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Case Report

A case of mucopolysaccharidosis type VI in Indian family: importance of clinical characteristics, urinary GAG and enzyme assay in diagnosis of mucopolysaccharidosis

Mohammad Amir Ali, Shivangi Maheshwari, Mrunmay Das Mohapatra*, Dillip Kumar Dash

Department of Pediatrics, IMS & SUM Hospital, Bhubaneswar, Odisha, India

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***Correspondence:**
Dr. Mrunmay Das Mohapatra,
E-mail: mrunmay.mohapatra@gmail.com

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ABSTRACT

Mucopolysaccharidosis (MPS) are hereditary progressive disease caused by mutations in genes coding for lysosomal enzymes essential to breakdown GAG. The inadequate degradation process leads to accumulation GAG in lysosome of diverse tissues, which interfere with cell functioning and leads to characteristic patterns of clinical, radiologic and biochemical problems. Patient appears to be healthy at birth and, symptoms start about 2-3 years of age. Clinical characteristics, radiographic findings, and notably enzyme assays have allowed us to make a clear diagnosis in these situations. There are extremely few cases of MPS VI reported in India. Here we are reporting a case of 14 yr. old female patient with a combination of clinical, radiological and biochemical characteristics confirmed as a case of MPS type VI. This example illustrates that atypical clinical symptom, such as growth failure, coarse facial features, and joint difficulties, are key pointers for further investigations linked to MPS disease. However, in low- and middle-income countries, it is difficult to make a definite diagnosis of one of the MPS due to insufficient enzyme assay.

Keywords: Mucopolysaccharidoses, Urinary GAG, ARSB gene, enzyme assay, Maroteaux-Lamy syndrome

INTRODUCTION

MPS is a category of metabolic illness defined by deficiency of enzymes involved in metabolism of GAGs at lysosomal level. Prevalence of MPS varies country to country. In general, for MPS, a prevalence of roughly 0.22 per 100,000 births was observed for MPS I, whereas for MPS II, the prevalence is 0.45 cases per 100,000 births; for MPS IV A and B it is 0.14 per 100,000 births; and for MPS VI, 0.03 per 100,000 births. The incidence of MPS VI varies substantially amongst populations.

There is wide variation of prevalence of MPS VI among the different populations and range from 0.0132 per 100,000 live births in Poland to 7.85 per 100,000 live births in Eastern Saudi Arabia. However, in certain small communities in Northeast Brazil due to high rates of endogamy and parental consanguinity could be the reason for increased incidence up to 20 per 100,000 live births as recorded by Costa-Motta. When considering all MPSs, MPS VI is the most frequent in Saudi Arabia followed by Malaysia, while the lowest numbers are reported for Poland.[1] However, these are likely underestimated prevalences, as the diagnosis rely mostly on the clinical signs and symptoms. A more precise evaluation of the prevalence can be estimated by early identification through the use of newborn screening programs.[2] In India we don't have appropriate statistics regarding incidence & prevalence MPS.

Different form of MPS were described individually thought the 20th century. Clinical manifestations of MPS differ based on kind of enzyme deficiency, the end organ affected, and the glycoprotein deposited. The principal GAGs include chondroitin-4-sulphate, chondroitin-6-sulphate, heparan sulphate, dermatan sulphate, keratin

sulphate and hyaluronin. As a general, defective breakdown of heparan sulphate is associated with cognitive and behaviour disorder and that associated with chondroitin, dermatan and keratan sulphate with mesenchymal abnormalities.[3]

Mucopolysacchradosis VI or Maroteaux–Lamy syndrome (MIM# 253200), is autosomal recessive genetic disease caused by low to absent activity of the lysosomal hydrolase N-acetylgalactosamine- 4-sulfatase (arylsulfatase B or ASB) that catalyses the degradation of the glycosaminoglycans (GAGs) in particular dermatan sulphate and chondroitin 4 sulfate.

Deficiency of Aryl Sulphatase-B leads to formation of partially degraded product and their accumulation in lysosome and extracellular matrix progressively take to pathological condition, often starting from osteoarticular apparatus and progressively involving all organ and finally leading to multisystem organ failure.[4]

The ARSB gene is located on chromosome 5 (5q13-5q14) and spans a region of approximately 208 kb; it contains 8 exons and encodes a transcript of 4852 bp, which is processed and translated into the 533 amino acids mature form of the ASB protein.[5] To the best of our knowledge, till date, more than 220 distinct variants of ARSB gene have been discovered.

The highest percentage is contributed by missense variants (59.5%); followed by small deletions, non-sense, splice site and intronic variants, small duplications and big deletions.[6] The gene displays a significant genetic variability with roughly 1/3rd (31.7%) of unique variants reported only once and an additional 28.5% reported twice.[7]

Most of them are unique to specific families although a few have been attributed to the founder effect. This heterogeneity is main contributing factor for the vast spectrum of symptoms in MPS VI individuals.[1]

The classical clinical symptoms of Maroteaux–Lamy syndrome are represented by osteoarticular deformity with dysostosis multiplex, low stature and motor dysfunction. In addition, ophthalmic and ENT signs were reported rather regularly, as well as Oro- dental abnormalities. Hypoplastic condyles is the commonest oral manifestation reported followed by malposition of unerupted teeth, large dental follicles, anterior open bite, maxillary constriction and taurodontism. Other signs, such as organomegaly and cardio-pulmonary insufficiencies, typical of MPSs in general, are also present in MPS VI.

