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Case report

GM2 activator protein deficiency, mimic of Tay-Sachs disease

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ABSTRACT

GM2 Gangliosidoses are a group of autosomal recessive genetic disorders caused by intra-lysosomal deposition of ganglioside GM2 mainly in the neuronal cells.GM2-Activator protein deficiency is an extremely rare type of GM2 gangliosidosis (AB variant) caused by the mutation of *GM2A*.We report a case of a female child who presented with clinical features similar to classical Tay-Sachs disease, but with normal beta hexosaminidase enzyme levels. Molecular study revealed a novel homozygous intronic mutation which confirmed the diagnosis of GM2 Activator protein deficiency. GM2 Activator protein deficiency is a mimic of Classical Tay-Sachs disease and should be a differential diagnosis in children who present with neuroregression, cherry red spots without hepatosplenomegaly and with normal beta hexosaminidase enzyme levels.

1. Introduction

GM2-Activator protein deficiency (OMIM 272750) is an extremely rare neuroregressive disorder which is clinically indistinguishable from classical Tay- Sachs disease. Konrad Sandhoff coined it as GM2 gangliosidosis AB variant in 1971. GM2 gangliosidosis AB variant is an autosomal recessive genetic disorder caused by the mutation of *GM2A* encoding for GM2 Activator protein.[1,2] Only 16 patients with GM2 Activator protein deficiency have been reported so far and the underlying mutation was proven in only 9 cases.[3–11] We report a homozygous intronic mutation proven case of GM2 activator protein deficiency which is the 10th case report proven by molecular studies.

2. Case report

A nineteen month old female child was referred to the Department of Pediatric Genetics for evaluation of neuroregression. She was the second child born to third degree consanguineous parents. She was born after an uneventful antenatal and post natal period with the birth weight of 3500 gm. Her development was age appropriate till seventh month. She had already attained head control and could sit without support. At seventh month, her parents had noticed squint following which they noticed regression of previously acquired motor and mental milestones. She started developing excessive startle response from 14 months of age and also had two episodes of seizures at 14th and 18th months.

On examination, she was found to be floppy with complete head lag and was not fixing on objects. Excessive startle response was elicited and there was no organomegaly. Fundus examination revealed pale disc with bilateral classical cherry red spots. MRI Brain done at 11 months of age was normal. Patient underwent three EEGs during the whole course of her illness. The first EEG which was done at 16th months of age was reported as a normal sleep record, without any awake record. The second EEG at 18th months of age did report generalized long interval periodic complexes with correlation with the myoclonic jerks. The third

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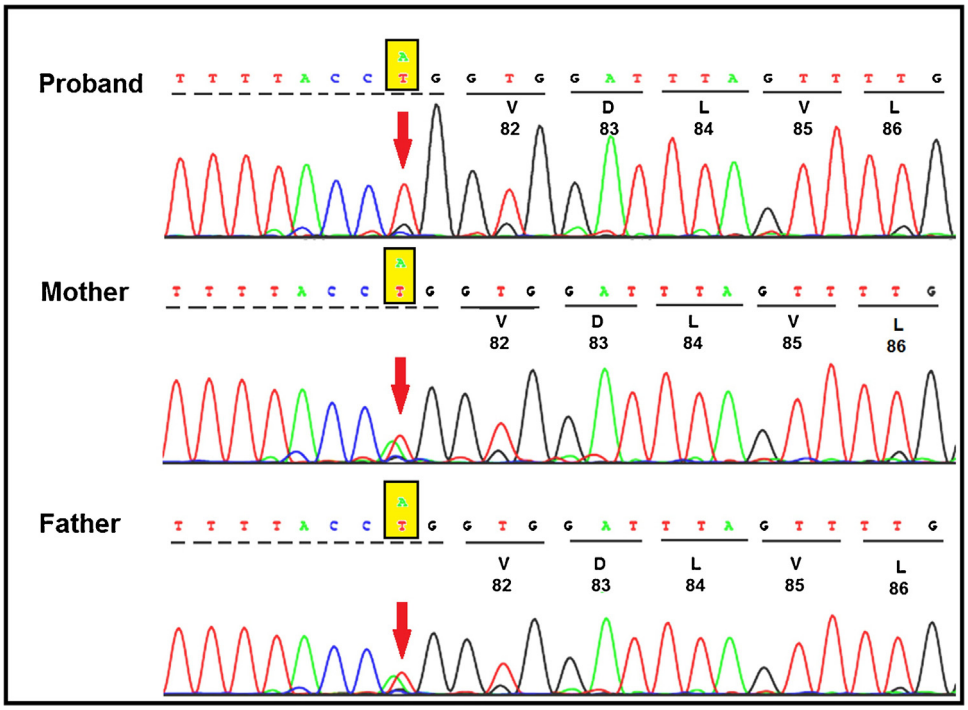

