately. Although complete remission is possible in bronchial carcinoids, ACs tend to have a more aggressive nature. A multidisciplinary approach and follow-up will improve quality of life and survival.

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sema Nilay Abseyi, Zeynep Şıklar, Elif Özsu, Zehra Aycan, Nurdan Taçyıldız, Ayten Kayı Cangır, Merih Berberoğlu, Concept: Sema Nilay Abseyi, Zeynep Şıklar, Merih Berberoğlu, Design: Sema Nilay Abseyi, Zeynep Şıklar, Merih Berberoğlu, Data Collection or Processing: Sema Nilay Abseyi, Analysis or Interpretation: Sema Nilay Abseyi, Literature Search: Sema

Nilay Abseyi, Writing: Sema Nilay Abseyi, Zeynep Şıklar, Merih Berberoğlu.

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CASE REPORT

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Early-onset Chronic Keratitis as the First Presenting Component of Autoimmune Polyendocrine Syndrome Type 1: A Case Report and Review of the Literature

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What is already known on this topic?

Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autosomal recessive disease. APS-1 is characterized by the clinical triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and primary adrenocortical insufficiency. It has been reported that the complete triad is present in only 50% of patients by the age of 20 years. When a rare or atypical component is the presenting feature of APS-1 and the diagnosis is made based on the classic triad, the diagnosis is usually delayed.

What this study adds?

This case presented with CMC and recurrent idiopathic keratitis. Pediatric ophthalmologists should consider APS-1 in the differential diagnosis of early-onset recurrent keratitis in children if it is associated with one or more of the major triad of APS-1.

Abstract

Autoimmune polyendocrine syndrome type 1 (APS-1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, is a rare monogenic autosomal recessive autoimmune disease. It is caused by mutations in the autoimmune regulator *(AIRE)* gene. APS-1 is diagnosed clinically by the presence of two of the three major components: chronic mucocutaneous candidiasis, hypoparathyroidism (HPT), and primary adrenocortical insufficiency. A 3.3-year-old girl presented with a carpopedal spasm to the pediatric emergency clinic. She had a history of recurrent keratitis, and chronic candidiasis, manifesting as urinary tract infections and oral thrush. HPT was diagnosed based on low serum concentrations of calcium and parathyroid hormone and elevated serum concentrations of phosphate, and treatment with calcium and calcitriol supplementation was started. Genetic testing identified a homozygous nonsense mutation, c.769C > T (p.R257X), in exon 6 of *AIRE* which has been reported previously. At the age of 5.6 years, she presented with adrenal crisis, and treatment with hydrocortisone and fludrocortisone was started. This case demonstrates that unexplained chronic keratitis in children may be the first and most severe component of this syndrome. The classic triad of APS-1 may also appear in the first decade of life.

Keywords: *AIRE* mutation, APS1, keratopathy, children, hypoparathyroidism

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Introduction

Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autosomal recessive disease caused by mutations in the human autoimmune regulator (*AIRE*) gene located on chromosome 21q22.3 (1,2). *AIRE* encodes a protein, AIRE, which acts as a regulator of the process of gene transcription and is essential for self-tolerance. AIRE deficiency leads to the escape and extra-thymic dissemination of autoreactive T-cell clones leading to the onset of autoimmune reactions against several tissue-specific self-antigens (1,2). Autoantibodies against type 1 interferons (IFN) (IFN-α and IFN-ω) are specific findings for APS-1 (3).

APS-1 is characterized by the clinical triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism (HPT), and primary adrenocortical insufficiency (PAI). Other endocrine and non-endocrine components, such as type 1 diabetes mellitus, Hashimoto thyroiditis, various ectodermal abnormalities (keratopathy, alopecia, vitiligo, chronic dermatitis, and dental enamel hypoplasia), pernicious anemia, chronic diarrhea, autoimmune hepatitis, cutaneous vasculitis, and primary gonadal failure may occur with different prevalences (4). Clinically, APS-1 is diagnosed by the presence of two major components of the triad or only one if a sibling has already been diagnosed with APS-1 (4). CMC is the most common first clinical manifestation in APS-1 (5). The age at diagnosis of CMC is usually < 5 years old (1.0-6.5 years) (6). HPT and adrenal insufficiency arise sequencially following CMC. However, when a rare or atypical component is the presenting feature of the syndrome, the diagnosis of APS-1 is often delayed.

The prevalence of APS-1 varies considerably from population to population. The highest prevalence is found among Persian Jews (1:9000) (7), Sardinians (1:14 000) (8), Finns (1:25 000) (9), and Norwegians (1:90 000) (10).

