CASE REPORT OLGU SUNUMU

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A Rare Syndrome Leading to Immunodeficiency: Zhu-Tokita-Takenouchi-Kim Syndrome

İmmün Yetmezliğe Yol Açan Nadir Bir Sendrom: Zhu-Tokita-Takenouchi-Kim Sendromu

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ABSTRACT Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome, a rare autosomal dominant genetic disease, is caused by a loss-of-function mutation in the *SON* gene, first described in 2015. The clinical features of the disease are dysmorphic craniofacial appearance, hypotonia, brain malformations, intellectual disability, musculoskeletal abnormalities, and congenital heart and genito-urinary system defects. The literature about ZTTK syndrome is limited, and the majority of them focus on clinical and genetic findings. Here, we present an immunocompromised patient with ZTTK syndrome due to a de novo mutation in the SON gene. There are no published data about the detailed immunologic parameters of ZTTK syndrome.

Keywords: Immune deficiency disease; genetics

ÖZET Nadir bir otozomal dominant genetik hastalık olan Zhu-Tokita-Takenouchi-Kim (ZTTK) sendromu, ilk kez 2015 yılında tanımlanan *SON* genindeki fonksiyon kaybı mutasyonundan kaynaklanmaktadır. Hastalığın klinik özellikleri dismorfik kraniyofasiyal görünüm, hipotoni, beyin malformasyonları, mental retardasyon, kas-iskelet sistemi anormallikleri ve konjenital kalp ve genito-üriner sistem bozuklukları-dır. ZTTK sendromu ile ilgili literatür sınırlıdır ve çoğunluğu klinik ve genetik bulgulara odaklanmaktadır. Bu vaka takdiminde, SON genindeki de novo mutasyon nedeniyle ZTTK sendromlu, immün yetmezlikli bir hastayı sunuyoruz. ZTTK sendromunun ayrıntılı immünolojik parametreleri hakkında yayınlanmış veri bulunmamaktadır.

Anahtar Kelimeler: İmmün yetmezlik hastalığı; genetik

Zhu-Tokita-Takenouchi-Kim syndrome (ZTTK syndrome) is a autosomal dominant multisystemic disorder characterized by intellectual disability and caused by variants in the SON gene.[1]

The SON gene, located in the human chromosomal region 21q22.11, consists of 12 exons. It encodes the SON protein, an important RNA splicing co-factor that plays a vital role in the splicing complex.[2] The SON gene is also involved in the cell cycle, genome stability, and centrosome maintenance. SON is involved in pluripotency and survival of embryonic stem cells as well as in the alternative splicing of other genes involved in epigenetic regulation and apoptosis.[3] Taking into account the many different functions of SON, it is to be expected that pathogenic variants in this gene can cause diverse clinical symptoms. The syndrome manifests with a range of symptoms, including dysmorphic facial features, brain malformations, craniosynostosis musculoskeletal abnormalities, short stature, eye abnormalities, diges-

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tive system and urogenital system deformities, congenital heart disease, enamel hypoplasia, as well as skin and nail abnormalities.[4]

CASE REPORT

A 9-year-old male patient diagnosed with Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome was referred to us for immunological evaluation. The WES analysis disclosed a heterozygous de novo pathogenic variant (NM_138927.2) C.2849_2850dup (p.Leu951 Aspfs*2) was detected in the *SON* gene. The variant was also confirmed by Sanger sequencing, and both parents did not have the mutation. There is no other promising gene involving the immune system.

He is the second child of a consanguineous family. The neurological examination revealed hypotonia, neuromotor retardation, speech delay, sensorineural hearing loss, and moderate intellectual disability. An ophthalmological examination showed myopia and astigmatism. His electroencephalogram (EEG) and brain magnetic resonance imaging were normal, both performed at the age of seven.

On physical examination, his weight was 16 kg (-4.87 SDS), his height was 115 cm (-3.73 SDS), and his head circumference was 50 cm (-2.38 SDS). He had facial dysmorphism with a long asymmetric face, midface retrusion, smallmouth, broad nasal bridge, hypertelorism, epicanthus, strabismus, and low-lying ears (Figure 1). The distal phalanges of his fingers were short. He had bilateral clinodactyly of the little fingers, onychodystrophy of toenails. His fingernails were normal. He had no gastrointestinal or urogenital abnormalities.

