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By the time she diagnosed with GM1 Gangliosidoses she is no more: Case Presentation

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Abstract

Beta-galactosidase-1 deficiency is rare lysosomal storage disorder which is also called as GLB1 deficiency or Landing disease. It is an autosomal recessive disorder whose age of onset is usually child hood. Deficiency of beta – galatosidase enzyme due to mutations of GLB1 gene results in toxic accumulation of gangliosides in either body tissues or particularly in the central nervous system which ultimately ends up in neurovisceral, ophthalmological and dysmorphic features. The types of GM1 gangliosidosis is based on the age of onset; infantile form which is severe and rapidly progressive, a late infantile or juvenile form with onset usually from seventh month to 3 years of age accompanied with delayed motor and cognitive development and thirdly an adult or chronic form with late onset characterized by generalized dystonia. The severity of disease depends on the level of beta – galactosidase activity. Due to the wide spectrum of disease, the diagnosis may be difficult. Facial coarsening, hypertrophic gums, cherry -red macula, visceromegaly, dysostosis and psychomotor are some signs of storage disorders which may help to diagnose GM1 gangliosidosis. The confirmative diagnosis is biochemical assay of beta – galactosidase activity by molecular genetic testing. GLB1 molecular analysis can be done either by chorionic villus or amniotic cells as prenatal diagnosis. There is no specific treatment for GM1 gangliosidosis; treatment is symptomatic as well as supportive. Extremely poor prognosis found in severe infantile form.

Key Terms: *GM1 Gangliosidosis, Beta-galactosidase-1 deficiency, landing disease, GLB1 deficiency, β -galactosidase-1 deficiency, Lysosomal disorders*

INTRODUCTION

GM1 gangliosidosis is broadly classified under lysosomal storage disorder. It is an inherited autosomal recessive disorder that gradually degenerates nerve cells (neurons) in the brain and spinal cord [1,2]. Absence or significantly reduced level of vital enzyme called beta – galactosidase cause GM1 gangliosidosis [3,4]. Each child has 25% of having the disease if both the parents are carriers. In general population, the carrier rate is 1/250. Natives of French Canadians, Louisiana Cajuns and Ashkenazi Jews (1/27) have an increased risk with a carrier state compared to Irish/ British Isle (1/50 to 1/150) [5]. Lysosomal storage disorders include nearly 50 different diseases with a combined incidence of 1:1500 to 1:7000 births. Prevalence of GM1 among Maltese Islands is 1:3,700, Roma ancestry is 1:10,000, and from Brazil is 1:17,000 [6]. Studies have proved that siblings are prone to get GM1 Gangliosidosis. For instance, Gascon et al. (1992) reported that two Saudi Arab siblings (brother and sisters of 9 and 7 years respectively) were diagnosed with GM1 Gangliosidosis and presented

with developmental arrest, gait disturbance and dementia. In addition, both were confined to bed by 2 years of age, had progressive myoclonic epilepsy syndrome with hyperacusis and in due course, they had spastic quadriparesis which led to a decerebrate state. The CT scans revealed global brain atrophy and the deficiency of ß-galactosidase activity was confirmed by bone marrow biopsies. They had another sibling with same complaints but passed away at the age of three [7].

Based on the onset or the first appearance of the clinical manifestation, GM1 gangliosidoses are classified as ***type 1*** - early or classic infantile**,** ***type 2*** - late infantile or juvenile or ***type 3*** - adult or chronic [8]. The child with type 1 or early infantile usually doesn't survive beyond infanthood [2,9]. Neurodegeneration, convulsions, exaggerated startle response, early psychomotor deterioration such as decreased activity, lethargy in the first weeks like initial hypotonia (hypotonic infant with regression in milestones and hepatomegaly occur not only in *gangliosidoses* (i.e., GM1 type I, Tay-Sachs, Sandhoff, fucosidosis, α-mannosidosis) but also in *mucolipidoses* (i.e., sialidosis, I-cell disease, multiple sulfatase deficiency), *mucopolysaccharidoses* (i.e., Hurler syndrome), and *glycogen storage disorders* (i.e., Pompe disease)[10,11], followed by spasticity, delayed milestones, feeding problems, visual failure by 6 months, secondary microcephaly, decerebrate rigidity by 1 year are neurological signs of GM1 gangliosidosis. In addition, skeletal abnormalities, particularly, joint stiffness, flexion contractures by 3 months, early subperiosteal bone formation, diaphyseal widening later, demineralization, thoracolumbar vertebral hypoplasia leading to fracture around age 3–6 months; kyphoscoliosis, dysostosis multiplex are some of the initial stage clinical manifestations. Also, gastro intestinal disorders like hepatosplenomegaly at around 6 months, distended abdomen; muscle weakness; macular cherry red spots in the eye by 6- 10 months or corneal opacities and deaf and blind by age 1 and hyperacusis (increased sensitivity to certain frequency) may be present in child. Over and above facial dysmorphology, frontal bossing, wide nasal bridge, facial edema or puffy eyelids, peripheral edema, epicanthus, long upper lip, microretrognathia, gingival hypertrophy (thick alveolar ridges), macroglossia, developmental regression (losing acquired skills) and profound intellectual disability are also seen. The child may die due to cardiac complication or pneumonia/ respiratory failure [12]**.**