Here, we present a case of APS-1 in a Turkish girl who presented with CMC and recurrent keratitis in the first year of life, while the other major components presented within the first decade of life.

Case Report

A 3.3-years-old girl of consanguineous Turkish parents (first-degree cousins) was referred by a local outpatient clinic with carpopedal spasms and tetany. She had a history of chronic keratitis, recurrent oral thrush, onychomycoses, and recurrent vulvovaginal candidiasis since 14-months of age. Hospital records from ophthalmology revealed that there was a circular corneal epithelial erosion in the inferior temporal cornea in the left eye (Figure 1A). She was commenced on moxifloxacin and lubricating eye drops, and ciprofloxacin ointment. The ulcerated area became epithelialized in 15 days, and a very slight corneal haze remained (Figure 1B). The patient was admitted four or more times in a year with the same complaints. At each admission, a similar lesion was observed in the same focus on the cornea. Two years after the first admission, she presented with severe blepharospasm and photophobia. Ophthalmological examination revealed spontaneous corneal perforation at the old ulcerated region. The Seidel test was positive and the iris prolapsed into the perforated corneal region. A corneal haze due to recurrent keratitis was detected in the upper periphery of the cornea in the left eye (Figure 1C). Iris adhesion was improved by a contact lens placement, and the pupil returned to its normal shape. Chronic keratitis was treated by combinations of local antibiotics and corticosteroids.

Her family history revealed that she had healthy parents and a little brother (Figure 2), and no family history of chronic illness, including autoimmune diseases. On physical examination, she was 99 cm tall (75th percentile) with a weight of 15 kg (50-75th percentile), and a body mass index of 14.5 kg/m^2 (25th percentile). Chvostek and Trousseau's signs were positive. Initial biochemical tests revealed that serum concentration of total calcium was 6.7 mg/dL [reference range (RR) 8.6-10.2]; phosphate, 7.0 mg/dL (RR 3.3-5.6); alkaline phosphatase, 45 U/L (RR 82-325); intact parathyroid hormone, 5.0 pg/mL (RR 10-65); and 25-hydroxyvitamin D, 69 ng/mL (RR 32-85). Based on the clinical and laboratory findings, she was diagnosed with HPT and commenced on oral elementary calcium (50 mg/kg three times daily) and calcitriol (oral, 0.25 mg twice daily). Her plasma calcium level increased to 8.1 mg/dL on the third day of treatment. Based on the presence of the diagnostic dyad of CMC and HPT and the coexistence of chronic keratitis, our presumptive diagnosis was APS-1.

During the Coronavirus disease-2019 pandemic, she was lost to follow-up for 2.5 years. The patient was admitted to our pediatric emergency clinic again at the age of 6.5 years with a high temperature, nausea, vomiting, and drowsiness. On physical examination, her skin was pale, mucous membranes dry, eyes sunken, skin turgor poor, and axillary temperature 38.7 °C. Vital signs and laboratory findings are shown in Table 1. Laboratory test results revealed hyponatremia (125 mEq/L), hypochloremia (84 mEq/L), hyperkalemia (7.2 mEq/L), metabolic acidosis (pH, 6.9 and HCO_3, 12 mEq/L), and hypoglycemia (38 mg/dL), low serum cortisol value (1.2 mg/dL) and elevated serum adrenocorticotropic hormone value (653 pg/mL). Based on the clinical and laboratory findings, she was diagnosed with adrenal crisis. Unfortunately, renin activity

was not measured during the adrenal crisis. Tests on organ-specific autoantigens associated with APS-1 were performed. Serum 21-hydroxylase antibody level was 3.9 U/mL (reference < 1.0). Antithyroid (antithyroid peroxidase and antithyroglobulin), anti-islet cell, anti-insulin, anti-glutamic acid decarboxylase 65, antimitochondrial and anti-tissue transglutaminase antibodies were all negative. She was hospitalized for twelve days for an adrenal crisis. Intravenous fluid and hydrocortisone replacement therapies were started. Three days later, she was followed up with maintenance doses of oral hydrocortisone (15 mg/m^2 three times daily), with dose adjustments according to concurrent illnesses and stresses, and mineralocorticoid (100 mg once daily). The patient gained weight and remained asymptomatic under replacement therapy with oral elemental calcium, calcitriol, hydrocortisone, and fludrocortisone. Since APS-1 patients may develop asplenia insidiously, the patient was vaccinated against encapsulated bacteria (*pneumococcus, meningococcus*, *Haemophilus influenza* type b), and annual influenza vaccination was recommended. One year later, there was widespread vitiligo on her face (Figure 3A) and patch-like hair loss on her occipital scalp (Figure 3B). Six months later, at the age of seven years, the patchy hair loss had been replaced by depigmented hair (Figure 3C).

