White Matter Changes in GM1 Gangliosidosis

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Background: GM1 gangliosidosis is a disorder due to *GLB1* gene mutation. **Case characteristics**: A 4-yr-old boy with neuroregression and optic atrophy with periventricular hyperintensity on magnetic resonance imaging. **Outcome:** Beta galactosidase enzyme activity was low which was confirmed by *GLB1* sequencing. **Message**: We highlight the white matter changes in late infantile GM1 gangliosidosis.

Key words: *Convulsions, Magnetic resonance imaging, Neuro-metabolic disorders.*

GM1 gangliosidosis is a rare genetic disorder caused by mutations in *GLB1* gene leading to the deficiency of enzyme beta galactosidase. [1]. The clinical manifestations are varied due to accumulation of ganglioside in the lysosomes. It can be divided into three types depending on the age of onset. Type 1 is an infantile form, which presents between birth and 6 months of life. Type 2 is the late infantile form, the onset varies between 6 months and 3 years of age, the clinical features of which include neurological deterioration, and cerebellar and extrapyramidal symptoms. Organomegaly, cherry red spot and skeletal changes are usually not observed in this form. Type 3 (chronic/adult form) presents between 3 and 30 years. It is a gray matter disease and diagnosis is confirmed by enzyme assay or mutation detection. We present a patient with late infantile form of GM1 gangliosidosis.

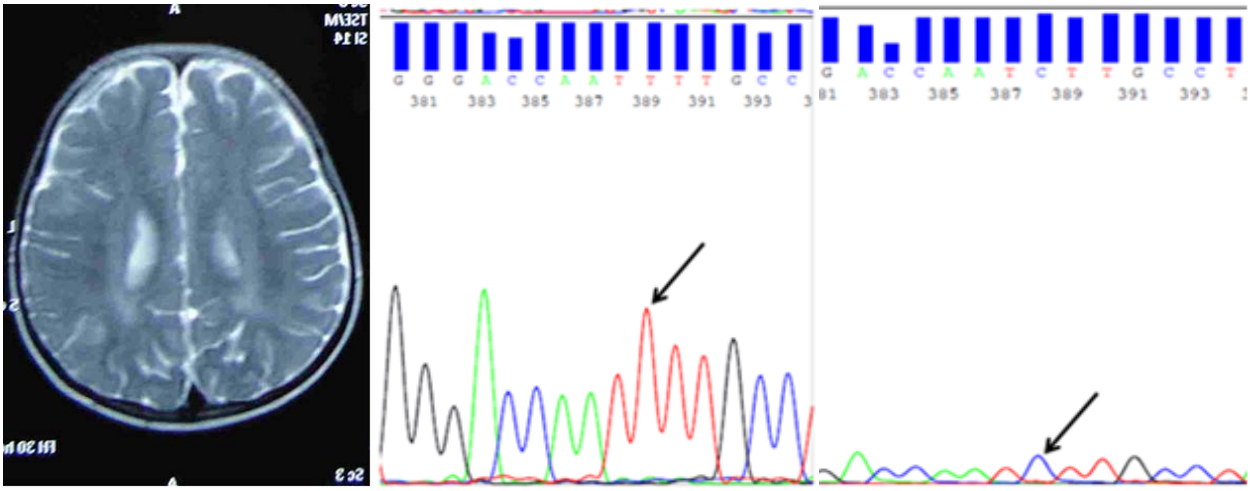
CASE REPORT

A four-year-old boy was brought with the complaint of loss of all developmental milestones. He gained normal developmental milestones till the age of 1 year. After 1 year, he had gradual loss of all acquired skills. He had high-grade fever following which he developed hypertonicity of the entire body, and then later at around 1½ years of age, he had unsteadiness of gait and had frequent falls. He was bed-ridden since 2 years of age. There was a history of seizures with onset at 1 ½ year of age, and apparent vision loss from the same age. There was no history of any consanguinity in the family. Antenatal period of the mother was uneventful. He was born by normal delivery with no history of any postnatal or neonatal complications. There was a history of similarly affected elder female sibling who died at 7 years of age.