He suffered from recurrent upper respiratory tract infections and pneumonia since his infancy. Serum immunoglobulin (Ig)G and IgA levels were low; however, IgM level was normal. There was no antibody response to the hepatitis and tetanus vaccines. Lymphocyte subsets were normal, including total T cells, T helper cells, T suppressors, B cells and NK cells. However, memory B cells were low compared to controls. Lymphocyte proliferation was normal. The patient's laboratory data are summarized in Table 1. Intravenous immune globulin therapy was initiated. Following intravenous immunoglobulin (IVIg) treatment, the frequency of infections decreased, and growth was accelerated.

FIGURE 1: Syndromic facial features of our patient.

TABLE 1: Patient's laboratory findings.

	Patient	Normal values
IgG (g/L)	528	(842-1943)
IgM (g/L)	71	(54-392)
IgA (g/L)	46	(62-398)
CD3% (AC)	67.4% (1179)	(65-85%)
CD4% (AC)	30.3% (530)	(29-59%)
CD8% (AC)	33.9% (593)	(19-48%)
CD19% (AC)	15.3% (267)	(7-23%)
CD19+IgM-IgD-CD27+% (AC)	1% (17)	(2.7-29%)
AntiHbs, Anti tetanus IgG	Negative	

AC: Absolu count; Ig: Immunoglobulin.

Written consent was obtained from the family to publish this case report. Uludağ University Ethics Committee number is 2023-22/30, date 31.10.2023.

DISCUSSION

SON is a nuclear protein involved in multiple cellular processes, including transcription, RNA-splicing, and cell cycle regulation. It has an essential role in maintaining embryonic stem cell pluripotency. Abnormal RNA splicing may impair multi-organ development and immune system functions.

Patients with ZTTK syndrome exhibit dysmorphic features and various symptoms owing to many

TABLE 2: Overview of phenotypic characteristics of individuals with variants in Zhu-Tokita-Takenouchi-Kim syndrome.

	Our patient	Dingem-ans et al.[6]	Kim et al.[2]	Tokita et al.[7]	Slez-ak et al.[11]	Kim et al.[12]	Quinta-na Castan-edo et al.[1]	Yang et al.[5]	Takenouchi et al.[13]	Tan et al.[14]
Head circumference <P3	1/1	6/18	4/18	3/7	NR	NR	NR	NR	0/1	NR
Height <P3	1/1	11/18	10/20	3/7	0/2	0/1	NR	1/1	1/1	1/1
Weight <P3	1/1	10/17	1/1	3/7	1/2	NR	NR	NR	1/1	NR
Motor delay	1/1	17/18	NR	5/5	2/2	NR	NR	1/1	1/1	1/1
Speech delay	1/1	17/17	NR	7/7	2/2	NR	NR	NR	1/1	NR
Intellectual disability	1/1	15/16	20/20	7/7	2/2	1/1	1/1	1/1	1/1	1/1
Neurological abnormality	0/1	16/18	18/20	7/7	2/2	NR	1/1	0/1	1/1	1/1
Abnormality of the brain	0/1	11/13	17/1	5/6	1/2	NR	1/1	1/1	0/1	1/1
Autistic behavior	1/1	1/18	2/20	3/7	0/2	NR	0/1	0/1	0/1	NR
Horizontal eyebrow	0/1	0/17	12/17	1/7	0/2	NR	0/1	1/1	0/1	0/1
Facial asymmetry	1/1	0/17	12/17	1/7	1/2	NR	0/1	0/1	0/1	0/1
Midface retrusion	1/1	2/17	12/17	0/7	0/2	NR	1/1	0/1	0/1	0/1
Strabismus	1/1	6/17	11/17	1/7	2/2	NR	1/1	0/1	0/1	0/1
Deeply set eye	0/1	0/17	12/17	0/7	0/2	NR	0/1	0/1	0/1	0/1
Epicanthus	1/1	4/17	0/17	2/7	2/2	NR	0/1	0/1	1/1	1/1
Short or smooth philtrum	0/1	2/17	12/12	6/7	1/2	NR	0/1	0/1	0/1	1/1
Thin upper lip vermilion	1/1	1/17	0/12	3/7	1/2	NR	0/1	1/1	0/1	0/1
Abnormality of the nasal bridge	1/1	5/17	12/12	1/7	1/2	NR	0/1	1/1	1/1	1/1
Low-set ears	1/1	6/18	12/12	1/7	1/2	NR	0/1	1/1	0/1	1/1
Posteriorly rotated ears	0/1	5/18	0/12	0/7	0/2	NR	0/1	0/1	1/1	0/1
Hypermobility	0/1	7/18	8/20	1/7	1/2	NR	0/1	0/1	0/1	0/1
Pes planus	1/1	4/18	6/20	0/7	1/2	NR	0/1	0/1	0/1	0/1
Abnormality of the foot	1/1	8/18	9/20	1/7	1/2	NR	1/1	0/1	0/1	0/1
Abnormality of the fingers	0/1	3/18	5/20	3/7	1/2	NR	1/1	0/1	0/1	0/1
Feeding difficulties	1/1	6/16	13/19	7/7	2/2	NR	0/1	0/1	1/1	1/1
Cardiac abnor.	0/1	2/15	6/20	4/7	1/2	1/1	1/1	0/1	1/1	0/1
Urogenital abnor.	0/1	4/14	8/20	3/7	1/2	1/1	0/1	1/1	1/1	1/1
Skin hair nail abnormalities	1/1	8/16	5/20	3/7	2/2	NR	1/1	1/1	1/1	0/1
Visual impairment	1/1	8/18	9/20	3/7	1/2	NR	0/1	0/1	0/1	0/1
Abnormal hearing	1/1	4/18	3/20	0/5	0/2	NR	0/1	0/1	0/1	0/1
Abnormality of immunological system	1/1	4/15	3/20	5/6	2/2	1/1	0/1	0/1	0/1	0/1
IgG and/or IgA deficiency	1/1	NR	NR	1/5	0/2	NR	0/1	0/1	0/1	0/1