Nervous system involvement reported in literature include white matter lesions, communicating hydrocephalus and ventricular enlargement, have been described, associated with spinal cord compression, myelopathy and carpal tunnel syndrome.

Phenotypic classification, based on severity (mild, moderate and severe) were used in past to describe MPS VI. Today, a continuum of phenotypes is frequently recognized, from a fast-progressing form to a slowly progressing one, based on the age of onset, rate of advancement and severity of clinical signs and symptoms.

CASE REPORT

14 years old female child was admitted to our hospital with complain of headache, blurring of vision, slurring of speech and on and off seizure for last 2-month duration. The first detected symptom by mother was joint stiffness and growth retardation.

The girl was from the first pregnancy, first delivery, born by normal vaginal delivery in 38-week, APGAR Score 9/10, birth weight About 2600 g, with no evidence of intra uterine dystrophy. The parents were not connected to one another. There was no family history of any sickness. Pregnancy was uneventful.

The general condition was poor. Physical examination suggestive of coarse facial features in form of frontal bossing, depressed nasal bridge, expanded mouth with big protruded tongue, thick eyebrows. Her calvarium was huge disproportionately, dentature was misaligned, neck was short, chest was small, non-distended stomach with shortening of limbs with little fingers and toe (Figure 1). Her skin was pale thick and gritty. Her height was 120 cm, US/LS 1.063, arm span 126 cm, weight 22 kg.

Her systemic evaluation during period of hospitalization revealed the following features. IQ and cerebellar function were normal with intact cranial nerve. Bulk of all muscle was reduced with enhanced tone but reflexes were normal.

Per abdominal examination suggestive of no organomegaly with normal external genital. Ophthalmoscopic examination suggestive of bilateral corneal opacity (Figure 2), with slightly raised intraocular pressure, with optic atrophy. Examination of auditory system showed there was bilateral moderate hearing loss. Haematological testing showed iron deficient anaemia. Echocardiography showed mild AR with thickened MV.

Radiological examination indicated features skeletal dysplasia

X-ray of hand shows bullet shaped phalanges with proximal tapering and angulation of metacarpals. X-ray skull and spine s/o Dolichocephalic with J shaped Sella and anterior beaking of vertebral bodies.

X-ray pelvis showed rounded iliac wings, inferior tapering of ilea with poorly formed acetabulum with coxa valga. CT head s/o J-shaped Sella with bilateral dilatated optic nerve sheath. MRI brain s/o mild hydrocephalus.

Figure 1: MPS image.

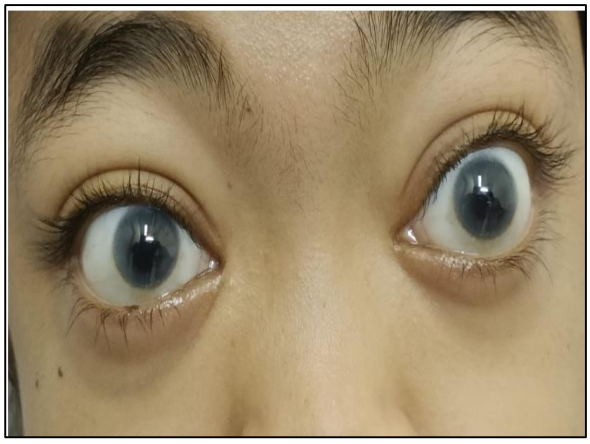

Figure 2: Cloudy cornea, depressed nasal bridge.

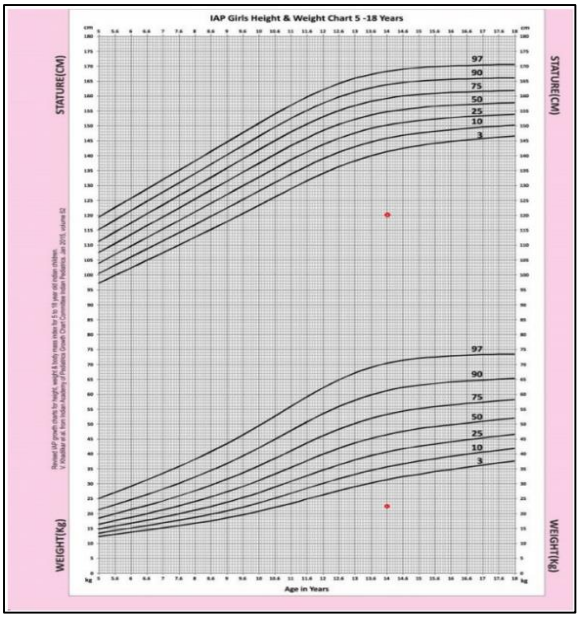

Figure 3: Growth retardation as depicted in image.

