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MABRY SYNDROME (HYPERPHOSPHATASIA WITH MENTAL RETARDATION SYNDROME): A CASE REPORT OF AN 8-YEAR-OLD GIRL.

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ABSTRACT **Introduction:** Mabry syndrome, also known as Hyperphosphatasia with Mental Retardation Syndrome (HPMRS), is a rare autosomal recessive congenital disorder of glycosylation caused by defects in glycosylphosphatidylinositol (GPI) anchor biosynthesis. **Case Report:** 8-year-old girl presenting with global developmental delay, seizures, and persistently elevated ALP, ultimately diagnosed with Mabry syndrome. **Investigation:** Laboratory evaluation showed normal liver function, normal thyroid function, normal levels of serum proteins, calcium, phosphate, vitamin D, parathyroid hormone and blood counts with an isolated marked elevation of serum alkaline phosphatase, suggestive of a non-hepatic cause such as Mabry syndrome. **Conclusion:** This case highlights that isolated hyperphosphatasia with developmental delay and dysmorphic features should prompt evaluation for Mabry syndrome, with early diagnosis enabling targeted management, multidisciplinary care, and genetic counselling to improve outcomes.

KEYWORDS : Mabry syndrome, Hyperphosphatasia, Mental Retardation Syndrome, glycophosphatidylinositol (GPI) biosynthesis disorder (GPIBD); congenital disorder of glycosylation, developmental delay.

INTRODUCTION

Mabry syndrome is a condition characterized by intellectual disability, distinctive facial features, increased levels of an enzyme called alkaline phosphatase in the blood (hyperphosphatasia), and other signs and symptoms. People with Mabry syndrome have intellectual disability that is often moderate to severe. They typically have little to no speech development and are delayed in the development of motor skills (such as sitting, crawling, and walking). Many affected individuals have low muscle tone (hypotonia) and develop recurrent seizures (epilepsy) in early childhood.

Hyperphosphatasia begins within the first year of life in people with Mabry syndrome. Hyperphosphatasia with Mental Retardation Syndrome (HPMRS), is a rare inherited disorder belonging to the group of congenital disorders of glycosylation[1]. It results from mutations in genes involved in GPI-anchor biosynthesis, such as PIGV, PIGO, PGAP2, PGAP3, and PIGW[2] which impairs the attachment of certain proteins to cell membranes. The proteins produced from the PIGV and PIGO genes are involved in piecing together the GPI anchor. After the complete GPI anchor is attached to a protein, the protein produced from the PGAP2 gene adjusts the anchor to enhance the anchor's ability to bind to the cell membrane. Mutations in the PIGV, PIGO, or PGAP2 gene result in the production of an incomplete GPI anchor that cannot attach to proteins or to cell membranes. Proteins lacking a functional GPI anchor cannot bind to the cell membrane and are instead released from the cell. The release of non-GPI anchored alkaline phosphatase elevates the amount of this protein in the blood, causing hyperphosphatasia in people with Mabry syndrome.

GPI anchors are essential for attaching many proteins to the cell membrane; defects lead to abnormal neuronal signalling, skeletal development, and enzyme anchoring. A hallmark laboratory feature is markedly elevated serum alkaline phosphatase, which is disproportionate to liver or bone disease[3].

Case Report

An 8-year-old girl presented to the pediatric outpatient department with concerns of delayed developmental milestones, poor scholastic performance, recurrent generalized seizures, and short stature noted since early childhood. The girl's initial complaint was *"Unable to walk or stand"*. She was born at term by normal vaginal delivery and had a delayed cry at birth. The neonatal period was largely uneventful except for feeding difficulties during infancy. There was no history of similar illness in her siblings and no significant family history.

On examination, the child weighed 18 kg, which was underweight for her age. Her height was 112 cm, falling below the 3rd percentile, and her head circumference was 48 cm, consistent with microcephaly. Developmental assessment revealed global developmental delay.

