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Case Report

Infantile Sotos Syndrome: A Case Presenting with Mental Retardation and Overgrowth

Bebeklik Çağı Sotos Sendromu: Mental Retardasyon ve Aşırı Büyüme ile Başvuran Bir Olgu

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ABSTRACT

Sotos syndrome is a growth disorder characterized by distinctive facial features, advanced bone age, macrocephaly, congenital visceral malformations, developmental delay, and epilepsy. Its estimated incidence is 1/14,000, making it one of the most common overgrowth syndromes. In this case report, we aim to present an 8-month-old female infant who was admitted to our clinic with a diagnosis of overgrowth and Sotos syndrome.

The patient's prenatal period was uneventful, and the parents were cousins in a consanguineous marriage. Physical examination showed body weight at the 99.8th percentile, height at the 99.9th percentile, and head circumference at the 98.4th percentile. He had generalized hypotonia, hypertelorism, prominent forehead, depressed nasal bridge, retrognathia, high palate, and brisk deep tendon reflexes. Bone age was advanced, consistent with 18-20 months, and cranial magnetic resonance imaging (MRI) was normal. Clinical findings and anthropometric measurements suggested Sotos syndrome. Although other overgrowth syndromes such as Marfan syndrome, homocystinuria, Beckwith-Wiedemann syndrome, Weaver syndrome, and Fragile X syndrome were considered, they were deemed less likely due to the lack of typical features and presence of prominent neuropsychiatric findings. Genetic analysis identified a heterozygous NSD1 mutation.

This case report highlights the importance of considering Sotos syndrome in the differential diagnosis of infants presenting with advanced anthropometric measurements for age, acromegaly-like somatic features, and neurodevelopmental delay.

Keywords: *Overgrowth, Dysmorphic face, İntellectual disability, NSD1 mutation.*

ÖZET

Sotos sendromu; kendine özgü yüz hatları, ileri kemik yaşı, makrosefali (başın normalden büyük olması), doğuştan iç organ anormallikleri, gelişimsel gerilik ve epilepsi ile karakterize bir büyüme bozukluğudur. Tahmini görülme sıklığı 1/14.000'dir ve bu da onu en sık görülen aşırı büyüme sendromlarından biri yapmaktadır. Bu olgu sunumunda, kliniğimize aşırı büyüme şikayetiyle başvuran ve Sotos sendromu tanısı konan 8 aylık kız bir bebeği sunmayı amaçlıyoruz.

Hastanın doğum öncesi dönemi sorunsuzdu ve ebeveynler kuzen evliliği yapmışlardı. Fiziksel muayenede vücut ağırlığı 99.8'inci, boyu 99.9'uncu ve baş çevresi 98.4'üncü persentildeydi. Yaygın kas tonusu düşüklüğü (hipotoni), gözlerin birbirinden uzak olması

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(hipertelorizm), belirgin alın, basık burun kökü, alt çenenin geride olması (retrognati), yüksek damak ve canlı derin tendon refleksleri gözlendi. Kemik yaşı 18-20 aylık bir bebekle uyumlu olarak ileriydi ve beyin MRG'si normaldi. Klinik bulgular ve vücut ölçümleri Sotos sendromunu düşündürüyordu. Marfan sendromu, homosistinüri, Beckwith-Wiedemann sendromu, Weaver sendromu ve Fragile X sendromu gibi diğer aşırı büyüme sendromları da düşünüldü, ancak bu sendromlara özgü tipik özelliklerin olmaması ve belirgin nöropsikiyatrik bulguların varlığı nedeniyle olasılık dışı bırakıldılar. Yapılan genetik analizde heterozigot bir NSD1 mutasyonu saptandı.

Bu olgu sunumu, yaşa göre ileri vücut ölçümleri, akromegali benzeri bedensel özellikler ve nörogelişimsel gerilikle başvuran bebeklerin ayırıcı tanısında Sotos sendromunun göz önünde bulundurulmasının önemini vurgulamaktadır.

Keywords: *Overgrowth, dysmorphic face, mental retardation, NSD1 mutation.*

INTRODUCTION

Characterized by macrocephaly, typical facial features, and intellectual disability, Sotos syndrome is an overgrowth syndrome first described by Sotos and colleagues in 1964 [1, 2]. These three clinical features are considered core characteristics of Sotos syndrome [3]. With an estimated incidence of 1/14,000, it stands as one of the most common overgrowth syndromes [4]. It is inherited in an autosomal dominant manner, with *de novo* pathogenic variants occurring in more than 95% of individuals [2].

The characteristic findings of Sotos syndrome include a large and prominent frontal bossing, sparse frontotemporal hair, down-slanting palpebral fissures, malar flushing, dolichocephaly, a long and narrow face, and a prominent mandible. The syndrome is additionally associated with behavioral problems, advanced bone age, cardiac, cranial, and renal anomalies, scoliosis, facial features such as hypertelorism and a high-arched palate, as well as ophthalmological findings like cerebellar nystagmus and strabismus [3, 4, 5]. Furthermore, cardiovascular, central nervous system, and genitourinary system anomalies may accompany the syndrome. The primary causative gene for the syndrome encodes the nuclear receptor-binding SET domain-containing protein 1 (*NSD1*). The *NSD1* gene codes for the NSD1 protein, a histone methyltransferase enzyme that plays a critical role in normal growth and development. Mutations or deletions in the *NSD1* gene can lead to Sotos syndrome, resulting in overgrowth. This is primarily due to the insufficient production of functional NSD1 protein. The disruption in NSD1's histone methylation activity causes abnormal expression of target genes that regulate growth and development, contributing to uncontrolled cell growth and consequently the overgrowth phenotype. This epigenetic imbalance is a characteristic feature of Sotos syndrome.