Fig. 1. Electropherogram showing a homozygous mutation in the intron 3 of *GM2A* (c.243-2A > T) in the proband and heterozygous status in the parents confirming the GM2 activator protein deficiency.

EEG at 20th months of age showed only diffuse beta activity, probably related to drugs. There were no periodic complexes in this last EEG. Her seven year old elder sibling was normal.

In view of positive consanguinity, neuroregression, bilateral cherry red spots, exaggerated startle response and absence of organomegaly, possibility of Tay – Sachs disease was considered. Enzyme analysis was sent for confirmation of the diagnosis. The total hexosaminidase, hexosaminidase A and chitotriosidase estimations were within normal limits. The other storage disorders presenting with neuroregression and cherry red spots viz, Gauchers disease, Niemann pick and sialidosis were ruled out by enzymatic analysis.

Since the clinical phenotypes of infantile form of Tay- Sachs disease is indistinguishable from GM2 activator protein deficiency, we investigated in favour of the latter by molecular analysis. Mutation study of the *GM2A* revealed homozygous mutation in the intron 3 of *GM2A* (c.243–2 A > T) and her parents are heterozygous carriers for the same mutation, thereby confirming the diagnosis of GM2 activator protein deficiency in the proband (Fig. 1).

3. Discussion

GM2 Gangliosidoses are a group of lysosomal storage disorder caused by excessive intra – lysosomal deposition of GM2 ganglioside mainly in the neuronal cells. There are 3 types of GM2 Gangliosidoses. The most common type is Tay – Sachs disease (variant B) caused by the mutation of the *HEXA* which is associated with the deficiency of β hexosaminidase A (Hex – A) and normal levels of β hexosaminidase B (Hex – B) enzyme activity. Sandhoff disease (variant O) is caused by the mutation of *HEXB* with deficient activity of β subunit of Hex – A and Hex – B. GM2 activator protein deficiency (variant AB) is an extremely rare type due to defective GM2-Activator protein resulting from the mutation of the *GM2A*.[1]

Hexosaminidase is a dimer composed of 2 subunits. The alpha sub unit is encoded by the *HEXA* gene located on chromosome 15. The beta sub unit is encoded by the *HEXB* gene located on chromosome 5. Hex – A is a heterodimer of α β (alpha beta) and Hex – B is a homodimer of β (beta beta). The *GM2A* is located on chromosome 5q31.3–q33.1 and has 4 exons.[1,12] GM2 activator protein (GM2 – AP) is 22 kDa glycoprotein which is an essential cofactor for β hexosaminidase A for the conversion of GM2 to GM3. The GM2 activator protein is encoded by the *GM2A*. Mutation in *HEXA*,*HEXB* or *GM2A* can lead to classical Tay- Sachs disease, Sandhoff disease and GM2 activator protein deficiency respectively. The GM2 activator initially binds with GM2 gangliosides and this complex binds with β hexosaminidase A, thereby leading to the degradation of GM2 gangliosides. Hence the defective GM2 Activator protein is unable to produce a functional ganglioside GM2 Activator complex even with normal or elevated levels of Hexosaminidase A and B.[1,13] The binding of GM2 activator to a wide variety of negatively charged glycosphingolipids may indicate that the activator protein has functions other than assisting the enzymatic hydrolysis of GM2.[14] Failure of enzymatic hydrolysis results in the progressive intra – lysosomal accumulation of GM2 gangliosides in the neuronal cells and spinal cord leading to severe progressive psychomotor regression. Affected infants are normal at birth and later present with clinical features consistent with classical Tay – Sachs disease with psychomotor regression, exaggerated startle response and refractory seizures. Exact incidence of AB variant is not known. It is an extremely rare disease and only 16 cases have been reported so far, of which 9 cases only are proven by molecular studies (Table 1).[3–11]

