Case Study

EARLY INFANTILE GANGLIOSIDOSIS GM1 , A RARE CLINICAL ENTITY

Abstract:

Gangliosidosis is rarelysosomal storage disease, about 200 cases have been reported to date. Over all prevalence at birth of GM1 gangliosidosis is estimated to occur in one in 100,000 to 300,000. It is an inherited enzyme deficiency of beta-galactosidase, which results in the accumulation of glycosphingolipids within the lysosomes. It leads to neurological, skeletal, and dermatological manifestations. Inferred GM1 gangliosidosis is a lysosomal storage disorder affected by mutations in *GLB1*, encoding beta-galactosidase. The range of severity is from type 1 infantile disease, lethal in early childhood, to type 3 adult onset, resulting in gradually progressive neurological symptoms in adulthood. We relate to 13 months old patient with early infantile type of gangliosidosis.

Key Words: *Gangliosidosis, autosomal recessive inherited enzymedeficiency , beta-galactosidase, glycosphingolipids, Lysosomes*

Introduction

Landing et al. (1964) gave the first definitive description of this disease, it used to be previously called asHurler variant, pseudo hurler variant and Tay – Sachs disease with visceral involvement(1) O' Brein et al (1965) suggested the term "generalized gangliosidosis.(2)Gangliosidosis is an autosomal recessive lysosomal storage disease characterized by accumulation of ganglioside substrate in lysosomes due to deficiency of human beta-galactosidase enzyme.(3) clinically patients show variable degrees of neurodegeneration and skeletal abnormalities. Type 1 or infantile form shows rapid psychomotor deterioration beginning within 6 months of birth, generalized central nervous system involvement, skeletal dysplasia, hepatosplenomegaly, facial dysmorphism, macular cherry red spots, and early death. Dysplastic changes in long bones and vertebrae have been observed(4). General edema (5) or pitting edema of hands and feet is also significant (6)

Gangliosidosis is a rare clinical disorder, the exact prevalence is not known. About 200 cases have been reported to date. Overall prevalence at birth of GM1 gangliosidosis is estimated to occur in one in 100,000 to 300,000.(7) the prevalence in Brazil (1:17,000), in persons of Roma ancestry (1:10,000), and in the Maltese Islands (1:3,700) is much higher than in other areas and likely represents founder effects.(8)Infantile formis the most frequent form of GM1 gangliosidosis. It involves cardiac manifestations. EKG(Electrocardiogram) showed an incomplete bundle branch block and pathology shows vacuolated and hypertrophied myofibers. The mitral valve leaflets are thick and nodular with vacuolated histiocytes and fibrous tissue. In some cases, the right coronary artery is partially occluded by an atherosclerotic plague containing ballooned cells(9)

Skin manifestations include angiokeratoma corporisdiffusumwhich appears with GM1-gangliosidosis. The angiokeratomasdoesn't form clusters but are scattered widely over the body and proximal extremities. No angiokeratomasare observed on the penis and scrotum(9)

Extensive dermal melanocytosisis reported in association with GM1-gangliosidosis type 1, clinically, dermal melanocytosisis associated with lysosomal storage disease . It is characterized by extensive blue cutaneous pigmentation with dorsal and ventral distribution, indistinct borders, and persistent and/or 'progressive' behavior(10)

GM1 also involves glomerular epithelium, a renal biopsy revealed storage of mucopolysachharide in vacuoles of glomerular epithelium, vacuoles were considered as lysosomes(11)

Currently no effective medical treatment is available forinfantileGM1 gangliosidosis. Bone marrow transplantation was successful in an individual with infant lie GM1 gangliosidosis, however no long-term benefit was reported. (12)

Presymptomatic cord-blood hematopoietic stem cell transplantation has been advocated by some as a possible treatment because of success in other lysosomal storage disorders.[14].

Prognosis is not good. Death usually occurs during the second year of life because of infection and cardiopulmonary failure(7)

Presentation of Case :

13 months old baby girl was attended and history was narrated by mother, mother complainedof non-bloody Diarrhea for 1 month, 3 episodes /day, contains mucous, grade 3-4, partiallyalleviated with medicine. Associated with non-documented and low-grade fever which wassudden in onset, intermittent, aggravated at morning and night had no alleviating factors. Motherdenied history of vomiting, dysuria, fits, loss of consciousness, cyanosis.