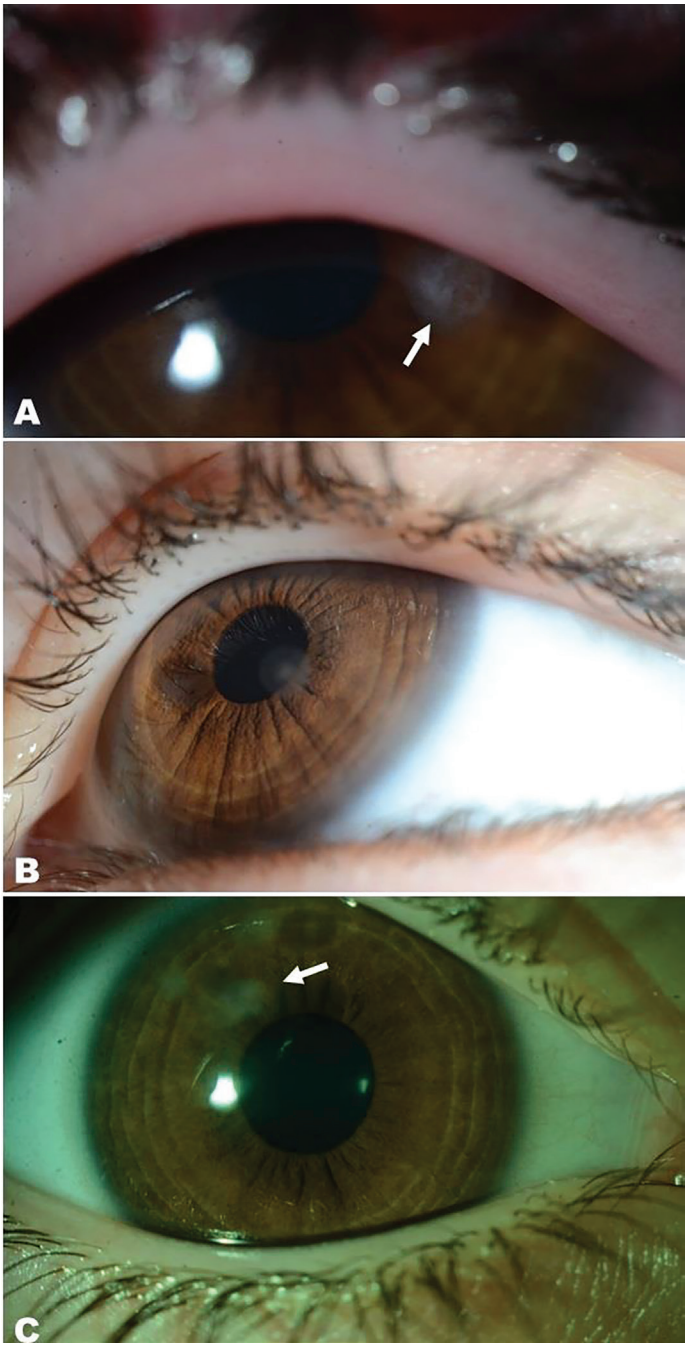

Figure 1. (A) Corneal ulcer and infiltrate (arrow) in the left eye; B) Healing of the keratitis after treatment; C) Haze in the peripheral cornea of the left eye (arrow) due to previous keratitis attacks

The concomitant diagnosis of HPT and PAI with a history of oral and urinary candidiasis fulfilled the clinical diagnostic criteria for APS-1. Mutation analysis by next-generation sequencing of the *AIRE* gene identified a documented homozygous missense mutation: c.769C > T (p.R257X)

