CASE REPORT

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A Rare Cause of Hypergonadotropic Hypogonadism: Transaldolase Deficiency in Two Siblings

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What is already known on this topic?

Transaldolase deficiency is a multisystemic disease that is characterized by intrauterine growth restriction, dysmorphism, cytopenia, hepatosplenomegaly, liver cirrhosis, endocrine problems, and skin, renal and cardiac abnormalities. Several endocrine system problems, such as abnormal external genitalia, primary hypothyroidism, short stature, bone abnormalities and hypergonadotropic hypogonadism may occur in transaldolase deficiency.

What this study adds?

Gonadal dysfunction with hypergonadotropic hypogonadism may occur in both girls and boys with transaldolase deficiency. Hypergonadotropic hypogonadism may become hormonally apparent in adolescence in girls with transaldolase deficiency although puberty starts on time. Transaldolase deficiency should be included in the differential diagnosis of cryptogenic cirrhosis and multisystemic involvement, especially if concomitant hypergonadotropic hypogonadism is present. Patients with transaldolase deficiency should be evaluated for gonadal functions, especially during puberty.

Abstract

Transaldolase deficiency is a rare inborn autosomal recessive disorder caused by biallelic mutations in the *TALDO1* gene. It is characterized by intrauterine growth restriction, dysmorphism, cytopenia, hepatosplenomegaly, liver cirrhosis, endocrine problems, and skin, renal and cardiac abnormalities. We present two siblings of Turkish origin with an early-onset form of transaldolase deficiency and hypergonadotropic hypogonadism in both sexes. The girl (index) was followed-up for cryptogenic cirrhosis, leukopenia and thrombocytopenia, skin abnormalities, congenital heart defects, hypercalciuria, nephrolithiasis, proteinuria, and chronic kidney disease throughout childhood. She developed hypergonadotropic hypogonadism in adolescence. Whole exome sequencing due to the multisystemic involvement revealed a previously described homozygous, inframe deletion in *TALDO1*. Her brother was born small for gestational age and was also followed-up with cryptogenic cirrhosis from infancy, together with cytopenia, congenital heart defects, bilateral cryptorchidism, short stature, hypercalciuria, proteinuria and chronic kidney disease in childhood. He presented with testicular microlithiasis and hypergonadotropic hypogonadism in adolescence. Sanger sequencing of *TALDO1* confirmed the presence of the same homozygous deletion as his sister. The mother was found to be a heterozygous carrier for this deletion. We describe two patients with multisystemic involvement since the neonatal period who presented with additional hypergonadotropic hypogonadism in adolescence. The diagnosis of transaldolase deficiency should be kept in mind for these patients, and they must be evaluated for gonadal functions, especially during puberty.

Keywords: Transaldolase deficiency, hypergonadotropic hypogonadism, whole exome sequencing, TALDO1

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Introduction

Transaldolase is a key enzyme in the pentose phosphate pathway (PPP), an alternative route for glucose oxidation. Glucose metabolism through PPP has two important functions: formation of ribose 5-phosphate for the synthesis of essential biomolecules, such as adenosine triphosphate (ATP), RNA, and DNA; and formation of NADPH for biosynthetic reactions and neutralization of reactive oxygen intermediates. In the absence of this enzyme, some intermediate products, such as polyols and seven-carbon sugars, accumulate in body fluids, mostly in the urine (1). Transaldolase deficiency was first described in 2001 in a Turkish girl with prominent liver involvement during early infancy (2). It is a rare, inborn, autosomal recessive disorder caused by biallelic mutations in the *TALDO1* gene and characterized by intrauterine growth restriction, dysmorphism, abnormal skin (telangiectasia, dryness, thinness), cytopenia, hepatosplenomegaly, liver cirrhosis, endocrine problems, and renal and cardiac abnormalities (3). Patients may exhibit either an early-onset presentation (prenatally or before one month of age) with severe symptoms during the neonatal period or a relatively milder late-onset presentation.

It has been reported that evaluation of the endocrine system in patients with transaldolase deficiency may show abnormal external genitalia, primary hypothyroidism, short stature, bone abnormalities and/or gonadal dysfunction with hypergonadotropic hypogonadism (3). Here, we present two siblings of Turkish origin with the early-onset form of transaldolase deficiency and hypergonadotropic hypogonadism with an overview of multisystemic manifestations throughout childhood in both sexes. Molecular diagnosis was established with whole exome sequencing (WES) in the index due to the multisystemic involvement, just before transition.