Type 2 involves intermediate form of condition and hence, includes late infantile (around 18 months) or juvenile forms (3 - 5 years) [12]**.** Usually these children have normal development initially, later develop developmental regression, distinctive facial features, or enlarged organs. Even though type 2 progresses are slower than type 1, but still it causes a shortened life expectancy. ***Type 3*** is adult or chronic form as the onset is between 3 and 30 years and represents the mildest end of the disease. Furthermore, muscle atrophy leading to dystonia (involuntary tensing of various muscles), abnormalities of the spinal cord, corneal clouding and angiokeratomas are also found.

Acid β -galactosidase genotyping (molecular diagnosis of the beta – 1 galactosidase gene - GLB1) to detect heterozygous carriers and affected patients [13,14]**,** lumbar puncture to rule out GM1 ganglioside levels which may be increased in CSF, skin biopsy to establish acid β -galactosidase activity in cultured fibroblasts, prenatal diagnosis such as amniocentesis or chorionic villi testing to find β -galactosidase activity in cultured

amniocytes or amniotic chorionic villi, the screening test includes acid β - galactosidase activity in peripheral blood leukocytes, not opted for the screening of heterozygote carriers as an overlap is often present between homozygotes without GM1 gangliosidosis and heterozygote carriers, an ancillary diagnostic test for galactose-containing oligosaccharides in urine, Complete Blood Count for Vacuolation of lymphocytes (nonspecific indicator in lysosomal storage disorders) and dried blood spots from new born screening filter paper (even after 15 months in storage enable to diagnose)[15]. Skeletal radiographs may reveal dysostosis multiplex including thickened calvaria, J-shaped enlarged sella turcica, wide spatula-shaped ribs, flared ilia, acetabular dysplasia and flat femoral heads, wide wedge-shaped metacarpals, shortened long bones with diaphyseal widening, and hypoplastic and anteriorly beaked thoracolumbar vertebrae. Delayed bone age also may be demonstrated. In the adult form, only mild vertebral changes may be observed [14]**.** Neuroimaging by CT scan or MRI generally reveals diffuse atrophy and white matter demyelination with or without basal ganglia changes. Bilateral T2-weighted hyperintensities in the putamen are a frequently reported MRI finding in adult-onset disease. Mild cerebral atrophy may also be observed in the adult form. MR spectroscopy has demonstrated increased striatal myoinositol. An ultrasound of the abdomen may demonstrate organomegaly, signs of cardiomyopathy or valvulopathy may be observed by echocardiography or electrocardiography and generalized dysrhythmia and epileptogenic foci electroencephalography. Bone marrow aspiration not recommended as diagnostic test since of nonspecific large foam cells, Gaucher cells, and ballooned cells have been reported in bone marrow but are typically reported in lower concentrations than in other lysosomal storage disorders [14]**.** Presence of Galactosyl-oligosaccharides in amniotic fluid with high-performance liquid chromatography (HPLC) at 14 weeks gestation may help to diagnose GM1 gangliosidosis prenatally [16].

CASE PRESENTATION

This is 27 years old female with obstetric Score $G_1P_0L_0A_0$ presented with meconium stained liquor and delivered a single live term female baby with APGAR 7 and 9 at 1 and 5 minutes by Caesarean Section. Both couples had family history of infant death with unidentified cause. Although she had history of mild anaemia since childhood, she was diagnosed to have minor thalassemia.