Table 1. Vital signs and laboratory findings at admission

Clinical and laboratory findings (reference range)	
Vital signs	
Systolic BP, mmHg	85
Diastolic BP, mmHg	55
Heart rate, beats/min	112
Respiratory, rate/min	35
Laboratory findings	
Sodium, mEq/L (135-145)	125
Potassium, mEq/L (3.5-4.5)	7.2
Chloride, mEq/L (96-106)	84
HCO_3, mEq/L (22-26)	12
pH, (7.35-7.45)	6.9
Calcium, mEq/L (8.6-10.2)	7.1
Phosphorus, mEq/L (3.5-5.6)	6.9
Glucose, mg/dL (65-99)	38
Blood urea, mg/dL (5-18)	> 100
Creatinine, mg/dL (0.5-1.2)	1.1
Hemoglobin, g/dL (13-16)	10.2
WBC, K/mL (4.8-13.1)	18.4
Neutrophil, % (33-77)	84
Lymphocyte, % (11-59)	10
Platelets, K/mL (189-394)	218
CRP, mg/L (0.0-5.0)	266
Procalcitonin, ng/mL (0.0-0.046)	2.25
Fibrinogen, mg/dL (170-420)	532
Cortisol, mg/dL (during hypoglycaemia; ≥20.0)	1.2
ACTH, pg/mL (8.5-65.5)	653
PTH, pg/mL (15-65)	4.7
25-OH vitamin D, ng/mL (32-85)	19.8
FT4, ng/dL (0.96-1.77)	1.39
TSH, mIU/mL (0.7-5.97)	1.86
Urinary sodium, mEq/L (*)	111

*During hyponatremia high or low urine sodium concentrations (typically with 20 mEq/L as cutoff) can be used for differential diagnosis.
BP: blood pressure, WBC: white blood cell count, CRP: C-reactive protein, ACTH: adrenocorticotropic hormone, PTH: parathyroid hormone, FT4: free thyroxine, TSH: thyroid-stimulating hormone, TPO-Ab: thyroid peroxidase antibody

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in exon 6. In addition, her parents and brother were identified as heterozygous carriers of the same mutations (Figure 2), which is consistent with the autosomal recessive pattern.

Discussion

APS-1 is a rare autosomal recessive autoimmune disease that is caused by variants in the *AIRE* gene. The classic clinical triad of APS-1 is CMC, HPT, and PAI. It has been reported that the complete triad was present in only half of patients with APS-1 by the age of 20 years (2,11). CMC, except in Persian Jews, is the most common and the first presenting component, typically developing in infancy or early childhood (11). However, in a study of 23 Persian Jews (12), only four patients presented with CMC. The median age of onset for CMC was 3 years (range 0.08-33 years). In the present case, CMC appeared at 14 months old as recurrent moniliasis and urinary tract candidial infections. HPT usually appears next after CMC, with the peak incidence between the age of 2-11 years (6,11), and it is the most common endocrine component in APS-1 patients. PAI appears most commonly following CMC and HPT in the second or third decades (11,13). PAI is generally the second most common endocrinopathy in patients with APS-1 with the peak incidence around 12 years of age. The diagnosis of PAI is usually made when the patient presents with the symptoms and signs of adrenal crisis. Thus, if the diagnosis of APS-1 is made based on the complete classical triad, the diagnosis is usually delayed. Even if a component of the classical triad is accompanied by one of the other minor components, such as alopecia, vitiligo, nail dystrophy, dental enamel dysplasia, or keratopathy, investigating APS-1 may be a reasonable approach. Once the diagnosis is confirmed, life-long follow-up through a multidisciplinary team should be planned without delay. Close monitoring of calcium, calcitriol, and glucocorticoid, and mineralocorticoid maintenance doses are important to avoid life-threatening events, including hypocalcemia and/or adrenal crisis. In the present case, following CMC and keratitis, HPT was diagnosed at the age of 3.2 years. The coexistence of CMC and HPT suggested the diagnosis of APS-1.

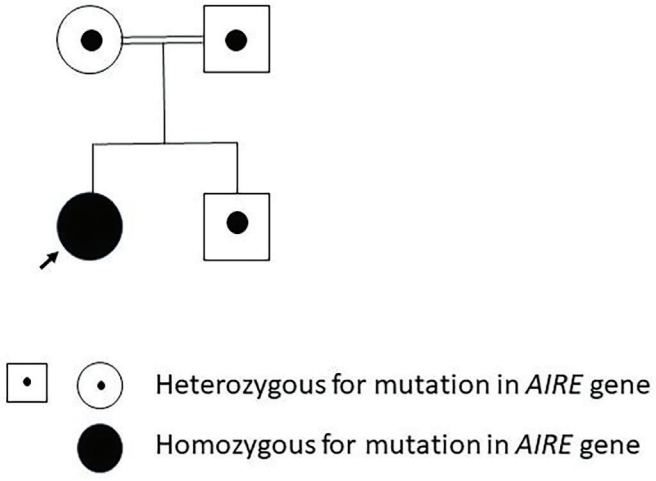

Figure 2. Family pedigree

The reported ocular manifestations of APS-1 include chronic persistent keratoconjunctivitis, dry eye, iridocyclitis, cataract, retinal detachment, and optic atrophy (14). Keratitis is the first manifestation in only 3-14% of APS-1 cases and the frequency varies between 25% and 50% (11,14). Chronic keratitis was reported as the first presenting sign before any evidence of systemic disease in three of 69 Finnish patients with APS-1, and 25% of cases with keratitis were bilateral (15). APS-1-associated keratopathy has been suggested to be an essential feature of APS-1 rather than

