CASE REPORT

Mabry Syndrome in a Child of South Asian Descent

Amir Humza Sohail[1], Muhammad Younus Khan Durrani[2], Shahnaz Hamid Ibrahim[3] and Khadija Nuzhat Humayun[3]

ABSTRACT

Mabry syndrome is the triad of seizures, hyperphosphatasia, and mental disability. It usually manifests in first year of life and has an autosomal recessive mode of inheritance. Besides the usual triad, other manifestations of Mabry syndrome include hypoplasia of distal phalanges, brachytelencepahly, gastrointestinal malformations and constipation, hypertelorism, short nose with a broad nasal bridge and dip, and thin upper lip with down turned corners of the mouth. More than 20 cases of Mabry syndrome have been reported in medical literature. Herein, we report the case of a six-month child with Mabry syndrome that presented with decreased neck holding, hypotonia and delayed motor milestones. The child also had a high-arched palate and hyperplastic malar eminences. Constipation was present but had a delayed onset, starting at 19 months of age. This is the first case of Mabry syndrome occurring in a child of South Asian descent.

Key Words: *Mabry syndrome. South Asia. Mental retardation. Epilepsy. Hyperphosphatasemia.*

INTRODUCTION

Mabry syndrome is the triad of seizures, hyperphosphatasia and mental disability. It usually manifests in first year of life with severe developmental delay and tonic-clonic seizures.[1,2] Mabry *et al*. first reported Mabry syndrome in three affected sibs of different sexes and an affected first cousin presenting with mental retardation, neurologic abnormalities and hyperphosphatasia, born to a multiply consanguineous family.[3] From pedigree analysis, the mode of inheritance of this disease was identified to be autosomal recessive. Kruse *et al.* confirmed the association of mental retardation and hyperphosphatasia in a case series comprising of nine patients.[4]

Rabe *et al*. reported two patients with features of severe mental retardation without speech development, persistently elevated alkaline phosphatase (AP) levels, hypoplasia of distal phalanges and facial abnormalities while Marcelis *et al*. reported two similar patients in 2007.[5,6] The combination of mental retardation with distal phalangeal hypoplasia caused both Rabe and Marcelis to consider the diagnosis of Coffin-Sirs Syndrome. Since these initial reports, more than 20 patients with the triad of Mabry syndrome have been identified and reported in medical literature.[1]

A subtype of Mabry syndrome associated with mutations in 1-6 manosyltransferase 2, phosphatidylinositol glycan V (PIGV) gene has also been identified.[7] Besides the classic triad of Mabry syndrome, mutations in PIGV gene may be responsible for many of the anomalies seen in Mabry syndrome, for example brachetelephalangy and anal abnormalities.[6,8]

Herein, we report the case of a child that presented at 6 months of age with decreased neck holding, hypotonia and delayed motor milestones and was later diagnosed to have Mabry syndrome.

CASE REPORT

A six-month male child of consanguineous parents presented to the pediatrics clinic with complaints of decreased neck holding, hypotonia and delayed motor milestones. He was born via emergency lower segment Cesarean section due to decreased fetal movements (second degree fetal distress) at 36 weeks of gestation. Antenatal history was positive for gestational diabetes mellitus and ultrasound scans showed polyhydramnios. Birth weight and head circumference were 2.9 kg and 49.0 cm, respectively; and Apgar scores were good. Postnatal history was unremarkable. At this initial visit, a broad wrist was noted and wrist X-ray was carried out but no abnormality was seen.

The child presented again at 12 months of age with partial neck holding and inability to sit. According to the mother, partial neck holding was achieved at 9 months of age. Physical examination showed that social smile and babbling were present; the child was able to roll over. Weight-for-age and height-for-age were within normal limits. Neurological examination showed decreased tone, positive reflexes of grade +2 and power of 4/5 in all four limbs. Scissoring was seen on holding. Eye examination was unremarkable. Other abnormalities noted were a high-arched palate, hypertelorism and hyperplastic malar prominences. No musculocutaneous abnormalities were noted. Laboratory findings for the various stages of follow-up are reported in Table I. CT scan of the brain showed atrophic findings in the frontal lobe.