MANAGEMENT AND OUTCOMES

Currently, there is no particular management for GM1 gangliosidosis. Although symptomatic treatment could help to reduce neurologic signs and symptoms but then does not significantly alter the progression of the condition. Mostly, the principle of treatment includes restoring the missing enzyme or decreasing the waste accumulation [1]**.** Within 24 hours of the birth, the child had generalized convulsions and was referred to NICU. After blood investigations, the child was diagnosed with imbalanced electrolytes, particularly potassium and calcium within few hours of birth. Generalized convulsions were relieved by calcium gluconate whereas hypoxia by oxygen administration via nasal prongs, bilevel positive airway pressure (BiPAP) and oxygen concentrator later in life. Symptomatic (anticonvulsants for seizures) and supportive therapy like proper nutrition, hydration, maintaining clear airway, etc. was provided with care [17]. Physical examination discovered facial and peripheral edema, kyphoscoliosis, gingival hypertrophy and angiokeratomas (red to blue colour benign cutaneous lesions of capillaries) on thorax,

abdomen and upper extremities since birth. She was diagnosed with delayed myelination with unmyelination deep white matter of corona radiata and centrum semiovale as expected for this age; wide spaced frontal horn of bilateral ventricles and mild colpocephaly by MRI at 5 months. At 6 months, the leukocyte enzyme activity which is measured by beta galactosidase (nmol/h/mg) was highly diminished (1.2) in comparison to the normal range (70-324). USG stated hepato splenomegaly while visual evoked potential test revealed sign of visual pathway dysfunction at 7th month. Piracetam is a gamma amnio butyric acid (GABA) analogues (protect brain against shortness of oxygen) was the major treatment. Neither bone marrow transplantation (though reported successful in infantile/juvenile for short- term benefit) nor pre-symptomatic cord- blood hematopoietic stem-cell transplantation (recommended due to its success in other lysosomal storage disorders) was not done. Occupational and Physiotherapy found to be beneficial**.** The child had feeding difficulty and was started on tube feeding. She developed abdominal distention, severe chest congestion and ended up with pneumonia. She breathed last on her 10th birthday.

Nursing management

Adequate information, support and counselling were made available for parent to make a future decision which indeed is essential. Infant was laid on comfortable position and position was changed every two hourly as the baby could not move by her own. The child with infantile type may have feeding problems which could be overcome by tube feeding with adequate nutrients. Proper neck support, either by neck collar or towel, could prevent the complications of atlantoaxial instability. Steam inhalation and nebulization followed by chest physiotherapy was beneficial during chest congestion. A nurse plays a vital role in educating families of patients with GM1 gangliosidosis. Planned adequate physical activity by occupational or physiotherapy could reduce skeletal difficulties.

DISCUSSION

GM1 gangliosidoses is an inherited autosomal recessive disorder with prevalence at birth is approximately 1:100,000 to 200,000 live births across the globe [18]. It is due to the marked deficiency of beta – galactosidase resulting in abnormal acidic lipid materials in the nerve cells. Generally, GLB1 (galactosidase beta -1) gene help to make a vital enzyme called beta – galactosidase and resides in cell compartments (called lysosomes) in order to metabolize certain molecules like GM1 ganglioside which is important for nerve cell function. Any mutation in GLB1 gene may decrease or eliminate the β -galactosidase enzyme. Consequently, it accumulates to toxic levels in tissues and organs, particularly in brain. Therefore, a fatty substance or lipid (called GM-1 ganglioside) accumulates abnormally in the nerve cells. Hence, this accumulation (called substrate) leads to progressive destruction of nerve cells [3]**.**

A study was conducted between 2011 and 2014 among patients referred from all over India and Pakistan. The coarse facies, short stature, multiplex dysostosis (bone development disorder, particularly ossification), corneal clouding and hepatosplenomegaly were the most common phenotype considered for referred case. The study reported that 4 were diagnosed with GM1 gangliosidosis by biochemically as well as confirmed by DNA analysis [19]. As India is a developing country, several cases could be unobserved due to difficulty in interpretation/ unawareness and cost of the investigations.

CONCLUSION

The untreated GM1 gangliosidosis result in devastating consequences on neurological system and eventually result in aspiration pneumonia, recurrent respiratory infections subsequent to neurologic compromise, congestive heart failure due to secondary cardiomyopathy (weakening of heart muscle) resulting in heart failure and atlantoaxial instability (AAI), i.e, characterized by excessive movement at the junction between atlas (C1) and axis (C2) leading to abnormally shaped cervical vertebrae**.** To conclude, genetic screening must be considered as priority suggestion for common public before conception in order to reduce grief and bereavement.

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