Case Report

Diagnosing a Rare and a Fatal Lysosomal Storage Disorder

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A B S T R A C T

Introduction: Infantile GM1 Gangliosidosis is rare and a fatal Lysosomal storage disorder caused by deficiency of the β-Galactosidase enzyme resulting in deposition of gangliosides and other metabolites in various organ systems. We present and discuss clinical, radiological findings in a 10 months old term female child who had generalised hypotonia, coarse facial features and bluish-black skin pigmentation over trunk and limbs. She was thoroughly investigated and diagnosis was confirmed by decreased β-Galactosidase activity.

Case Report: A 10 months old term female child born to non-consanguineous parents presented with complaints of feeding problems, absence of neck holding, inability to sit with or without support, constantly opening of mouth and persistent bidextrous reach till date which implicates generalised hypotonia and global developmental delay. In view of age of presentation, presence of skeletal changes and imaging features Infantile GM1 Gangliosidosis was diagnosed. The diagnosis was confirmed by decraesed β-galactosidase activity.

Conclusion: Infantile GM1 gangliosidosis presents as an early onset global developmental delay with extensive dermal melanocytosis, cherry red spot on macula. In addition, skeletal changes in form of vertebral beaking. MRI shows hypomyelination and T2 hyperintense bulky basal ganglia. In future with availability of enzyme replacement/ gene therapy these signs will be helpful in arriving at the diagnosis as early as possible.

Keywords: GM1 Gangliosidosis, Lysosomal Storage Diseases (LySD), Dermal Melanocytosis, Hypomyelination.

INTRODUCTION

Infantile GM1 (Monosialotetrahexosylganglioside) Gangliosidosis is an autosomal recessive lysosomal storage disorder caused due to mutation in GLB1 gene, Chromosome 3p22.3 which lowers or eliminates the activity of the β-Galactosidase enzyme, preventing the breakdown of gangliosides and leading to its deposition in various organ systems especially nervous system and leads to destruction of nerve cells.[1]

Armstrong-Javors A et. al[2] in a study stated that the child diagnosed with Infantile GM1 Gangliosidosis may present with loss of vision and deafness by age 1 and often die by age 3 from cardiac complications or pneumonia. Till now about 200 cases of GM1 Gangliosidosis have been reported in the literature. The prevalence of GM1 Gangliosidosis is estimated to be approximately 1/200,000 live births.[3]

CASE REPORT

A 10 months old term female child born to non-consanguineous parents presented with complaints of feeding problems, absence of neck holding, inability to sit with or without support, constantly opening of mouth and further examination revealed persistent bidextrous reach till date which implicates generalised hypotonia and global developmental delay.

Further inspection revealed extensive dermal melanocytosis over trunk and limbs [Figure 1A], increased inter-canthal distance, depressed nasal bridge, coarse facial features and low set ears [Figure 1B].All the anthropometric measurements were found within normal limits.One of her elder siblings died at the age of 3 months due to pneumonia.Biochemical analysis showed elevated liver enzymes in the form of Aspartate Transaminase 123 IU/L; Alanine Transaminase 36 IU/L;Serum Alkaline Phosphatase 781IU/L with normal bilirubin levels. Cherry-red spot in macula and optic disc atrophy bilaterally was noted on fundus examination. Hepatosplenomegaly [Figure 2A, 2B] was demonstrated on sonographic examination and antero-inferior beaking of body of first three lumbar vertebrae was noted on lateral view of infantogram [Figure 2C]. On MRI, T2 Hyperintensity involving bilateral lobar and periventricular white matter, posterior limb of internal capsule and dorsal aspect of brainstem was noted [Figure 3A, 3D], these signal changes were isointense on T1 [Figure 3B], which was suggestive of hypomyelination. In addition, T2 hyperintense bilateral bulky basal ganglia were noted [Figure 3C]. In view of age of presentation and presence of skeletal changes, these features suggested Infantile GM1 Gangliosidosis. The diagnosis was

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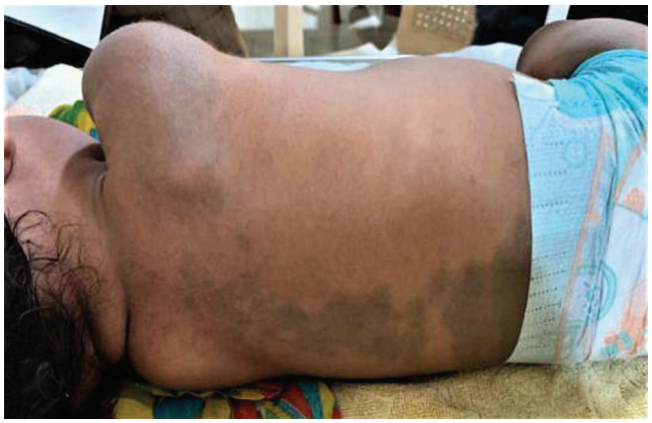

