CASE REPORT

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A Rare Presentation of HIST1H1E Syndrome with Short Stature and Multiple Pituitary Hormone Deficiencies

İlayda Altun, Elvan Bayramoğlu, Hasan Karakaş, Gökçe Velioğlu Haşlak, Mert Uçar, Hande Turan, Olcay Evliyaoğlu

İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye

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ABSTRACT

Histone Gene Cluster 1 Member E (HIST1H1E) syndrome is a rare autosomal dominant disorder resulting from a heterozygous variation in the *H1-4* gene located on chromosome 6p22.2. Mental retardation, recognizable facial features, skeletal abnormalities and overgrowth are the main clinical manifestations of this syndrome. A 17-year-old male presented to the pediatric endocrinology clinic due to short stature. He had a characteristic facial appearance with neurodevelopmental delay. Genetic analysis revealed a heterozygous pathogenic variation in the *H1-4* gene located on chromosome 6p22.2 which confirmed his diagnosis of HIST1H1E syndrome. This presentation was distinguished by the co-occurrence of short stature and obesity accompanying central hypothyroidism and growth hormone deficiency due to a hypoplastic pituitary gland, which is in marked contrast to the somatic overgrowth characterizing this syndrome. Furthermore, the presented case is the second patient reported with HIST1H1E syndrome with hyposecretion of multiple pituitary hormones caused by hypoplasia of the pituitary gland.

Keywords: Central hypothyroidism, growth hormone deficiency, hypoplastic pituitary gland, HIST1H1E, short stature

What is already known on this topic?

Mental retardation, recognizable facial features, overgrowth and skeletal abnormalities are the main clinical manifestations of Histone Gene Cluster 1 Member E (HIST1H1E) syndrome. Hypoplastic corpus callous, ventriculomegaly, small posterior fossa, partial decent of cerebellar tonsils were detected the common finding of brain magnetic resonance imaging of the patients diagnosed HIST1H1E syndrome.

What this study adds?

In our case, distinguished by the co-occurrence of short strature accompanying central hypothyroidism and growth hormone deficiency, which differs from the somatic overgrowth characterizing this syndrome. Pituitary hypoplasia has been reported in our case.

Corresponding Author: İlayda Altun, MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye
E-mail: ilaydaauslu@gmail.com **ORCID:** orcid.org/0000-0002-2329-9223

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Introduction

Histones play a key role in dynamic packaging of nuclear DNA in chromatin, epigenetic modifications and the regulation of chromosome structure (1). Histone Gene Cluster 1 Member E (HIST1H1E), located at chromosome 6p22.2, a member of the *H1* gene family, encodes Histone H1.4, responsible for higher order chromatin structure. HIST1H1E syndrome (also known as Rahman syndrome, OMIM #617537) was first described as autosomal dominant intellectual disability syndrome and is associated with pathogenic frameshift variations in the C-terminal domain of the *H1-4* gene. It has been associated with a distinctive facial features (2) (micrognathia, deep-set eyes, down-slanting palpebral fissures, high hairline, hypertelorism, telecanthus), hypotonia, behavioral issues and mental problems (combinations of obsessive behaviors, anxiety/phobias, autistic spectrum disorder/traits, attention-deficit/hyperactivity disorder and others), cardiac and skeletal abnormality, cryptorchidism, abnormal dentition including dental erosions, thin enamel, crumbling teeth, and multiple dental caries, ectodermal abnormalities and hypothyroidism (3). Autism spectrum disorder and intellectual disability has been described as a component of the presentation in a patient with HIST1H1E syndrome (4).

HIST1H1E syndrome also serves as a mnemonic form for some of key features of the syndrome: H for hypotonia, I for intellectual disability, S for skeletal abnormalities, T for testicular and thyroid anomalies, H for heart anomalies and E for ectodermal features.

HIST1H1E syndrome was first described as an overgrowth syndrome. However, Takenouchi et al. (5) suggested that overgrowth is not a hallmark clinical feature of HIST1H1E syndrome. A few case reports (2,3,4) evaluating growth patterns in Rahman syndrome have also focused on height variability. We report a case of HIST1H1E syndrome in a patient with obesity, short stature and deficiency of multiple pituitary hormones.