She was born at term by Simple Vaginal Delivery at hospital, mother had no history of prenatal/Natal/ postnatal complications. She had cried well soon after birth though her family had noticedthe dysmorphic face and increased weight of 4.5 kg. Parents considered increased weight to benormal. Patient at age of 12 months, developed Respiratory infection and was treated for it.Patient had normal developmental milestones but was unable to stand or walk. Patient is third child ofconsanguineous parents. The eldest child passed away due to meningitis at age of 1 while the second child is doing fine.

On Examination the baby had dysmorphic face. Her skin was generally pale. Head circumference wasmeasured to be 50 cm. Anteriorfontanellewas open and flat which measuredas 1.5 cm x 1.5 cm.There wasfrontal bossing and depressed nasal bridge. On musculoskeletal examination it showedasymmetry of both upperand lower limb,rocker bottom feet and B/L(Bilateral) pittingedema of lower limbs up till thighs[Figure no 1]. There were wrinkles on arms. Abdominal examination showed Harrison sulcus[Figure no 3] hepatomegaly with liver span of 8 cm below costal margin but no splenomegaly. Cardiacand Chest exams were normal.

Imaging studies were run, where X-Ray Skeletal survey showed J shaped SellaTurcica andanterior beaking of thoracolumbar vertebrae [Figure no 2] . Liver Trucut Biopsy showed

Mild Macrovesicularsteatosis.. Eye Examination revealed squinted eyes and did not show any Cherry Red Spot. Her Echocardiogram, Ultrasound KUB (Kidney Ureter and Bladder) and ThyroidProfile were normal

At the end of history parents were counselled to undergo testing and the scope of prenatal diagnosis was discussed for next pregnancy

Discussion:

Gangliosidosis aninherited enzyme deficiency of beta-galactosidase which results in the accumulation of glycosphingolipids within the lysosomes. It leads to neurological, skeletal, and dermatological manifestations. Inferred GM1 gangliosidosis is a lysosomal storage disorder affected by mutations in *GLB1*, encoding beta-galactosidase. The range of severity is from type i infantile disease, lethal in early childhood, to type iii adult onset, resulting in gradually progressive neurological symptoms in adulthood.
Gangliosidosis is a rare clinical disorder ,About 200 cases have been reported to date . The prevalence of GM1 gangliosidosis at birth is estimated to occur in one in 100,000 to 300,000 Childs.

The patient is diagnosed on the basis of several clinical features which are typical of generalized GM1-gangliosidosis. These include vertebral changes which included Upper and lower limb asymmetry, dysmorphicfacies(4), characteristic pitting bilateral lower limb edema(5, 6)since birth and upper respiratory tract infection.
Other unique clinical features of the patient included J shaped SellaTurcica andanterior beaking of thoracolumbar on X-Ray Skeletal survey

Conclusion :

Since this is a rare clinical entity , therefore it needs to be documented. About 200 cases have been reported to date .The prevalence of GM1 gangliosidosis at birth is estimated to occur in one in 100,000 to 300,000 Childs.
This case report emphasize on reporting of a rare disorder and also focuses in the aspected that can help in diagnosing Gangliosidosis. Clinical and radiological aspects better helps in this regard. The clinical aspects in the present case are vertebral changes which includes bilateral lower limb asymmetry and edema. Edema either generalized or present only in lower limbs .Radiological features of the patient includes J shaped SellaTurcica and anterior beaking of thoracolumbar on X-Ray skeletal survey. Therefore both clinical and radiological aspected can assist in diagnosing Gangliosidosis GM1 in infants.

CONSENT:

All authors declare that 'written informed consent was obtained from the guardians of patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office/chief editor/editorial board members of this journal.

