

## Lysosomal Storage Disease

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### ABSTRACT

We report a case of lysosomal storage disease diagnosed by lysosomal enzyme assay in a two year old boy with a history of gradual onset of weakness of body, poor vision, flaccid neck and spasticity in all four limbs with hyper-reflexia. On fundus examination cherry red spots were noted at macula. On performing lysosomal enzyme assay, beta-galactosidase level was considerably low. This indicates that the child is affected by lysosomal storage disease most likely GM1 gangliosidosis. The diagnosis is important because the disease is rare and it may be missed as the symptoms are similar to other neurological conditions and the diagnosis can help with future conception.

**Key Words:** *beta-galactosidase, GM1 gangliosidosis, lysosomal storage disease*

### INTRODUCTION

Lysosomal storage disease is a group of diseases which results due to genetic defect in a lysosomal system protein leading to accumulation of partially degraded molecules within lysosomes.<sup>1,2</sup> Over 40 lysosomal storage diseases are known and they have a collective incidence of approximately 1 in 7000-8000 live births.<sup>1</sup> Most of these disorders are autosomal recessively inherited, however a few are X-linked recessively inherited like mucopolysaccharidosis II (MPS II) and Fabry disease.<sup>1</sup> Although these diseases are considered in the differential diagnosis on the basis of clinical findings, they are not confirmed due to the lack of advanced laboratory techniques in Nepal.

This case, as per the clinical findings and the laboratory findings of beta-galactosidase level, was diagnosed as GM1-Gangliosidosis.

### CASE REPORT

A two year old boy from Jibjibe, Rasuwa presented with developmental regression from the age of eight months, the prior growth and development being normal. Then the child had progressive weakness of the body. The child was unable to hold his head, unable to breastfeed, had poor vision, had recurrent history of dyspnea, on and off fever and constipation. There was no history of seizures and vomiting. There was no history of similar disorder and other neurological disorder in the family. There was no history of drug intake or maternal illness during the time of pregnancy.

On examination the child was ill-looking. Head size was normal. The child had flaccid neck and spasticity in all four limbs with hyper-reflexia. The child also had dysmorphic facial features like depressed nasal bridge with broad nasal tip, large low set ears and long philtrum.

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Large mongolian spots were presents on the child's back. The child had macroglossia. Hepatosplenomegaly was present. Cardiovascular and respiratory systems were normal.

Plain Computed Tomogram (CT) of head showed a normal study. On, ophthalmological consultation, only perception of light was present in both eyes with nystagmus of wandering type. Pupillary reaction was sluggish. On fundus evaluation, optic disc pallor, attenuated blood vessels and cherry red spots at the macula were noticed. On further evaluation, sleep electroencephalogram (EEG) showed evidence of epileptiform activity over the left parietal region.

The child's clinical features suggested a neurological disorder. His blood sample showed beta-galactosidase level 0.2 nmol/min/mg of protein. Other lysosomal enzymes were within normal range (Table 1.)

Analysis of the child's leucocyte lysosomal enzyme activities revealed a low beta- galactosidase activity. This indicates that the child most likely had GM1 gangliosidosis.

Similar findings were noticed in his sister's blood examination. Her beta-galactosidase activity was 0.1 nmol/min/mg of protein. His sister who is twelve months old also showed similar clinical features.

## DISCUSSION

GM1 gangliosidosis is an autosomal lysosomal storage disorder due to deficiency of the beta-galactosidase enzyme. This deficiency results in accumulation of GM1 gangliosides and related glycoconjugates in the lysosomes leading to lysosomal swelling, cellular

damage, and organ dysfunction.<sup>3,4</sup> It is a very rare disease, however unusually high incidence has been found in Southern Brazil and an incidence of 1 case per 3700 live births has been reported in the population of Malta.<sup>5,6</sup>

GM1-Gangliosidosis is characterised by generalized accumulation of GM1 ganglioside, oligosaccharide and mucopolysaccharide keratin sulphate and their derivatives. Acid beta-galactosidase is a lysosomal hydrolase that catalyzes the removal of the terminal beta-linked galactose from glycoconjugates (e.g. GM1 ganglioside), generating GM2 ganglioside. It also functions to degrade other beta-galactose-containing glycoconjugates, such as keratan sulfate. Deficiency of acid beta-galactosidase results in the accumulation of glycoconjugates in body tissues and their increased excretion in urine. Various mutations have been seen with the beta-galactosidase gene.

