

## $\beta$ -mannosidase deficiency in two mentally retarded girls with intractable seizures

Mathew Punnachalil Cherian, MD, DCH, FRCPI

$\beta$ -mannosidosis is a rare lysosomal storage disease of glycoprotein catabolism, caused by an autosomal recessively inherited deficiency of  $\beta$ -mannosidase, the final enzyme involved in the catabolism of oligosaccharide side-chains of glycoproteins. This disorder was originally described in goats in 1981<sup>1</sup> and then humans in 1986.<sup>2,3</sup> Unlike the severe clinical presentation of the caprine disease, a rapidly fatal neurological disease leading to neonatal death, the human disease is milder. To date, only twelve patients with this condition have been reported in the literature throughout the world, and the clinical manifestations have been heterogeneous, including various degrees of mental retardation associated with speech impairment,<sup>2-7</sup> hearing loss,<sup>4,6,8</sup> aggressive behavior and emotional instability,<sup>5,8,9</sup> angiokeratoma,<sup>2</sup> recurrent respiratory infections<sup>6,9</sup> and epileptic encephalopathy.<sup>7</sup> The most recently reported case was an infant who presented with hypotonia, and abnormalities in esophageal motility and swallowing, resulting in recurrent respiratory infections.<sup>10</sup>

My report is about two girls of consanguineous Saudi parents who presented with intractable seizures, mental retardation, severe speech and language impairment. One of the girls showed deficiency of  $\beta$ -mannosidase in plasma, leukocytes and cultured fibroblasts, together with excretion of an abnormal disaccharide in urine. The enzyme level in the second girl was not depleted to the same extent as the first. The clinical and biochemical features of these two patients are compared to those of previously reported patients. The majority of the twelve previously reported cases of  $\beta$ -mannosidosis were of European ancestry. To my knowledge, these are the first cases reported from the Arabian Peninsula.

### Case 1

The first case was a girl who was the second of five children of a consanguineous Saudi family. She first presented to our hospital at the age of 2 years with a history of very frequent generalized tonic-clonic seizures, beginning at the age of 6 months. She was the product of a normal pregnancy, born in a local hospital and there was no history of antenatal or post-natal insult. Her developmental milestones were delayed. The tonic-clonic seizures were always associated with fever with no apparent focus of infection. She had been on treatment with phenobarbitone with no amelioration of seizure activity. On examination at the age of 2 years, she was thin-built, with a weight and head circumference on the 3rd percentile and height on the 50th percentile. There were no facial dysmorphism, organomegaly or skeletal

*From the Ras Tanura Primary Care Services Division, Saudi Aramco Medical Services Organization, Ras Tanura, Saudi Arabia*

*Dr. Mathew P. Cherian  
Saudi Aramco  
PO Box 1356  
Ras Tanura 31311  
Saudi Arabia  
Email: mathew.cherian@aramco.com*

*Accepted for publication:  
October 2003*

*Ann Saudi Med 2004; 24(5): 393-395*

defects. She showed severe mental retardation, speech impairment and alternating esotropia. No hearing loss was detected on audiogram. EEG showed diffuse disorganization of cerebral rhythm as well as a potential epileptiform focus arising from the left parasagittal region. The brain-stem auditory evoked response was normal on both sides. A CT scan of the brain did not show any abnormality. Her seizure frequency and severity did not improve despite adequate blood levels of phenobarbitone and valproic acid, which prompted further investigations. Serum electrolytes, glucose, ammonia, lactic acid, carnitine, lead, uric acid, TSH and amino acids were all normal. Urinary amino acids and organic acids were normal.

