



Sotos syndrome: a case report

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Abstract

Background and Objective: This clinical case study analyzed the characteristics of Sotos syndrome. Since it is a rare syndrome and is related to the occurrence of behavioral disorders. Health professionals who work with this population were informed so that this condition is recognized, enabling appropriate treatment and consequently a good quality of life. This study was analyzed and approved by the Research Ethics Committee according to the reasoned opinion number, under number 6,089,691, and the patient's consent was obtained through the Free and Informed Consent Form.

Final Considerations: Sotos Syndrome should be considered when the patient presents macrocrania, growth acceleration, and behavioral changes associated with varying degrees of delay. The diagnosis is clinical, but complementary tests help, as they rule out other possible causes for such an association of symptoms since there is no specific test for the syndrome to date. The treatment of these patients must be individualized, using pharmacological and non-pharmacological strategies according to the needs of the moment. Clinical follow-up is always necessary, due to complications that may arise.

Keywords: Sotos syndrome. Behavioral disorders. Physical changes. Treatments.

Introduction

Sotos Syndrome, also called cerebral gigantism, is a congenital anatomical megalencephaly characterized by rapid bone growth up to four years of age and macrocephaly with dolichocephalus [1,2]. The first description of Sotos Syndrome (MIM 117550) was made

in 1964 by Sotos and collaborators. In 1990, Cole and Hughes described that aspects of the syndrome were milder than previously believed and that these aspects tended to improve with age [1].

The gene associated with Sotos Syndrome is NSD1, located on chromosome 5. Around 80% to 90% of those affected have a point mutation or deletion in NSD1. The essential function of NSD1 is to produce several proteins that control the activity of genes that are involved in normal growth, development, and maturation. Its prevalence is 1:14,000 live births [3-5].

Genetically, the syndrome is inherited in an autosomal dominant manner. More than 95% of individuals have a de novo pathogenic variant. If neither parent of a proband has Sotos syndrome, the risk to the proband's siblings is low (<1%). The risk to the offspring of affected individuals is 50%. Prenatal testing for an increased-risk pregnancy and preimplantation genetic testing is possible if the NSD1 pathogenic variant has been identified in an affected family member [5].

Sotos Syndrome is characterized by a distinctive facial appearance (wide, prominent forehead with dolichocephalic head shape, sparse frontotemporal hair, downward-sloping palpebral fissures, malar flush, long, narrow face, long chin); learning disability (early developmental delay, mild to severe intellectual disability); and overgrowth (height and/or head circumference ≥ 2 SD above the mean). These three clinical features are considered the cardinal features of Sotos Syndrome. Other features include behavioral findings (primarily autism spectrum disorder), advanced bone age, cardiac anomalies, MRI/head CT/EEG abnormalities, joint hyperlaxity with or without pes planus, maternal pre-eclampsia, neonatal complications,

renal anomalies, scoliosis and convulsions, slight prognathism, high palate, premature tooth eruption and malar flushing [5].

Tumors occur in approximately 3% of people with Sotos syndrome. The wide range includes sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia, smallcell lung cancer, and astrocytoma [5]. In general, these characteristics are more evident in early childhood and attenuate with age. Neonatal jaundice and early feeding problems are found in more than 40% of affected children and may be related to difficulties during the birth of these babies [3].

Depending on the degree, behavioral problems may be associated with this syndrome, including aggression, difficulties in socialization, attention deficits, and emotional immaturity. Problems are often more noticeable at home than at school. Based on a phenotype with large body size, accelerated growth, advanced bone age, characteristic facial appearance, and developmental delay, the hypothesis of Sotos Syndrome is raised and its diagnosis is made through genetic examination. When clinical manifestations are identified, referral to a specialist is recommended. It is possible to carry out interdisciplinary monitoring to offer a better quality of life [6].

Genetic counseling is the process of providing individuals and families with information about the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. When neither parent of a proband with Sotos syndrome has the NSD1 pathogenic variant or clinical evidence of the disorder, the proband likely has a de novo pathogenic variant. Once the NSD1 pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for Sotos syndrome and preimplantation genetic testing are possible [1,6].

Phenotypic expression may vary from one generation to another; therefore, it is not possible to accurately predict the phenotype based on the results of prenatal molecular genetic testing. Prenatal diagnosis cannot be accurately performed by ultrasound: features of Sotos syndrome that can be detected by ultrasound, such as macrocephaly and increased length, are nonspecific [6].

The objective of this work was to review the characteristics of this syndrome and report them based on a clinical case, since it is a rare syndrome and is related to the occurrence of behavioral disorders. We sought to inform health professionals who work with this population, so that this condition is recognized, enabling appropriate treatment and consequently a good quality of life.

Case report

The present study was elaborated according to the rules of **CARE case report**. Available at: <https://www.care-statement.org/>. Accessed on: 09/10/2023_

Ethical Aspects

This study was analyzed and approved by the Research Ethics Committee according to the reasoned opinion number, under number 6.089.691, and the patient's consent was obtained through the Free and Informed Consent Form.

