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Case Report

An infant who cannot open her eyes and does not smile: a case report

K. Venkataramana Reddy*, Chapay Soren, Sujatha Chunduri, Sravani N., Bandi Vineeth Kumar

Department of Pediatrics, S. V. S. Medical College, Mahabubnagar, Telangana, India

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***Correspondence:**
Dr. K. Venkataramana Reddy,
E-mail: reddy.venkataramana1@gmail.com

ABSTRACT

Noonan syndrome (NS) is a genetically heterogeneous disorder, with distinctive facial features, short stature, chest deformity, and congenital heart diseases. Germline mutations in the RAS-MAPK (mitogen-activated protein kinase) signal transduction pathway result in Noonan syndrome. It shares clinical features with other RASopathies like Costello syndrome, and cardio-facio-cutaneous syndrome. Ocular findings like hypertelorism, ptosis, refractive errors, strabismus, amblyopia, and external eye abnormalities. It is often difficult to differentiate from other syndromes. Molecular genetic testing can confirm the diagnosis in 70% of cases and plays an important role in genetic counselling and management.

Keywords: Noonan syndrome, Genetic, Strabismus, Ptosis, RAS-MAPK, RASopathies

INTRODUCTION

Noonan syndrome (NS) is a multi-systemic, autosomal dominant condition characterized by facial dysmorphism and short stature, first described by Jacqueline Noonan and Ehmke in 1963. Its incidence ranges from 1/1000 to 1/2500 live births.[1]

NS involves mutations in genes of the RAS-MAPK signaling pathway. Similar genetic disorders, such as Costello syndrome, cardio-facio-cutaneous syndrome, Noonan syndrome with multiple lentigines (NS-ML), and neurofibromatosis type 1, are known as RASopathies or neuro-cardio-facio-cutaneous syndromes.[2,3]

Facial features include a broad forehead, hypertelorism, down-slanting palpebral fissures, ptosis, and low-set posteriorly rotated ears. Cardiac defects like pulmonary valve stenosis, atrial septal defects, and hypertrophic cardiomyopathy are common. Individuals may have mild intellectual disabilities, developmental delays, and a higher risk of malignancies later in life.[4]

CASE REPORT

We presented a 5-month-old girl with a history of incomplete eyelid opening and persistent eye watering since birth. Born at term via LSCS due to non-progression of labor, she had a birth weight of 2.5 kg. She cried right after birth and was promptly breastfed. Her mother noticed that the infant couldn't fully open her eyes and had no facial expressions while crying. There were no issues with facial asymmetry, milk pooling, or choking. The baby appeared less vigorous, had poor head control, and did not respond with a smile, despite looking at her mother during feeding. The mother, who had seizures and was treated with levetiracetam during pregnancy, reported no decreased fetal movements or polyhydramnios, and the infant had no NICU admissions. She was exclusively breastfed.

Developmentally, the infant can roll over but lacks stable head control, social smiling, and reaching for objects.

Her examination revealed a weight of 4.9 kg (<3rd centile), length of 65 cm, and head circumference of 39 cm (3rd centile) with an open anterior fontanel. Notable findings included drooping eyelids, down-slanting palpebral fissures, a flat nasal bridge, hypertelorism, a long philtrum, a bulky upper lip, an expressionless face, loss of nasolabial folds, no eye movement, and inability to follow objects. Pupils were reactive. Muscle tone was decreased, deep tendon reflexes were normal, and there were no neurocutaneous markers or skin bruising. Systemic examination was normal.

