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Case Report

Extensive mongoloid spots in mucopolysaccharidosis Type I Hurler syndrome

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ABSTRACT

Lysosomal storage diseases are inherited metabolic disorders that are caused by enzyme deficiencies within the lysosomes. The most common lysosomal storage disorder associated with Mongolian spots (MSs) is GM1 gangliosidosis Type-1. We are reporting a case of Hurler disease with extensive MS. A 9-month-old girl, born to a consanguineously married couple, presented with a developmental delay with uneventful birth history. The presence of multiple mongoloid spots over the lumbosacral region and lateral abdominal wall was noticed since birth. Examination showed coarse facies with a depressed nasal bridge and a low-set ear. Multiple mongoloid macules were noted in the lumbosacral region. Serum enzyme assay level had decreased activity of alpha-L-iduronidase (*IDUA*). Exome sequencing revealed a homozygous mutation in exon 8 of the *IDUA* gene. Extensive MS can be seen in mucopolysaccharidosis (MPS) Type 1 in addition to commonly described GM1 gangliosidosis. The early diagnosis helps to start enzyme replacement therapy in MPS Type I, compared to currently no specific treatment available for GM1 gangliosidosis.

Keywords: Mucopolysaccharidosis Type I, Hurler's disease, Mongolian spots, Alpha-L-IDURONIDASE gene

INTRODUCTION

Lysosomal storage diseases are inherited metabolic disorders that are caused by enzyme deficiencies within the lysosomes. The storage of undegraded substrate leads to various clinical manifestations based on substrate and site of accumulation.[1] Mongolian spots (MSs) are non-blanching hyperpigmented macules over the gluteal region that are usually present at birth. These MSs are most prominent at the age of 1 year and start regressing thereafter. Most MSs disappear by early childhood.[2] The average prevalence of MS is around 10% in White infants, 50% in Hispanics and 90–100% in Asians and Africans.[3] Usually, MS have been regarded as benign. Recent data suggest that MS may be associated with inborn errors of metabolism (IEM) and neurocristopathies.[4] Weissbluth *et al.* have the first to recognise an association between generalised MS and various storage disorders.[5] The most common lysosomal storage disorder associated with MS is GM1 gangliosidosis 1.[4] Apart from GM1 gangliosidosis, MSs have been reported in association with Mucopolysaccharidosis (MPS) Type II, Mucolipidosis, Niemann-Pick disease and Mannosidosis.[6,7] Recognition of these extensive MS associations with storage disorders helps in the early diagnosis of treatable conditions; hence, we are reporting a child with Hurler Syndrome (MPS-I) with extensive MS.

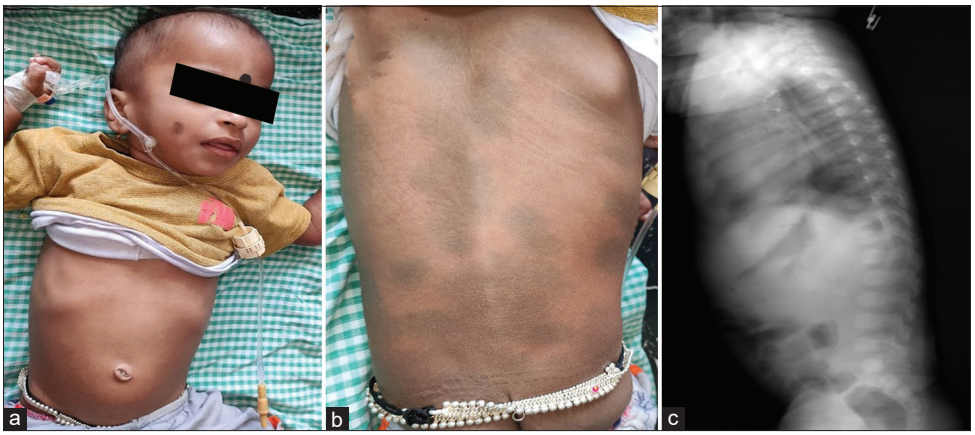

Figure 1: (a) Coarse facies, (b) Mongoloid macules in the lumbosacral region and (c) A lateral X-ray of the thoracolumbar spine with anterior beaking of vertebrae.

CASE REPORT

A 9-month-old girl, born to a consanguineously married couple, presented with a developmental delay with uneventful birth history. The presence of multiple macular bluish pigmentations over the lumbosacral region and lateral abdominal wall is noticed since birth. Developmentally child attained partial neck control at 5 months of age, cooing at 6 months, and social smile at 4 months of age. On examination, coarse facies with depressed nasal bridge, low set ear, [Figure 1a] and head circumference of 43 cm between (−1 standard deviation and median). Multiple mongoloid macules were presented in the lumbosacral region of the body [Figure 1b]. A corneal haze with normal fundus was presented in both eyes. The tone was normal without hepatosplenomegaly. Clinical possibilities of GM1 gangliosidosis were considered.

On investigations, complete blood count, renal function test and liver function tests with low thyroid stimulating hormone were normal. A lateral X-ray of the whole spine showed ovoid vertebral bodies [Figure 1c]. Serum enzyme assay level had decreased activity of alpha-L-Iduronidase (*IDUA*). Exome sequencing revealed homozygous mutation c.1096_1099del (p. Thr 366ArgfsTer73) in exon 8 *of* the *IDUA* gene.

DISCUSSION

We report a child of a 9-month-old girl with developmental delay, coarse facies, and extensive mongoloid spots with reduced enzyme activity of *IDUA* suggestive of Hurler Syndrome and confirmed by exome sequencing.

Mongoloid spots are bluish-black birthmarks over the gluteal region, more commonly seen in African or Asian populations. Usually, spontaneous lightning is expected, persistence of the same is termed atypical and may be associated with IEM.[1,2] The term atypical is used for multiple and extensive, extra-sacral, deeply pigmented MS and mongoloid spot-in-spot. The lysosomal storage disorders associated with atypical presentation include GM1 gangliosidosis.[2,3]

Exome sequencing showed a homozygous frameshift deletion c.1096_1099del (p.Thr366Argfs*73) in exon 8 of the *IDUA* gene. This variant has not been reported in 1000 genomes and gnomAD databases. The *in silico* prediction is a disease caused by MutationTaster. The variant is reported in ClinVar as Pathogenic (VCV001065522.1). The variant is classified as pathogenic as per ACMG classification. A missense variant p.Thr366Pro, upon mutant p.Thr366Pro and wild-type transfection into Cos-1 cells, revealed less than 1% of the a-L-Iduronidase activity.

Diagnosis of MPS 1 is challenging for physicians in recognising the early stages of the disease. Delayed diagnoses are still common and even efforts to increase awareness may have a limited impact. Few cases of coexistence of MS with storage disorders reported till now. Extra sacral, extensive, persistent, and dark-coloured spots should be looked on with suspicion, especially in the presence of a consanguineous marriage or a strong family history of storage disorders. Recognition of this extensive MS helps the physician to diagnose the treatable cause of storage disorder. The mucopolysaccharidoses respond well to stem cell transplantation or enzyme replacement therapy if instituted at an early stage before irreversible organ damage occurs.

CONCLUSION

The diagnosis of MPS 1 or Hurler can be made by evaluating the patients with signs and symptoms and measuring enzyme activities and identification of genetic variants. Further studies should be done to correlate the extensive MS and MPS 1 so that diagnosis can make at the early stage of disease progression and therapeutic measures should be instituted.

Ethical approval

The research/study is approved by the Institutional Ethics Committee at Indira Gandhi Institute of Child Health, number IEC/2023/08/23, dated 3rd February 2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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