Case Reports

Patient 1

A $7^{6/12}$ year-old girl (index) was referred to the pediatric endocrinology clinic due to development of pubic hair. She was born after an uneventful pregnancy at term, with a birth weight of 2800 g [-1.44 standard deviation score (SDS)] and birth length of 49 cm (-0.51 SDS). She was the second child of healthy, consanguineous parents of Turkish origin. There was no family history of infertility. Soon after the newborn period, she underwent diagnostic work-up due to splenomegaly, elevated transaminase levels, direct hyperbilirubinemia, and prolonged coagulation tests. She was diagnosed with chronic liver disease of unknown cause. At the age of $2^{9/12}$ years, the diagnosis of cryptogenic liver disease was established after liver biopsy and etiological investigations. She was followed up for portal hypertension and managed conservatively for gastrointestinal bleeding. Bone marrow aspiration for evaluation of possible storage diseases showed hypercellular and heterogenous bone marrow associated with hypersplenism, but no evidence of storage cells. She was also regularly followed-up due to secundum atrial septal defect (ASD), mitral valve prolapse, mild dilatation of the aortic root, and aortic regurgitation since infancy. She had primary nocturnal enuresis, history of a kidney stone due to hypercalciuria, and proteinuria. Furthermore, she was under medication due to attention-deficit/hyperactivity disorder. Endocrine pancreas functions were normal, with blood glucose, insulin and HbA1c in normal ranges. Clinical manifestations are given in Table 1.

On physical examination at referral she had a body weight of 19.8 kg (-1.34 SDS), height of 122.6 cm (-0.32 SDS) [target height 160 cm (-0.53 SDS)], a small triangular face, microretrognathia, flat nasal bridge, long eyelashes, high palate, diffuse telangiectasias, thin and dry skin, hemangiomas, and a 3 cm palpable splenomegaly. Neurodevelopmental milestones and systemic examination were otherwise normal. She had Tanner stage 2 pubic hair but no breast development or clitoromegaly. Pubertal examination findings, and pubertal hormones at admission and subsequently are given in Table 2. Laboratory investigation for premature adrenarche found normal levels of dehydroepiandrostenedione sulphate and total testosterone. Slightly elevated 17-hydroxyprogesterone (1.29 ng/mL) and 1.4-delta androstenedione (1.5 ng/mL) levels prompted a 250 µg adrenocorticotropic hormone stimulation test which resulted in normal cortisol response and adrenal precursor concentrations. Thyroid hormone levels were within normal limits. Bone age was consistent with $8^{10/12}$ years, and slightly advanced.

During follow-up, breast development started at $9^{5/12}$ years and pubertal development proceeded with menarche at $12^{7/12}$ years. Inappropriately increased follicle stimulating hormone (FSH) levels for her pubertal stage were consistent with a hypergonadotropic state with menarche. Subsequently, primary ovarian insufficiency (POI) became clinically apparent, with secondary amenorrhea and hormonally apparent because of low anti-Mullerian hormone levels (<0.08 ng/mL). Pelvic ultrasound imaging revealed a pubertal uterine volume of 8 mL (13x23x53 mm) and ovarian volumes of 2.4/1.7 mL. Diagnostic work-up for the etiology of POI resulted in a normal 46,XX karyotype, negative genetic testing for the fragile X mental retardation

Table 1. Clinical manifestations of two siblings throughout childhood

Clinical features	Patient 1 (index)	Patient 2
Gender	Female	Male
Molecular diagnosis	Homozygous p.Ser171del c.512_514delCCT	Homozygous p.Ser171del c.512_514delCCT
Birth weight	2800 g (-1.44 SDS)	2500 g (-2.94 SDS)
Dysmorphism	+	+
Skin abnormalities	Telangiectasia, hemangiomas	Telangiectasia
Hepatological problems	Splenomegaly, cryptogenic cirrhosis, portal hypertension	Splenomegaly, cryptogenic cirrhosis, portal hypertension
Liver transplantation	+	-
Impaired coagulation tests	+	+
Cytopenia	Leukopenia and thrombocytopenia	Leukopenia and thrombocytopenia
Urinary system problems	Primary nocturnal enuresis, hypercalciuria, nephrolithiasis, proteinuria, chronic kidney disease	Primary nocturnal enuresis, hypercalciuria, proteinuria, membranous glomerulopathy, chronic kidney disease
Cardiac problems	Secundum ASD, MVP, aortic regurgitation	Secundum ASD (surgically corrected)
Endocrine system problems	Hypergonadotropic hypogonadism	Bilateral cryptorchidism (orchiopexy), short stature, hypergonadotropic hypogonadism
Mental problems	ADHD	None
At transition	Adult height: 165.7 cm Regular menses with HRT	Adult height: 165 cm On testosterone treatment

