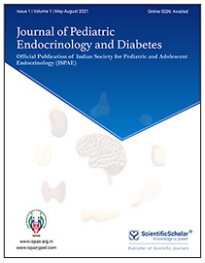
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ispae-jped.com/

Journal of Pediatric Endocrinology and Diabetes



Case Report

Those blue eyes; an eye opener – A rare case report of Marshall-Smith syndrome

Amina Shamsudeen[1], Veena Viswambharan Nair[1], Kamala Swarnam[1], Parameswaran Madhavachandran Nair[1], Mili Thomas[1], Gopika Sekhar Remadevi[1]

[1]Department of Pediatrics, Ananthapuri Hospital and Research Institute, Thiruvananthapuram, Kerala, India.

***Corresponding author:**
Amina Shamsudeen,
Department of Pediatrics,
Ananthapuri Hospital
and Research Institute,
Thiruvananthapuram, Kerala,
India.

aamishams@gmail.com

Received : 06 February 2023
Accepted : 10 March 2023
Published : 11 April 2023

DOI
10.25259/JPED_2_2023

Quick Response Code:

ABSTRACT

We report a 6-month-old female baby, with dysmorphic facies, recurrent respiratory tract infections, and failure to thrive. A detailed search for genetic causes of failure to thrive including next-generation sequencing revealed the diagnosis of a very rare entity; Marshall–Smith syndrome, a syndrome with very high early mortality. On further evaluation, she was noted to have disordered osseous maturation. She is now on regular follow-up for early intervention and rehabilitation.

Keywords: Marshall–Smith syndrome, Accelerated skeletal maturity, Blue sclera, Genetics, Dysmorphic facies

INTRODUCTION

Marshall–Smith syndrome (MRSHSS) is a genetic disorder caused by genetic changes in the *NFIX* gene, in which individuals typically have advanced bone age, failure to thrive, unique facial features, and intellectual disability. It was initially described by Marshall *et al.* in 1971.[1] Only 60 cases have been reported so far in the world literature, including one from our country.[2] We report a 6-month-old female infant who presented with characteristic features of MRSHSS, with confirmed nuclear factor 1 X (*NF1X*) mutation due to exon 10 deletion (c1451del variant).

CLINICAL PROFILE

The child is an early term (37 weeks and 4 days), 2.46 kg, low birth weight baby girl with normal length and head circumference who was second born to non-consanguineous parentage. At birth, the baby was noted to have dysmorphic features including triangular facies, prominent forehead, protruding eyes, blue sclera, megalocornea, depressed nasal bridge, anteverted nares, posteriorly rotated ears [Figure 1], high arched palate, hypertrichosis along with clitoromegaly, genital and axillary hyperpigmentation [Figure 2] and long, and slender limbs. There was no history of exposure to any known teratogen. Family history was non-contributory. Antenatal ultrasound was suggestive of polyhydramnios.

The baby was initially evaluated for probable congenital adrenal hyperplasia since she had clitoromegaly, hypertrichosis, and genital hyperpigmentation. However, hormonal and genetic evaluation ruled out congenital adrenal hyperplasia. She had stridor and feeding issues in the

postnatal period, for which laryngology evaluation and swallowing assessment were done which were normal except for a narrow nasal cavity.

The baby had frequent hospital visits for recurrent respiratory infections, poor weight gain, noisy breathing, and feeding difficulty. On follow-up, baby had feeding difficulty which became worse with recurrent vomiting and poor weight gain, and she needed nasogastric feeding in between. Severe failure to thrive despite resolving the feeding issues and the prominent dysmorphic features including blue sclera prompted us to do next-generation sequencing (NGS) to look for genetic causes, which turned out to be positive for Marshall–Smith syndrome. NGS showed heterozygous 1 base pair deletion in exon 10 of the *NF1X* gene (chr19: g.13090347del; Depth: ×413). A radiographic skeletal survey at 6 months of age revealed a markedly advanced bone age. Radiological assessment also showed wide proximal and middle phalanges of the hands [Figure 3]. Terminal phalanges were markedly short and narrow.

Figure 1: A 6-month-old baby with characteristic facies of Marshall–Smith syndrome: Prominent forehead, protruding eyes, blue sclera, telecanthus, triangular facies, and megalocornea.

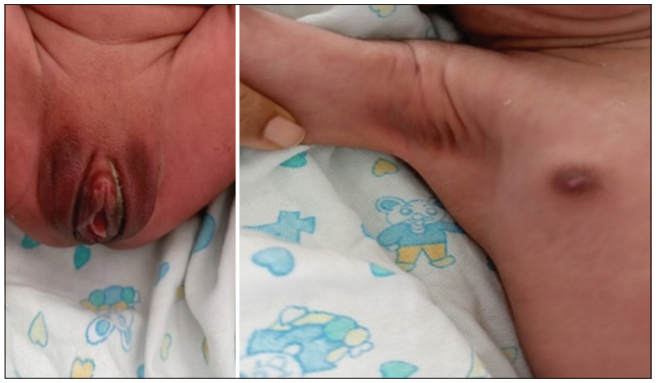


Figure 2: Prominent clitoris and genital and axillary hyperpigmentation noticed at birth.

