REVISTA ECUATORIANA DE PEDIATRIA
rev-sep.ec

CLINICAL CASE

Noonan syndrome associated with SOS1 gene mutation, case report

Andrea Nájera *[1], Diana Granda[1], María Emilia Arteaga Espinosa[2]

1. Department of Pediatrics, VIDA Pediatric Center, Complementary Health Network, Quito, Ecuador.
2. Department of Medical Genetics, Gynemedic, Mexico City, Mexico.

Received: May 2, 2021
Accepted: November 26, 2021
Published: December 30, 2021
Editor: Dr. Paúl Astudillo Silva.

Bibliographic letterhead:

Nájera A, Granda D, Arteaga M. Freites M, Alvear M. Noonan syndrome associated with a mutation of the sos1 gene, case report. Ecuadorian Journal of Pediatrics 2021; 22 (3): Article 26: 1-7 doi: https://doi.org/10.52011/93

Summary

Introduction: Noonan syndrome is a dominant autosomal inherited genetic disorder with variable phenotypic expression. It is found within diseases known as rasopathies and is produced by mutations in RAS genes. Patients are characterized by facial dysmorphism, short stature, congenital heart disease, musculoskeletal disorders, and, in some cases, intellectual disability.

Clinical case: This report describes the case of a one-month-old male patient who comes to the outpatient clinic, presenting with facial dysmorphism and pulmonary stenosis, for which a multidisciplinary follow-up is carried out due to suspicion of Noonan syndrome. From the fourth month, the patient developed lymphedema in the deltoid area.

Evolution: At 7 months of age, exome sequencing was performed, finding a pathogenic variant in the SOS1 gene and confirming the diagnosis of this syndrome.

Conclusion: This case documents the presence of Noonan syndrome with a mutation of the SOS1 gene with typical facial dysmorphology, pulmonary valve stenosis, cryptorchidism and lymphatic dysplasia with deltoid.

Keywords:

DeCS: Noonan Syndrome, Genes, Congenital Heart Disease, Congenital Anomalies, Craniofacial Anomalies

* Corresponding author:

Email: andreanaul@hotmail.com (Andrea Nájera). Address: Av. Mariana de Jesús, Quito 170147 Telephone: (02) 226-3393

Introduction

Noonan syndrome is a disease of genetic origin, and it has a prevalence of 1/1000-2500 live newborns [1]. It is characterized by typical facial dysmorphism, short stature, congenital heart abnormalities, and varying degrees of intellectual disability. Among the phenotypic characteristics we find: eyelid ptosis, hypertelorism, downward oblique eyelid fissures, low implantation of ear pavilions with posterior rotation and thickened helix, short neck with excess skin on the nape and low posterior hairline, deformation of the rib cage and cryptorchidism [2]. In addition, lymphatic dysplasia, clotting disorders, and feeding problems can occur during childhood. Among the cardiological alterations, the most common are pulmonary valve stenosis and hypertrophic cardiomyopathy [1, 2]. At the cutaneous level, its manifestations will depend on the causal mutation, and café-au-lait spots, pigmented nevi and lentigo can be observed [3].

It has an autosomal dominant mode of inheritance, the karyotype is normal, and nonsense mutations are found in the PTPN11 gene (12q24.1) in 50% of patients. However, mutations in genes of the RAS MAPK metabolic pathway, such as SOS1, RAF1, RIT1 and KRAS, have been discovered in a small proportion of patients. In some cases, the pathogenic variant occurs for the first time in the affected individual, known as a de novo mutation; however, an affected parent is identified in 30 to 75% of families [2].

Cardiological and genetic evaluation, monitoring of growth and psychomotor development, and a guide for eating problems should be included in the management of patients. Most affected children can lead normal lives into adulthood and do not require any particular medical treatment [4].

Clinical case

Male patient product of the second pregnancy, born by iterative cesarean section, son of nonconsanguineous parents, 40-year-old mother and 45-year-old father with a history of testicular cancer in remission. Six-year-old brother diagnosed with Asperger's syndrome. In the first trimester of pregnancy, she presented retroplacental hematoma with progesterone administration, and there were no ultrasound dataof the first trimester sieve. In the second trimester structural ultrasound performed at week 21, bullous pelvic dilation was evidenced, predominantly in the right kidney, with no other positive marker. In the third trimester, polyhydramnios and calcified placenta are evident. He was born by cesarean section at 38 weeks of gestation without complications, birth weight 3382

Fig. 1 Presence of palpebral ptosis, ocular hypertelorism.