ASD: atrial septal defect, MVP: mitral valve prolapse, ADHD: attention-deficit/hyperactivity disorder, HRT: hormone replacement therapy, SDS: standard deviation score

Table 2. Clinical and hormonal profile of the cases at admission and pubertal milestones

	Tanner stage	FSH (mIU/mL)	LH (mIU/mL)	Estradiol (pg/mL)	Total testosterone (ng/mL)
Patient 1					
Admission ($7^{6/12}$ years)	P2, T1/1	0.6	0.1	18.5	-
Pubertal onset ($9^{5/12}$ years)	P2, T1/2	7.1	1.6	21	-
Menarche ($12^{7/12}$ years)	P4, T4/4	18	11.1	29.6	-
Secondary amenorrhea ($13^{10/12}$ years)	P5, T5/5	56.2	33.5	15.6	-
Patient 2					
Admission (9 years)	P1, bilateral NP testis	3.4	0.23	-	< 0.01
At the time of pubertal delay (14 years)	P2, TV 0.5/0.5 mL	128	88.8	-	0.28

FSH: follicle stimulating hormone, LH: luteinizing hormone, P: pubic hair, T: thelarche, NP: non-palpable, TV: testicular volume

1 premutation (29/32 CCG repeats), negative 21-hydroxylase antibody testing, and negative screening for reducing substances in urine. There had been no sign of autoimmune or adrenal disease, nor history of a cytotoxic treatment to the ovaries. She was evaluated for the consequences of estrogen deficiency. Dual energy X-ray absorptiometry scan revealed a low L1-4 bone mineral density of 0.782 g/cm^2 (Z score -2.5). Since there had been no history of any bone fracture, she was put on calcium and vitamin D prophylaxis. Transdermal estrogen and an oral progesterone regimen was preferred as hormone replacement therapy because of her well-established chronic liver disease.

At the age of 15 years, she was diagnosed with chronic kidney disease. At the age of 17.5 years, a hypoechoic nodular mass on cirrhotic liver was detected on ultrasonography and magnetic resonance imaging (MRI). Due to suspicion of hepatocellular carcinoma, she underwent living related liver transplantation from her father. The histopathological assessment of the explanted liver did not confirm the diagnosis of hepatocellular carcinoma. The features of nodular cirrhosis, focal dysplastic changes, and macro-microvesicular steatosis were reported after histopathological examination. Owing to the multisystemic involvement, chromosomal microarray and WES was perfomed. Xgen® Exome Research Panel v1.0 (Integrated DNA Technologies, USA) in Novaseq Platform (Illumina, USA) for exome sequencing and Cytoscan 750K Array kit in Affymetrix Platform (Thermo-Fisher Scientific, USA) for

microarray analysis were used. A previously described, homozygous, inframe deletion in exon 5 of *TALDO1* was detected (NM_006755.2; c.512-514delCCT; p.Ser171del). This mutation was previously reported in a Turkish girl (2).

Patient 2

Patient 2, the older brother of Patient 1, was referred to the pediatric endocrinology clinic due to bilateral cryptorchidism at the age of 9 years. He was born after an uneventful pregnancy at term, with a birth weight of 2,500 g (-2.94 SDS), and thus was classified as small for gestational age. He was also investigated for chronic liver disease since the newborn period, and the diagnosis of cryptogenic cirrhosis was established at the age of $4^{9/12}$ years. He had portal hypertension, esophageal varices, leukopenia, and thrombocytopenia. He was operated for secundum ASD. He had primary nocturnal enuresis, hypercalciuria, and proteinuria. Clinical manifestations of both siblings are given in Table 1.

Physical examination at referral revealed a body weight of 20.8 kg (-2.23 SDS), height of 122 cm (-1.83 SDS) [target height 173 cm (-0.52 SDS)], sitting height/height ratio 0.54, small triangular face, micrognathia, diffuse telangiectasia, thin and dry skin, 3/6 systolic murmur, and a 4 cm palpable splenomegaly. Neurodevelopmental milestones were normal. His pubertal development was consistent with Tanner stage 1, both testes were non-palpable, and stretched penile length was 4 cm (normal penile length for age: >4.72 cm). FSH, luteinizing hormone (LH) and testosterone concentrations were within prepubertal ranges. Testicular ultrasonography revealed bilateral small testes (0.5/0.5 mL) in the proximal inguinal canal. Human chorionic gonadotrophin (hCG) stimulation test (intramuscular hCG 1,500 IU/day, for 3 days) revealed no testosterone response. He underwent bilateral orchiopexy due to bilateral undescended testes soon after admission. Pubertal examination findings, and pubertal hormones at admission and subsequently for both siblings are given in Table 2.

