Joint hypermobility as a manifestation of neonatal Sotos syndrome

Vanesa Botella López [1,2], Eva García Cantó [1], Alberto Marin Muñoz [1], Caridad Tapia Collados [1,3]

[1]Pediatric Department, Alicante Hospital General, Alicante, Spain
[2]Alicante Institute for Health and Biomedical Research, ISABIAL, Alicante, Spain
[3]ISABIAL, Alicante, Spain

Correspondence to
Dr Eva García Cantó;
egcanto@gmail.com

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Summary Sotos syndrome is associated with hypergrowth, macrocephaly, intellectual disability and characteristic facial features, the diagnosis of which becomes more evident during childhood. We present the case of a full-term newborn, who was admitted to the Neonatology Unit with early hypoglycaemia, hypotonia, a peculiar phenotype and joint hyperlaxity, with dislocation of both wrists. An interventricular communication with haemodynamic repercussions was detected. During his hospitalisation, he presented with feeding difficulties and cholestasis of multifactorial aetiology. Genetic testing detected a pathogenic variant in heterozygosity in the NSD1 gene (c.5990A>G p.Tyr1997Cys) with an autosomal dominant de novo inheritance pattern. Therefore, in a newborn with hypotonia associated with typical facial features, together with joint hyperlaxity, jaundice, hypoglycaemia and feeding difficulties, this syndrome should be suspected and a genetic study requested. In more than 95% of cases, Sotos syndrome is caused by mutations or microdeletions in the NSD1 gene. Given the associated complications, multidisciplinary follow-up is recommended.

BACKGROUND

Sotos syndrome is a syndrome that associates postnatal predominant hypergrowth, macrocephaly, intellectual disability and characteristic facial features. In the neonatal period, hypotonia and feeding problems are prominent.

In most cases, it is due to mutations or microdeletions of the NSD1 gene (5q 35), which is involved in normal growth. The diagnosis becomes more evident in infancy, with typical facial features such as dolichocephaly, elongated face, prominent forehead, downslanting palpebral fissures and pointed chin, as well as delayed acquisition of motor milestones.

CASE PRESENTATION

We present the case of a male newborn admitted to the neonatal unit for early hypoglycaemia and hypotonia. Controlled pregnancy, with pregnancy-induced hypertension and maternal history of vitiligo and autoimmune hypothyroidism. He was born by planned caesarean section and presented with neonatal depression with Apgar test 3/8, which improved with intermittent positive airway pressure.

Examination revealed low birth weight (percentile 3–10) with low adipose panniculus, broad forehead with relative macrocephaly (head circumference percentile 50–75), retrognathia, ogival palate and long, thin arms with muscular hypotrophy (figure 1). The hands were in maximum dorsal flexion, with dislocation of both distal radio-ulnar joints, in relation to a marked joint hyperlaxity (figure 2). Intense axial hypotonia, incomplete Moro reflex and weak and biting suction were prominent. Osteotendinous reflexes were present, and the level of wakefulness was normal. No other associated malformations.

DIFFERENTIAL DIAGNOSIS

In the presence of hypotonia, joint hyperlaxity with wrist dislocations, macrocephaly and the remaining clinical findings, a differential diagnosis was conducted to rule out other neonatal conditions, including inborn errors of metabolism, Weaver syndrome, Bannayan-Riley-Ruvalcaba syndrome, FG syndrome, Marfan syndrome and Down syndrome.

An initial diagnostic workup was performed, consisting of transfontanellar and abdominal ultrasound, as well as cardiologic, ophthalmologic and first-tier metabolic evaluations.

In the initial study protocol, imaging tests such as cerebral and abdominal ultrasound and ophthalmological study were normal. A metabolic cause was ruled out by specific analytical tests. The cardiological study detected a moderate perimembranous ventricular septal defect (VSD) with moderate posterior extension (4–4.4 mm) from left to right, small associated gerbode-type defect (1.36 mm) with early dilation of left-sided chambers.

A genetic study was requested with targeted exome and analysis of the variants present in the genes associated with human phenotype ontology according to the phenotype described.