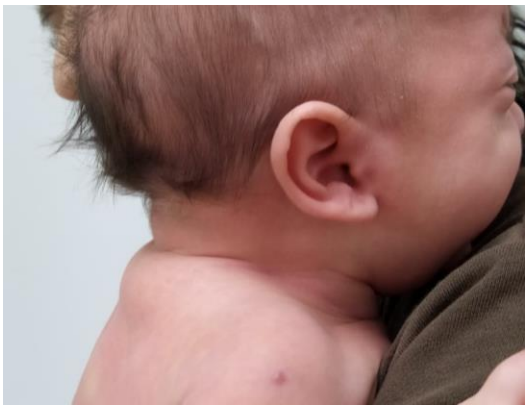

Fig. 2 Presence of a short neck and low implantation of the pinna.

Fig. 3 Abnormal distribution of the folds of the hand.

grams and height 48 cm. In the first hours of life, it presents desaturation and tachypnea. They perform tests showing elevated IL-6, which is why they diagnose early sepsis and administer intravenous antibiotic therapy for 7 days.

On physical examination, they auscultated a systolic murmur in the left sternal border, so on the fourth day of life, it was assessed by pediatric cardiology, and the echocardiogram showed a slightly thickened pulmonary valve with mild stenosis, aortic arch and tortuous descending aorta with slight narrowing and a gradient greater than 22 mmHg and pulmonary hypertension without oxygen 41 mmHg, which decreased to 23 mmHg with O2. Therefore, the use of oxygen was indicated for one month.

He came to the consultation at 27 days of life, and the physical examination revealed a 0.5 cm hemangioma in the right leg and the gluteal region, palpebral ptosis with bilateral pupillary red reflex, grade II systolic murmur in tricuspid focus and hyperphonetic R2 and teletelia. On neurological examination, archaic reflexes were normal, but there were no upward movements.

At 2 months, in consultation, the physical examination revealed a weight of 5.2 kg (P25) and height 56cm (P15), slight dolichocephaly, eyelid ptosis, ocular hypertelorism (Figure 1), downward oblique palpebral fissures and proptosis; short neck (Figure 2), depressed nasal bridge with bulbous nose tip, high palate, low pinna implantation, rectus abdominis diastasis, umbilical hernia, right cryptorchidism, abnormal distribution of the hand crease (Figure 3), overlapping toes (Figure 4). In psychomotor development, he does not smile, babbles little, and does not hold his head.

Diagnostic workshop

Genetics is consulted, who requests a karyotype in peripheral blood reported with a modal number of 46 chromosomes with XY chromosomal sex complement, without evidence of numerical or structural alterations, due to phenotypic characteristics, Noonan syndrome is suggested (Figure 5).

At 4 months of age, a smooth mass without defined borders was evidenced in the left posterior deltoid region (Figure 6). Ultrasound of the lesion was performed, showing a process compatible with lymphedema (Figure 7).

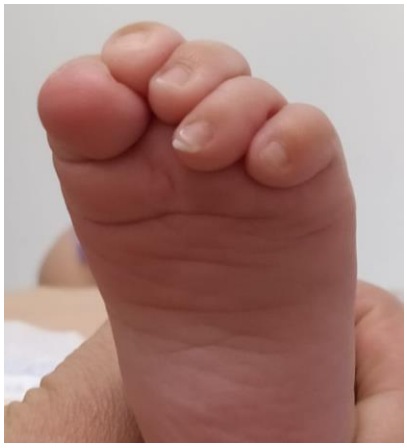

Fig. 4 Presence of overlapping toes.

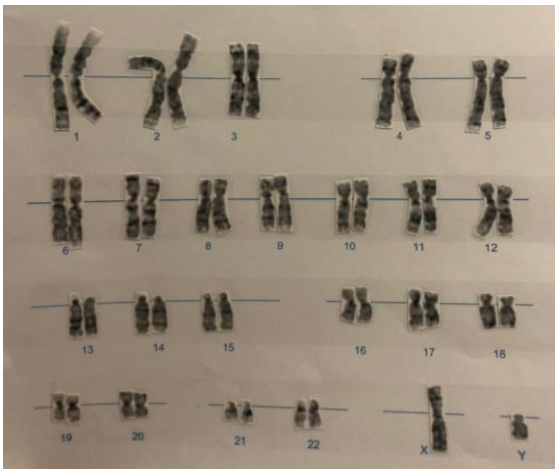

Fig. 5 Karyotype with normal distribution

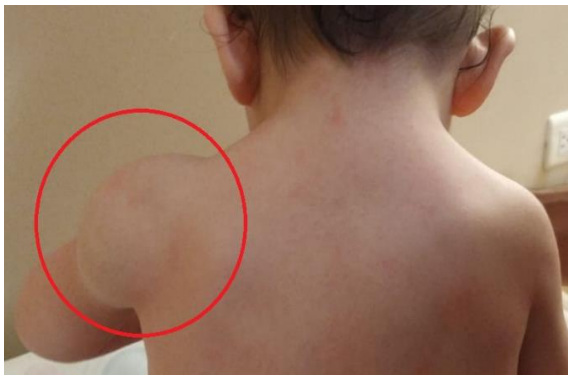

Fig. 6 Mass in the deltoid area at 4 months of age.

