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Sotos syndrome: Report of a new pathogenic variant in the *NSD1* gene in an adolescent

Nicolle D. Becerra Páez[1], *Dubán S. Hernández Rodríguez*[1], *Leidy A. Forero Cisneros*[2], *Gustavo A. Contreras García*[2,3], *Víctor C. Mendoza Rojas*[2,4]

ABSTRACT

Sotos syndrome is a genetic disorder characterized by distinctive facial features, intellectual disability, and excessive growth. It is associated with pathogenic variants in the *NSD1* gene, most of which *are de novo*.

We present the case of an 11-year-old girl with overgrowth (height more than 2 standard deviations above the mean), typical craniofacial dysmorphisms, global neurodevelopmental delay, and borderline intelligence. A *de novo nonsense* variant was detected in the *NSD1* gene [NM_022455.5:c.1782dup p.(Glu595Ter)], confirmed by family segregation analysis, which has not been previously described in the literature. The patient also presented with hypotonia, hypoglycemia, neonatal jaundice, strabismus, scoliosis, seizures, and attention-deficit disorder.

This report contributes to our understanding of the phenotypic spectrum of Sotos syndrome in Latin America and highlights the importance of a multidisciplinary approach, as well as timely access to genetic testing to confirm the diagnosis and guide comprehensive patient care.

Keywords: *Sotos syndrome;* NSD1 *gene; growth disorders; intellectual disability; facial features.*

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[1] *Universidad Industrial de Santander, Colombia;* [2] *Pediatrics, Universidad Industrial de Santander, Colombia;* [3] *Genetics, Universidad Industrial de Santander, Colombia;* [4] *Pediatric Endocrinology, Universidad Industrial de Santander, Colombia.*

Correspondence to *Nicolle D. Becerra Páez: becerrapaezn@gmail.com*

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INTRODUCTION

Sotos syndrome (SS) (OMIM #117550) is characterized by the presence of characteristic facial features, intellectual disability, and excessive growth (height and/or head circumference ≥2 standard deviations –SD– above the mean).[1] Overgrowth syndromes (OGS) often go unrecognized; SS is the second most common, with an estimated prevalence of 1 in 14 000 live births.[1,2] Alterations in the *NSD1* gene, located on chromosome 5q35, account for 75% of cases; 95% occur *de novo*, with an autosomal dominant inheritance pattern.[1-3] Partial or total deletions of *NSD1* can be detected using various molecular tests; point mutations can be detected through direct sequencing.[2]

Management should focus on improving the patient's quality of life and addressing complications as they arise.[2] The prevalence and specific clinical characteristics of SS within the Latin American population, and particularly in Colombia, have not been sufficiently studied. This situation poses challenges for both physicians and families, who face delayed diagnosis and inadequate treatment. The objective of this report is to present the case of an adolescent with overgrowth and typical signs of SS, with a previously undescribed variant of the *NSD1* gene.

CLINICAL CASE

An 11-year-old adolescent, the second child of non-consanguineous parents, with a bichorial, biamniotic pregnancy and preterm delivery at 32 weeks with normal anthropometry. She developed neonatal jaundice, hypoglycemia of unknown origin with secondary encephalopathy, neonatal sepsis, and bronchopulmonary dysplasia. Metabolic testing ruled out an inborn error of metabolism. At 2 years of age, bilateral inguinal herniorrhaphy was performed. At 4 years of age, she developed a seizure disorder, which was initially managed with anticonvulsant therapy; in the absence of seizures for more than 2 years and with a normal video-EEG, the medication was discontinued.

During her development, she showed a general delay in reaching developmental milestones for her age group, a neuropsychological evaluation with a full-scale IQ of 71, inattentive-type attention-deficit/hyperactivity disorder (ADHD), and auditory evoked potentials showing mild impairment in the right ear. In addition, she had chronic constipation and was tall for her age. Menarche occurred at age 10. At this age, a carpogram was performed, showing a mild bilateral increase in the metacarpal index of the second and third phalanges, and endocrinological studies were conducted, the results of which are presented in *Table 1*, all within normal ranges. Renal and urinary tract, abdominal, and pelvic ultrasounds, as well as an echocardiogram, were normal.

Mother's menarche at age 10; average parental height of 165 cm. Older sister with treated central precocious puberty (current height 166 cm) and a learning and attention disorder. Twin brother with no height abnormalities.

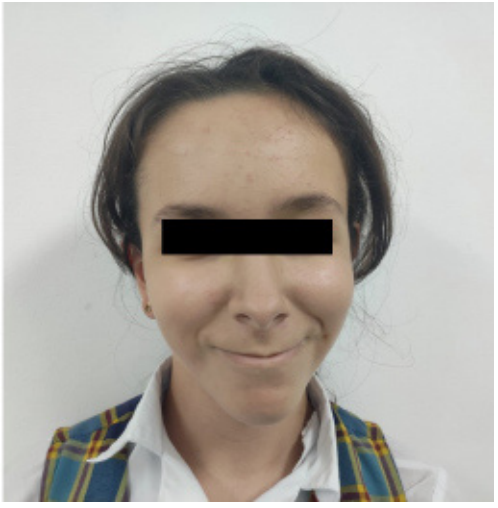
On physical examination, she presented with macrocephaly, a broad and prominent forehead, receding hairline, an elongated face, downward-slanting palpebral fissures, and a long chin (*Figure 1*), as well as scoliosis, amblyopia, and strabismus. Neurologically, she showed hypotonia and hyperlaxity; she did not engage in abstract thinking or make analogies appropriate for her age, and she performed simple calculations.