[1] *Department of Surgery, Howard University, Washington, USA.*
[2] *Department of Surgery / Paediatrics[3], The Aga Khan University, Karachi.*

Correspondence: Dr. Amir Humza Sohail, Resident, General Surgery, Howard University Hospital, Georgia Avenue, Washington D.C., USA.
E-mail: ameer.hamzasohail@gmail.com

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At 19 months of age, the child presented with mild constipation and tonic-clonic seizures with a frequency of 50 jerks/hour. The parents reported sudden head dropping during the seizure episodes. Electro-encephalogram, echocardiogram, electromyography, brain and brainstem evoked response audiometry (BERA) were unremarkable. The patient was started on valproic acid but did not show any improvement and was shifted on pyridoxine phosphate, which led to a better response.

The child achieved complete neck holding, sitting and standing (without support) at the ages of 18, 30 and 42 months, respectively. Screening of other family members and children, and genetic counselling was also recommended.

DISCUSSION

The triad of hyperphosphatasia, mental retardation and neurological deficits, most commonly seizure, has been described to characterise Mabry syndrome.[3-5] We report the case of a child with persistently elevated serum AP levels, generalised tonic-clonic seizures, developmental delay, hypertelorism, high-arched palate and hyperplastic malar eminences, who was diagnosed to have Mabry syndrome based on clinical and laboratory evidence.

Because of developmental delay with poor speech and language development, our patient, like most previously reported cases, was suspected to have severe mental retardation.[2,3,6] However, this could not be confirmed via formal IQ testing. Other neurological deficits that have been reported in these patients include hypotonia and seizures, which were present in our patient.[9] The severity of hyperphosphatemia shows considerable variability.[9] In our patient, AP levels were consistently found to be high (Table I).

Growth parameters in patients of Mabry syndrome have generally been reported to be normal or higher than normal.[8,9] However, growth parameters at birth and subsequent height-for-age and weight-for-height charting was found to be within normal limits in our patient.

PIGV mutations in Mabry syndrome tend to be associated with a broader phenotype than that reported by Mabry *et al*.[1,3,8] These mutations may be responsible for the great phenotypic diversity found in patients of Mabry syndrome. Similarly, the range of coarsening of facial features and hand abnormalities can be quite variable amongst patients who have the core syndrome.[3,10] Hand abnormalities, i.e., brachitelephalangy, were described as a consistent sign by Horn *et al*.[9] However, in other cases, such as ours, hands and feet may be completely normal.[1]

The recurring pattern of hypertelorism, large appearing eyes, a short nose with broad nasal bridge and dip, thin upper lip with down turned corners of the mouth, have also been noted.[9] Our case is particularly important because, out of these previously reported facial abnormalities, our patient only had hypertelorism. However, a high-arched palate and hyperplastic malar eminences were noted in our patient, which have not been previously reported in Mabry syndrome. This underscores the need for reporting of more patients of Mabry syndrome to identify the complete spectrum of abnormalities associated with it.[9]

Constipation, Hirshsprung disease, and anorectal abnormalities have been reported in association with Mabry syndrome.[8] This is consistent with the finding of constipation in our patient. However, the reason for delayed onset of constipation (at 19 months) is unclear. Hearing defects have also been reported in Mabry syndrome, but were not seen in our patient.

While many reports of patients with Mabry syndrome from the Western populations are available in medical literature, no such case has been previously reported in South Asian population. Our case is the first reported patient of South Asian descent with Mabry syndrome.

In conclusion, in children with delayed development, epilepsy, dysmorphic features and hypoplastic terminal phalanges, AP levels should always be checked in order to make a confirmatory diagnosis of Mabry syndrome.

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Table I: Laboratory investigations' findings for the reported case.

Age (months)	6	8	11	12	15	18	22
Alkaline phosphatase (IU/L)	2275	2640	4099	3376	3069	2752	2724
Serum calcium (mg/dL)	11.0	9.4	9.0	9.9	14.1	10.8	10.2
Serum phosphorus (mg/dL)	7.5	5.4	6.0	6.0	4.8	5.2	4.8
Vitamin D3 (ng/mL)					105.5	94.3	105.0
Creatine kinase (U/L)	71.1		98.0				
Thyroid stimulating hormone (TSH) (mIU/L)	3.4		4.1				

TSH = Thyroid stimulating hormone.

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