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White Matter Changes in GM2 Gangliosidosis

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Abstract

Background: GM2 gangliosidosis is a neuro-metabolic disorder due to deficiency of β hexosaminidase activity in lysosomes. *Case Report*: One and half year old male child presented with regression of milestones and seizures since age of 8 months. Clinical examination showed hypotonia, exaggerated deep tendon reflexes and cherry red spot. MRI brain showed predominant white matter degenerative changes along with grey matter involvement. Enzyme assay for GM2 gangliosidosis showed decreased β hexosaminidase activity. *Conclusion*: We highlight the white matter changes in late infantile GM2 gangliosidosis.

Keywords: GM2 Gangliosidosis, Grey Matter, Lysosomes, Muscle Hypotonia, Seizures.

Introduction

Infantile Tay Sach's disease is autosomal recessive genetic disorder that is part of larger group of GM2 gangliosidosis. The disease manifests itself in infants with deficiency of lysosomal enzyme, β hexosaminidase A. The onset is typically seen in infancy with clinical manifestations including loss of motor skills, increased startle reaction, macular pallor and retinal cherry red spots. Affected infants usually develop normally until 4-5 months of age when decreased eye contact and an exaggerated startle response to noise (hyperacusis) are noted. Child develops seizures by two years which are refractory to anticonvulsant drugs. Neurodegeneration is relentless, with death occurring by the age of 4 or 5 years. It is a gray matter disease and diagnosis is confirmed by enzyme assay or mutation detection. We present a patient with infantile form of TSD with predominant white matter changes on MRI.

Case Report

A one and half year-old boy, product of non-consanguineous marriage was brought with the complaints of loss of all developmental milestones and seizures since the age of 8 months. The child had normal milestones till 8 months of age when he developed multiple generalised tonic and clonic seizures. He then had progressive worsening of symptoms along with off and on seizures despite anticonvulsant therapy and gradual loss of all acquired skills.

Antenatal period of the mother was uneventful. He was born by normal delivery with no history of any postnatal or neonatal complications. On examination, child's weight, height and head circumference were below -2SD, with stable vitals. He was conscious but unaware of the surroundings, not maintaining eye contact and demonstrated complete head lag. Tone was reduced in all four limbs with exaggerated deep tendon reflexes with bilateral Babinski sign. Pupils were equal in size with normal reaction however, cherry red spots were seen in both eyes. Rest systemic examination was normal, child had no organomegaly.

Presence of cherry red spot had narrowed down the differential diagnosis to GM2 gangliosidosis, Gauchers or Nieman Pick

syndrome. MRI brain was done and enzymes for GM2 gangliosidoses were sent. MRI brain showed white matter changes with altered signal intensity in bilateral thalami and basal ganglia (high signal intensity on T2WI). Punctate T2 hyper-intensities were noted in caudate and lentiform nuclei bilaterally with high T1 signal intensity in thalami **[Fig.1]**. Global delay in myelination was seen with raised signal intensity of white matter on T2WI which is abnormal for patients age. These findings were in favour of grey and white matter disease. With the above findings, Krabbe disease, metachromatic leucodystrophy and neuronal ceroid lipofuscinosis were considered as the most probable diagnosis. Further investigations were planned keeping these in mind .

Meanwhile enzyme assay for GM2 gangliosides was positive for Tay Sacs disease. Total hexosaminidase were 1217 nmol/hr/mg (normal value: >1150) in blood while enzyme hexoaminidase A was only 19% as compared to > 55% required for normal activity. Hence further investigations were withheld and parents were advised further for gene studies.

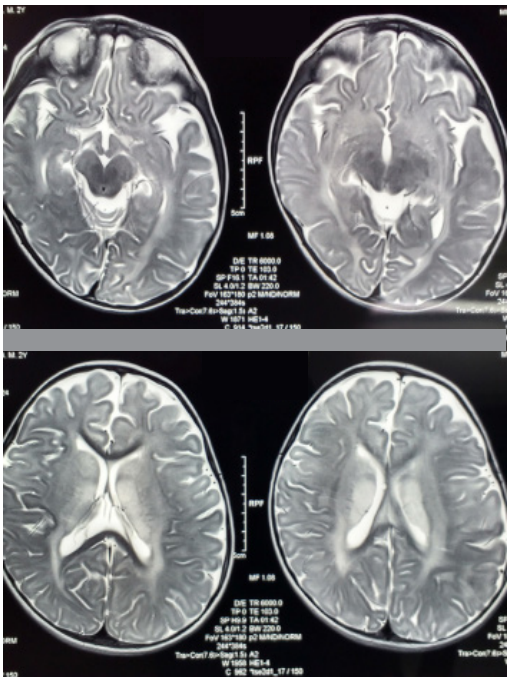

Fig.1: *Altered signal intensity in bilateral thalami and basal ganglia (high signal intensity on T2WI). Punctate T2 hyperintensities are noted in caudate and lentiform nuclei bilaterally with high T1 signal intensity in thalami.*

Discussion

White matter abnormality in late infantile GM1 gangliosidosis have rarely been reported previously [1]. In India also recently one case report of GM1 gangliosidoses with white matter changes in brain was published. A case was reported from southern part of India with similar complaints of regression of all developmental milestones, seizures and spastic changes in limbs. [2]. MRI showed periventricular hyper-intensities in bilateral parieto-occipital regions with subcortical white matter changes. On further investigations, beta galactosidase activity (2.1 nmol/hr/mg) (normal 70-324 nmol/hr/mg) was found deficient. This proved to be GM1 gangliosidosis which is a grey matter disease with white matter involvement [2]. Similarly white matter abnormality in late infantile Sandoffs gangliosidosis have also been reported previously [3]. Gangliosides have been found to be present primarily within grey matter nuclei. To a lesser degree, it is also found within myelin sheaths of the white matter [3]. GM2 ganglioside accumulation within lysosomes of cortical neurons due to the deficiency in enzymes responsible for the hydrolysis of the gangliosides, results in distension of neuronal cell bodies and nucleus displacement [4]. Over time, this cellular enlargement results in neuronal dysfunction and severe neurodegeneration. Thus ganglioside storage has been found to induce degeneration of white matter [4]. Neuroimages of cases with GM2 gangliosidases were reported with varied involvement of white matter and grey matter in different patients [4]. These white matter changes have been believed secondary to the grey matter disease as studied through the study done feline models suffering from GM2 gangliosidosis [5].

One study reported progressive neurodamage on neuroimaging of a patient

diagnosed with GM1 gangliosidosis from the age of 18 months, MRI series showed progression of hypomyelination, cerebral and cerebellar atrophy with involvement of the white matter and cerebral cortex without affecting basal ganglia [6]. This case report highlights the MRI imaging in a late infantile Tay Sac's disease (GM2 gangliosidoses) which have been rarely reported previously. Tay Sacs disease is well known as a grey matter disease, which can have significant white matter involvement. Thus the disease can clinically present accordingly with upper motor neuron lesions like spasticity and brisk deep tendon reflexes despite the presence of cherry red spot on ophthalmic examination. Thus this report broadens the phenotypic spectrum of this disorder.

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