Their weight growth continues at the same percentiles, and psychomotor development improves with stimulation without encountering red flags in their development.

At 7 months of age, exome sequencing was performed, finding a pathogenic variant: c.1654A> G (p. Arg552Gly) identified in the SOS1 gene, a variant associated with autosomal dominant RASopathies spectrum disorders, confirming the diagnosis of syndrome by Noonan.

Discussion

The diagnosis of Noonan syndrome is mainly clinical; however, on certain occasions, it may not be so clear since there is great variability in expression, and the phenotype becomes less pronounced with increasing age [5].

Several scoring systems have been designed to aid the diagnostic process, the most recent being developed in 1994 by Van der Burgt [6] and is presented in the table 1

Table 1 Diagnostic criteria for S. Noonan

Clinical manifestation	A Major criteria	B. Minor criteria
1.Facial	Typical facial dysmorphology	Suggestive facial dysmorphology
2. Cardiac	Pulmonary valve stenosis, hypertrophic obstructive cardiomyopathy and / or typical NS ECG	Other flaw
3.Size	Percentile <3	<10th percentile
4 thoracic wall	Pectus carinatum / excavatum	Broad chest
5. Family history	First-degree relative with confirmed SN	First-degree relative with data suggestive of NS
6.Other	Have all: Cryptorchidism Intellectual disability, Lymphatic dysplasia	One of them

Definitive SN: 1 "A" plus another major criterion or two minor ones; 1 "B" plus two major or three minor criteria

In the case of the patient presented in this report, he met the major criteria of typical facial dysmorphology, pulmonary valve stenosis, andcryptorchidism and lymphatic dysplasia, so it could be classified as a definitive diagnosis of Noonan syndrome.

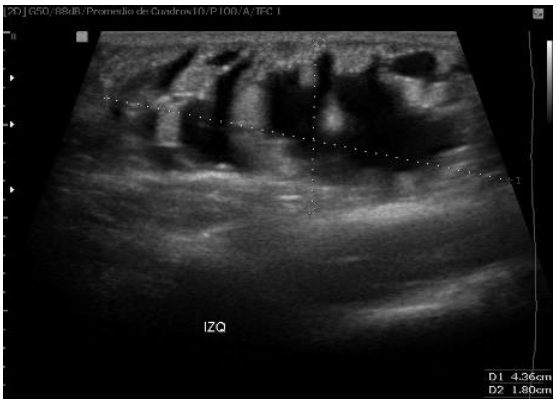

Fig. 7 Presence of lymphedema in the deltoid area.

It should be noted that our patient presented lymphedema in the posterior region of the left shoulder, a characteristic not described in the literature. However, lymphatic vessel dysplasia, hypoplasia, or aplasia is evidenced in 20% of patients, a condition that leads to generalized lymphedema, peripheral lymphedema, pulmonary lymphangiectasia, or intestinal lymphangiectasia. The most common manifestation is lymphedema of the dorsal region of the hands and feet, which generally disappears during childhood [1].

Contrary to what is described in the bibliography, our patient did not present any problems in weight-bearing growth and had a slight delay in psychomotor development that was overcome with early stimulation.

In recent years, a group of genetic diseases called rasopathies, disorders of the RAS/MAPK signaling pathway or neuro-facial-cutaneous disorders have been described, which have alterations in the genes involved in this pathway as a common denominator. Mutations are found in the germline, unlike somatic mutations found in cancer [7].

Within this group, there is Noonan syndrome, which clinically can overlap with other disorders of the same signaling pathway, such as Leopard syndrome, cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis-Noonan syndrome, type 1 neurofibromatosis, Noonan-like syndrome (NLS) presenting with anagen-phase hair loss, Watson's syndrome, and Legius syndrome [3].

The Ras/mitogen-activated protein kinase (MAPK) pathway plays a vital role in development and

is activated by extracellular input in the form of growth factors. It is essential for regulating the cell cycle and cell growth, differentiation, and senescence, all of which are essential for normal mammalian development [7].