Figure-1A: Extensive dermal melanocytosis over the trunk and limbs

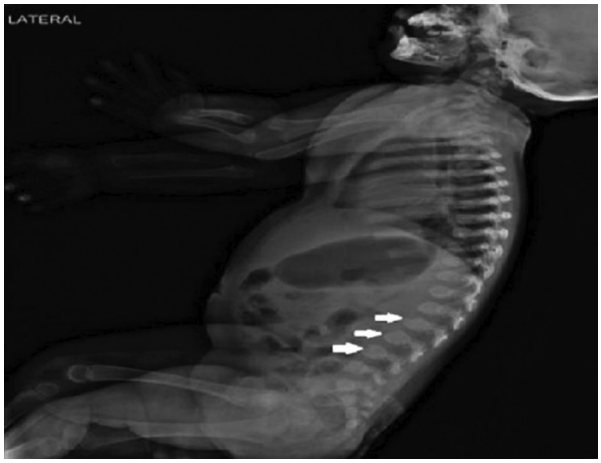

Figure-1B: Antero-inferior beaking of first three lumbar vertebral bodies as marked by arrows

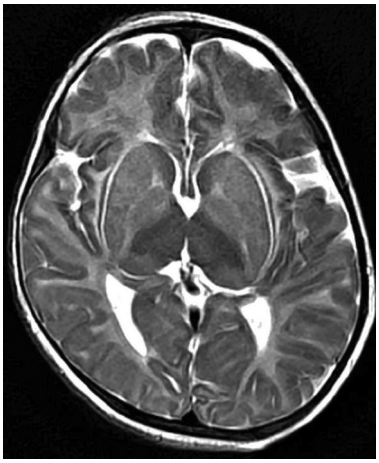

Figure-2A: Axial T2 MRI (right) shows bilateral thalami hypointensity with bulky Basal Ganglia.

confirmed by decraesed β-galactosidase activity.

DISCUSSION

Gangliosidosis are a group of lysosomal storage disorders (LySD) which involves accumulation of lipids in multiple organ systems. They are broadly grouped into 2 types- GM1 Gangliosidoses caused due to a deficiency of the enzyme β-Galactosidase and GM2 Gangliosidosis caused by deficiency of the enzyme β-Hexosaminidase.[4]

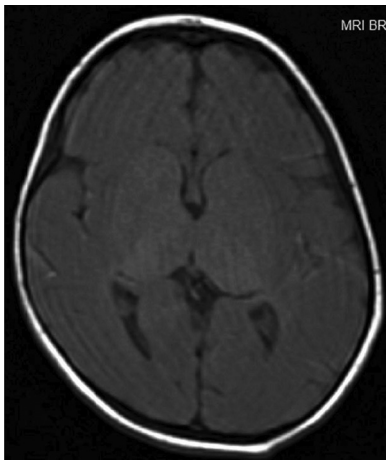

Figure-2B: Axial T1 MRI shows bilateral thalami hyperintensity with bulky Basal Ganglia.

Further, GM1 Gangliosidosis may be grouped into three major types based on the age at which signs and symptoms first appear: Type 1- Classic infantile type GM1, Type 2- Late infantile or Juvenile type GM1, Type 3- Adult or Chronic type GM1.[5]

Our patient presented with generalised hypotonia, bluish-black skin pigmentation over the trunk and limbs and global developmental delay. Extensive dermal melanocytosis is an rare association with lysosomal storage diseases. Until 2014, only 54 cases were reported in which extensive dermal melanocytosis was noted in association with Lysosomal storage disorders, out of which only 17 cases were reported to be GM1 Gangliosidosis. It is hypothesized that the accumulated metabolites in GM1 binds to tyrosine kinase protein, leading to increased level of nerve growth factors which bind to melanocyte chemotactic receptors preventing melanocyte migration and thus produces extensive dermal melanocytosis.[6] Cherry-red spot in macula noted on fundus examination in our patient excluded Mucopolysaccharidosis. Imaging features of GM1 gangliosidosis include hepatosplenomegaly, skeletal changes and hypomyelination and T2 hyperintense bilateral bulky basal ganglia on MRI. Other findings which have been described include hyperdense, T2 hypointense thalami, and blooming involving globus pallidus.

On MR Spectroscopy of the thalamus, a lowered N-acetylaspartate/Creatinine ratio and an raised Choline/Creatinine ratio is seen.[7] Brunetti-Pierri et. al[8] stated in a study that in some cases prenatal manifestations like hydrops fetalis and intrauterine growth retardation is noted.

Currently no definitive medical management is available for the condition, only symptomatic and supportive treatment in the form of proper nutrition, hydration, anti-convulsants to control seizures and maintaining an open airway. Allogenic bone marrow transplantation has been attempted but the patient continued to deteriorate neurologically. Active research for enzyme replacement and gene therapy is ongoing.

Our case shows typical neuroimaging and skeletal findings in this rare entity of GM1 gangliosidosis which are helpful in reaching a correct diagnosis for proper genetic counselling and explaining the prognosis. Presence of extensive dermal melanocytosis adds to the limited literature of cases of GM1

gangliosidosis having these skin changes.

CONCLUSION

Infantile GM1 gangliosidosis presents as an early onset global developmental delay with extensive dermal melanocytosis, cherry red spot on macula. In addition, skeletal changes in form of vertebral beaking. MRI shows hypomyelination and T2 hyperintense bulky basal ganglia. In future with availability of enzyme replacement/ gene therapy these signs will be helpful in arriving at the diagnosis as early as possible.

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