Assay of white cell and plasma lysosomal enzymes was performed to rule out lysosomal storage disorders, including Sandhoff disease, ACP deficiency  $\alpha$ - and  $\beta$ -mannosidosis, Tay-Sachs disease, Sly's disease, GM1-gangliosidosis, Fabry's disease, fucosidosis, Wolman's disease, metachromatic leukodystrophy, Gaucher's disease, Neimann-Pick disease A&B, Krabbe's leukodystrophy and Schindler's disease. All values were normal except for a marked deficiency of plasma  $\beta$ -mannosidase activity suggesting a diagnosis of  $\beta$ -mannosidosis. Further  $\beta$ -mannosidase assays of leukocytes and skin-fibroblasts of both girls, as well as plasma and leukocyte assays of both parents were performed, as previously described by Cooper et al<sup>11</sup> (Table 1).

Case 1 showed consistently reduced  $\beta$ -mannosidase activity when compared to controls and parental samples in all tissues investigated. Her urine was tested for disaccharide excretion. Thin-layer chromatography of urinary oligosaccharides showed a single prominent band with the mobility of a disaccharide. On further testing the band was identified as  $\beta$ -mannosyl<sup>1-4</sup> N-acetyl-glucosamine, the

**Table 1.** Results of β-mannosidase assays in plasma, leukocytes and fibroblasts.

	Plasma β-mannosidase (nmol/hr/ml)	Leukocyte β-mannosidase (nmol/hr/mg of protein)	Fibroblast β-mannosidase (nmol/hr/mg of protein)
Case 1	21	33	18
Case 2	121	91	24
Father	115	144	–
Mother	83	118	–
Controls	200-1500	245-467	77-95

characteristic urinary disaccharide excreted in patients with β-mannosidosis.

**Case 2**

The 3-1/2-year-old sister of the proband had a similar presentation: intractable seizures beginning at the age of 6 months, mental retardation and severe speech impairment. Her birth and immediate neonatal period was uneventful. The seizures were of the generalized tonic-clonic type and were always associated with fever. This girl was also treated in a local hospital with phenobarbitone, without any seizure control. Examination revealed a mentally retarded child with no facial dysmorphism. Her speech was severely impaired and an audiological evaluation was normal. EEG showed evidence of a multifocal epileptiform process with some predominance over the left hemisphere. The general organization of baseline was abnormal, with relatively poorly developed sleep activity for her age, suggesting a global encephalopathic process with the associated irritability. Seizures could not be controlled with a combination of phenobarbitone, valproic acid and, later, phenytoin. This girl was also investigated on the same lines as the proband. Blood biochemistry, plasma amino acids, urine amino acids and organic acids were all normal. CT scan of the brain was unremarkable. Plasma, leukocyte and fibroblast β-mannosidase levels showed only mild to moderate deficiency (Table 1).

The family left the city and thus our care soon after the above tests; therefore an estimation of urinary disaccharide could not be performed on this patient. Both patients are now lost for follow-up, and the subsequent progress or deterioration of their condition could not be assessed.

**Discussion**

The clinical manifestations of the human form of β-mannosidase deficiency are relatively less severe compared to the neurological involvement in caprine β-mannosidosis, which consists of intense tremor, nystagmus, ataxia, inability to stand and a fatal outcome. Clinical heterogeneity is evident in most cases of the human disease even between affected members of the same family.<sup>9</sup> This heterogeneity is further complicated by its association with other metabolic

disorders such as combined deficiencies of β-mannosidase and heparin sulfamidase resulting in mucopolysacchariduria<sup>3</sup> and detection of significant ethanolinouria.<sup>4</sup> Of twelve patients reported to date (who ranged in age from one to forty four years), the majority presented with severe speech impairment and varying degrees of mental retardation.<sup>2,7</sup> The two girls in the present report had identical presentations, consisting of intractable tonic-clonic seizures, mental retardation and severe speech impairment. According to the literature, the only occurrence showing an association of the disease with seizures was in a one-year old girl who presented with developmental delay and epileptic encephalopathy.<sup>7</sup> Though hearing loss has been the hallmark in a few cases,<sup>4,6,8</sup> audiological evaluation of patients in this report was normal. Other rare clinical manifestations reported in the past include angiokeratoma of the scrotum and penis,<sup>2</sup> cranio-facial dysmorphism and emotional instability,<sup>5</sup> bone deformity, gargoylism, recurrent skin and respiratory infections,<sup>9</sup> and demyelinating peripheral neuropathy.<sup>12</sup>