NR: Not reported; Ig: Immunoglobulin.

organ involvement. Facial dysmorphism findings are facial asymmetry, midface retrusion, eye, nose, ear, and mouth abnormalities.[5] Neurological abnormalities are characterized by intellectual disability, hypotonia, seizures, and EEG abnormalities. Brain malformations include cortex, cerebral white matter, ventricles, cerebellum malformation, or corpus callosum abnormality. Autism is prevalent.[6,7] Our patient had mental retardation, autistic behaviors, and visual and hearing impairments, but neither brain malformation nor epileptic attacks were detected. Musculoskeletal abnormalities are represented by short stature, scoliosis, joint hypermobility, and pes planus. Our patient showed finger and nail abnormalities. Gastrointestinal abnormalities are reported in ZTTK patients having feeding difficulties and various structural abnormalities.[8] Compared with our patient the systematic review of the cases published in the literature is given in Table 2.

Immunodeficiency was not reported in cases with ZTTK syndrome until this year; Kylat et al. informed an association of mutations in Foxp3 leading to the clinical triad of enteropathy, endocrinopathies, and dermatitis provides the definitive diagnosis of IPEX syndrome and the *SON* gene in a patient.[9] The patient had respiratory insufficiency and failure to thrive. An immunologic evaluation included normal Ig M, G, E, and A levels but abnormal FOXP3 and regulatory T cell panel. He did not have the classic findings of Ipex syndrome and died of pneumonia and respiratory failure before the anticipated BMT at six months of age. Our case has a heterozygous de novo pathogenic variant (NM_138927.2) C.2849_2850dup (p.Leu951Aspfs*2) in the *SON* gene. The immunological workup revealed hypogammaglobulinemia and antibody production defects. IVIg treatment was effective in reducing infections.

One of the interacting proteins for the *SON* gene is Smad nuclear-interacting protein 1; required for pre-mRNA splicing as a component of spliceosome down-regulates nuclear factor-kappa-B (NF-κB) signaling. NF-κB regulates a large array of genes involved in different processes of the immune and inflammatory responses. The NF-κB transcription factor initiates the expression of genes that drive B cell proliferation and differentiation.[10]

We suggest that it is important to review the immunologicl data of patients with ZTTK syndrome and to provide supportive treatments in case of immunodeficiency, including prophylactic antibiotics or IVIg.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sara Şebnem Kılıç Gültekin;* ***Design:*** *Sara Şebnem Kılıç Gültekin, Gözde Özkan;* ***Control/Supervision:*** *Sara Şebnem Kılıç Gültekin;* ***Literature Review:*** *Gözde Özkan, Sara Şebnem Kılıç Gültekin;* ***Writing the Article:*** *Gözde Özkan, Sara Şebnem Kılıç Gültekin.*