She achieved neck control at 6 months, sat without support at 14 months, and started walking independently at around 3 years of age. Her speech was limited to disyllables with poor comprehension, and a formal psychological evaluation suggested moderate intellectual disability.

She had global developmental delay, with delayed attainment of major milestones—head control was achieved around 6 months, independent sitting at 12 months, and walking only after 2.5 years of age. Speech development was markedly delayed, with limited vocabulary and poor sentence formation for her age. As she grew older, she exhibited poor scholastic performance, characterized by difficulty in understanding lessons, impaired attention span, and dependence on special assistance at school, suggestive of underlying intellectual disability.

Physical examination revealed characteristic facial dysmorphism, including a broad nasal bridge, long philtrum, tented upper lip, high-arched eyebrows, and coarse facial features. Neurological examination showed generalized hypotonia, brisk deep tendon reflexes, poor coordination, and intermittent generalized tonic seizures. Musculoskeletal examination revealed brachytelephalangy, nail hypoplasia, and mild scoliosis. Abdominal examination showed mild hepatomegaly, approximately 2 cm below the right costal margin. Cardiovascular examination was unremarkable, with no audible murmur.

Laboratory evaluation revealed normal liver function parameters, with total bilirubin 0.32 mg/dL, direct bilirubin 0.11 mg/dL, AST 29.57 U/L, and ALT 12.94 U/L, all within age-appropriate reference ranges. Serum total proteins (7.95 g/dL), albumin (4.88 g/dL), globulin (3.07 g/dL), and A/G ratio (1.59) were also normal.

However, there was a marked isolated elevation of serum alkaline phosphatase (400 U/L). The presence of hyperphosphatasia in the setting of otherwise normal liver enzymes and bilirubin suggested a non-hepatic source, consistent with a metabolic or genetic disorder such as hyperphosphatasia with intellectual disability syndrome (Mabry syndrome).

Serum calcium, phosphate, vitamin D, and parathyroid hormone levels were also normal. Thyroid function tests and complete blood counts were also within normal limits.

Radiological evaluation reveals Reimer Index 29% left Hip, indicating a very high risk of hip subluxation. (Fig 1)

Magnetic resonance imaging of the brain showed a few chronic lacunar infarcts noted in the bilateral gangliocapsular regions.

In view of the clinical phenotype and persistent isolated hyperphosphatasia, a genetic evaluation was pursued. Clinical exome sequencing identified a homozygous pathogenic mutation in the PIGV gene, confirming the diagnosis of hyperphosphatasia with mental retardation syndrome (Mabry syndrome), a GPI-anchor biosynthesis defect belonging to the congenital disorders of glycosylation.

The child was managed with a multidisciplinary approach. Antiepileptic therapy was optimized to achieve seizure control, along with regular neurological follow-up. She was enrolled in early intervention programs, including physiotherapy, occupational therapy, and speech therapy, to address hypotonia, motor delay, and expressive language impairment. Special education support was initiated for cognitive and scholastic difficulties. Nutritional rehabilitation and growth monitoring were advised, and orthopaedic follow-up was arranged for scoliosis and skeletal anomalies. The family received detailed counselling regarding the autosomal recessive inheritance pattern, recurrence risk, and the importance of prenatal diagnosis in future pregnancies. At present, treatment for Mabry syndrome remains supportive and symptomatic, with long-term management focused on these domains.

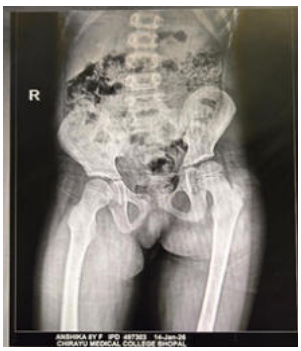

Fig 1: Left Hip, indicating a very high risk of hip subluxation

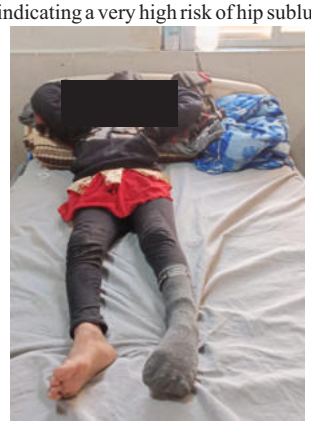

Fig 2: 8-Year-Old Girl positioned supine with the left leg indicating possible limitation of movement or deformity, while the right leg appears normal.

