

Dysostosis Multiplex (G_M-1 Gangliosidosis: Type II)

Madhu KJ^{1*}, Vijyalakshmi IB², Chitra Narsimhan² and CN Manjunath¹

¹Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, India

²Department of Pediatrics Cardiology, Sri Jayadeva Institute of cardiovascular Sciences and Research, India

Abstract

G_M1 gangliosidosis is an autosomal recessive lysosomal storage disorder characterized by the generalized accumulation of G_M1 ganglioside, oligosaccharides, and the mucopolysaccharide keratan sulfate (and their derivatives). Deficiency of the lysosomal hydrolase, acid β-galactosidase, causes G_M1 gangliosidosis. G_M1 gangliosidosis is a rare disorder, and the estimated incidence is 1:100,000-200,000 live births. G_M1 gangliosidosis is found in all races, although specific alleles can be identified in certain ethnic groups. A high frequency of G_M1 gangliosidosis has been reported from Southern Brazil, and a large number of Japanese patients with the adult form have been reported. All 3 types of G_M1 gangliosidosis are inherited as autosomal recessive traits and have equal sex distributions.

Key words : Mucopolysachroid; Keratan sulphate; Dermal melanocytosis; Autosomal recessive.

Introduction

G_M1 gangliosidosis is an autosomal recessive lysosomal storage disorder characterized by the generalized accumulation of G_M1 ganglioside, oligosaccharides, and the mucopolysaccharidekeratan sulfate (and their derivatives). Deficiency of the lysosomal hydrolase, acid β-galactosidase, causes G_M1 gangliosidosis [1]. G_M1 gangliosidosis is a rare disorder, and the estimated incidence is 1:100,000-200,000 live births [2]. G_M1 gangliosidosis is found in all races, although specific alleles can be identified in certain ethnic groups. A high frequency of G_M1 gangliosidosis has been reported from Southern Brazil, and a large number of Japanese patients with the adult form have been reported [3]. All 3 types of G_M1 gangliosidosis are inherited as autosomal recessive traits and have equal sex distributions.

Case Report

5 years old boy with normal birth history born to a non-consanguineous parents, presented with mild developmental delay, gait difficulties and stiffness of limbs since 4 year of age. Initially parents noticed child had tiptoe walking, later he had stiffness of both upper and lower limbs which is gradually progressive. Child is still able to walk but unable to run. There is history of febrile seizures at 1.5 year of age. Younger sibling also having similar complaints

On examination

Boy is alert, cooperative GPE revealed, Coarse facial features, proptosis, prominent forehead, tented upper lip, hepatosplenomegaly, melanotic patches over back, elbow, finger & hamstrings contracture, protrubent abdomen with umbilical hernia, brisk reflexes, power 5/5 and spastic gait.

Investigations

CBC showed normocytic hypochromic with mild relative monocytosis, LFT & RFT's were normal, Urine test positive for MPS, Serum Hexosaminidase. A enzyme levels raised above normal limits, Aryl sulfatase negative, Beta galactosidase enzyme levels were reduced.

Cardiac evaluation

Mild MR, MVP, dilated LV, pericardial thickening, depositions over heart valves, chordae, endocardium and pericardium

X-ray

Thick calavaria, J shaped sella, Beaked vertebra

MRI brain

Prominent elongated perivascular spaces were noted in bilateral posterior periventricular and lobar white matter, as well as corpus callosum and centrum semiovale. T2 FLAIR white matter signal changes are also noted in these regions (sparing the corpus callosum [4]). Sella appears J shaped (Figures 1-4)

Discussion

Acid β-galactosidase is a lysosomal hydrolase that catalyzes the removal of the terminal β-linked galactose from glycoconjugates (eg, G_M1 ganglioside), generating G_M2 ganglioside. It also functions to degrade other β-galactose-containing glycoconjugates, such as keratan sulfate.

Enzyme activity is markedly reduced in patients with G_M1 gangliosidosis. Deficiency of acid β-galactosidase results in the accumulation of glycoconjugates in body tissues and their excretion in urine. G_M1 ganglioside and its derivative asialo-G_M1 ganglioside (GA1), glycoprotein-derived oligosaccharides, and keratan sulfate are found at elevated intracellular concentrations[1,5-8]. The gene has been isolated and is located on chromosome band 3p21.33. Various types of mutations have been identified in the acid β-galactosidase gene, including missense/nonsense, duplication/insertion, and splice site abnormalities [9].

Three clinical subtypes

There are of G_M1 gangliosidosis are recognized

The infantile form (Type 1): Typically presents between birth and

***Corresponding author:** Madhu KJ, Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, India, Tel: +9902783016; E-mail: madhujumla@gmail.com

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Figure 1: Showing prominent forehead, hypertelorism, proptosis, flat nasal bridge, tented upperlip, umbilical hernis, elbow contracture.



