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MORQUIO SYNDROME: A CASE REPORT

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ABSTRACT

Type IV Mucopolysaccharidosisincludes type IVA and type IVB, causing defective degradation of keratan sulfate. We report a rare case of Morquio syndrome type IVA an autosomal recessive mucopolysaccharidosis due to deficiency of N-acetylgalctosamine-6-sulfatase. Diagnosis requires agreement of clinical, radiographic, and laboratory findings.In our case, diagnosis was confirmed by testing for enzyme levels. It is very relevant to diagnose this disease, as enzyme replacement therapy isnow available.

KEYWORDS

Introduction:

Mucopolysaccharidoses (MPSs) are a group of inherited lysosomal storage disorders caused by enzymatic defects in the catabolic pathway of glycosaminoglycans (GAGs). Eleven different enzymatic defects result in seven different types of MPS, MPS I toMPS VII, each with its specific set of manifestations [1]. The specific enzyme deficiency leads to accumulation of tissue-specific intracellular substrates, which cause organ dysfunction.

Type IV MPS is referred to as Morquio syndrome, which is an autosomal recessive disorder and includes two types - Type IV A, due to deficiency of N-acetylgalactosamine-6-sulfatase (GALNS), and Type IV B, due to deficiency of beta-galactosidase(GLB), each resulting in the defective degradation of keratansulfate[2].The gene for N-acetylgalactosamine-6-sulfatase is located on chromosome 16q24.3, and for beta galactosidase on chromosome 3p21.33[3]. The incidence of MPS in British Columbia, Canada is 1 per 200,000 live births, and in Europe the incidence varies from 1 per 76,000 to 1 in 450,000 live births, and hence these are a rare group of disorders[1].

Morquio syndrome predominantly affects cartilage and cornea, as these are rich in keratan sulfate [4]. Heparan and dermatan sulfate have a more generalized tissue distribution and are normally catabolized in patients with Morquiosyndrome, hence these patients do not have mental retardation anddisease manifestations observed in other types of MPSs. More than 100 different mutationshave been identified in the GALNS gene, and this heterogeneity may be the cause of the variability observed in the phenotypic presentation [5].

We report an enzymatically proven case of MPS 4A with typical radiological manifestations. It is very relevant to know and diagnose this MPS as enzyme replacement therapy is now available.

Case report:

A 10 year old female child born out of a non-consanguineous marriage, presented with complaints of short stature and deformed knees.She was apparently normal at birth till about 1 year of age. Weight was 10.5 kg and height was 86 cm (both less than 3 S.D for age). Upper segment to lower segment ratio was 0.87: 1. Her parents and 3 siblings were of normal weight and height. Various skeletal abnormalities included short neck, pectuscarinatum, hypermobile wrist joints, bilateral genu valgum and flat feet(Figure-1). The child had corneal haziness with normal fundus, widely spaced incisors with serrated margins, and enamel hypoplasia. Her intelligence was normal. There was no organomegaly. She had difficulty in breathing on exertion for the last 2 years.

Routine blood tests (hemogram, LFT, RFT, Calcium and Phosphorus) were normal.

Skeletal survey showed J-shaped sella, platyspondyly, anterior central beaking of vertebrae, oar/paddle shaped ribs(Figure-2),distal ends of ulna and radiusof both upper extremities slanting towards each other, short and wide metacarpals, proximal and middle phalanges with tapering of distal phalanges,pointed proximal ends of metacarpals(Figure-3), generalized osteopenia,flared iliac wings with slightly obliquely directed acetabular roof, poorly formed acetabulam,coxa valgus(Figure-3) genu valgus and metaphyseal expansion and sclerosis of long bones(Figure-4).

CT scan of cervical spine showed hypoplastic dens, small and fragmented appearance of atlas arches, and J-shaped sella(Figure-5).

Urine mucopolysaccharides were significantly raised (44.9mg GAG/mmolcreatinine). Enzyme assay (Dries blood sample fluorometry method) showed significantly reduced level of

galactose 6 sulfatase (1.31 nmol/hr/ml) and normal level of β-Galactosidase(32.46 nmol/hr/ml) consistent with the diagnosis of MPS IV-A.