DISCUSSION

Nampoothiri et al. [5] in their study described two siblings with global developmental delay, facial dysmorphism, and elevated alkaline phosphatase due to a novel *PGAP3* mutation identified on whole-exome sequencing, highlighting the utility of genetic testing in establishing a definitive diagnosis when biochemical and clinical features raise suspicion of a GPI-anchor defect. Like our patient, these siblings had persistent hyperphosphatasia and dysmorphic features, reinforcing that elevated ALP combined with neurodevelopmental impairment should prompt evaluation for rare GPI-biosynthesis disorders in the Indian pediatric population.

Comparatively, although large cohort studies specific to India are limited, the *PGAP3*-related Mabry syndrome documented in the report by Nampoothiri and colleagues demonstrates overlap with our case in terms of developmental delay, severe intellectual impairment, and biochemical markers, suggesting a shared phenotypic spectrum within the country's genetic landscape. Furthermore, international case series and genetic studies have shown that GPI-anchor defects due to various gene mutations (including *PIGV*, *PIGW*, and *PGAP2*) present with a consistent core of intellectual disability, seizures, hyperphosphatasia, and brachytelephalangy, even as facial phenotypes and additional anomalies vary, underscoring the diagnostic significance of elevated serum alkaline phosphatase as a biochemical clue in Mabry syndrome across populations[6].

Prateek Kumar Panda et al. [7] in their study also described a toddler with global developmental delay, isolated hyperphosphatasia, and a GPI-anchor biosynthesis defect confirmed on genetic testing, consistent with Hyperphosphatasia with Impaired Intellectual Development Syndrome (HPMRS). Similar to this our report, presented with persistent elevated alkaline phosphatase in the setting of normal calcium, phosphate, and vitamin D levels, excluding rickets and pointing toward a genetic etiology. Along with seizures, dysmorphic facial features, brachytelephalangy, and mild scoliosis, reflecting the phenotypic spectrum of Mabry syndrome.

These observations reinforce the diagnostic value of serum alkaline phosphatase as an early biochemical clue and the critical role of genetic testing in establishing a definitive diagnosis**,** guiding management, and enabling family counselling. Ultimately, recognition of this rare syndrome allows for timely multidisciplinary interventions, developmental support, and anticipatory care.

CONCLUSION

This case highlights the importance of considering Mabry syndrome (hyperphosphatasia with intellectual disability syndrome)[8] in children presenting with global developmental delay, seizures, dysmorphic features, and isolated persistent elevation of serum alkaline phosphatase. The identification of a pathogenic *PIGV* mutation confirmed the diagnosis of this rare GPI-anchor biosynthesis defect belonging to the congenital disorders of glycosylation. Early recognition is crucial, as it allows appropriate seizure management, developmental interventions, and surveillance for multisystem involvement. This report also reflects the value of isolated hyperphosphatasia as a key biochemical clue to an otherwise under-recognised genetic syndrome and emphasizes the role of multidisciplinary care and genetic counselling in improving long-term outcomes.

Recommendation

Children presenting with global developmental delay, epilepsy, dysmorphic features, and isolated elevation of serum alkaline phosphatase should be systematically screened and evaluated for hyperphosphatasia with intellectual disability syndrome[9].

Early referral for genetic testing is recommended to establish a definitive diagnosis and avoid unnecessary investigations. Prompt initiation of multidisciplinary interventions, including seizure control, developmental therapies, and special education services, is essential to optimize functional outcomes[10]. Genetic counselling and access to early intervention and government-supported rehabilitation programs should be integral components of management and follow-up.

Conflict Of Interest: None.

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