Case Report

Sandhoff disease (GM2 Gangliosidoses) in a premature patient with bronchopulmonary dysplasia

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ABSTRACT

We report a female premature infant with bronchopulmonary dysplasia and Sandhoff disease. The clue for diagnosis was the fundoscopy examination. We discuss this rare disease with unusual presentation of intrauterine growth retardation, premature delivery, and bronchopulmonary dysplasia.

Keywords: Cherry-red spot, GM2 ganglioside, hexosaminidases A & B, Tay Sachs disease, Sandhoff disease.

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The first clinical description of GM2 gangliosidosis was in 1881 by a British ophthalmologist, Warren Tay who described the peculiar bright-red macula in a child with mental and physical retardation.[1] Svennerholm[2] determined that GM2 ganglioside was the primary ganglioside stored in Tay-Sachs disease. The term GM2 gangliosidosis refers to all disorders that are associated with GM2 ganglioside (acidic glycosphingolipids) accumulation.[3] These acidic glycosphingolipids were called gangliosides due to their highest concentrations in normal brain, and because they were found in ganglion cells.[4] Both Tay-Sachs and Sandhoff diseases are neurometabolic disorders due to lysosomal dysfunction, which cause abnormal storage of glycosphingolipids. A deficiency of lysosomal enzyme beta-hexosaminidase A causes Tay-Sachs disease while a combined deficiency of beta-hexosaminidase A and B causes Sandhoff disease.[5,6] Our patient is a premature infant who had bronchopulmonary dysplasia and Sandhoff disease and the clue for diagnosis was the fundoscopy examination. Diagnosis is important for genetic counseling. Our report discusses this rare disease with unusual presentation of intrauterine growth retardation, premature delivery, and bronchopulmonary dysplasia.

Case Report. A female patient who was born at 30 weeks of gestation, was delivered by cesarean section due to intrauterine growth retardation. Apgar score is 5 at one minute and 9 at 5 minutes. Her birth weight was 1.1 kg (10th) percentile, height was 35cm (10th) percentile and head circumference was 26 cm (10th) percentile. She was mechanically ventilated for 30 days due to respiratory distress. She had been oxygen dependent for 3 months. At the 5th month of life, she was discharged from the nursery with a clinical and radiological finding of bronchopulmonary dysplasia, maintained on hydrochlothiazide and aldactone. Her parents are first cousins, they have 2 boys and 2 girls, both healthy. Examination at 7 months showed developmental delay, normal features, alert smiling look, generalized hypotonia, generalized weakness,

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brisk deep tendon reflexes and no organomegally. This was wrongly explained as a cerebral palsy due to stormy prenatal and postnatal problems in the absence of regression of milestones. However, we noticed a regression in her milestones at the end of her first year of life as she lost her ability to role over and sit with support with rapid progressive course until she became vegetative at 20 months of age. Fundoscopy examination at the age of 5 months showed normal findings, and 2nd fundoscopy at one year showed characteristic cherry red spot, immediately raising the possibility of neurodegenerative storage disease. Her leukocytic enzymes are consistent with a diagnosis of Sandhoff variant GM2 gangliosidosis. Family screening for leukocytic enzymes proved hetrozygote disease in both parents and other siblings (**Table 1**). At 20 months, she had generalized spasiticity, brisk deep tendon reflexes and up going planter reflexes. She died at the age of 2 years due to respiratory failure (**Figure 1**).

Table 1 - Result of leukocytic enzyme study.

Family member	Total b-hexomindases (normal 0.58 - 3.0 µmol/ml/hr)	Total b-hexomindase A (normal 134 - 700 µmol/ml/hr)
Patient	0.028	25
Mother	0.47	110
Father	0.71	160
1st brother	0.55	128
2nd brother	0.33	80
1st sister	0.49	111
2nd sister	0.56	134

Homozyote range: total b-hexomindase (0.02 - 0.17); hexomindase A (40 - 156). Hetrozyote range: total b-hexomindase (0.33-0.91); hexomindase A (70 - 341).

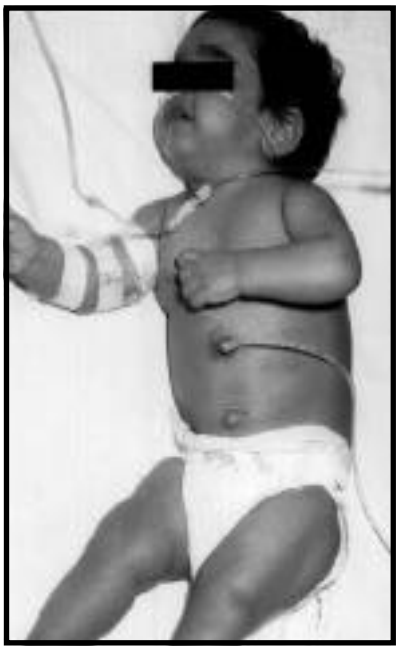

Figure 1 - Patient at one year of age, became hypertonic with stiffness and fisting of both hands.