Case Report

Patient Information and Clinical Findings, Timeline, Diagnostic Assessment, Therapeutic Intervention and Follow-up

G.S.S 10 years old, female, white, born and living in Tupã- SP, second daughter of three pregnancies, lives with her mother, father, and two brothers. She was born with a head circumference of 38cm, 51.5cm in length, and 3,515kg. Cesarean delivery, at 38 weeks due to polyhydramnios and the baby's head circumference being larger. At birth, the mother reported that the child had his eyes closed for a long time, had tremors in his arms, and had excess skin.

At 15 days of birth, she went to an ophthalmologist because the child remained with her eyes closed for a long time. The specialist determined that the child had no ocular changes, just eyelid ptosis, where she remained opening her eyes a little until she was 4 months old.

She had a delay in NPMD until she was 4 months old, and was referred to a Neuropediatrician, followed up until she was 4 years old due to normal childhood hydrocephalus and febrile seizures, and was monitored by a physiotherapist, speech therapist, and occupational therapy. She sat up at 7 months, crawled at 11 months, and walked at 1 year and 3 months.

Until she was 4 years old, she had food allergies (egg, milk protein, soy) and several medications. After this situation, she was referred to a pediatric endocrinologist, where she underwent genetic testing and follow-up with a geneticist, finalizing the diagnosis of Sotos Syndrome, with the presence of a mutation in the NSD1 gene.

Due to the accentuated growth, at the age of 8, he began follow-up with a pediatric endocrinologist due to thelarche that began at the age of 7, with additional tests being carried out that revealed a 2-year advance in bone age, a normal uterus, and ovaries compatible with the pre-pubertal stage and pre-pubertal hormonal levels. puberty (LH 0.23MUI/mL, E2 19.0 PG/mL). She

reported her complaints as being impulsive and angry, having difficulty gaining weight despite eating well, and having difficulty with hair growth. She presents with astigmatism and joint hypermotility.

Today the patient is 10 years old, 1.55m tall, and has no difficulties at school. She learned to read and write at age 7. She has symptoms of aggression, impatience, and impulsiveness, tried therapy with Risperidone and methylphenidate with guidance from a Neuropediatrician, requiring suspension due to significant weight loss. She is not taking any medication.

Genetic test for customized NGS panel: Material: whole blood. Result: a heterozygous, probably pathogenic variant was identified in the NSD1 gene. Interpretation: Sotos Syndrome 1 [OMIM:117550], autosomal dominant inheritance, NSD1 gene, variant NM 022455.4:c.1313dup:p., heterozygosity (59.65%).

Discussion

The present study described the characteristics of Sotos syndrome through a clinical case. Sotos syndrome is caused by pathogenic variants of NSD1 and is characterized by a distinct facial appearance, intellectual disability, tall stature, and/or macrocephaly. Other associated clinical features include scoliosis, seizures, renal anomalies, and cardiac anomalies. Many of the published clinical descriptions of Sotos syndrome are based on studies with children, such as the present study. In this sense, disruption of NSD1 causes Sotos syndrome [7].

A retrospective study of 8 pregnancies analyzed fetal ultrasound findings associated with Sotos syndrome caused by deletions at 5q35 including NSD1 and a point mutation. Two cases did not present significant fetal anomalies and were only diagnosed after birth. A case presented in the first trimester with increased nuchal translucency. The remaining five fetuses were identified at the end of pregnancy. One of the five fetuses presented mild ventriculomegaly in the second trimester and four in the third trimester presented mild ventriculomegaly, macrocephaly, and polyhydramnios. Chromosomal microarray was performed in all cases and revealed 5q35 deletions in seven cases, and whole exome sequencing detected a maternally inherited NSD1 variant in one case. Thus, fetal ultrasound findings in cases with Sotos syndrome, associated with deletions in 5q35 and point mutation in NSD1, are not specific, with the most common finding being mild ventriculomegaly [8].

Furthermore, a recent study carried out by authors Lourdes et al. (2023) analyzed clinical and genetic data from a cohort of 31 patients diagnosed with Sotos syndrome. All presented excessive growth, typical

dysmorphic features, and different degrees of developmental delay. Non-structural diseases such as pericarditis were highlighted. Five patients suffered from recurrent onychocryptosis that required surgical procedures [9].

Final Considerations

Sotos Syndrome should be considered when the patient presents macrocrania, growth acceleration, and behavioral changes associated with varying degrees of delay. The diagnosis is clinical, but complementary tests help, as they rule out other possible causes for such an association of symptoms since there is no specific test for the syndrome to date. The treatment of these patients must be individualized, using pharmacological and non-pharmacological strategies according to the needs of the moment. Clinical follow-up is always necessary, due to complications that may arise.

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Ethical Approval

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Informed consent

Data from the child under study were obtained through the collection and analysis of information contained in the patient's medical record, duly authorized by those responsible using signing the Informed Consent Form.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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It was applied by Ithenticate®.

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It was applied.

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