In this case report, we aim to highlight the importance of considering Sotos syndrome in the differential diagnosis of overgrowth and intellectual disability by presenting a case referred to our clinic by pediatric neurology due to intellectual disability and overgrowth, who was subsequently diagnosed with Sotos syndrome.

CASE REPORT

The 8-month-old female infant, referred to our clinic due to overgrowth, was reported to have started undergoing investigations for neuromotor developmental delay at the age of 4 months. The prenatal history was unremarkable. She was the second living child from the 23-year-old mother's third pregnancy, born at term via normal spontaneous vaginal delivery, weighing 4200 grams. Parental consanguinity at the third-degree was reported. Newborn hearing and vision screening, and hip ultrasound were noted to be normal. The patient reportedly achieved head control at approximately 6 months of age.

Physical examination revealed generalized hypotonia and hypertelorism. Dysmorphic features included a prominent forehead, depressed nasal bridge, retrognathia, high palate, brisk deep tendon reflexes, macrocephalic appearance, and a wide and prominent forehead. Patient weighed 10.2 kg, which corresponds to standard deviation score (SDS): +1.64 (approximately 95th percentile) according to Neyzi reference data. Her height was measured as 80 cm, with an SDS: +3.58 (>99.98th percentile), indicating a markedly tall stature for her age. The body mass index (BMI) was 15.94 kg/m^2, corresponding to SDS: -0.72 (approximately 24th percentile), within the normal range. The mother's height was 156 cm and the father's height was 170 cm, yielding a target height of 156.5 cm (SDS: -1.12). Accordingly, the patient's current height is markedly above her genetic target height. Hemogram and biochemical parameters yielded normal results.The hormonal evaluation revealed normal thyroid function and a normal GH-IGF-1 axis. Bone age was consistent

with 18-20 months. Cranial magnetic resonance imaging, requested due to macrocephaly, micrognathia, frontal bossing, intellectual disability, triangular face, and acromegaloid appearance, was reported as normal for the parenchyma.

Given the patient's anthropometric measurements exceeding two standard deviations, the presence of dysmorphic features, and developmental delay, Sotos syndrome was considered the primary diagnosis. Genetic analysis identified a heterozygous c.4928G>C (p.Gly1643Ala) pathogenic variant in the NSD1 gene, which is classified as *pathogenic* according to ACMG and ClinVar criteria. Considering the clinical findings and the pathogenicity of the variant, the patient was diagnosed with Sotos syndrome, and segregation analysis is planned to further support this finding.

DISCUSSION

In this case presentation, the findings of macrocephaly, overgrowth, dysmorphic facial features (frontal bossing, hypertelorism, long face, etc.), advanced bone age, and neurodevelopmental delay in an 8-month-old female infant support the diagnosis of Sotos syndrome. Although the patient's prenatal history was unremarkable, significant overgrowth and neuromotor developmental delay, which became apparent from the 4th month, were notable.

Central nervous system anomalies such as ventriculomegaly and corpus callosum hypoplasia, observed in patients with Sotos syndrome, play a significant role in the pathophysiology of their neurodevelopmental delay and neurological findings. These findings are observed in approximately 60-80% of patients [6]. In our patient, brain magnetic resonance imaging was reported as normal for the brain parenchyma. Most patients exhibit a phenotype characterized by non-progressive neurological symptoms and impaired coordination. Delays in the development of language and motor skills are particularly common in the early period. Although cognitive functions show significant variability, learning difficulties have been reported in 97% of 239 *NSD1*-positive individuals in the Tatton-Brown series [7].

Sotos syndrome frequently leads to hyperactivity, impulsivity, and attention problems as a manifestation of attention deficit hyperactivity disorder in affected individuals [8]. Our 8-month-old patient also presented with neuromuscular developmental delay. A comprehensive systematic meta-analysis conducted on individuals with Sotos syndrome demonstrated that the anxiety levels identified in this group showed statistically significant elevation when compared with data from the general population and individuals with Rubinstein-Taybi and Fragile X syndromes [9].

Once patients are diagnosed with Sotos syndrome, they should be screened for potential associated pathologies. For this purpose, a hearing test was performed on our patient, but due to effusion, a clear evaluation could not be made, and a follow-up test was planned. Congenital heart diseases such as atrial septal defect, ventricular septal defect, patent ductus arteriosus, tricuspid atresia, and mitral valve prolapse are observed in 8% of individuals with Sotos syndrome [10]. Our patient's echocardiography was evaluated as normal. Various ocular manifestations such as megalocornea, iris hypoplasia, cataract, megalophthalmos, strabismus, nystagmus, and retinal dystrophy can be seen in individuals with Sotos syndrome [11]. Our patient was evaluated for potential accompanying eye findings. Retina and corneal examination were found to be normal in our patient. A follow-up ophthalmological examination for visual field assessment is planned.

The comparison of the clinical features of our case with those reported in the literature is given in table 1.

In our patient, who was evaluated with a preliminary diagnosis of Sotos syndrome, other syndromes characterized by overgrowth were also considered in the differential diagnosis. Particularly, conditions such as Marfan syndrome, homocystinuria, Beckwith-Wiedemann syndrome, Weaver syndrome, and Fragile X syndrome were carefully evaluated due to their potential for overlapping clinical features. In our case, in addition to the observed overgrowth and dysmorphic features, the presence of neuromotor developmental delay, coordination problems in fine and gross motor skills, and findings suggestive of autism spectrum disorder create a clinical picture more consistent with the characteristic features of Sotos syndrome.

In conclusion, Sotos syndrome should be considered primarily in the differential diagnosis of cases characterized by anthropometric measurements above the 97th percentile, acromegaly-like somatic features, neurodevelopmental delay, and multisystemic anomalies.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

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