Three clinical subtypes of GM1 gangliosidosis exist, they are:

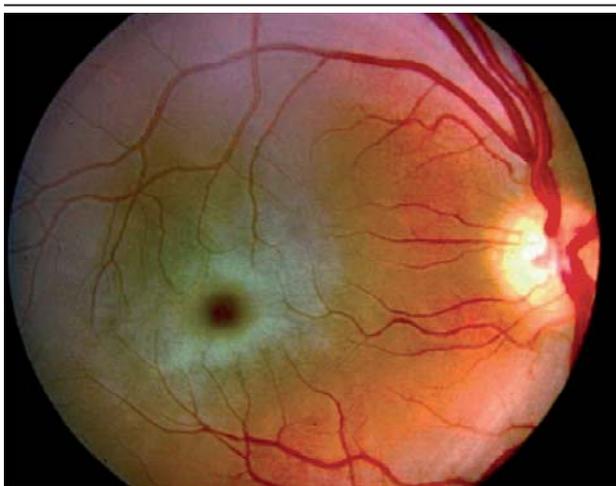
1. Infantile: It is most common and typically presents between birth and age six months of age. It shows coarse facial features, hepatosplenomegaly, generalized skeletal dysplasia (dysostosis multiplex), macular cherry-red spots, and developmental delay/arrest followed by progressive neurologic deterioration which usually occur within the first six months of life.<sup>3,7-9</sup> An increased incidence of Mongolian spots has also been reported.<sup>10</sup> Death usually occurs during the second year of life because of infection (usually due to pneumonia that results from recurrent aspiration) and cardiopulmonary failure.

**Table 1.** Lysosomal Enzymes study of the child carried out in National Reference Laboratory in Australia. Specimen type: EDTA blood

Lysosomal enzymes	Measured value in nmol/min/mg protein	Reference range
Beta-galactosidase	0.2 (low)	1.0-6.0
Total beta-Hexosaminidase	65 (high)	10-50
Beta-Hexosaminidase A	20	3-20
Arylsulphatase A	5.1 (high)	1-5
Beta-glucuronidase	2	0.5-3.4
Alpha-mannosidase	20	2-25
Alpha-fucosidase	2.7	0.4-2.7
<b>Measured value in pmol/min/mg protein</b>		<b>Reference range</b>
Sphingomyelinase	81	20-120
<b>Measured value in nmol/min/ml plasma</b>		<b>Reference range</b>
Alpha-NAc-galactosaminidase	0.2	0.1-0.6



**Figure 1.** Child with Lysosomal Storage Disease



**Figure 2.** Macular cherry red spot observed under Fundoscopy

2. Juvenile: The juvenile form is characterized by a later age of onset, less hepatosplenomegaly (if any), fewer cherry-red spots (if any), dysmorphic features, or skeletal changes (vertebral dysplasia may be detected radiographically). Death usually occurs before the second decade of life.
3. Adult: The adult form is characterized by normal early neurologic development with variable age of clinical presentation. Slowly progressing dementia with parkinsonian features and extrapyramidal disease is common. Intellectual impairment may be initially absent or mild but progresses with time. Generalized dystonia with speech and gait disturbance is the most frequently reported early feature.<sup>11</sup>

In lab studies acid beta-galactosidase activity in peripheral blood leukocytes is decreased. Galactose-containing oligosaccharides are excreted in the urine. Their presence may be used as an ancillary diagnostic test, and the concentration of the metabolites is proportional to disease severity. Skeletal radiographs may reveal changes characteristic of dysostosis multiplex. Neuroimaging using CT scan or magnetic resonance imaging (MRI) generally reveals diffuse atrophy and white matter demyelination with or without basal ganglia changes. An ultrasound of the abdomen may reveal organomegaly. On echocardiography, signs of cardiomyopathy or valvulopathy may be observed. EEG may reveal generalized dysrhythmia and epileptogenic foci.<sup>12</sup>

On many cases, the disease is recognized on the basis of diffuse vacuolization of cyto- and syncytiotrophoblasts, stromal cells and amniocytes on histological analysis of the placenta. The placental examination is prompted by the prenatal detection of intrauterine growth retardation (IUGR) and oligohydramnios at 32 weeks of gestation.<sup>13</sup>

Currently, no effective medical treatment is available for the underlying disorder. Bone marrow transplantation was successful in an individual with infantile/juvenile GM1 gangliosidosis; however, no long-term benefit is reported.<sup>14</sup> A recent study has suggested that galactose or its derivatives with potential chaperone properties could be used in the development of non-invasive therapies of GM1-gangliosidosis.<sup>15</sup> Symptomatic treatment for some neurologic sequelae is available but does not significantly alter the clinical course. The management is usually a team work requiring clinical geneticist, neurologist, cardiologist, orthopedist, ophthalmologist, otolaryngologist and audiologist.