During follow-up, he was evaluated for short stature and low annual growth rate, when he was 13 years old. Thyroid hormone levels were within normal limits. Insulin-like growth factor-1 (IGF-1) was 8.08 ng/mL (-2.3 SDS), IGF binding protein-3 (IGFBP-3) was 1790 ng/mL (-2.1 SDS), and bone age was 11 years. Growth hormone (GH) stimulation tests revealed GH deficiency with peak GH levels of 4.96 ng/mL and 5.37 ng/mL. MRI scan of his hypophysis was normal. During the investigations for delayed puberty at the age of 14 years, hypergonadotropic hypogonadism was detected. Inhibin-B level was 13 ng/L (100-444 ng/L). Testicular ultrasonography revealed atrophic testes with testicular microlithiasis. Monthly testosterone replacement was started. A normal 46,XY karyotype excluded chromosomal anomaly.

At the age of 13 years, he was diagnosed with membranous glomerulopathy and, after adolescence, with chronic kidney disease. He did not have hepatic decompensation throughout the childhood period and liver transplantation was not needed. Sanger sequencing of *TALDO1* confirmed the presence of the same homozygous deletion as his sister. The mother was found to be a heterozygous carrier for this deletion. She had not exhibited any evidence of relevant manifestations of the disease and was still having normal menses at the age of 48. Genetic analysis could not be performed for the father.

Discussion

In this report two patients with multisystemic involvement since the neonatal period are described, who presented with additional hypergonadotropic hypogonadism in adolescence. After years of diagnostic work-up, a homozygous *TALDO1* gene mutation causing transaldolase deficiency was detected with WES. The clinical diagnosis was considered as an early-onset form of transaldolase deficiency. Both patients had displayed normal prepubertal concentrations of gonadotropins before puberty. With the onset of puberty, hormonal status became hypergonadotropic in a few years.

Hypergonadotropic hypogonadism was reported in 18% of transaldolase deficient patients in a study performed by a retrospective questionnaire and literature review of 34 patients from 25 families (3). All these six reported patients also had early-onset phenotype. Recently, a boy with a late-onset presentation of transaldolase deficiency was reported with the prominent clinical finding of hypergonadotropic hypogonadism for the first time (4). Several hypotheses have been proposed to explain the mechanism of gonadal dysfunction in patients with transaldolase deficiency. As cirrhosis has been suggested to result from increased cell death of hepatocytes, gonadal insufficiency was thought to occur due to cell damage. Enzyme-activity and metabolic studies of transaldolase deficient lymphoblasts had revealed coordinated changes in mitochondrial homoeostasis, oxidative stress, and Ca^{2+} fluxing (5). Shortage of NADPH and antioxidant glutathione lead to decreased mitochondrial transmembrane potential and reduced ATP/ADP ratio in the liver of mice lacking transaldolase (*TALDO1 -/-*) (6). Increased levels of reactive oxygen intermediates and depleted neutralization, together with toxic accumulation of C5 polyols and seven-carbon sugars may lead to apoptosis,

and direct damage to gonadal cells in these patients (1). On the other hand, decrease in the ratio of NADPH/NADP may cause abnormal gonadal steroid hormone biosynthesis (5). *TALDO1* is significantly expressed in almost all tissues in the body. It has relatively higher expression in bone marrow and the gastrointestinal tract, while it is also expressed to some extent in the ovary and testis (7). Therefore, oxidative stress due to dysfunction of PPP to metabolize glucose could account not only for defects in liver tissue or bone marrow but also for gonadal damage. Patients should also be assessed carefully in terms of other system dysfunctions during follow-up.