Figure 2: Showing large and low set ear, beaded appearance of ribs, lumbar lerosis, hamstrings contracture, finger contracture, protrubrent abdomen with hepatosplenomegaly.

age 6 months with progressive organomegaly, dysostosis multiplex, facial coarsening, and rapid neurologic deterioration with the first year of life. Death usually occurs during the second year of life because of infection (usually due to pneumonia that results from recurrent aspiration) and cardiopulmonary failure [10]

The juvenile form (Type 2): Typically presents at age 1-2 years with progressive psychomotor retardation. Little visceromegaly and milder skeletal disease are present compared to the infantile form. Death usually occurs before the second decade of life.

The adult form (Type 3): Typically presents during childhood or adolescence as a slowly progressive dementia with prominent parkinsonian features and extrapyramidal disease, particularly dystonia. Marked phenotypic variability may occur. Age at death may widely vary.

Other clinical features of G_{MI} Gangliosidosis are

Neurological features: Developmental delay [11], arrest, and regression, Generalized hypotonia initially, developing into spasticity, Exaggerated startle response, Hyperreflexia, Seizures, Extrapyramidal disease, Generalized dystonia (adult subtype) [12], Ataxia, Dementia, Speech and swallowing disturbance [13].

Ophthalmologic features: Macular cherry-red spots, Optic atrophy, Corneal clouding

Dysmorphic features: Frontal bossing, Depressed nasal bridge and broad nasal tip, Large low-set ears, Long philtrum, Gingival hypertrophy and macroglossia [1], Coarse skin, Hirsutism, Cardiovascular - Dilated and/or hypertrophic cardiomyopathy, valvulopathy.

Per abdomen: Hepatosplenomegaly, Inguinal hernia.

Skeletal abnormalities: Lumbar gibbus deformity and kyphoscoliosis, Dysostosis multiplex, Broad hands and feet, Brachydactyly, Joint contractures, Prominent dermal melanocytosis [14-17].

Diagnosis

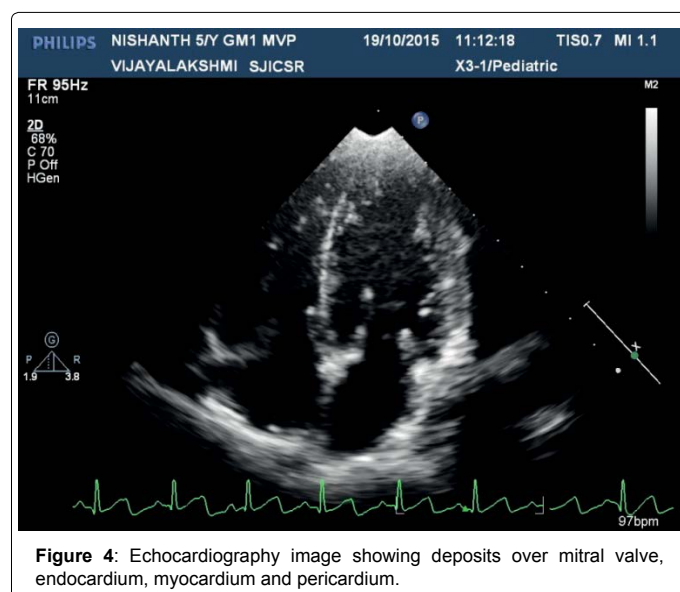
Diagnosis of G_{MI} gangliosidosis can be confirmed by measurement of acid β -galactosidase activity in peripheral blood leukocytes. Patients with the infantile form have almost no enzyme activity, whereas patients with the adult form may have residual activity of 5-10% of reference values.

Urine

Galactose-containing oligosaccharides are excreted in the urine. Their presence may be used as an ancillary diagnostic



Figure 3: Showing Dermal Melanocytosis, characterized by extensive blue cutaneous pigmentation with dorsal and ventral distribution with indistinct border.



test, and the concentration of the metabolites is proportional to disease severity.

CBC count

Vacuolation of lymphocytes may be present in patients with G_{M1} gangliosidosis but is a nonspecific.

Dried blood spots

Diagnosis of G_{M1} gangliosidosis has been made based on dried blood spots from newborn screening filter paper, even after 15 months in storage [18].

Molecular analysis

Molecular analysis of the β -1 galactosidase gene (GLB1) is clinically available [9].

Prenatal diagnosis

Prenatal diagnosis has been performed successfully by assay of β -galactosidase activity in cultured amniocytes or amniotic chorionic villi [1]. Mutation identification allows prenatal or preimplantation genetic diagnosis [19,20].

Treatment

Currently, no effective medical treatment is available for the underlying disorder in patients with G_{M1} gangliosidosis. Bone marrow transplantation was successful in an individual with infantile/juvenile G_{M1} gangliosidosis; however, no long-term benefit was reported [21]. Presymptomatic cord-blood hematopoietic stem-cell transplantation has been advocated by some as a possible treatment because of success in other lysosomal storage disorders [22]. Symptomatic treatment for some neurologic sequelae is available but does not significantly alter the clinical course. Active research in the areas of enzyme replacement and gene therapy for G_{M1} gangliosidosis is ongoing but has not advanced to human trials [2].

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