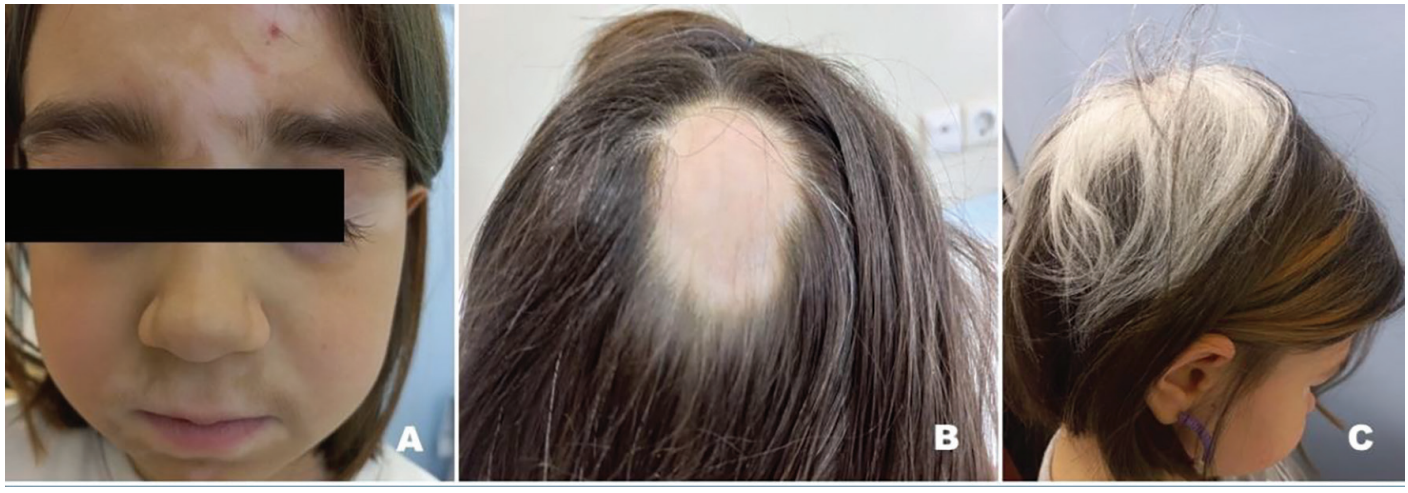

Figure 3. (A) Widespread vitiligo on her face; B) Patch-like hair loss on occipital area; and C) Hair regrew in the hair loss area but was depigmented

a secondary manifestation. Chronic keratitis is usually accompanied by severe photophobia, blepharospasm, conjunctival redness, and decreased visual acuity. Keratitis in APS-1 patients is characterized by recurrent attacks and may lead to irreversible scarring, deep vascularization, and blindness (15). In the present case, keratitis was the second manifestation of the syndrome, following CMC. Alopecia, vitiligo, and nail dystrophy were also later accompanying manifestations. Topical steroids and antibiotics were used for the treatment of keratitis. The presentation of this case suggests that pediatric ophthalmologists should consider APS-1 in the differential diagnosis of early-onset and recurrent keratitis in children.