Discussion. Accumulation of GM2 ganglioside has been observed in 18 to 20 weeks fetuses,[7] however, infants with Tay-Sachs disease and Sandhoff disease generally appear normal at birth. The intrauterine growth retardation in our patient, wether related to her problem or incidental finding needs to be confirmed. To our knowledge there are no reports of intrauterine onset of the disease. The earliest sign of the disease is mild motor weakness at 3 to 5 months of age followed by progressive weakness and loss of gross motor skills at 6 to 10 months of age. We had been misled by the stormy prenatal and neonatal periods, along with this absence of a definite history of regression of her milestones. The clinical phenotypes in GM2 gangliosidosis are categorized according to the type of enzymatic deficiency. The initial characterizations were determined according to the presence or absence of beta-hexosaminidase isoenzymes. The beta-hexosaminidase enzyme is composed of alpha and beta-subunits, beta-hexosaminidase A contains one alpha and one beta-subunit whereas beta-hexosaminidase B is composed of 2 beta-subunits. The Tay-Sachs variant is due to a deficiency of the alpha-subunit for the enzyme, which causes a loss of beta-hexosaminidase A so that only the B isoform of the enzyme is biologically active. Since, beta-hexosaminidase B is the only isoenzyme present, this variant is also called the B variant. The Sandhoff variant, caused by a defect in the beta-subunit, has a loss of both beta-hexosaminidases A and B (zero hexosaminidase activity) and thus is referred to as the O variant.[8] Characteristics of infantile Sandhoff disease, such as age of onset, duration, neurologic symptoms and ophthalmologic signs are identical to those seen in Tay-Sachs disease. The only clinical differences that may rarely be present in patients

with Sandhoff disease are mild hepatosplenomegaly (secondary to storage of globoside) and bony deformities.[9] On bone marrow biopsy, foam cells had been demonstrated in a few patients.[10] The first symptom is an excessive startle in response to noise, tactile stimuli, or light flashes. As the disease progresses the motor development slows and other motor skills, such as rolling, purposeful hand movements, head control, vocalizations and awareness are frequently lost. One of the characteristics of ophthalmologic findings is the presence of a macular cherry red spot that occurs in over 90% of infants with this disease. The storage of lipid within the retinal ganglion cells causes a whitish discoloration mostly of the retina. The fovea, however, which does not contain the bipolar ganglion cells, retains the normal red color, which appears accentuated by the contrasting white retina. The fovea gradually becomes a cherry-brown color and the retina assumes a yellow-white appearance.[11] During the 2nd year of life, macrocephaly becomes apparent, presumably caused by the intraneuronal storage of gangliosides and other lipids, reactive gliosis, and the disturbance of fluid balance.[9] The children may develop seizures that can be induced, on occasion, by auditory stimuli. The visceral organs, skeletal structures, and peripheral nervous system are spared in this form of disorder. Between 2 and 3 years of age, the children become severely cognitively impaired, decerebrate, blind and unable to respond to most stimuli. All of the variant forms of GM2 gangliosidosis are inherited as an autosomal recessive trait. The genes for each of the beta-hexosaminidase subunits were found to map into different chromosomes; the alpha-subunit localized to chromosome 15 and the beta-subunit mapping to chromosome 5.[12,13] This patient is the first reported patient from Qatar. Other cases are reported from the Middle East, Kingdom of Saudi Arabia and Lebanon.[14] Out of the 11 cases clinically diagnosed in Lebanon as infantile Tay-Sachs, 9 were affected with Sandhoff's disease.[14] Thus, the gene frequency for the disease is thought to be higher in Lebanon than elsewhere. Tay-Sachs disease was reported in 3 families, from Kuwait and 6 families from Egypt.[15] As consanguineous marriages are common in our area, we believe that the disease is more common than expected. Under reporting may be due to the absence of disease registry or lack of diagnosis in our area. Genetic counseling is important for families at risk. The rate of new cases in the Jewish population has been reduced from 60 patients per year in the pre-1970 era to 3, and 5 per year due to the successful implementation of carrier screening and prenatal diagnosis.[16] Carrier testing in high-risk populations (Ashkenazi Jews) has provided an effective means to identify couples at risk of having an affected infant. Prenatal testing is widely available by means of enzyme analysis of tissue, obtained after chorionic villus sampling at 8 to 12 weeks of gestation or later in the pregnancy from cultured cells obtained by amniocentesis. Pre-implantation genetic diagnosis is also possible in Tay-Sachs disease using pre-embryo biopsy and gene amplification by polymerase chain reaction.[17] Children with Tay-Sachs disease or Sandhoff disease have a shortened life span, with complications of cachexia and aspiration pneumonia causing death by 4 to 5 years of age. There are no effective means of treatment for the GM2 gangliosidosis at the present time. Numerous attempts, which have included enzyme replacement, cellular infusions, and bone marrow transplantation, have proven unsuccessful.[18] Bone marrow transplantation, performed in 10 to 16 day old Sandhoff disease mice, were found to have prolonged life span and reduced neurologic signs.[19] Gene therapy in the near future may provide new hope for the diseased children.

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