The β-mannosidase levels in the plasma, leukocytes and skin fibroblasts of the proband showed a substantial reduction when compared to controls and parents. However, the level of enzyme activity in her tissues was much higher than in the originally reported cases. The presence of the characteristic disaccharide, β-mannosyl<sup>1-4</sup> N-acetyl glucosamine in urine, together with her clinical presentation could be attributed to a form of β-mannosidosis. In Case 2, the enzyme level in plasma was similar to that of her parents, but significantly decreased activity was found in leukocytes and fibroblasts when compared to controls. Since the urine of Case 2 could not be examined for the presence of the disaccharide excretion, the diagnosis of β-mannosidosis could not be confirmed and the presence of another deficiency or a neurodegenerative disease could not be ruled out. Both of the parents had intermediate β-mannosidase activity, suggesting a carrier status and thus confirming an autosomal recessive mode of inheritance.

Caprine β-mannosidosis is associated with accumulation of the disaccharide, β-mannosyl-(1-4)- N-acetyl-glucosamine as well as the trisaccharide, β-mannosyl-β-(1-4)-N-acetyl-glucosaminyl-(1-4)N-acetyl-glucosamine in the brain



and their excretion in urine. This specific trisaccharide, demonstrated in the urine of affected goats, is not present in human counterparts. Instead, the human disease is associated with variable excretion of urinary disaccharide,  $\beta$ -mannosyl-(1-4)-N-acetyl glucosamine.<sup>2,3,6,8,9</sup> Studies have shown the accumulation of the same disaccharide in cultured human fibroblasts and, to a lesser extent, leukocytes.<sup>11,13</sup> In human glycoprotein catabolism, unlike in ruminants, the chitobiose linkage appears to be preferentially cleaved and hence the disaccharide rather than the trisaccharide is the major accumulated and excreted oligosaccharide.<sup>3,11</sup> The possible roles of accumulated oligosaccharides in the pathogenesis of neurological manifestations of this disease have not yet been established in man or animals. No human autopsy studies have been reported to date.

$\beta$ -mannosidosis is thought to be of autosomal recessive inheritance. Though consanguinity is found only in this study and in one previous report,<sup>6</sup> the recessive inheritance is further substantiated by occurrence of the disease in both sexes, together with the finding of reduced  $\beta$ -mannosidase activity in parents. Studies have suggested that human and caprine  $\beta$ -mannosidosis are both most likely caused by allelic mutations in the structural  $\beta$ -mannosidase genes.<sup>14</sup> Recent studies on mutation analysis have identified the gene localized to chromosome 4q22-25,<sup>15</sup> and the gene consisting of 17 exons.<sup>16</sup> Prenatal diagnosis is possible

in this condition since  $\beta$ -mannosidase activity is highly expressed in chorionic villi and amniotic cells.<sup>5,17</sup> The level of enzyme activity in tissues is much higher in these patients than in the originally reported cases. However, the symptomatology of intractable seizures, mental retardation and speech impairment could not be attributed to any other etiology and may represent another rare entity of the disease spectrum in  $\beta$ -mannosidosis. The genotype might have contributed to the milder residual enzyme activity in these patients.

### Acknowledgments

The author acknowledges the use of Saudi Aramco Medical Services Organization (SAMSO) facilities for the research data utilized in this manuscript. Opinions expressed in this article are those of the author and not necessarily of SAMSO. The author wishes to thank Dr. Revi Mathew (Department of Pediatric Endocrinology, Vanderbilt University Medical Center, Tennessee, USA) for his involvement in the diagnosis and management of these patients and Ms. Susan Newby for her assistance in typing the manuscript. The author also acknowledges the assistance from Dr. J.E. Wraith and A. Cooper of Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, United Kingdom for performing most of the assays.