Anti-IFN-α and anti-IFN-ω autoantibodies have high specificity for APS-1 (3,10). Testing for anti-IFN antibodies when there is clinical suspicion may be helpful for rapid and more convincing diagnosis of APS-1. In the present case, we could not assay anti-IFN antibodies, because this test was not available in our hospital at the time. The diagnosis was confirmed by sequencing of the *AIRE* gene mutation to differentiate APS-1 from APS-1-like conditions, including APS-2 and X-linked immunoregulation, polyendocrinopathy, and enteropathy syndromes. APS-1 is a monogenic, autosomal recessive disease caused by a mutation in the *AIRE* gene. In the present case there was a homozygous nonsense c.769C > T (p.R257X) mutation in the *AIRE* gene. To date, more than 140 different mutations in the *AIRE* gene have been reported worldwide (16). The c769C > T (p.Arg257stop) nonsense mutation is the most common variant with documented in at least 125 cases previously (1,2,17,18,19). It is a frequent mutation in Finnish (1,2,18), Norwegian (5), Italian (19), Turkish (20), and Serbian patients (17). R257X in exon 6 changes an arginine codon to a stop codon at amino acid position 257, which encodes a truncated, non-functional protein of 256 amino acids. The second most frequent mutation is c.967_979del13 (p.C322del13) which is prevalent in Norwegian, British, French, North American, and Indian patients (5,21,22). The other frequent mutation c.415C > T (p.139X) is prevalent in Sardinian patients (4). In contrast, p.V80G and p.X46L + 59aa mutations were reported only from Indian patients (22). Other variants have been reported as isolated cases. Heterozygous dominant-negative *AIRE* mutations in the plant homeodomain 1 domain have also been described in Persian Jews (23). These dominant-negative mutations are associated with milder diseases.

APS-1 is characterized by high phenotypic heterogeneity, with wide variability in the number of clinical manifestations and there is often a delay in the diagnosis. PAI usually presents as a life-threatening adrenal crisis. Therefore, early diagnosis of APS-1 is important, even in the absence of the main triad. APS-1 should be considered in children who have one of the major components of the classical triad with coexistence of one of the minor manifestations. The presented case had HPT by the time she attended pediatric endocrinology, and she had a history of CMC and chronic keratitis. This case highlight that early diagnosis of APS-1, close monitoring of affected children by pediatric endocrinologists, and periodic evaluation of biochemical and hormonal parameters are essential to prevent severe and life-threatening events. Patients and their parents should be educated in regard of symptoms and sick day management for adrenal insufficiency and HPT.

Conclusion

The diagnosis of APS-1 is usually delayed due to wide variations in clinical presentations. The presented case highlighted that early diagnosis of APS-1 is important to avoid severe and life-threatening events associated with this syndrome and also shows that recurrent keratitis in children may be an early and severe manifestation of APS-1. The diagnosis of APS-1 should be considered in all patients presenting with one of the major clinical manifestations coexistent with other minor manifestations of the disease. The diagnosis can be confirmed by sequencing the *AIRE* gene where available.

Ethics

Informed Consent: Written informed consent for publication of clinical details and images were obtained from parents.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Enver Şimşek, Tülay Şimşek, Oğuz Çilingir, Concept: Enver Şimşek, Tülay Şimşek, Design: Enver Şimşek, Tülay Şimşek, Data Collection or Processing: Enver Şimşek, Tülay Şimşek, Oğuz Çilingir, Analysis or Interpretation: Enver Şimşek, Tülay Şimşek, Oğuz Çilingir, Literature Search: Enver Şimşek, Writing: Enver Şimşek, Tülay Şimşek.

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BRIEF REPORT

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Making Teachers and School Health Nurses Part of Pediatric Diabetes Teams

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What is already known on this topic?

Children with type 1 diabetes require comprehensive care and support to manage their condition effectively in educational settings. Integrating teachers, school nurses, and staff into diabetes care teams has been shown to improve diabetes management and quality of life for these children, although challenges in providing optimal care and preventing discrimination persist.

What this study adds?

This study highlights the significant progress made by the Diabetes at School Program in Türkiye, demonstrating effective strategies for integrating diabetes care into school environments. It underscores the importance of government support, comprehensive training, and designated caregivers in ensuring consistent and equitable care for children with type 1 diabetes in a school environment.

Abstract

Children with diabetes need consistent care across all environments, including school, where they spend significant time. Türkiye's Diabetes at School Program, initiated in 2010, has made substantial progress in integrating diabetes care into the school system. The program's achievements include government support, annual awareness activities, communication between diabetes teams and schools, policy implementation, and training for school staff. A recent meeting of Provincial Health Service Officers highlighted ongoing efforts and future directions for the program, emphasizing the importance of continuous support for children with diabetes in educational settings. Key outcomes of this meeting included designated caregivers for children with diabetes at school, optional administration of insulin by trained staff, mandatory diabetes education for teachers, and health-conscious policies for school activities. The program's success is attributed to the collaborative efforts of teachers, healthcare professionals, and government officials. Ensuring robust support for children with diabetes in schools is vital for their well-being and academic success.