In summary, children with developmental delay, seizures, dysmorphic features, neuromuscular defects and organomegaly with or without positive urinary screening for common metabolic disorders, need to be investigated for lysosomal storage diseases. Variability of clinical expression is commonly observed which require further confirmation by specific leukocyte enzyme study.

Lysosomal storage disease is a debilitating genetic disorder which looks similar to other neurological conditions but can be diagnosed with proper laboratory investigation. Though rare in incidence, any genetic disease like lysosomal storage disease cannot be overlooked in a developing country like Nepal where the diagnosis if made early with proper prenatal counseling can be of significant help in future conception.

## REFERENCES

1. Ballabio A, Gieselmann V. Lysosomal disorders: from storage to cellular damage. *Biochim Biophys Acta*. 2009 Apr;1793(4):684-96.
2. Winchester B, Vellodi A, Young E. The molecular basis of lysosomal storage diseases and their treatment. *Biochem Soc Trans*. 2000 Feb;28(2):150-4.
3. Yoshida K, Yanagisawa N. Beta galactosidosis: GM1 gangliosidosis and Morquio B disease. *Nippon Rinsho*. 1995 Dec;53(12):2960-6.
4. Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects. *Mol Genet Metab*. 2008 Aug;94(4):391-6.
5. Severini MH, Silva CD, Sopelsa A, Coelho JC, Giugliani R. High frequency of type 1 GM1 gangliosidosis in southern Brazil. *Clin Genet*. 1999 Aug;56(2):168-9.
6. Lenicker HM, Vassallo Agius P, Young EP, Attard Montalto SP. Infantile generalized GM1 gangliosidosis: high incidence in the Maltese Islands. *J Inherit Metab Dis*. 1997 Sep;20(5):723-4.
7. Steczkowska M, Gergont A, Krocicka S, Nowak A. Clinical features of GM1 and GM2 gangliosidosis in own observation. *Przegl Lek*. 2008;65(11):819-23.
8. Beck M. Variable clinical presentation in lysosomal storage disorders. *J Inherit Metab Dis*. 2001;24(Suppl 2):47-51.
9. Chamoles NA, Blanco MB, Iorcansky S, Gaggioli D, Specola N, Casentini C. Retrospective diagnosis of GM1 gangliosidosis by use of a newborn-screening card. *Clin Chem*. 2001 Nov;47(11):2068.
10. Ashrafi MR, Shabani R, Mohammadi M, Kavusi S. Extensive Mongolian spots: a clinical sign merits special attention. *Pediatr Neurol*. 2006 Feb;34(2):143-5.
11. Muthane U, Chickabasaviah Y, Kaneski C, Shankar SK, Narayanappa G, Christopher R, et al. Clinical features of adult GM1 gangliosidosis: report of three Indian patients and review of 40 cases. *Mov Disord*. 2004 Nov;19(11):1334-41.
12. Gascon GG, Ozand PT, Erwin RE. GM1 gangliosidosis type 2 in two siblings. *J Child Neurol*. 1992 Apr;7 Suppl:S 41-50.
13. Brunetti-Pierri N, Mian A, Luetchke R, Graham BH. Intrauterine growth retardation and placental vacuolization as presenting features in a case of GM1 gangliosidosis. *J Inherit Metab Dis*. 2007 Oct;30(5):823.
14. Wu XR, Bao XH. Recent advances in the diagnosis and treatment of lysosomal storage diseases. *Beijing Da Xue Xue Bao*. 2005 Aug 18;37(4):440-4.
15. Caciotti A, Donati MA, d'Azzo A, Salvioli R, Guerrini R, Zammarchi E, et al. The potential action of galactose as a "chemical chaperone": increase of beta galactosidase activity in fibroblasts from an adult GM1-gangliosidosis patient. *Eur J Paediatr Neurol*. 2009 Mar;13(2):160-4.