Table 1. Endocrinological tests performed on the patient

Hormone	Result
FSH	2.9 mIU/ml
LH	0.74 mIU/ml
Estradiol	6.06 pg/ml
Dehydroepiandrosterone	93.4 µg/dl
Prolactin	6.69 ng/ml
TSH	1.28 µIU/ml
Free thyroxine	1.19 ng/dl
IGF-1	204.9 ng/ml

FSH: follicle-stimulating hormone, LH: luteinizing hormone, TSH: thyroid-stimulating hormone, IGF-1: insulin-like growth factor 1.

Figure 1. Adolescent with Sotos syndrome



Characteristic facial features are evident: A broad and prominent forehead, receding hairline, an elongate face, and a long, prominent chin.

Anthropometry: height 162 cm (99th percentile), weight 55.7 kg (91st percentile), growth velocity 2.5 cm/year, Tanner stage 3-3.

Given these findings, it was decided to conduct a molecular study to evaluate OGS, using an NGS (next-generation sequencing) panel for OGS. The variant NM_022455.5(*NSD1*):c.1782dup p.(Glu595Ter) was detected in the *NSD1* gene. A family segregation analysis was performed, which confirmed that the variant was *de novo*.

The differential diagnoses considered included parental tall stature, precocious puberty, gigantism, hyperthyroidism, and Beckwith-Wiedemann syndrome; these were ruled out based on the facial phenotype, age at menarche, and the absence of advanced bone age, hormonal abnormalities, organomegalies, or tumors.

DISCUSSION

Research on growth disorders has primarily focused on short stature; the pathological processes underlying tall stature have received less attention.[4] OGSs may be associated with life-threatening conditions; therefore, clinicians must recognize them early to ensure timely intervention. Some of the phenotypic findings previously used for diagnosis have been correlated with their molecular bases; we now know that SS is a single-gene constitutional disorder.[5]

Ninety percent of patients exhibit the diagnostic triad: 1) excessive growth (tall stature, macrocephaly, long limbs), 2) characteristic facial features, and 3) learning and intellectual disabilities.[2,4] Bone age is typically advanced; however, after age 4, rapid growth stabilizes and final height falls within the average range, although adults with molecularly confirmed SS are tall.[4,6] There appears to be a genotype-phenotype relationship indicating more prominent overgrowth in patients with an *NSD1* intragenic variant than in those with a microdeletion.[7]

Notable facial features include a prominent forehead with dolichocephaly, sparse frontotemporal hair, downward-slanting palpebral fissures, malar erythema, an elongated face due to bitemporal narrowing, a prominent chin, early eruption of deciduous teeth, and an arched palate.[2,4] On the other hand, most patients have mild intellectual disability or borderline intelligence; difficulty with verbal processing, abstract reasoning, and writing; delayed development of motor skills; and difficulty with verbal language development.[2,8]

We present the case of a female patient with the classic triad: tall stature, characteristic facial features, and intellectual disability (early delay in developmental milestones and neuropsychological testing indicating borderline intelligence).[2,8]

The most common behavioral disorders include autism spectrum disorder, ADHD, anxiety, and aggression/tantrums.[9] Between 5–50% of patients have a seizure disorder; half of these cases are febrile.[10] In a multicenter study,

64% of patients with SS and febrile seizures developed epilepsy; 47% of the seizures were generalized tonic-clonic, and 40% were temporal lobe seizures. Most patients responded to monotherapy with anticonvulsants.

Approximately 70% of patients exhibit hypotonia, which contributes to delays in motor development milestones, evident from the neonatal stage, such as difficulty breastfeeding and, later on, in the onset of walking.[4] These problems tend to improve with age, although other issues often arise with expressive language.[4] Other common complications include hypoglycemia, neonatal jaundice (75%), congenital heart defects (20%), maternal preeclampsia (17%), urogenital malformations (19%), renal anomalies (15%), joint laxity and scoliosis (15-30%), four of which were documented in the patient. In monozygotic twins with a variant in the gene, significant phenotypic differences may exist due to post-conception changes, epigenetic factors, and/or environmental factors.[11] Since SS generally results from *de novo* variants, it is less likely that both dizygotic twins will be affected.

The diagnosis is based on detailed medical history and genetic testing to confirm the diagnosis or consider differential diagnoses.[1,4] The clinical presentation varies widely; patients with distinctive clinical findings will be diagnosed through gene-specific testing, while patients with atypical findings will undergo comprehensive genomic testing. In the Colombian cohort, two case reports were identified: one identified a heterozygous *missense* variant in the *NSD1* gene[12] and the other, a 2.028 Mb deletion in the 5q35.2-q35.3 region encompassing the *NSD1* gene.[6] Most variants causing SS are point mutations.[4]

In this case, molecular analysis confirmed a *de novo nonsense* variant caused by a thymine duplication at position 1782, which generated a stop codon, meeting the ACMG variant classification criteria: PVS1, PM2, and PS2, which allows to classify it as a pathogenic variant associated with SS. This change has not been reported in the Database (gnomAD) and ClinVar databases, nor has it been previously described in the literature to date.[13,14]

These patients have a wide range of needs; both a thorough assessment of the extent of the disease and interdisciplinary collaboration are required to determine their treatment options. To this end, the following evaluations are recommended: echocardiogram, renal ultrasound, retrograde cystourethrography, audiological evaluations, and, of course, evaluation and follow-up by clinical genetics and pediatrics.[1] Interventions to address developmental delays and intellectual disability include timely access to occupational therapy, speech-language therapy, physical therapy, and applied behavior analysis therapy. The latter aims to improve areas of social and behavioral functioning.[1] ■

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