Case Report

The male proband is the first child of healthy, consanguineous Turkish parents. He was born at 38 weeks, with a weight of 2,600 g [-1.78 standard deviation (SD)] and a length of 48.0 cm (-0.91 SD). Anthropometric measurements were appropriate for the gestational age. He stayed in the neonatal intensive care unit for a month due to hypotonia and respiratory distress. Cardiac problems, including secundum atrial septal defect and patent ductus arteriosus, were detected in the neonatal period. He was able to sit without support at the age of one year. He attained independent walking by the age of two years, and began to produce phrase-level speech after the age of three years. Cryptorchidism was detected and he had bilateral orchiopexy at 2 years of age. At 3 years of age, his weight was 20 kg (+2.08 SD), height 104 cm (+1.81 SD).

The patient demonstrated intellectual disability and neuromotor developmental delay. He had a history of afebrile seizure at the age of nine years. Brain magnetic resonance imaging (MRI) performed at the time showed focal hypoplastic corpus callosum. At the age of 17 years, he was referred to our tertiary pediatric endocrinology center with obesity and short stature. His body mass index (BMI) was 34.5 kg/m^2 with a weight of 87.6 kg (1.48 SD) and a height of 159.4 cm (-2.53 SD). His pubertal development was appropriate to his chronological age. He had a characteristic facial appearance with bitemporal narrowing, a high hairline, deep set eyes, hypertelorism and downslanting palpebral fissures. In addition, he exhibited problems of abnormal dentition, including dental erosions, crumbling teeth, thin enamel and multiple dental caries. His ectodermal issues included thin nails, sparse hair and hyperkerotosis. Informed consent was obtained from his parents and himself for publication of an image of the patient's face (shown in Figure 1). Skeletal anomalies included kyphoscoliosis and hallux deformity. The patient demonstrated moderate intellectual disability.

In the routine laboratory examination performed to assess the short stature of the patient, thyroid function tests were compatible with central hypothyroidism, with free thyroxine of 0.75 ng/dL [normal range (NR) 0.98-1.63], free triiodothyronine of 2.67 ng/dL (NR 2.56-5.01), thyroid-stimulating hormone of 3.2 mIU/L (NR 0.51-4.3). Furthermore, his insulin-like growth factor-1 (IGF-1) of 92 ng/mL [-2.91 SD score (SDS)] was low. Evaluation of other anterior pituitary hormones revealed: adrenocorticotropic hormone 38.3 pg/mL (NR 0-46); cortisol 14.4 µg/dL (NR 6.2-19.4); and prolactin (132 µg/L), all of which were normal. Gonadotropins, luteinizing hormone (LH) 8.96mU/mL and follicle stimulating hormone (FSH) 10.2 mU/mL were at the upper limit of the reference range but total testosterone levels (265 ng/dL) were not compatible with hyogonadism. His hypothyroidism was managed with levothyroxine 50 µg daily. Growth hormone (GH) deficiency was demonstrated in the GH stimulation tests performed after euthyroidism was achieved; peak GH in an L-Dopa stimulation test was 2.51 ng/mL and the peak GH in a clonidine stimulation test was 1.53 ng/mL. Wrist X-ray reported normal bone age consistent with the chronological age of the patient of 17 years. GH stimulation testing served a diagnostic rather than therapeutic purpose as part of adult endocrine evaluation because growth plates were closed. Therefore, the purpose and clinical utility of this functional assay was explained to the patient and his family before proceeding. A brain and sellar MRI showed pituitary hypoplasia. On the basis of these findings, the patient was diagnosed with central hypothyroidism and GH deficiency. Bone mineral density was measured at 1.11 g/cm^3 (1.9 SDS), which is within the NR (6).