On examination, weight height and head circumference were below -2SD. He was indifferent to the surroundings. There was no startle response, no fixation to light, no nystagmus and no hepatosplenomegaly. There was spasticity in the upper and lower limbs and the deep tendon reflexes were absent. Fundus examination showed bilateral optic atrophy. Nerve conduction velocity was normal and MRI (magnetic resonance imaging) brain showed subtle T2 periventricular hyperintensity in bilateral parieto-occipital regions extending to frontal region. The subcortical white matter was also involved at places (***Fig* 1a**). There was thinning of corpus callosum with no significant changes in basal ganglia, no evidence of cortical atrophy. Ventricles were normal sized. Posterior fossa showed prominent cistern magna and hypoplasia of inferior part of vermis.

With the above findings, Krabbe disease, Metachromatic leucodystrophy and Neuronal ceroid lipofuscinosis were considered as the most probable diagnosis. The enzyme activities for palmitoyl protein thioesterase, tripeptidyl peptidase 1, beta galacto-cerebrosidase and aryl sulfatase A were normal. There was deficient beta galactosidase activity (2.1 nmol/hr/mg) (normal 70-324 nmol/hr/mg) which was tested as a control enzyme. The white matter changes in MRI were not in the favor of GM1 gangliosidosis, which is a gray matter disease. Hence, further GCMS (gas chromatography mass spectrometry), TMS (tandem mass spectrometry) and lactate were also done and were found to be normal. The enzyme assay for beta galactosidase was repeated and showed deficient enzyme activity. The confirmation of the diagnosis was done by sequencing of *GLB1* gene (c.940T>C, p.Phe314Leu (homozygous) mutation in exon 9 of *GLB1* gene) (***Fig.* 1b** and **1c**). This was a novel mutation.

Bioinformatics analysis was conducted to access the potential effect of this missense mutation on the protein; five bioinformatics tools were used: the PolyPhen-2, SIFT, PROVEAN, Mutation Taster and PANTHER. All the



(*a*) (*b*) (*c*)

Fig. 1 *(a) MRI brain showing mild T2 hyperintensities in the central periventricular as well as subcortical white matter; (b) Sequencing result of wild type of exon 9 of GLB1 gene; and (c) Sequencing result of patient showing c.940T>C (homozygous) mutation in exon 9 of GLB1 gene. (See color image at website)*

bioinformatics analyses predicted that p.Phe314Leu is expected to be damaging to the protein function and hence it is likely to be a disease-causing mutation. Parents were also sequenced and they were found to be heterozygous for the same mutation. Radiographs were not done as GM1 gangliosidosis was not suspected at the initial evaluation.

DISCUSSION

White matter abnormality in late infantile GM1 gangliosidosis have rarely been reported previously [2-4]. Moreover, optic atrophy is a rare eye manifestation seen in this disorder [5-7]. Neuroimaging findings in late infantile GM1 gangliosidosis have been rarely reported. Gururaj, *et al*. [2] reported MRI findings in two infants with GM1 gangliosidosis and found delayed myelination and abnormal appearance of the subcortical white matter, internal capsule, and basal ganglia. Thalamic hyperdensity on CT scans and hypointense signal of the thalami on T2-weighted MR images have also been reported [3].

This case report highlights the MRI imaging and eye findings in late infantile GM1 gangliosidosis which have been rarely reported previously. This report broadens the phenotypic spectrum of this disorder. Infantile GM1 presents with paucity of myelin in MRI and the clinical and radiological picture of late infantile GM1 is entirely different from infantile GM1 gangliosidosis.

Contributors: MT: clinical evaluation of child; AMB: sequencing of *GLB1* gene; KMG: analysis of sequencing; SP: supervision and intellectual inputs. All authors contributed to manuscript writing and its final approval.
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