The RAS genes constitute a multigene family that includes HRAS, NRAS, and KRAS. RAS proteins are small guanosine nucleotide-linked GTPases that function as critical signaling centers within the cell [7].

To date, rasopathies have been closely related to 8 genes belonging to the RAS/MAPK signaling pathway in etiology: PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, and CBL3. There are no exclusive phenotypic characteristics of a specific genotype, since genetic and epigenetic factors probably influence both the penetrance and the expressiveness of the syndrome.

In the case of Noonan syndrome, seven causal genes and their chromosomal locations have been identified (Table 2).

Table 2 Genetic alterations in Sd. by Noonan

Affected gene	Chromosomal location	Presentation percentage
PTPN11	12q24.1	fifty%
SOS1	2p22.1	10%
RAF1	3p25	3-17%
KRAS	12p12.1	<5%
NRAS	1p13.2	4 cases
MAP2K1 (MEK1)	15q22	<2%
BRAF	7q34	<2%

Taken and modified from: Heredia Ramírez CE, Barros F, Conde JB, Castro-Feijóo L, Cabanas Rodríguez P, Arias MP. Rasopathies. Rev Esp Endocrinol Pediatr. 2013: 68-86

Nonsense mutations in the SOS1 gene are the second most common cause of Noonan syndrome, accounting for approximately 15% of all cases [8].

SOS1 encodes the guanine nucleotide exchange factor protein Ras (RasGEF), which is responsible for stimulating the conversion of Ras from the inactive GDP-bound form to the active GTP-bound form [7]. Most SOS1 missense mutations disrupt the self-inhibition of RasGEF activity, resulting in a gain of SOS1 function, a subsequent increase in the active form of Ras, and an increase in Ras/MAPK pathway signaling. [7]. A study carried out in 2007 by Tartaglia et al. in 22 patients with Noonan syndrome and a mutation in the SOS1 gene showed a high prevalence of congenital heart disease (81%), pulmonary valve stenosis (62%), septum defects (25%), pectus deformities (100%), short and winged neck (94%) and facial dysmorphism, in particular palpebral ptosis and low implantation of the ears, downward oblique palpebral fissures and macrocephaly (56%). He emphasized the more frequent occurrence of ectodermal abnormalities such as keratosis pilaris (50%) and curly hair (88%) and a higher probability of normal development and stature in these individuals compared to others with the syndrome and other mutations [9].

Roberts et al. reported 14 individuals with Noonan syndrome who had a pathogenic variant in SOS1. In this study, no differences were found in terms of development and height from other individuals with the syndrome. Similarly, heart septal defects were found more frequently than in individuals with Noonan syndrome and pathogenic variants in PTPN11 [8].

While cognitive impairment was common among individuals with PTPN11 mutations and those with unknown mutations, all individuals with SOS1 mutations exhibited average or higher verbal and nonverbal cognitive abilities.

Pierpont et al. studied the intellectual abilities in Noonan syndrome and the different genes involved, finding that cognitive impairment was common among individuals with PTPN11 mutations and those with unknown mutations, while all individuals with SOS1 mutations exhibited verbal and nonverbal cognitive abilities in the average or higher range [10].

In cases with a de novo mutation, that is, those where there is no known family history, as in the case of our patient, it has been universally found that the pathogenic variant is of paternal origin. In addition, there is a relationship with advanced paternal age (> 40 years), together with a significant bias in the proportion of affected sexes, favoring transmission to male children, a finding that has not been explained so far but suggests a higher rate of point mutations in paternal spermatogenesis [11].

The reviewed studies suggest that the wide range of clinical manifestations in patients with Noonan syndrome is related to the variable expressiveness typical of autosomal dominant diseases, as well as the allelic and locus heterogeneity present in rasopathies.

This information supports the fact that although the diagnosis can be suspected clinically, assessment by an interdisciplinary group and the establishment of a definitive diagnosis through massive sequencing

with increasingly accessible multigene panels are necessary.

Having a molecular result allows for an adequate genotype-phenotype relationship, which facilitates follow-up and adequate counseling for parents, both in management, prognosis, and risk of recurrence.

Conclusions.

This case documents the presence of Noonan syndrome with a mutation of the SOS1 gene with typical facial dysmorphology, pulmonary valve stenosis, cryptorchidism and lymphatic dysplasia with deltoid lymphedema, a finding not described in previous cases.

Abbreviations

Sd: syndrome.

Supplementary information

Supplementary materials were not declared.

Acknowledgments

We thank the patient's tutors who authorized the publication of the case.