References:

1. LANDING BH, SILVERMAN FN, CRAIG JM, JACOBY MD, LAHEY ME, CHADWICK DL. Familial Neurovisceral Lipidosis: An Analysis of Eight Cases of a Syndrome Previously Reported as Hurler-

Variant, Pseudo-Hurler Disease, and Tay-Sachs Disease With Visceral Involvement. American Journal of Diseases of Children. 1964;108(5):503-22.
2. Yoshida T, Wilson J, editors. Phenotype-genotype correlation in GM1-gangliosidosis. Molecular Approaches to the Study and Treatment of Human Diseases: Proceedings of the International Symposium on Genetic Intervention in Diseases with Unknown Etiology, Tokyo, Japan, 30 November-1 December 1990; 1992: Excerpta Medica.
3. Okada S, O'Brien JS. Generalized gangliosidosis: beta-galactosidase deficiency. Science. 1968;160(3831):1002-4.
4. Fricker H, O'brien J, Vassella F, Gugler E, Mühlethaler J, Spycher M, et al. Generalized gangliosidosis: Acid β-galactosidase deficiency with early onset, rapid mental deterioration and minimal bone dysplasia. Journal of neurology. 1976;213(4):273-81.
5. Cabral A, Portela R, Tasso T, Eusébio F, Moreira A, Dos Santos HM, et al. A case of GM1 gangliosidosis type I. Ophthalmic paediatrics and genetics. 1989;10(1):63-7.
6. Benson P, Brown S, Babarik A, Mann T. GM1-generalized gangliosidosis variant with cardiomegaly. Postgraduate medical journal. 1976;52(605):159-65.
7. Regier DS, Tifft CJ. GLB1-related disorders. 2013.
8. Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects. Molecular genetics and metabolism. 2008;94(4):391-6.
9. Hadley RN, Hagstrom JW. Cardiac lesions in a patient with familial neurovisceral lipidosis (generalized gangliosidosis). American journal of clinical pathology. 1971;55(2):237-40.
10. Hanson M, Lupski JR, Hicks J, Metry D. Association of dermal melanocytosis with lysosomal storage disease: clinical features and hypotheses regarding pathogenesis. Archives of dermatology. 2003;139(7):916-20.
11. Kelly DA, Portmann B, Mowat AP, Sherlock S, Lake BD. Niemann-Pick disease type C: diagnosis and outcome in children, with particular reference to liver disease. The Journal of pediatrics. 1993;123(2):242-7.
12. Ong W-Y, Kumar U, Switzer RC, Sidhu A, Suresh G, Hu C-Y, et al. Neurodegeneration in Niemann-Pick type C disease mice. Experimental brain research. 2001;141(2):218-31.