Laboratory investigations for obesity were performed. These showed a high fasting glucose (105 mg/dL) with concurrent

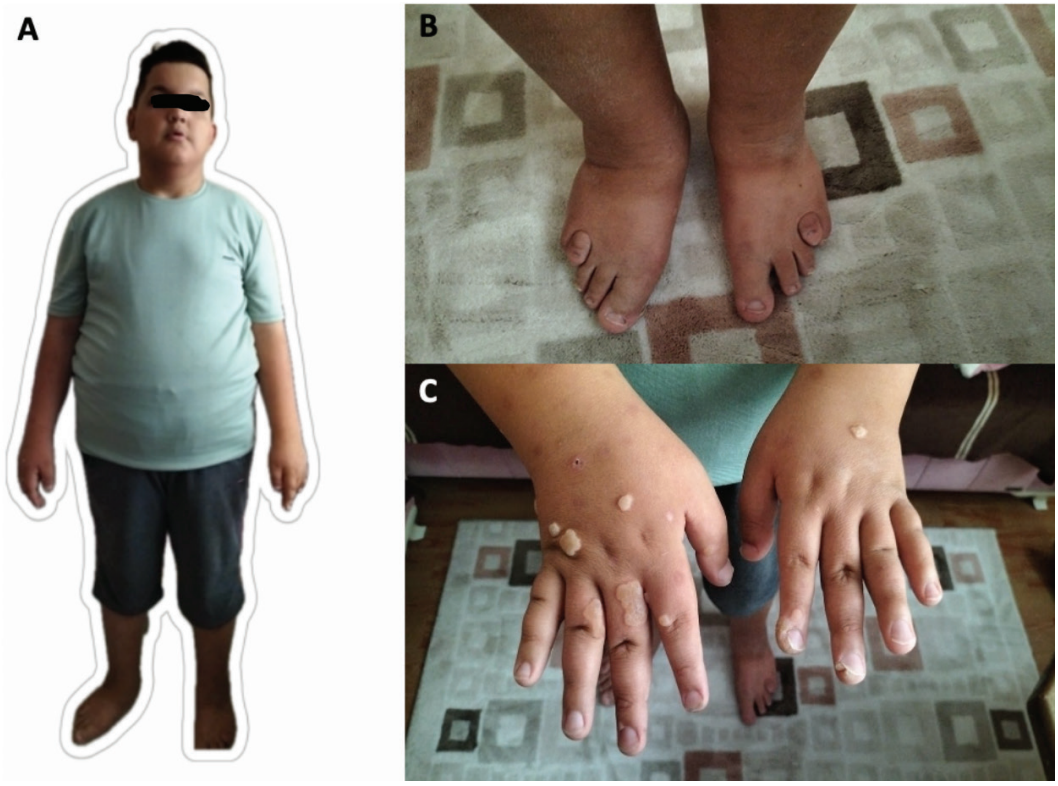

Figure 1. A) Distinctive external features including characteristic facial appearance, obesity, and short stature. **B)** Skeletal anomalies including hallux deformity. **C)** Ectodermal anomalies including hyperkeratosis

insulin of 13.4 mU/mL, C-peptide of 2.72 ng/mL, Homeostatic Model Assessment of Insulin Resistance of 3.5 and HbA1c of 28.96 mmol/mol (4.8%). Impaired glucose tolerance was demonstrated on glucose tolerance test with a 1 hour postprandial level of 168 mg/dL and a 2 hour postprandial level of >140 mg/dL. Total cholesterol was 216.8 mg/dL with triglyceride 252 mg/dL, low-density lipoprotein 147 mg/dL and high-density lipoprotein 30.4 mg/dL. Grade 2 fatty liver disease was detected by abdominal ultrasound. The patient was treated with metformin.