Because of specific clinical and radiological features MPS VI was suspected and for conformation of diagnosis urinary GAG excretion test was done which revealed increased level of urinary GAG of 22.9 mg/mM creatinine (biological reference interval:1.5-5.0) and leucocyte enzyme activity of arylsulfatase B was found to be 56.9 nmol/hr/mg (Biological reference range: 84-452, Mean±SD: 231.6±22.3). Child was stabilised and started on antiepileptics for control of seizures. During hospital stay infant developed pneumonia and was treated successfully. In view of moderate hydrocephalus, neurosurgical opinion was taken and VP shunting was done effectively. Post OP patient was monitored for 1 year. Post OP patient was seizure free. There was not significant improvement in other systemic examination.

DISCUSSION

In this study, we are presenting a case of MPS VI in an Indian family. The diagnosis of MPS VI often starts with particular clinical features, suggestive of a metabolic disease. Most common clinical features reported are coarse facies, short height, dysostosis multiplex, hepatosplenomegaly, macrocephaly, inguinal or umbilical hernia, corneal clouding, cardiac valve thickening. The differential diagnosis for MPS is mucolipidosis and oligosaccharidosis. Mucolipidosis and oligosaccharidosis exhibit with the same clinical and radiological characteristics as MPS. In these cases, urinary conditions of GAGs are not raised. Hurlers like facial characteristics, joint contractures, dysostosis multiplex and high urine GAG excretion identify the MPS from other neurodegenerative and dwarfism diseases.

In our case the patient was suspected to be suffering from either MPS I or VI. The first component of that we want to emphasize is the relevance of clinical examination in diagnosis of MPS. Based on our clinical experience and clinical signs & symptoms, we excluded MPS I. In MPS I, the patient had intellectual disability, which was a marker of Hurler syndrome. The cognition begins to regress at about the age of two. Child was delivered by normal vaginal delivery with non-consanguineous marriage and without any family history of MPS or any past illnesses.

The girl had multiple classic clinical features of MPS VI, largely linked to skeletal deformity without mental retardation. The first observed symptom in the girl was joints stiffness of finger and later growth retardation. Our patient had ocular clouding, which goes in favour of MPS VI. Ashworth et al, in his study reported ophthalmologic abnormalities in MPS type VI and reported that these patients are prone to corneal clouding (95%) and glaucoma (50%).[7]

Our patient was also having history of recurrent respiratory tract infection and this might be the explanations for bilateral moderate hearing loss. Our patient likewise had mild AR with thickened MV. Azak

and Golda in his echocardiographic study reported, valvular heart disease with 96% of mitral valve involvement, tricuspid valves (71%), and aortic (43%).[8] Therefore, cardiac evaluations are indicated every 1 to 2 years and should involve a blood pressure monitoring, ECG and 2D ECHO.

The second aspect that we want to discuss here the role of radiological examination in MPS. Radiological examination revealed bullet shaped phalanges with proximal tapering and angulation of metacarpals, dolichocephalic skull with J shaped Sella, X-ray spine revealed anterior beaking of vertebral bodies with hydrocephalus. All the radiological features found in our case goes in favour of MPS. In spite of all the above clinical and radiological features suggests a case of MPS but do not provide a definite diagnosis.

The 3rd aspect that we want to highlight is the importance of urinary GAG and enzyme assay that provide definite diagnosis of MPS. In our case urinary GAG was elevated. This positive result was followed by measurement of ARSB enzyme activity, which was low, suggesting MPS VI. Swedler et al, reported GAG as a potential prognostic biomarker in MPS VI patients.

Urinary GAG >200 µg /mg creatinine were associated with an accelerated clinical course and poor prognosis whereas levels below 100 µg/mg. creatinine were reported with slowly progressing phenotypes and longer-term survival.[9] These findings were further confirmed in 2014 by Giugliani et al, when he resurveyed analysed data from same patients.[10]

The final diagnosis of MPS VI is based on molecular analysis of the ARSB gene, which enables the identification of the specific variations linked to the disease. Typically, molecular analysis is conducted on both parents to determine if the variants are located on different chromosomes (segregation analysis).

Additionally, if only one variant is found, the analysis is used to confirm whether it is homozygous or to identify the presence of large deletions.[11] The results of the molecular study in the proband and both parents are valuable for enhancing genetic counselling, particularly for preconception or prenatal testing, in families with MPS VI patients.[12,13]

CONCLUSION

In conclusion, authors present not only the case study, but we try to emphasize the importance of clinical examination and high value of Urinary GAG and enzyme assay in the context of diagnosing mucopolysaccharidosis. Early diagnosis will lead to early therapeutic intervention. Multidisciplinary management approach is needed for these patient as per recently published Systematic evidence and consensus-based guidelines.

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