REFERENCES

1. Quintana Castanedo L, Sánchez Orta A, Maseda Pedrero R, Santos Simarro F, Palomares Bralo M, Feito Rodríguez M, et al. Skin and nails abnormalities in a patient with ZTTK syndrome and a de novo mutation in SON. Pediatr Dermatol. 2020;37(3):517-9. [Crossref] [PubMed]
2. Kim JH, Shinde DN, Reijnders MRF, Hauser NS, Belmonte RL, Wilson GR, et al. De Novo Mutations in SON Disrupt RNA splicing of genes essential for brain development and metabolism, causing an intellectual-disability syndrome. Am J Hum Genet. 2016;99(3):711-9. [PubMed] [PMC]
3. Lu X, Göke J, Sachs F, Jacques PÉ, Liang H, Feng B, et al. SON connects the splicing-regulatory network with pluripotency in human embryonic stem cells. Nat Cell Biol. 2013;15(10):1141-52. [Crossref] [PubMed] [PMC]
4. Kushary ST, Revah-Politi A, Barua S, Ganapathi M, Accogli A, Aggarwal V, et al.; DDD Study; TUDP Consortium; Anyane Yeboa K. ZTTK syndrome: Clinical and molecular findings of 15 cases and a review of the literature. Am J Med Genet A. 2021;185(12):3740-53. [Crossref] [PubMed] [PMC]
5. Yang Y, Xu L, Yu Z, Huang H, Yang L. Clinical and genetic analysis of ZTTK syndrome caused by SON heterozygous mutation c.394C>T. Mol Genet Genomic Med. 2019;7(11):e953. [Crossref] [PubMed] [PMC]
6. Dingemans AJM, Truijen KMG, Kim JH, Alaçam Z, Faivre L, Collins KM, et al. Establishing the phenotypic spectrum of ZTTK syndrome by analysis of 52 individuals with variants in SON. Eur J Hum Genet. 2022;30(3):271-81. [Crossref] [PubMed] [PMC]
7. Tokita MJ, Braxton AA, Shao Y, Lewis AM, Vincent M, Küry S, et al. De Novo truncating variants in SON cause intellectual disability, congenital malformations, and failure to thrive. Am J Hum Genet. 2016;99(3):720-7. [Crossref] [PubMed] [PMC]
8. Kim JH, Park EY, Chitayat D, Stachura DL, Schaper J, Lindstrom K, et al. SON haploinsufficiency causes impaired pre-mRNA splicing of CAKUT genes and heterogeneous renal phenotypes. Kidney Int. 2019;95(6):1494-504. [Crossref] [PubMed] [PMC]
9. Kylat RI, Stanley K, Simon S, Erickson RP. Immune dysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX) syndrome due to a mutation in FOXP3, modified by a pathogenic variant in SON (SON DNA-binding protein). J Appl Genet. 2023;64(1):141-4. [Crossref] [PubMed]
10. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol. 2009;1(4):a000034. [Crossref] [PubMed] [PMC]
11. Slezak R, Smigiel R, Rydzanicz M, Pollak A, Kosinska J, Stawinski P, et al. Phenotypic expansion in Zhu-Tokita-Takenouchi-Kim syndrome caused by de novo variants in the SON gene. Mol Genet Genomic Med. 2020;8(10):e1432. [Crossref] [PubMed] [PMC]
12. Kim JH, Park EY, Chitayat D, Stachura DL, Schaper J, Lindstrom K, et al. SON haploinsufficiency causes impaired pre-mRNA splicing of CAKUT genes and heterogeneous renal phenotypes. Kidney Int. 2019;95(6):1494-504. [Crossref] [PubMed] [PMC]
13. Takenouchi T, Miura K, Uehara T, Mizuno S, Kosaki K. Establishing SON in 21q22.11 as a cause a new syndromic form of intellectual disability: Possible contribution to Braddock-Carey syndrome phenotype. Am J Med Genet A. 2016;170(10):2587-90. [Crossref] [PubMed]
14. Tan Y, Duan L, Yang K, Liu Q, Wang J, Dong Z, et al. A novel frameshift variant in SON causes Zhu-Tokita-Takenouchi-Kim Syndrome. J Clin Lab Anal. 2020;34(8):e23326. [Crossref] [PubMed] [PMC]