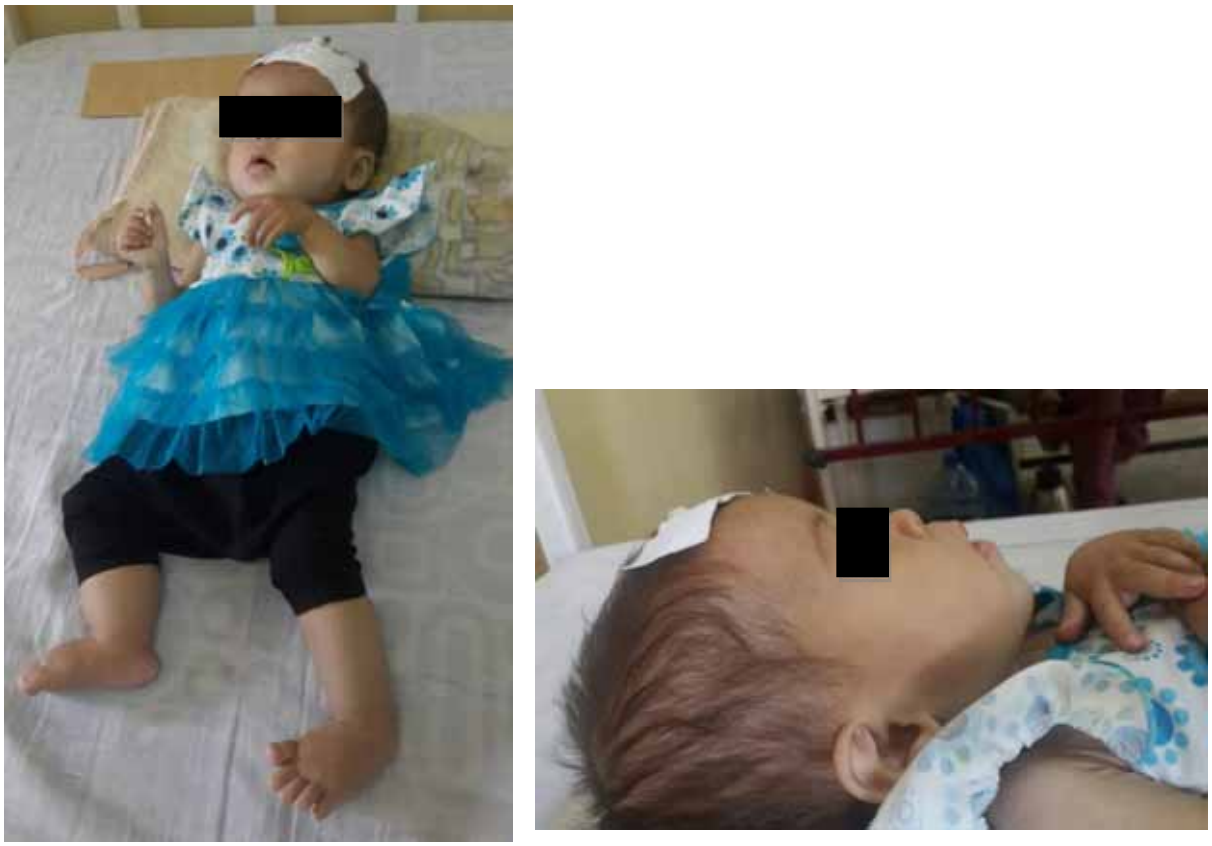

Figure 1: shows frontal bossing, Depressed nasal bridge. Upper and lower limb asymmetry with B/L pitting edema of lower limbs, Rocker Bottom feet and Frontal Bossing

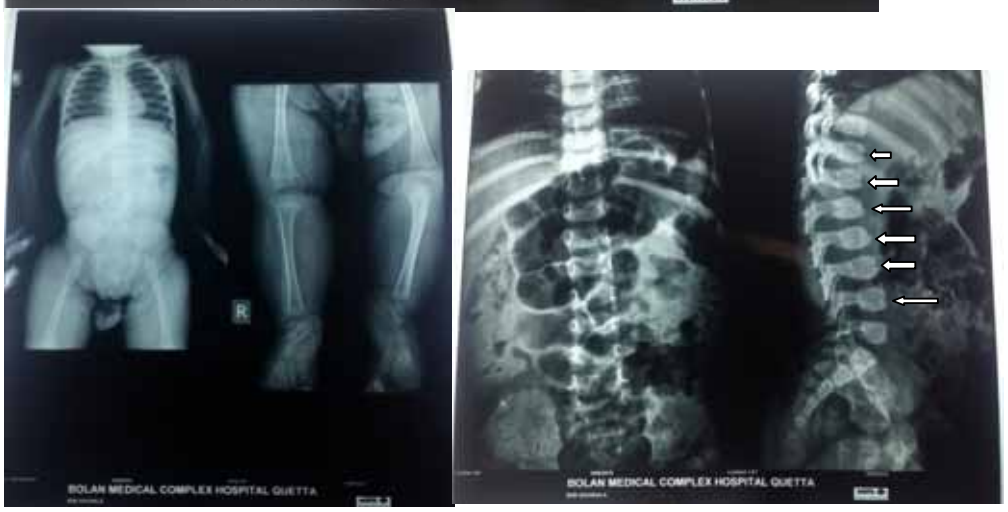

Figure 2: Skeletal survey, J shaped Sellaturcica is prominent, skeletal asymmetry and Skeletal survey showing Anterior Beaking of Thoracolumbar vertebrae

Figure 3: showing Harrison's sulcus and wrinkling of Skin.