Keywords: Children, diabetes, school

Introduction

For children with diabetes to live healthy, happy, and high-quality lives, they need comprehensive education about their condition. This education should cover the language and math of diabetes, understanding the need for insulin due to non-functioning pancreatic beta cells, and the use of technology, such as sensors and insulin pumps if necessary. It should also include guidance on consuming carbohydrates with a low glycemic index in moderation and maintaining a regular daily routine. This need for comprehensive diabetes management persists at all times and in all settings where children live. Since children spend more than 30 hours a week at school, the diabetes care and glycemic targets

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during school hours should be consistent with those in other settings. Therefore, improving diabetes care at school and considering diabetes management on a 24-hour basis is crucial (1).

The World Health Organization and the ÇÖZGER directive in Türkiye recognize diabetes as a "special needs condition". Therefore, schools must plan to address the needs of children with diabetes, including supervision, assistance with low blood glucose, administration or monitoring of insulin via injection or insulin pump, nutritional support, participation and encouragement in physical activities and school trips, and prevention of discrimination, stigmatization, and bullying. Supporting children with diabetes in schools remains a challenge in many countries. On April 24, 2023, a U.S. federal court approved the settlement of a class action lawsuit brought by three parents of students attending public schools in New York city (NY, USA). The plaintiffs alleged that New York city, the Department of Education, the Department of Health and Mental Hygiene, and the Office of School Health violated the Americans with Disabilities Act by failing to ensure that students with diabetes could attend school safely and enjoy the same educational opportunities as their classmates (2).

The essence of this case and of living with diabetes in school is that students with type 1 diabetes should participate in school life on an equal basis with their peers and that parents cannot be expected to make up for a lack of school resources and be involved in their child's medical care all day long.

Outcomes of the Diabetes at School Program

The Diabetes at School Program, launched in Türkiye in 2010, aimed to support children with type 1 diabetes in the school environment and integrate teachers and school nurses into diabetes teams. Despite significant progress, with 38 activities conducted over 14 years, many challenges remain (3). The program's key achievements include (4):

Government Support: The Ministries of National Education and Health have taken ownership of the program, assigning relevant personnel centrally.

Awareness Initiatives: November 14, World Diabetes Day, is recognized in schools, with awareness activities organized annually.

Communication with Schools: Pediatric diabetes teams send "Letters to Teachers" and "Diabetes Management Plans" to schools.

Provincial Health Service Assignments: Provincial health service officers from the Ministry of National Education are designated to focus on this issue.

Policy Implementation: The "Directive on the Care and Support of Students with Type 1 Diabetes at School" was published on October 14, 2020.

Educational Platform: The Diabetes in School Program Education Platform was launched (https://okuldadiyabet.meb.gov.tr).

School Training: Community health nurses from the Ministry of Health provide training in schools.

School Healthcare Staff Recruitment: The number of school health nurses has increased, and dietitians are being appointed in various provinces.

New Phase in the Diabetes at School Program: Ministry of National Education Provincial Health Service Officers Meeting

A meeting of the Provincial Health Service Officers of the Ministry of National Education for the Diabetes in School Program was successfully held on May 17-18, 2024. This meeting aimed to evaluate the conditions and challenges faced by approximately 26,000 children with type 1 diabetes, most of whom are in primary school, in the school environment.

Currently, school health initiatives within the Ministry of National Education are managed by the Health Services Branch under the General Directorate of Support Services, Department of Workplace Health and Safety. Health Service Officers operate in the provinces and districts of large cities under this branch. The Diabetes at School Program is a key initiative managed by this branch, highlighting the commitment to addressing the needs of students with diabetes in the educational setting.

On the first day of the meeting, awards were presented to 15 individuals selected from among teachers, school administrators, school health nurses, and other school staff who could be "Diabetes in School Program Ambassadors." These individuals were recognized for their exemplary efforts in identifying children with diabetes symptoms in their classrooms, ensuring early diagnosis, and supporting the care of children with diabetes. During the award ceremony, each awardee and the provincial health service officer from the Ministry of National Education of their province were invited to the stage together. The awardees were thanked with the words, *"Thank you very much for your support to children with diabetes by taking responsibility and making an exemplary effort in line with the objectives of the Diabetes in School Program. Your students and we will always remember the value of your contribution,"* and they were presented with a plaque. Following the presentation, the awardees gave brief speeches about their work in their respective provinces. These speeches highlighted that the Diabetes in School

Program had even effectively reached the mountain villages. They demonstrated that school administrators, teachers, and school nurses, acting as "diabetes ambassadors," had made significant contributions in various areas. This included supporting children with diabetes sensors, aiding in insulin pump treatment, encouraging children with type 1 diabetes to be open about diabetes and stop them hiding their diabetes, and helping them achieve academic success.