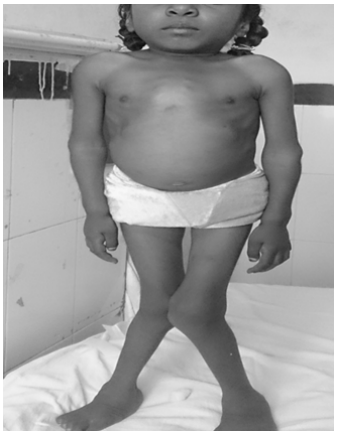

Figure 1 - Patient having short stature, short neck, pectuscarinatum, bilateral genu valgum and flat feet.

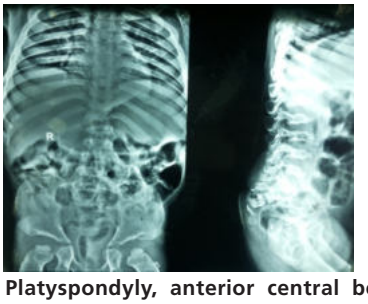

Figure 2 - Platyspondyly, anterior central beaking of vertebrae, oar/paddle shaped ribs.

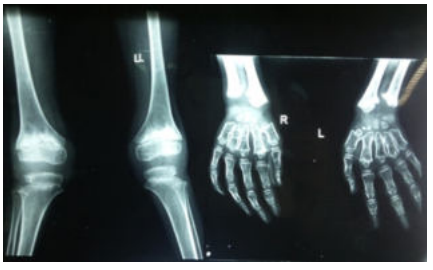

Figure 3 - Genu valgum, metaphyseal expansion, sclerosis of long bones, distal ends of ulna and radius of both upper extremities slanting towards each other, short and wide metacarpals and proximal and middle phalanges with tapering of distal phalanges, pointed proximal endsof metacarpals.

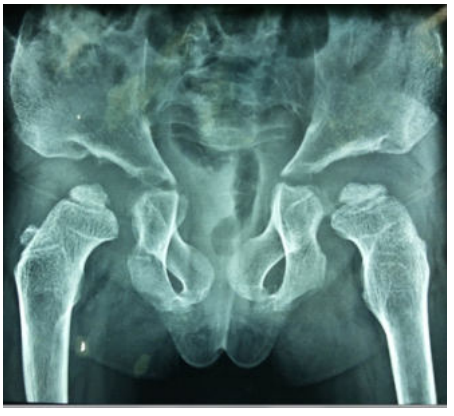

Figure 4 - Flared iliac wings with slightly obliquely directed acetabular roof, poorly formed acetabulam, coxavalga.

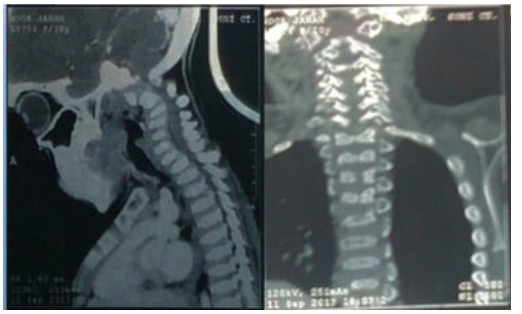

Figure5 - CT scan of cervical spine showing hypoplastic dens and small and fragmented appearance of atlas arches, J-shaped sella is also visible.

Discussion:

Patients with MPS IV-A appear normal at birth, but initial presenting symptoms often manifest after 1 year of age. Musculoskeletal features are the most common presenting features of MPS IV-A. Patients may also develop complications involving the cardiac, respiratory, and digestive systems. Unlike most other MPS types, MPS IV-A does not have any neurological manifestation, and patients exhibit normal intelligence, although behavioral problems such as anxiety and depression have been associated with MPS IV-A[6].

Common patient-reported initial skeletal symptoms include short stature, abnormal gait, genu valgum, pectuscarinatum (rarely pectusexcavatum), and spinal abnormalities like odontoid hypoplasia, cervical instability, kyphosis/gibbus, and scoliosis [7]. Gibbus is often the first sign noticed in MPS IVA. Joint hypermobility, especially of the wrist joints, may develop and is an important clinical sign as it is specific to MPS IV [7].

Extra-skeletal abnormalities are also important manifestations and may also be useful for clinical diagnosis of MPS IVA. Respiratory compromise, frequent respiratory tract infections, obstructive sleep apnea, snoring, mitral and/or aortic value regurgitation and thickening, conductive and sensorineural hearing loss, and muscle weakness may be seen. Corneal clouding and astigmatism can occur. Dental abnormalities include spaced dentition, pointed cusps, spade-shaped incisors, and enamel hypoplasia [8].