The phenomenon of accumulation of metabolites, such as polyol and a sugar phosphate due to an enzyme deficiency in a pathway is also seen in galactosemia due to galactose-1-phosphate uridyltransferase deficiency (8). Ovarian failure in galactosemia is suggested to be due to direct toxic effect of galactose or its metabolites on ovarian parenchyma. Gonadal dysfunction is acquired and varies in severity with the age of the patient at onset (9). However, clinically significant gonadal dysfunction is not reported in boys, except for cryptorchidism. There has been evidence for both mild Sertoli and Leydig cell dysfunction in the testes, but these would have little impact on fertility (10). In contrast, gonadal dysfunction and hypergonadotropic hypogonadism has been reported in both sexes with transaldolase deficiency (3). Fertility of spermatozoa depends on the maintenance of the mitochondrial transmembrane potential and is regulated by an oxidation-reduction equilibrium of reactive oxygen intermediates. In a murine study, *TALDO1 -/-* male mice exhibited defective forward motility of spermatozoa, thus associating transaldolase deficiency with sperm dysmotility and potential male infertility (11). In Patient 2, low inhibin B concentrations suggested Sertoli cell dysfunction and potential subsequent infertility. However, the pathogenesis of gonadal dysfunction in males has not yet been entirely elucidated.

In this report, the girl (Patient 1) with transaldolase deficiency had spontaneous pubertal onset within the expected time frame with gonadotropins in the normal range. She had normal pubertal development but hypergonadotropic hypogonadism became hormonally apparent at the time of menarche, and several years prior to her liver transplantation. In contrast, puberty of the boy (Patient 2) was delayed, and no testicular enlargement was observed, as in the previously reported boy with late-onset presentation (4). This might be either due to the primary cellular damage in testis or damage to gonadal tissue due to late orchiopexy. Furthermore, coexistence of these two conditions may have exacerbated the clinical presentation. The onset and timing of the damage causing gonadal dysfunction in transaldolase deficiency in both sexes remains unclear, as it is for ovarian dysfunction in galactosemia (12). Further studies are needed to understand if transaldolase expression in ovary and testis differ, and if gonadal cells are affected in a different manner from the increased levels of reactive oxygen intermediates and oxidative stress.

Short stature was described in some patients with transaldolase deficiency, with a concomitant IGF-1 deficiency in a few (3). It has been suggested that IGF-1 deficiency may be due to delayed puberty, malnutrition, or liver disease. The presence of chronic systemic diseases in transaldolase deficiency could further contribute to poor growth. Short stature and IGF-1 deficiency observed in Patient 2 was possibly due to the combination of all these mechanisms. GH therapy has not been considered due to underlying chronic diseases of unknown etiology in young patients.

The mutation in the presented patients was same as in the first reported Turkish girl with transaldolase deficiency (2). This girl was evaluated for an enlarged clitoris, but dehydroepiandrosterone, androstenedione, and testosterone in serum were normal. Our index case was also evaluated for signs of hyperandrogenism, but the final clinical diagnosis was premature adrenarche with slightly elevated adrenal precursors. The condition may exhibit variable expressivity or intrafamilial phenotypic variability, as previously reported (13). Follow-up of these patients is extremely important since defects in a range of organ systems may appear at various times due to ongoing oxidative stress.

Conclusion

In conclusion, patients with cryptogenic cirrhosis and multisystemic involvement should be evaluated for gonadal function, especially during puberty. Transaldolase deficiency may be included in the differential diagnosis of these patients, especially if concomitant hypergonadotropic hypogonadism is present. In patients with transaldolase deficiency, puberty may begin spontaneously but managing clinicians should be aware of the possibility of developing hypergonadotropic hypogonadism during follow-up. Cryptorchidism may be an alarming symptom. Early diagnosis of these patients may present an opportunity for tissue cryopreservation to preserve fertility in the long term. The presented cases only had definitive diagnosis of transaldolase deficiency with WES after years of follow-up with multisystemic involvement throughout childhood. Testing for pathogenic variants in *TALDO1* gene may be considered earlier in these patients.

Ethics

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

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Melek Yıldız, Zerrin Önal, Tuğçe Göksu Kabil, Güven Toksoy, Şükran Poyrazoğlu, Özlem Durmaz, Concept: Melek Yıldız, Tuğçe Göksu Kabil, Güven Toksoy, Şükran Poyrazoğlu, Özlem Durmaz, Design: Melek Yıldız, Tuğçe Göksu Kabil, Şükran Poyrazoğlu, Data Collection or Processing: Melek Yıldız, Gözde Yeşil, Firdevs Baş, Özlem Durmaz, Feyza Darendeliler, Literature Search: Melek Yıldız, Zerrin Önal, Gözde Yeşil, Tuğçe Göksu Kabil, Güven Toksoy, Şükran Poyrazoğlu, Firdevs Baş, Feyza Darendeliler, Writing: Melek Yıldız, Zerrin Önal, Gözde Yeşil.

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