At 1 month of life, the results of the genetic study were received, which identified the presence in heterozygosis of the pathogenic variant c.5990A>G p. Tyr1997Cys in the NSD1 gene, a result compatible with Sotos syndrome, with an autosomal dominant inheritance pattern inherited de novo. A genetic study was performed on the parents, and the mutation identified in the child was not found in either parent, suggesting a de novo mutation.

TREATMENT

There is no specific treatment and a multidisciplinary approach is recommended for the complications associated with the syndrome. Although no specific protocols are available, it is recommended to perform periodic abdominal ultrasound scans to rule out abdominal tumours, brain ultrasound scans

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Figure 1 Frontal view of the newborn with retrognathia, broad forehead and relative macrocephaly, highlighting the craniofacial features.

with possible electroencephalogram study, and urine catecholamine and BHCG determinations.

OUTCOME AND FOLLOW-UP

The patient presented with early hypoglycaemia and feeding difficulties, requiring intravenous glucose and orogastric tube feeding during the first 6 days of life. He developed hyperbilirubinaemia, initially of indirect predominance, with a subsequent increase in the direct fraction (maximum 3 mg/dL). The cholestasis study was normal, so it was considered to have a multifactorial cause, requiring treatment with ursodeoxycholic acid, with progressive improvement.

After 14 days of life, the patient developed heart failure secondary to VSD, and anti-congestive treatment with diuretics was started with furosemide, captopril and spironolactone.

After adequate stabilisation of the child, with feeding by suction, the patient is discharged from the hospital to home. A follow-up is scheduled with rehabilitation, traumatology, cardiology, paediatric neurology and the early intervention programme. Prophylaxis with nirsevimab was administered according to the current immunisation schedule prior to hospital discharge.

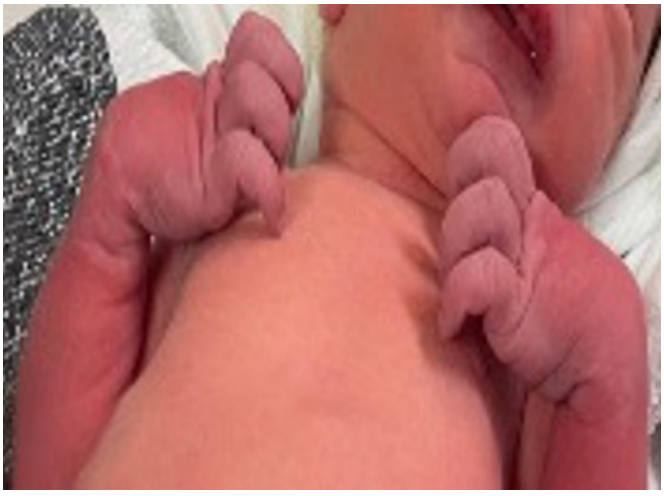

Figure 2 Newborn's hands in maximal dorsal flexion, with bilateral dislocation of the distal radioulnar joints.

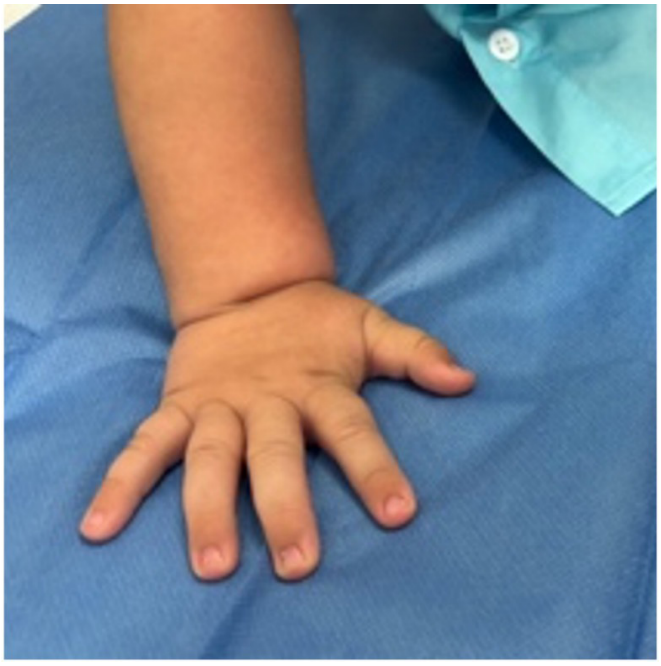

Figure 3 Patient's hand at 8 months of age with joints in normal alignment and no dislocation.