### References

- Jones MZ, Dawson G. Caprine  $\beta$ -mannosidosis: Inherited deficiency of  $\beta$ -D-mannosidase. *J Biol Chem.* 1981; 256: 5185-5188.
- Cooper A, Sardharwalla IB, Roberts MM. Human  $\beta$ -mannosidase Deficiency. *N Engl J Med.* 1986;315: 1231.
- Wenger DA, Sujansky E, Fennessey PV, Thompson JN. Human  $\beta$ -mannosidase Deficiency. *N Engl J Med.* 1986; 315: 1201-1205.
- Wijburg H, de Jong J, Wevers R, et al. Beta-mannosidosis and ethanolanuria in a female patient. *Eur J Pediatr.* 1992;151:311.
- Poenaru L, Akli S, Rocchiccioli F, Eydoux P, Zamet P. Human  $\beta$ -mannosidosis: A 3-year-old boy with speech impairment and emotional instability. *Clin Genet.* 1992; 41: 331-334.
- Dorland L, Duran M, Hoefnagels FET, et al.  $\beta$ -mannosidosis in two brothers with hearing loss. *J Inher Metab Dis.* 1988;11 suppl 2: 255-258.
- Cooper A, Wraith JE, Savage WJ, Thornley M, Noronha MJ.  $\beta$ -mannosidase Deficiency in a female infant with Epileptic Encephalopathy. *J Inher Metab Dis.* 1991;14: 18-22.
- Cooper A, Hatton CE, Thornley M, Sardharwalla IB.  $\alpha$ - and  $\beta$ -mannosidosis. *J Inher Metab Dis.* 1990;13: 538-548.
- Kleijer WJ, Hu P, Thoomes R, et al.  $\beta$ -mannosidase deficiency: heterogenous manifestation in the first female patient and her brother. *J Inher Metab Dis.* 1990; 13: 867-872.
- Gourrier E, Thomas MP, Munnich A, Poenaru L, Asensi D, Jan D, Leraillez J. Beta mannosidosis: a new case. *Arch Pediatr.* 1997;4:147-151.
- Cooper A, Hatton CE, Thornley M, Sardharwalla IB. Human  $\beta$ -mannosidase deficiency: Biochemical findings in plasma, fibroblasts, white cells and urine. *J Inher Metab Dis.* 1988;11:17-29.
- Levade T, Graber D, Flurin V, et al. Human  $\beta$ -mannosidase Deficiency associated with peripheral neuropathy. *Ann Neurol.* 1994;35:116-119.
- Van Pelt J, Hokke CH, Dorland L, et al. Accumulation of mannosyl- $\beta$  (1-4)- N-acetyl glucosamine in fibroblasts and leukocytes of patients with a deficiency of  $\beta$ -mannosidase. *Clin Chim Acta.* 1990;187:55-60.
- Hu P, Wenger DA, Van Diggelen OP, Kleijer WJ. Complementation studies in Human and Caprine  $\beta$ -mannosidosis. *J Inher Metab Dis.* 1991;14:13-17.
- Alkhatat AH, Kraemer SA, Leipprandt JR, et al. Human beta-mannosidase c DNA Characterization and first identification of a mutation associated with human beta-mannosidosis. *Hum Mol Genet.* 1998;7:75-83.
- Bedilu R, Nummy KA, Cooper A, et al. Variable clinical presentation of lysosomal  $\beta$ -mannosidosis in patients with null mutations. *Mol Genet and Metab.* 2002;77:282-290.
- Kleijer WJ, Geilen GC, Van Diggelen OP, Wevers RA, Los FJ. Prenatal analyses in a pregnancy at risk for  $\beta$ -mannosidosis. *Prenat Diagn.* 1992;12:841-843.