Bone age was assessed to be around 5 years (carpal – 5 years, radial head – 1 year, and phalanges – 20 months) by Greulich and Pyle method. Ophthalmology evaluation showed hypertelorism, megalocornea, blue sclera, and fundus evaluation, which was normal. Cardiology evaluation and evaluation of other systemic evaluations were within normal limits. She is on regular follow-ups from genetic and nutrition clinics and is undergoing early interventional therapy.

DISCUSSION

The major manifestations of MRSHSS described include moderate to severe developmental delay, severe respiratory difficulties, characteristic facial features (high forehead, proptosis, anteverted nares, and retrognathia), abnormal bone ossification, and failure to thrive.[2] Other highly prevalent features reported are blue sclerae, visual impairment[3] hypertrichosis, gingival hypertrophy, and the development of kyphoscoliosis in later childhood and adolescence.[4]

Previous case reports suggest distinct frameshift and splice *NF1X* mutations that escaped nonsense-mediated mRNA decay in MRSHSS patients.[5]

NF1X gene belongs to the nuclear factor one family of transcription factors, and its specific function is presently unknown. Normally, *NF1X* is expressed prenatally during human brain development and skeletogenesis.

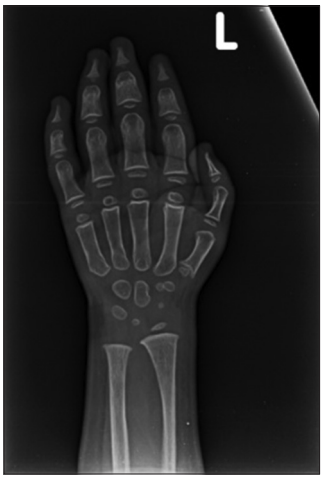


Figure 3: Bone age assessment showing advanced osseous maturation (Carpal 5 years, radial head 1 year, and phalanges 20 months) by Greulich and Pyle method.

The disorder appears to affect males and females equally.[3] Other close differentials to be considered in the differential diagnosis are Weaver syndrome[2,6] and Malan syndrome. Weaver syndrome is characterized by accelerated skeletal maturity and characteristic facies different from MRSHSS. A child with Weaver syndrome is usually thriving well and has normal development. Malan syndrome is a rare genetic syndrome due to *NF1X* gene mutation characterized by features like MRSHSS such as accelerated skeletal maturity, blue sclera, triangular facies, developmental delay, and skeletal abnormalities. Ophthalmologic features (deeply set eyes, down-slanting palpebral fissures), macrocephaly, and seizures seen in Malan syndrome make it characteristically different from MRSHSS.

Blue sclera can be a manifestation of many conditions such as osteogenesis imperfecta, Ehlers–Danlos syndrome, and Marfan syndrome and overgrowth syndromes like MRSHSS, Malan syndrome, and Sotos syndrome. Definitive diagnosis could be made possible only by molecular genetics.

MRSHSS is an autosomal dominant disorder characterized by abnormal bone maturation with skeletal anomalies, airway obstructions, failure to thrive, developmental delay, intellectual disability, and typical facial features.

Treatment of MRSHSS is based on symptoms and giving supportive care to the patient. Due to the developmental delay, special education programs and other supportive resources may be utilized early in such patients.[3]

Most of the reported cases died in the first 3 years of life due to respiratory problems. Aspiration pneumonia is frequent due to underdeveloped epiglottis and pharyngeal incoordination. Malnutrition and respiratory infections are dangerous complications encountered and should be aggressively treated.

CONCLUSION

The confirmation of diagnosis of MRSHSS is still a challenge, especially due to the extremely low incidence of this disorder. However, it should neither be neglected nor underestimated due to the variable prognosis and highly differing health complications that follow.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Marshall RE, Graham CB, Scott CR, Smith DW. Syndrome of accelerated skeletal maturation and relative failure to thrive: A newly recognized clinical growth disorder. J Pediatr 1971;78:95-101.
2. Sharma AK, Haldar A, Phadke S, Agarwal SS. Marshall-Smith syndrome: A distinct entity. Indian Pediatr 1994;31:1098-100.
3. Deshpande C, Forrest M, Russell-Eggitt I, Hall CM, Mehta R, Paterson J. Visual impairment and prolonged survival in a girl with Marshall-Smith syndrome. Clin Dysmorphol 2006;15:111-3.
4. Shaw AC, van Balkom ID, Bauer M, Cole TR, Delrue MA, Van Haeringen A, *et al*. Phenotype and natural history in Marshall-Smith syndrome. Am J Med Genet A 2010;152A:2714-26.
5. Malan V, Rajan D, Thomas S, Shaw AC, Dit Picard HL, Layet V, *et al*. Distinct effects of allelic *NFIX* mutations on nonsense-mediated mRNA decay engender either a Sotos-like or a Marshall-Smith syndrome. Am J Hum Genet 2010;87:189-98.
6. Adam MP, Hennekam RC, Keppen LD, Bull MJ, Clericuzio CL, Burke LW, *et al*. Marshall-Smith syndrome: Natural history and evidence of an osteochondrodysplasia with connective tissue abnormalities. Am J Med Genet A 2005;137:117-24.

How to cite this article: Shamsudeen A, Nair VV, Swarnam K, Nair PM, Thomas M, Remadevi GS. Those blue eyes; an eye opener – A rare case report of Marshall–Smith syndrome. J Pediatr Endocrinol Diabetes 2022;2:142-4.