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Case Report

Trouble doubled: a rare case of Schaaf Yang syndrome with severe acute malnutrition

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ABSTRACT

Schaaf-Yang syndrome is a genetic disorder caused by mutations in the paternal allele of the Melanoma antigen L2 (MAGEL2) gene. Developmental delay, feeding difficulties with joint contractures and a high prevalence of development disorders including autism are characteristic of this syndrome. We describe a unique case of an infant with Schaaf-Yang syndrome who presented with failure to thrive. The case emphasizes the need for genome sequencing for early diagnosis and management of this rare genetic disease. It also highlights the need to think beyond nutrition when it comes to severe acute malnutrition.

Keywords: Schaaf Yang syndrome, Failure to thrive, Development delay

INTRODUCTION

Schaaf-yang syndrome (SYS) is a rare genetic disorder caused by mutations in the paternal allele of the Melanoma antigen L2 (MAGEL2) gene.[1,2] MAGEL2 is a maternally imprinted, paternally expressed, protein coding gene present on chromosome 15q11, within the critical region of Prader Willi syndrome (PWS).[1]

Clinical manifestations include muscular hypotonia seen at birth with distal joint contractures in a majority of affected individuals. Gastrointestinal/feeding problems are seen in infancy leading to severe acute malnutrition. Respiratory distress is present in many individuals at birth with need of intubation and mechanical ventilation. Skeletal manifestations such as joint contractures, scoliosis, and decreased bone mineral density are usually seen.

All affected individuals show developmental delay, resulting in intellectual disability of variable degree, from low-normal intelligence to severe intellectual disability. Other clinical features may include short stature, seizures, eye anomalies, and hypogonadism.[3]

CASE REPORT

A 2-month-old male born to non-consanguineous marriage was brought to the pediatric outpatient unit with complaints of stiffness of all four limbs and poor feeding since birth. Antenatal scans showed intrauterine growth restriction. Baby had weak cry at birth with history of neonatal intensive care unit (NICU) admission in view of respiratory distress. On examination, child had dysmorphic facies with cranial synostosis, sunset sign, dilated veins over forehead, nystagmus with failure to thrive. Systemic examination revealed hypertonia of all four limbs, contractures of bilateral wrist with undescended testis. In view of suck rest suck cycle, pediatric cardiology opinion was taken and echo done revealed tiny patent foramen ovale (PFO) with patent ductus arteriosus (PDA) (left to right shunt). Magnetic resonance imaging (MRI) brain and lumbar puncture was done which was normal. Physiotherapy, neurodevelopmental stimulation and oromotor stimulation was taught to the mother and continued. Visual assessment was done and showed normal fundus with absence of fixation. Parents were counselled regarding the need for visual rehabilitation. Vitamin B12, homocysteine, serum creatine phosphokinase (CPK) and tandem mass

spectrometry (TMS) was done which were normal. In view of suspected genetic disorders whole exome sequencing was done which demonstrated a de novo heterozygous, frameshift variant c.1996dupC in exon 1 of the MAGEL2 gene that results in amino acid substitution p.Gln666fs*47 causing SYS. Child was continued on physiotherapy and neurodevelopmental stimulation and other supportive measures. Child was started on nutritional rehabilitation for severe acute malnutrition. Parents were counselled regarding need for genetic testing before next pregnancy.

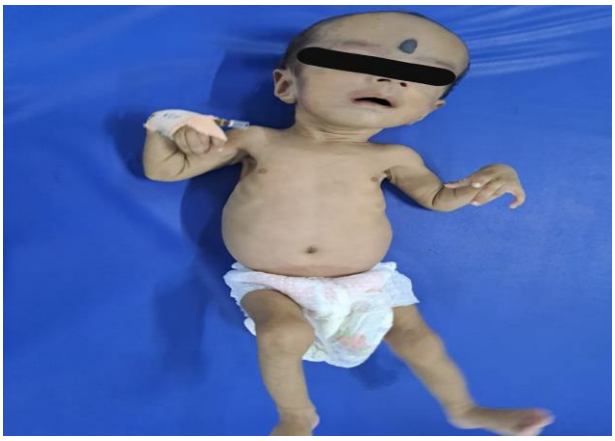

Figure 1: A male baby with Schaaf Yang syndrome with dysmorphic facies, severe wasting and bilateral contractures.

DISCUSSION

MAGEL2 is a paternally expressed, maternally imprinted, protein-coding gene located on chromosome 15. MAGEL2 is one of the genes that falls into the paternally expressed region of chromosome 15.

SYS is seen to have protean manifestations including infantile hypotonia, feeding difficulties, leading to failure to thrive, hypoglycemia which may progress to hyperphagia in childhood, developmental delay with joint contractures. Our child had failure to thrive owing to feeding difficulties seen since birth with joint contractures.[4] However unlike infants of SYS, our child exhibited hypertonia of all four limbs with associated undescended testis. The estimated prevalence is less than 1 per 1,000,000 and there are 160 cases published in the literature to date.[5,6]

Approximately 50% of individuals diagnosed with SYS inherited a MAGEL2 pathogenic variant from father who is asymptomatic and the remaining individuals have a de novo mutation. If the father of the proband is heterozygous for the MAGEL2 pathogenic variant identified in the proband, the risk to both male and female siblings is 50%.[2] The recurrence risk within the family of the proband's mother is similar to that of the general population. Once the MAGEL2 pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are viable options.

The c.1996dupC variant is the most prevalent pathogenic mutation, found in 40-50% of affected individuals as seen in our child. Compared to affected individuals who have other truncating variants, those with the c.1996dupC variant display a more severe phenotype, including a higher prevalence of joint contractures, more severe respiratory complications, more pronounced developmental delay and intellectual disability.[3]

With whole genome sequencing becoming more accessible in the current era, this diagnostic dilemma can be shortened, saving both time and other valuable resources for families and the community. An earlier diagnosis can also have a significant impact in care outcomes by guiding decision-making for general pediatricians and giving scope for early referral.[2]

Additional studies will be necessary to continue monitoring the expanding cohort of individuals with truncating mutations in MAGEL2 and their associations. Through the continued analysis of these patients, we hope to provide updated recommendations for physicians and families, to provide the best care for those affected by SYS.

CONCLUSION

This report exemplifies the need of early utilization of whole genome sequencing, especially in infancy, to facilitate early diagnosis of rare conditions like SYS, which, in turn, could help save considerable amount of time and resources and help to improve clinical outcomes of patients. It also emphasises the need to look beyond malnutrition as a cause of failure to thrive in a child with severe acute malnutrition. It also offers scope for genetic testing and preimplantation testing which will make a huge difference in the lives of families and parents caring for these children.

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