Picture of the Month

A. Engin Arisoy, MD; Serap Ozden, MD; E. Sami Arisoy, MD; Kenan Kocabey, MD; Huseyin Guvenco, MD (Contributors); Walter W. Tunnessen, Jr, MD (Section Editor).

Figure 1.

Retinal changes in an apathetic infant with progressive mental and physical retardation.

Figure 2.

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Contributed from the Departments of Pediatrics (Drs A. E. Arisoy, E. S. Arisoy, Kocabey, and Guvenco) and Ophthalmology (Dr Ozden), Firat University School of Medicine, Elazig, Turkey.
Reprint requests to The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Tunnessen).
Denouement and Discussion

Tay-Sachs Disease

Figs 1 and 2.—A classic cherry-red spot is visualized in the macula of both eyes.

Manifestations

The characteristic cherry-red spots of Tay-Sachs disease were first described in 1881 by Warren Tay, a British ophthalmologist, in a 1-year-old child with mental and physical retardation. Bernhard Sachs, a neurologist, coined the term familial amaurotic idiocy for this disorder and described the typical morphologic feature of the disease: distended cytoplasm of the neurons and ballooning of their dendrites. In the 1930s, Ernst Klenk, a biochemist, used the name gangliosides to describe the glycolipid accumulation in ganglion cells characteristic of this disease.

Tay-Sachs Disease, now referred to as GM₂ gangliosidosis, type 1, has a classic progression. Affected infants appear normal at birth. The earliest signs, beginning at age 3 to 5 months, are mild motor weakness and myoclonic jerks associated with sharp noises. Most often, these signs are not recognized by the parents, except in retrospect. Between ages 6 and 10 months, there is a progressive loss of motor function with weakness, hypertonia, poor head control, and decreased attentiveness to surroundings. The exaggerated response to auditory stimuli suggests hyperacusis. Visual signs, such as unusual eye movements and episodes of staring, or concerns about decreased visual acuity, may lead to ophthalmologic consultation, the discovery of the cherry-red spots (Figs 1 and 2), and ultimately the diagnosis of GM₂ gangliosidosis.

After age 1 year, the central nervous system steadily degenerates. Seizures may become prominent; spasticity with hyperactive reflexes, blindness, and deafness follow. The face takes on a doll-like expression, with translucent skin and long eyelashes. Macrocephaly secondary to cerebral glialosis becomes apparent by age 18 to 24 months. Intercurrent respiratory infections are common, and death usually occurs between ages 2 and 4 years.

The most characteristic feature of Tay-Sachs disease is the cherry-red spot of the macula. This finding actually represents a normal red macular area surrounded by a white area, the result of lipid accumulation in the retinal ganglion cells. The spot later becomes darker and brownish as the macula degenerates, and opaque whitish streaks along vessels may be observed. Cherry-red spots may be noted as early as age 3 months.

The cherry-red spots are not pathognomonic for Tay-Sachs disease. They can be seen in retinal ischemia and contusion of the globe, generalized gangliosidosis, Sandhoff disease, metachromatic leukodystrophy, Niemann-Pick disease, Farber disease, and sialidosis (types 1 and 2). However, the discovery of a cherry-red spot in a Jewish infant, a typical clinical course, and the absence of organomegaly are strongly suggestive of Tay-Sachs disease.

Diagnosis

The basic defect in this disorder is a deficiency of hexosaminidase A, which is responsible for hydrolyzing GM₂ ganglioside, the glycolipid that accumulates in neurons. The deficiency of hexosaminidase A can be demonstrated in serum, plasma, leukocytes, and cultured fibroblasts of affected infants. A simple and inexpensive measurement of this enzyme has enabled population screening for heterozygotes in Jewish communities. A newer DNA-based test with increased specificity and predictive value has proven useful when used as an adjunct to screen carriers for this disorder. Prenatal diagnosis can be accomplished by measuring this enzyme in amniotic fluid, cultured amniocytes, or chorionic villus samples.

Genetics

Tay-Sachs disease has an autosomal-recessive mode of inheritance. The two abnormal alleles of the hexosaminidase A locus on chromosome 15 account for almost all infantile cases in Ashkenazi Jews. The severity of the disease appears to correlate with the level of residual enzyme activity. An abnormal carrier state affects approximately one in 31 individuals of Ashkenazi Jewish ancestry, but only one in 167 individuals in the non-Jewish population.

Treatment

No specific therapy for the treatment of Tay-Sachs disease is available. Supportive care includes management of hydration, intercurrent infections, and seizures.

References