Supporting Children with Diabetes is Our Duty!

As the program coordinators, we are very pleased to see that the provincial health service officers and ministry officials from the Ministry of National Education who attended the meeting were working tirelessly to support children with diabetes. We believe that this meeting will be a turning point in terms of supporting children with diabetes in the school environment, and we can say that all of us returned home with the awareness that "Supporting Children with Diabetes is Our Duty." We can summarize the key outcomes of the meeting as follows:

- After the family informs the school administration or the relevant teacher, a person responsible for the care of the child with type 1 diabetes at school is designated.

- Although it is not a legal obligation, this person can, with the written consent of the family, administer glucagon and insulin injections to children in need, support blood glucose monitoring, and provide additional doses of insulin in consultation with the family when necessary.

- Ensuring that all teachers receive a "Training Certificate" through the Diabetes in School Program Education Platform.

- In schools without nurses, establishing a connection with the nearest family medicine center to provide rapid intervention and support in emergencies.

- Restricting activities such as "Canteen Day" and frequent birthday celebrations in schools, and ensuring that menus are healthy.

Conclusion

In conclusion, even the smallest support we provide to improve the lives of children with type 1 diabetes can create a positive ripple effect, making every effort worthwhile. With this in mind, we would like to thank the teachers who support children with diabetes and administer insulin with the meticulousness of parents, the team members who work with these children, the directors of the association, the officials of the Ministry of National Education and the Ministry of Health, everyone who works in schools, and Sanofi, which has unconditionally supported the Diabetes at School Program for 13 years.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Şükrü Hatun, Gül Yeşiltepe Mutlu, Zehra Aycan, Concept: Şükrü Hatun, Gül Yeşiltepe Mutlu, Zehra Aycan, Design: Şükrü Hatun, Gül Yeşiltepe Mutlu, Gülcan Kılınç, Zehra Aycan, Data Collection or Processing: Şükrü Hatun, Gül Yeşiltepe Mutlu, Gülcan Kılınç, Zehra Aycan, Analysis or Interpretation: Şükrü Hatun, Gül Yeşiltepe Mutlu, Zehra Aycan, Literature Search: Şükrü Hatun, Gül Yeşiltepe Mutlu, Zehra Aycan, Writing: Şükrü Hatun, Gül Yeşiltepe Mutlu, Zehra Aycan.

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Can Dietary Acid Load in Obese Adolescents Interfere with Cardiometabolic Risk, Psychological Resilience and Sleep Quality?

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Dear Editor,

Recently, Bozbulut et al. (1) published an article entitled "The Effect of Dietary Acid Load on Cardiometabolic Risk, Psychological Resilience and Sleep Quality in Adolescents with Obesity". This study addressed the effects of dietary acid load on cardiometabolic risk factors, psychological resilience and sleep quality in adolescents with obesity. This is a highly relevant study, and the authors deserve recognition for their scientific contribution to such a current and interdisciplinary topic. The results showed that a high dietary acid load is associated with greater cardiometabolic risk, insulin resistance, lower psychological resilience and worse sleep quality. To assess dietary acid load, the researchers used a three-day food record, a widely accepted methodology for estimating food consumption. Sleep quality, in turn, was measured by the Pittsburgh Sleep Quality Questionnaire, recognized for its accuracy and validity. Although food records are generally consistent, their use among adolescents may encounter challenges, such as underreporting or inaccuracies (2). Furthermore, we emphasize that lifestyle aspects in this age group, such as increased screen time and irregular eating patterns, can impair the circadian rhythm and, consequently, sleep quality. Given the close relationship between sleep quality, mental health, and metabolic risks, we suggest the inclusion of tools to assess chronotype, classifying adolescents as morning, intermediate, or evening types (3). The evening chronotype has been linked to lower sleep quality, poor dietary behaviors, and higher risk of cardiometabolic conditions (4).

Additionally, we recommend the use of actigraphy as an objective method for evaluating sleep parameters. Research indicates that self-reported sleep duration and actigraphy-measured sleep duration can differ by an average of about one hour (5).

Finally, we recommend the use of complementary tools that allow a more specific assessment of circadian preferences and dietary patterns in adolescents. Such approaches could enrich the study findings, deepening the understanding of the interactions between dietary acid load, metabolic risks, mental health and sleep quality in adolescents with obesity. These efforts are crucial to support more effective interventions to promote the physical and psychological health of this population.

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