Conventional G-banding cytogenetic analysis demonstrated a normal karyotype of 46,XY. He subsequently underwent whole exome sequencing (WES) incorporating copy number variant analysis. WES was performed using the Roche KAPA HyperExome capture kit (Roche Sequencing Solutions, Pleasanton, CA, USA) and sequenced on the Illumina NovaSeq 6000 (Illumina, Inc., San Diego, CA, USA) platform. Library preparation was conducted according to the manufacturer's protocols. Detected variants were annotated and interpreted using multiple population and disease databases, including ClinVar, OMIM, PubMed, and *in silico* tools. For pathogenicity classification, the Illumina BaseSpace Variant Interpreter, InterVar, VarSome, Franklin by Genoox, and other relevant resources were used, in accordance with the 2015 American College of Medical Genetics and Genomics (ACMG)-Association for Molecular Pathology guidelines. A *de novo* pathogenic frameshift variant in the *H1-4* gene: c.430dupG; p.(Ala144Glyfs*52) (OMIM 142220, NM_005321.3), located on chromosome 6p22.2 was found and was classified as pathogenic based on ACMG criteria. The analysis was guided by Human Phenotype Ontology terms, including short stature (HP:0004322), panhypopituitarism (HP:0000829), obesity (HP:0001513), and intellectual disability (HP:0001249).

Discussion

Although HIST1H1E syndrome was initially reported in 2017 as typically presenting with overgrowth and intellectual disability, recent studies have suggested that overgrowth may not be a hallmark feature of the syndrome (4). In the present report, a patient with a *de novo* truncating variant of the *H1-4* gene, exhibiting intellectual disability and the characteristic facial and skeletal features of HIST1H1E syndrome was described. However, in contrast to the typical presentation, the patient displayed marked decreased height over time and eventually short stature. Further investigation into the etiology of the short stature revealed multiple pituitary hormone deficiencies. Moreover, he also presented with obesity and impaired glucose tolerance. These findings suggest the clinical heterogeneity of the syndrome may be broader than previously reported in the literature.

Zhao et al. (3) systematically reviewed genotype-phenotype relationships based on data from a relatively large 52 patient cohort with HIST1H1E, and found 23 frameshift variants. These findings demonstrated that likely gene-disrupting variants in *H1-4* contribute to phenotypic heterogeneity. Variants in *H1-4* have frequently been associated with a specific subtype of neurodevelopmental disorders. Although the phenotypes of patients are complex, some clinical presentations that are common to most patients are observed, including developmental delay (50/52), prominent forehead (40/52), high hairline (45/52), downward slanting palpebral fissures (35/52), hypertelorism (37/52), and cryptorchidism (17/25), which were all exhibited by the patient in our case report. Furthermore, Zhao et al. (3) also reported that the 430 dupG;_p.(Ala144Glyfs*52) variant was most commonly detected among the 52 patients reviewed, which was also the variant detected in the patient we present.

The reported height SD range of patients with Ala144 frameshift variants has been very variable, ranging between -1.74 SD and +3.65 SD, but has not included clinical short stature. We wish to highlight the co-occurrence of short stature in the presented case with height ≤-2 SD. To the best of our knowledge, only one other case of HIST1H1E syndrome with short stature has been described by Tanabe et al. (7) with height ≤-2 SD.

Endocrine problems have been reported in several different case reports, including hypothyroidism. To date there has been no differential diagnosis between central hypothyroidism and primary hypothyroidism. Burkardt et al. (8) reported 30 unrelated individuals with frameshift *H1-4* variants. Twelve of them had 430 dupG; p.(Ala144Glyfs*52) variant which was the same variant found in our case and 25% were reported to have hypothroidism (8).

Zhao et al. (3) reported 4 (4/52) unrelated individuals diagnosed as HIST1H1E syndrome who had hypothyroidism and two of them had 430 dupG;_p.(Ala144Glyfs*52) variant.

Burkardt et al. (8) and Zhao et al. (9) reported highly variable brain MRI findings. Hypoplastic corpus callosum, ventriculomegaly, small posterior fossa, and partial descent of cerebellar tonsils were the most common MRI findings. Pituitary hypoplasia has been reported in one case who had a *de novo* c.360_361insA, p.(Ala123Glyfs*73) variant associated with hypothyroidism (3,8).

Tanabe et al. (7) reported first case of HIST1H1E syndrome with hyposecretion of multiple pituitary hormones, including central hypothroidism, GH deficiency and hypogonadotropic hypogonadism. The presented case is only the second case of HIST1H1E syndrome with short stature and multiple pituitary hormone deficiency (central hypothyroidism and GH deficiency) reported, after that of Tanabe et al. (7).