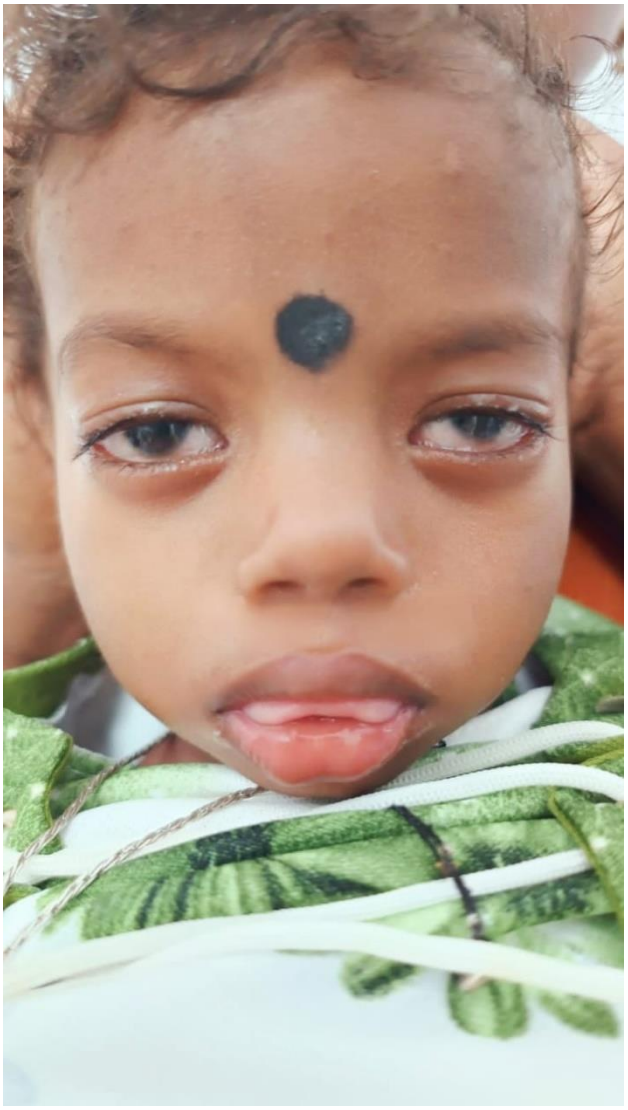
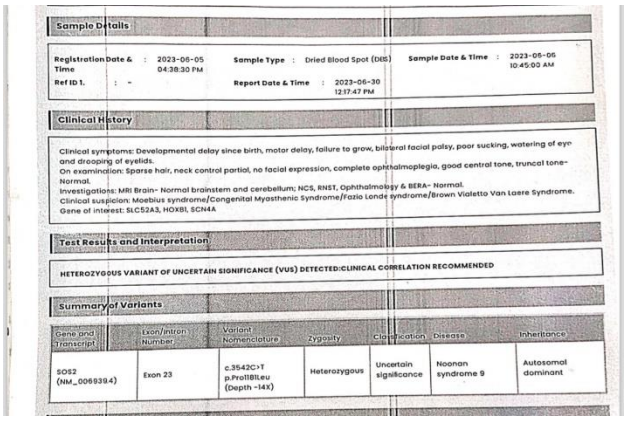


Figure 1: Bilateral ptosis with masked facial features.

These features suggested bilateral facial weakness, external ophthalmoplegia, dysmorphic facies, microcephaly, central hypotonia, and developmental delay, which made us to consider a syndrome (Figure 1).

Differential diagnoses included Noonan syndrome, Costello syndrome, congenital myasthenia (ruled out by normal repetitive nerve stimulation and no response to pyridostigmine), hereditary motor neuropathy (ruled out by normal nerve conduction studies), Brown-Vialetto-Van-Laere syndrome (no sensorineural hearing loss), Fazio-Londe syndrome (no response to riboflavin), Moebius syndrome (normal MRI), and Horner syndrome (normal pupillary responses).

Investigations showed normal MRI, repetitive nerve stimulation test (RNST), nerve conduction studies, and brainstem evoked response audiometry (BERA). Ophthalmic examination suggested external ophthalmoplegia with a normal fundus; visual evoked potentials were not performed. Additional tests, including CK-MB, thyroid function tests, and 2D echocardiography, were normal. Whole exome sequencing identified a heterozygous SOS2 gene mutation of uncertain significance (Figure 2).


Sample Details

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Clinical History

Clinical symptoms: Developmental delay since birth, motor delay, failure to grow, bilateral facial palsy, poor sucking, watering of eye and drooping of eyelids.
On examination: Sparse hair, neck control partial, no facial expression, complete ophthalmoplegia, good central tone, truncal tone- Normal.
Investigations: MRI Brain- Normal brainstem and cerebellum; NCS, RNST, Ophthalmology & BERA- Normal.
Clinical suspicion: Moebius syndrome/Congenital Myasthenic Syndrome/Fazio Londe syndrome/Brown Vialetto Van Laere Syndrome.
Gene of interest: SLC52A3, HOXB1, SCN4A

Test Results and Interpretation

HETEROZYGOUS VARIANT OF UNCERTAIN SIGNIFICANCE (VUS) DETECTED:CLINICAL CORRELATION RECOMMENDED

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature	Zygosity	Classification	Disease	Inheritance
SOS2 (NM_006939.4)	Exon 23	c.3542C>T p.Pro1181Leu (Depth -14X)	Heterozygous	Uncertain significance	Noonan syndrome 9	Autosomal dominant

Figure 2: Whole exome sequence SOS2 gene mutation.