Table 1
Comparison of present case with previous proven cases.[3-11]

	Schroder et al.,1991, Xie et al., 1992 [3,4]	Schroder et al., 1993 [5]	Schepers et al., 1996 [6]	Schepers et al., 1996 [6]	Chen et al., 1999 [7]	Kolodny et al., 2008 [8]	Renaud et al., 2015 [9]	Kustermann et al., 2015 [10]	Sheth et al., 2016 [11]	Our Case
Ethnicity	Afro American	Indian	Saudi Arab	Spanish	Laotian Hmong	Indian	Hmong	Turkish	Indian	Indian
Consanguinity	NA	–	+	+	–	–	–	+	+	+
Sex	F	F	F	F	M	F	F	F	M	F
Age of onset (months)	9	5	8	7	5	11	3	9	12	7
Presenting Symptoms	Neuro regression	Neuro regression	Motor Weakness, head lag	Neuro regression	Delayed motor milestones, weakness	Development delay, seizures	Poor visual fixation, global developmental delay	Ataxia, Developmental stagnation	Global developmental delay	Neuro regression
Squint	NA	NA	NA	NA	NA	NA	NA	NA	NA	+
Nystagmus	NA	+	+	+	NA	NA	NA	NA	+	+
Bilateral Cherry red spots	+	+	+	+	+	+	+	+	+	+
Hepatomegaly	NA	NA	+	NA	NA	NA	NA	+	–	–
Splenomegaly	NA	NA	NA	NA	NA	NA	NA	NA	–	–
Seizures	NA	+	+	+	+	+	+	–	NA	+
Hyperacusis	+	+	+	+	+	+	+	+	+	+
EEG	NA	NA	NA	NA	NA	NA	NA	NA	NA	Generalized periodic complexes
MRI brain	NA	NA	Diffuse Brain atrophy	Demyelination of both cerebral hemispheres & cerebellum	Abnormal signal in basal ganglia and white matter	NA	Delayed myelination with abnormal signal intensity in both thalami	periventricular dysmyelination	Abnormal signal intensity in putamen and thalamus	Normal
Hex-A & Hex-B Enzyme	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Mutation in *GM2A* gene (homozygous)	c.412T > C (p. C107R)[3] c.412T > C (p. C138R)[4]	c.506G > C (p.R169P)	c.262_264delAA (p.88Kdel)	c.410delA (p. H137PfsX34)	c.160G > T (p.E54X)	c.522T > G (p. L174R)	c. 160G > T (p.E54X)	c.164C > T (p. P55L)	c.472G > T (p.E158X)	c.243-2 A > T (IVS3-2 A > T)

NA – Not Available, F –Female, M – Male.

4. Conclusion

The diagnosis of GM2 Activator protein deficiency should be considered in infants who present with classical features of Tay-Sachs disease with normal levels of beta hexosaminidase A enzyme activity. Confirmation of the diagnosis is absolutely essential for genetic counselling and prenatal diagnosis, as the risk of recurrence in subsequent pregnancy is 25%.

Contributor's credits

SK prepared the manuscript & did detailed literature search. JS did the molecular studies and interpretation. DY did literature search and had helped in manuscript preparation. VP had evaluated the patient contributed in manuscript. NR had evaluated the case in detail and had helped in manuscript. SN had conceived the idea of drafting this paper and has done the final drafting and will act as the guarantor of the manuscript.

Conflict of interest

None stated.

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