Sandhoff disease in an extreme preterm baby with bilateral syndactyly

PMC Nair, *MD, DM,* ***Flor Bataclan,*** *MD,*
Anuradha Ganesh, *MRCP (Ophthal).*

Sandhoff disease (GM2 gangliosidosis) is much less common than Tay-Sachs disease. Both are autosomal recessive lysosomal storage disorders (GM gangliosidoses). But Sandhoff disease is caused by mutations of the gene encoding the beta sub-unit of hexosaminidase, on chromosome 5. In Tay-Sachs disease, the mutation is in the alpha sub-unit on chromosome 15.[1] Since both hexosaminidase A and hexosaminidase B contain beta subunits, the activity of both these 2 enzymes is lacking in this disorder. So GM2 gangliosides and other structurally related glycolipids accumulate in the brain, liver, spleen, and kidney. We report a case of Sandhoff disease in an extreme pre-term baby with bilateral syndactyly.

A female baby was born at 28 weeks of gestation with a birth weight of 770 gm to a gravida 3, para 2, 23-year-old Omani mother by assisted breech delivery. The Apgar score was 4 at one minute and 7 at 5 minutes. She was intubated and ventilated for 8 days for severe Respiratory Distress syndrome, received 2 doses of surfactant and was on nasal continuous positive airway pressure for 29 days. She had patent ductus arteriosus; closed with 3 doses of indomethacin and grade I intraventricular hemorrhage which resolved on subsequent ultrasound examinations. On clinical examination, she had bilateral syndactyly of 2nd and 3rd toes, but no other dysmorphic features. Chromosomal karyotyping was normal. Screening for retinopathy of prematurity was normal. She was discharged at 3 months of age (corrected post-conceptional age of 40 weeks) with a weight of 2 kg, normal growth pattern and reflexes, and breast-feeding. The earliest evidence of abnormality was noticed at corrected age of 3 months, when social smile was noticed to be absent. Repeat ophthalmic examination at this stage, showed normal disc and normal vessels, but macula showed definite pallor with some hypopigmentation at fovea suggestive of a cherry red spot. A metabolic storage disorder was

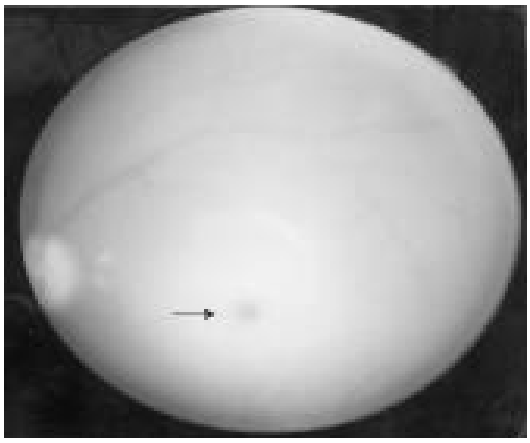

Figure 1 - Fundus showing cherry red spot at the macula and normal optic disk at 3 months of age.

Table 1 - Result of leukocyte and plasma enzyme studies.

Enzymes	Normal range	Baby	Father	Mother
Leukocyte enzymes				
Total b-hexosaminidases (umol/hour/mg protein) homozygote range: 0.02 - 0.17 heterozygote range: 0.33 - 0.91	0.58 - 3.0	0.11	0.43	0.77
Hexosaminidase A (nmol/hour/mg protein) homozygote range: 40 -156 heterozygote range:70 - 341	134 - 700	70	93	224
Plasma enzymes				
Total b-hexosaminidases (umol/hour/ml) homozygotes: 0 - 0.033 heterozygotes: 0.25 - 0.74	0.41 - 1.7	0.028	0.41	0.36
Hexosaminidase A (nmol/hour/ml) homozygotes: 0 - 25 heterozygotes: 52 - 134	76 - 269	18	110	88

considered at this point. By 6 months of corrected age, all developmental milestones were delayed with impaired hearing (brainstem evoked potential audiometry showed no response) and hepatomegaly of 4 cms. Ophthalmic examination under general anesthesia showed a typical cherry red spot at the macula with normal disc (**Figure 1**). Her leukocyte and plasma enzyme studies were consistent with a diagnosis of Sandhoff variant GM2 gangliosidosis and parental screening for leukocyte enzymes showed heterozygote disease in both the parents (**Table 1**). However, the other siblings were not screened. On examination, both the siblings had normal neurodevelopment. By one year of age, all the milestones of development in the index case were markedly delayed with generalized hypotonia and hyperreflexia.

Manifestations of Sandhoff disease are similar to Tay-Sachs disease with manifest hyperacusis, impaired vision with cherry-red spot on the macula, decerebrate rigidity and eventual development of megalencephaly. Unlike Tay-Sachs, Sandhoff disease patients have hepatosplenomegaly. There are no reports of intra-uterine onset of the disease. The earliest signs reported are mild motor weakness at 3-5 months of age, followed by progressive weakness and loss of gross motor skills to a vegetative state by 6 months to one year of age. A preterm baby with bilateral syndactyly presenting with cherry red spot at 3 months of age as in this case is rare. Literature search revealed only one similar report.[2] Macular cherry red spot is due to retinal ganglioside accumulation. Since consanguinity is more common, identification of the disease is important, as carrier detection and prenatal diagnosis is possible. Due to the nearly total absence of hexosaminidase activity in affected individuals, laboratory diagnosis of an affected child as well as prenatal diagnosis is accurate and reliable.[3] An accurate and inexpensive carrier detection test is available (serum or leukocyte hexosaminidase A) and the disease can be reliably diagnosed by chorionic villous sampling during the first trimester of pregnancy in couples at risk (heterozygote parents as in this case). Treatment is only supportive and most patients succumb to the disease by 4-5 years of age. Enzyme replacement, cellular infusions, substrate deprivation therapy and bone marrow transplantation have been tried. Gene therapy in the near future may provide the answer.[4,5]

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From the Neonatal Division, Child Health Department and Ophthalmology Department, Sultan Qaboos University Hospital, Muscat, Oman. Address correspondence and reprint requests to Dr. PMC Nair, Consultant, Neonatal & PICU, Department of Child Health, Sultan Qaboos University Hospital, PB-38, Al-Khod-123, Muscat, Sultanate of Oman. Fax. +968 513009. E-mail: dr_pmc@hotmail.com

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Erratum

In manuscript “Semiology of temporal lobe epilepsies” Neurosciences 2003; Vol. 8 (3): 139-142, reference number 48 in the references section should have appeared as follows:

48. Serles W, Caramanos Z, Lindinger G, Pataraia E, Baumgartner C. Combining ictal surface-electroencephalography and seizure semiology improves patient lateralization in temporal lobe epilepsy. ***Epilepsia*** 2000; 41: 1567-1573.