At the 8-month follow-up, the child demonstrated significant developmental progress, including crawling, sitting with support, and standing with assistance. She showed progress by crying and recognizing her parents but continued to have limited eye movements, persistent eye watering, and a subdued smile.

DISCUSSION

NS is a heterogeneous group of multiple congenital anomalies. With the emergence of these characteristics at different ages, clinical diagnosis is difficult in older age, as the changes are not easily noticed.

The first gene discovered to be responsible for NS was PTPN11 on chromosome 12q24.1. Dysfunction of this gene influences various developmental processes.[5] The RAS-MAPK cascade is a well-known intracellular signalling pathway resulting in transcription in the cell nucleus and is involved in cell proliferation, differentiation and apoptosis processes. Gain-of-function results in dysregulation of the RAS-MAPK pathway. This dysregulation of molecular pathways results in profound deleterious effects on developmental processes. More than 14 genes were identified with germline mutations responsible for NS. Gain-of-function mutations in

PTPN11 account for approximately 50% of all cases. The other gene mutations include SOS1 (10-15%) and RAF1 (5-10%). The less common causative genes for NS are KRAS, NRAS, RRAS, CBL, SOS2, LZTR1 and RIT1 which are rarely mutated in NS.[6,7]

Heterozygous variants in the gene SOS2 (MIM 601247) have recently been identified in a few patients with NS. SOS1 and SOS2 share 70% amino acid homology. Heterozygous variants in SOS2, encoding a guanine nucleotide exchange factor for RAS, have recently been identified in patients with NS. The phenotype associated with SOS2 variants has been described as fitting the general NS spectrum and resembling the phenotype of SOS1-related NS. A study published by Lissewski et al found an increased risk of lymphatic complications with SOS 2-related NS.[8]

The most frequent external features described in the literature include facial features that vary with age. Children usually lack an expression and mimic myopathic faces. NS due to a SOS1 mutation, the most frequent ocular findings were hypertelorism and ptosis.[5]

Ocular manifestations in NS

Ocular findings in these children include hypertelorism, down-slanting palpebral fissures, epicanthal folds, and ptosis (unilateral or bilateral). The most common are refractive errors (61%), strabismus (48-63%), and amblyopia (33%), etc. have been described in up to 95% of NS.[1,9,10] In 90% of children, the ears appear low, oval in shape, with thick helix and posteriorly rotated. The nose seems short and broad. The upper lip is distinctive with a deeply grooved philtrum, high, wide peaks to the vermillion of the upper lip (95%), and full lips. In 55% of the cases, the neck appears short with redundant skin and a low posterior hairline.[11,12] Other ocular abnormalities, including eyelid and external eye abnormalities, are the prevailing features.[13]

These patients usually appear with ocular alignment and motility disorders, including strabismus, absence of normal stereopsis, limited ocular motility, or nystagmus. The limited ocular motility may present as limited abduction, limited adduction, or limited elevation.[6] Other findings include congenital heart defects (pulmonic stenosis and HCM), a webbed neck, short stature, chest (pectus deformities) and spine abnormalities (scoliosis), cryptorchidism, and coagulation disorders (von Willebrand disease, deficiencies of factors XI and XII, and thrombocytopenia).[14,15]

As NS is inherited in an autosomal dominant manner, an affected parent has a 50% chance of passing the disorder to each child. If neither parent is affected, the risk for their children is less than 1%. Early diagnosis is crucial for counselling parents about the risks of future pregnancies.

CONCLUSION

NS presents with high phenotypical heterogeneity. Dysmorphic faces and poor skeletal growth are good pointers to suspect syndromic conditions. We conclude that SOS2 is one of the known gene mutations responsible for the clinical phenotype. This case highlights that all the clinical findings mentioned in our case will be helpful in the diagnosis of Noonan syndrome, particularly in a child who presents with a mild phenotype in the absence of cardiac anomalies. This case adds to the understanding of the Noonan syndrome clinical spectrum and guides clinicians to consider it as a differential diagnosis for congenital ptosis and expressionless face.

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