Authors' contributions

Andrea Nájera: Conceptualization, Data Conservation, Formal Analysis, Fund Acquisition, Research, Methodology, Project Management.
Diana Granda: Resources, software, supervision, validation, visualization.
María Emilia Arteaga Espinosa: Writing - original draft, Writing: revision and editing.
All authors read and approved the final version of the manuscript.

Financing

The authors financed the expenses incurred in this report. The costs of diagnostic studies were part of the normal clinical activity of the institution, and the patient did not assume costs for the report of this case.

Availability of data and materials

The data sets generated and/or analyzed during the current study are not publicly available but will be available through the corresponding author upon reasonable academic request.

Declarations

Ethics committee approval and consent to participate

Ethics committee approval is not required for publication of clinical cases. Consent of the guardians was requested for the present case.

Publication consent

The tutors authorized the publication of images of the physical examination and soft tissue ultrasound. The data were hidden to avoid the identification of the patient.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Authors' information

Andrea Nájera Ulloa, Surgeon from the Pontifical Catholic University of Ecuador, Specialist in Pediatrics from the Pontifical Catholic University of Ecuador. Pediatrician at VIDA Pediatric Center and Associate Pediatrician of the Metropolitan Hospital of Quito. Email: andreanaul@hotmail.com
Diana Granda González, Doctor in Medicine and Surgery from the National University of Loja, Specialist in Pediatrics from the International University of Ecuador. Pediatrician at VIDA Pediatric Center and Active Pediatrician of the Metropolitan Hospital of Quito. Email: dkgranda@hotmail.com
María Emilia Arteaga Espinosa, Doctor of Medicine from the International University of Ecuador, specialist in Medical Genetics from the Autonomous University of Mexico, High Specialty in Perinatal Genetics from the Autonomous University of Mexico. Email: emiliaar teaga@gynemedic.mx

References

1. van der Burgt I. Noonan syndrome. Orphanet J Rare Dis. 2007 Jan 14; 2: 4. doi: 10.1186 / 1750-1172-2-4. PMID:17222357; PMCID: PMC1781428.

2. Allanson JE, Roberts AE. Noonan Syndrome Summary Diagnosis Suggestive Findings. 2020: 1-36. PMBID:NBK1124

3. Heredia Ramírez CE, Barros F, Conde JB, Castro-Feijóo L, Cabanas Rodríguez P, Arias MP. Rasopathies. Rev Esp Endocrinol Pediatr. 2013: 68-86. doi:10.3266 / RevEspEndocrinolPediatr.pre2013.Jul.202

4. Cantabria AS de N de. Noonan syndrome. Orientation guide for families. 2014. SU:noonanasturias

5. Shrinuvasan S. Noonan Syndrome - a Rare Case Report. Indian J Med Case Reports. 2014; 3 (September): 12-16.

6. van der Burgt I, Berends E, Lommen E, van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. Am J Med Genet. 1994 Nov 1; 53 (2): 187-91. doi: 10.1002 / ajmg.1320530213. PMID:7856646.

7. Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet. 2013; 14: 355-69. doi: 10.1146 / annurev-genom-091212-153523. Epub 2013 Jul 15. PMID:23875798; PMCID: PMC4115674.

8. Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Kucherlapati RS. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet. 2007 Jan; 39 (1): 70-4. doi: 10.1038 / ng1926. Epub 2006 Dec 3. PMID:17143285.

9. Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, et al. Gain-of-function SOS1 mutations cause a

distinctive form of Noonan syndrome. Nat Genet. 2007 Jan; 39 (1): 75-9. doi: 10.1038 / ng1939. Epub 2006 Dec 13. Erratum in: Nat Genet. 2007 Feb; 39 (2): 276. PMID:17143282.

10. Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, Seidenberg MS. Genotype differences in cognitive functioning in Noonan syndrome. Brain Behav genes. 2009 Apr; 8 (3): 275-82. doi: 10.1111 / j.1601-183X.2008.00469.x. Epub 2008 Dec 11. PMID:19077116; PMCID: PMC2760992.

11. Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, Seidenberg MS. Genotype differences in cognitive functioning in Noonan syndrome. Brain Behav genes. 2009 Apr; 8 (3): 275-82. doi: 10.1111 / j.1601-183X.2008.00469.x. Epub 2008 Dec 11. PMID:19077116; PMCID: PMC2760992 ..

DOI: Digital Object Identifier PMID: PubMeD Identifier SU: Short URL

Editor's Note

The Ecuadorian Journal of Pediatrics remains neutral with respect to jurisdictional claims on published maps and institutional affiliations.