Following discharge from the neonatal unit at 2 months of age, the patient required admission to the paediatric intensive care unit due to bilateral pneumonia caused by *Chlamydophila pneumoniae*, which required non-invasive ventilation with bilevel positive airway pressure (BiPAP).

After this episode, mild respiratory distress persisted, and the patient was discharged home under the supervision of the paediatric home hospitalisation unit, continuing nocturnal BiPAP support due to hypotonia and persistent mild respiratory difficulty, as well as decongestive treatment prescribed by cardiology (captopril, furosemide and spironolactone).

Treatment with ursodeoxycholic acid was discontinued at 2.5 months of age following resolution of the condition.

Neurologically, the patient continues in a rehabilitation and early intervention programme, with significant improvement in hypotonia and joint dislocation resolution (figure 3).

At 8 months of age, psychomotor development is appropriate for age.

The VSD has decreased in size, and heart failure symptoms have improved, allowing discontinuation of spironolactone and furosemide, with captopril maintained as the sole treatment.

Likewise, due to respiratory improvement, non-invasive respiratory support has been withdrawn, although follow-up continues with the paediatric home hospitalisation unit.

In terms of growth, the patient presents with a head circumference above the 97th percentile, with dolichocephaly and a prominent forehead (see figure 4), while weight and height remain within normal percentiles (figure 3).

DISCUSSION

Sotos syndrome has a prevalence of 1/14 000 births.[1] It is an overgrowth syndrome of genetic origin, with a peculiar phenotype,

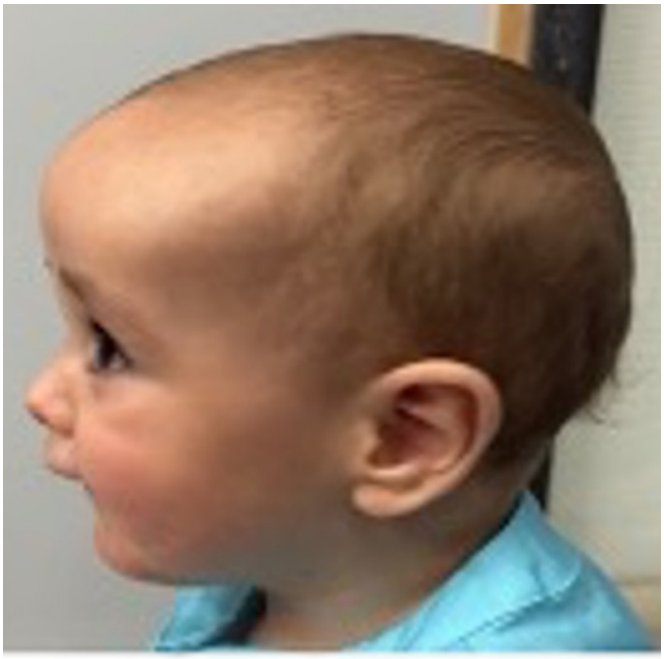

Figure 4 Facial appearance at 8 months of age showing macrocephaly, broad forehead and dolichocephaly.

macrocephaly disproportionate to height and variable intellectual disability.[2]

According to the classic diagnostic criteria of Cole and Hughes[3] from 1994, a clinical diagnosis of Sotos syndrome is highly probable if the three main criteria are met: characteristic facial appearance, excessive and accelerated growth (height and head circumference above the 97th percentile) with advanced bone age, and psychomotor developmental delay.

There are other supportive, non-mandatory criteria that reinforce the suspicion: attention deficit hyperactivity disorder, autism spectrum disorder (ASD), or other behavioural disorders, seizures, neonatal hypotonia, cardiopathies, or other malformations.

In the neonatal period, in addition to the typical facial features present in our case, hypotonia, hyperbilirubinaemia and feeding difficulties stand out, with a greater tendency to hypoglycaemia. The association with cutis laxa and joint hyperlaxity, understood as greater amplitude of normal joint movement, has been described previously in three cases by Robertson and Bankier[4] and in one infant reported by Cortés-Saladefont *et al*;[5] however, no cases have been described with such severe hyperlaxity associated with wrist dislocation, as in the case presented here.