Diagnosis of Morquio syndrome can be suspected from clinical and radiological findings but has to be confirmed by biochemical analysis (showing specific enzyme deficiency) or genetic analysis (detecting specific mutations in candidate genes). Radiographic findings in MPS IVA can include odontoid hypoplasia, atlantoaxial subluxation, thickened skull, J- or omega-shaped sellaturcica, flared ribs, short thorax with wide anterior posterior diameter, constricted iliac wings, underdeveloped acetabula, flattened capital femoral epiphyses, coxa-valga, universal platyspondyly, anterior beaking of the vertebrae, short ulna, and delayed bone age or dysplastic carpal/tarsal and metacarpal/metatarsal bones. Evaluation can be done for both the total amount of GAG excreted (quantitative analysis) and the specific types of GAG excreted (qualitative analysis). Diagnosis is confirmed by enzyme activity analysis using dried blood samples or cultures of fibroblasts or leucocytes. Mutation analysis by molecular methods can be used to confirm enzyme activity analysis and for genetic counseling.

Presently, mainstay of treatment is palliative and focused on alleviation of organ-specific complications. In February 2014, FDA (Food and Drug Association, USA) approved enzyme replacement therapy (Elosulfasealfa) for MPS 4A. Initial reports have been encouraging [9,10], although more long term studies are needed to establish long term benefits and safety profile.While the role of stem cell transplantation and gene therapy for the treatment of MPS IV-A has yet to be fully defined with further animal and human studies, the current data on enzyme replacement therapy is promising.

Conclusion

With availability of enzyme replacement therapy for many of these storage disorders, timely diagnosis may result in a better quality of life and improved life expectancy of such patients. Hence early diagnosis is necessary, which requires identification of specific clinical features and then confirmation by either enzyme assays or genetic mutation analysis.

Abbreviations :

MPS :Mucopolysaccharidoses
GAG: glycosaminoglycans
GALNS: N-acetylgalactosamine-6-sulfatase
GLB: galactosidase
LFT: Liver Function Test
RFT: Renal Function Test
mmol: millimole
mg: milligram
DBS: Dried Blood Spot
nmol/hr/ml: nanomole/hour/milliliter

Conflict of interest – None

Financial support - None

References:

1. Algahim M.F., Almassi G.H. Current and emerging management options for patients with Morquio A syndrome. Therapeutics and Clinical Risk Management.Dovepress 2013;9:45-53.
2. Koto A, Horwitz AL, Suzuki K, Tiffany CW. The Morquio syndrome: neuropathology and biochemistry.Annals of Neurology. 1978;4(1): 26–36.
3. Spranger J. Mucopolysaccharidosis.Kleigman R.M., Stanton B.F., St Geme III J.W., Schor N.F., Behrman R.E. Nelson Textbook of Paediatrics 19thedition,Philadelphia Elsevier Saunders, 2011:509-516.
4. HopwoodJ. J. andMorrisC. P. The mucopolysaccharidoses. Diagnosis, molecular genetics and treatment. Molecular Biology and Medicine. 1990;7(5): 381–404.
5. Tomatsu S, Montano AM, Nishioka T et al. Mutation and polymorphism spectrum of the GALNS gene in mucopolysaccharidosis IVA (Morquio A). Hum Mutat 2005; 26:500–512.
6. DavisonJE, Kearney S, HortonJ, Foster K, PeetAC,Hendriksz CJ. Intellectual and neurological functioning in Morquio syndrome (MPS IVa).J Inherit Metab Dis. 2013;36(2):323-8.
7. TomatsuS,Montario AM, Oikawa H, et al. Mucopolysaccharidosis type IVA (MorquioAdisease): clinical review and current treatment. Curr Pharm Biotechnol. 2011;12(6):931–945.
8. Hendriksz CJ, Al-Jawad M, Berger K.I. et al. Clinical overview and treatment options fornon-skeletal manifestations of mucopolysaccharidosis type IVA. J Inherit Metab Dis. 2013;36:309-322.
9. Hendriksz CJ, Burton B, Fleming TR, Harmatz P, Hughes D, Jones SA, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfasealfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. J Inherit Metab Dis. 2014;37:979–990.
10. Brian Long, Troy Tompkins, Celeste Decker, Lynne Jesaitis, Shahid Khan, Peter Slasor, Paul Harmatz, Charles A. O'Neill, Becky Schweighardt. Long-term Immunogenicity of Elosulfase Alfa in the Treatment of Morquio A Syndrome: ResultsFrom MOR-005, a Phase III Extension Study.ClinTher 2017 Jan;39(1):118-129.e3