Interestingly, the current case had normal height SDS early in life (+1.81 at 3-years old) with short stature developing later, so that by nine years of age his height was -2.53 SDS. In the literature, there are cases where the birth length was normal, but there was a loss of height later in life (3). Although the mechanism for the development of short stature has not been clarified, in our case, it is thought that short stature developed due to central hypothyroidism and GH deficiency. This hypothesis is supported by the data from Tanabe et al. (7) whose case report described a patient with HIST1H1E syndrome with GH deficiency and hypothyroidism and who had short stature (6).

Given that the FSH and LH levels in the presented case were at the upper limit of the reference range (10) according to pubertal levels, the patient should be monitored for potential development of hypergonadotropic hypogonadism, as this may reflect an early compensatory response to declining testicular function. Although hypogonadotropic hypogonadism has been reported in association with HIST1H1E syndrome previously (7), to date, there have been no documented cases of hypergonadotropic hypogonadism.

Although obesity is not the main component of the Ala144 frameshift variants, the presented case was obese, with impaired glucose tolerance associated with hypercholesterolemia. Ahmed et al. (11) reported the first case of HIST1H1E syndrome with raised BMI SD and diabetes mellitus. The weight SD range of patients with Ala144 frameshift variants reported by Zhao et al. (3) were between -0.88SD and +3.3SD. A raised BMI may increase the risk of glucose metabolism problems with hypercholesterolemia.

H1.4 is a structural part of chromatin involved in the control of DNA compaction, DNA replication, recombination, repair and gene expression regulation. We would like to highlight that dysfunction or abnormality of the *H1-4* gene may cause neurodevelopmental dysfunction, because of the important structural and regulatory roles of histones. A *H1-4* pathogenic frameshift c430. Dup; p.(Ala144glyfs*52) may cause defects in pituitary gland organogenesis. In recent years, genome-wide methylation array analysis has allowed researchers to detect and investigate epigenetic features of diseases. Ciolfi et al. (12) reported that a clinically relevant proportion of the genes containing hypomethylated regions in HIST1H1E variants are predominantly expressed in brain and encode different subunits essential for synaptic function, synaptic plasticity, and cognitive function. HIST1H1E-mediated regulation of chromatin compaction may contribute to neurogenesis defects (12). A better understanding of site-specific functions of variants is needed to clarify the connection between histone proteins and pituitary gland development.

Conclusion

HIST1H1E syndrome is a neurodevelopmental syndrome which may be recognizable through characteristic facial features. The generally described phenotypic features facilitate current knowledge regarding the spectrum of HIST1H1E variants, but skeletal overgrowth, initially believed to be a phenotypic characteristic of HIST1H1E, does not appear to be an essential feature. The syndrome may present with short stature, especially if the patients are only diagnosed at older ages, which appears to develop over time in a very few cases. Multiple pituitary hormones deficiency should be kept in mind in *H1-4* pathogenic frameshift variations. Additional investigations are required to elucidate the biological mechanisms underlying the pheotypic features of frameshift variants of HIST1H1E.

Ethics

Informed Consent: Informed consent was taken from the parents of patient for publication. Consent was obtained from the parents for publication of an image of the patient's image.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İlayda Altun, Elvan Bayramoğlu, Hasan Karakaş, Olcay Evliyaoğlu, Concept: İlayda Altun, Elvan Bayramoğlu, Olcay Evliyaoğlu, Design: İlayda Altun, Elvan Bayramoğlu, Olcay Evliyaoğlu, Data Collection or Processing: İlayda Altun, Analysis or Interpretation: İlayda Altun, Elvan Bayramoğlu, Hasan Karakaş, Gökçe Velioğlu Haşlak, Mert Uçar, Hande Turan, Olcay Evliyaoğlu, Literature Search: İlayda Altun, Writing: İlayda Altun, Elvan Bayramoğlu, Olcay Evliyaoğlu.

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