In newborns, with the exception of hip dislocation, other joint dislocations are uncommon. Most of the joint dislocations reported in neonatology involve the hips or knees. However, to the best of our knowledge, there is no literature describing wrist dislocation in this population. Joint dislocation has not been reported as a feature of Sotos syndrome. Nonetheless, hyperlaxity and hypotonia, which are commonly observed in Sotos syndrome, may predispose to joint dislocations and other musculoskeletal complications such as scoliosis.

Diagnosis in the neonatal period is rare, as it usually manifests with more marked postnatal growth in the first 4 years of life, with motor, cognitive, language and learning disabilities. In addition, they may present neurodevelopmental disorders, such as ASD features, brain anomalies (agenesis of the corpus callosum, ventricular dilatation), renal anomalies (vesicourethral reflux), advanced bone age, scoliosis, epilepsy and cardiac anomalies. Our case was associated with a VSD as a cardiac malformation. The cancer predisposition of this syndrome seems to be currently under debate.

The diagnosis of suspicion is based on the main clinical manifestations, already described, and must be confirmed by genetic testing. In more than 95% of cases, Sotos syndrome is caused by mutations or microdeletions of the NSD 1 gene (5q35) known as 'nuclear receptor SET domain-containing protein-1', involved in normal growth and development, and expressed in different organs such as brain, spleen, thymus, kidney, skeletal muscle and blood cells [6 7 7]Some bi-allelic mutations of the APC2 gene (19p13.3) have also been described.[1] In cases with a strong clinical suspicion but negative genetic studies, epigenetic analysis should be performed [8] .

In rare familial cases associated with the NSD1 gene, inheritance follows an autosomal dominant pattern, so genetic counselling should be offered to the family, and the risk of transmitting the disorder to the rest of the offspring should be reported to be 50%. Most patients have de novo mutations, and in these cases, the risk of recurrence is very low.

The general prognosis is marked by the wide spectrum of intellectual disability with the possibility of normal functioning to a completely dependent situation, hence the importance of multidisciplinary follow-up.

As in our case, early diagnosis is beneficial in order to implement rehabilitation and physiotherapy programmes, as well as to initiate immunisation protocols against respiratory syncytial virus, among others.

Learning points

- Diagnosing Sotos syndrome in the neonatal period can be challenging; however, certain features, such as macrocephaly, hypotonia and joint hypermobility, should raise clinical suspicion.
- When this syndrome is suspected, targeted genetic testing enables early and accurate diagnosis.
- In a newborn presenting with joint dislocations, Sotos syndrome should be considered part of the differential diagnosis.

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ORCID iDs
Vanesa Botella López https://orcid.org/0009-0002-7910-8075
Eva García Cantó https://orcid.org/0000-0002-4069-4532
Alberto Marin Muñoz https://orcid.org/0009-0000-4167-4931

REFERENCES

1 Orphanet. Paris: Orphanet; 2020. Available: https://www.orpha.net/es/disease/detail/821
2 Tatton-Brown K, Cole TRP, Syndrome RNS. Sotos syndrome. In: *GeneReviews*. 2025. Available: https://www.ncbi.nlm.nih.gov/books/NBK1479/#sotos.Summary
3 Cole TR, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. *J Med Genet* 1994;31:20–32.
4 Robertson SP, Bankier A. Sotos syndrome and cutis laxa. *J Med Genet* 1999;36:51–6.
5 Cortès-Saladelafont E, Arias-Sáez K, Esteban-Oliva D, *et al*. Síndrome de Sotos: nueva mutación «sin sentido» del gen NSD1 que presenta cutis laxa neonatal. *Anales de Pediatría* 2011;75:129–33.
6 Liu X, Chen C, Wan L, *et al*. A novel nonsense variant in NSD1 gene in a female child with Sotos syndrome: A case report and literature review. *Brain Behav* 2023;13:e3290.
7 Ren Z, Yue L, Hu HY, *et al*. Identification of Novel NSD1 variations in four Pediatric cases with sotos Syndrome. *BMC Med Genomics* 2024;17:116.
8 Lui JC, Baron J. Epigenetic Causes of Overgrowth Syndromes. *J Clin Endocrinol Metab* 2024;109:312–20.