Tay-Sachs Disease:
To Screen or Not to Screen?

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Medical aspects

History. In 1881, the British ophthalmologist Warren Tay first described degeneration of the macular region of the eye in a one-year-old child. Six years later, the American neurologist Bernard Sachs published the clinical and pathological findings. Sachs noted the familial nature of the condition, which he called amaurotic familial idiocy. There are six different types, including infantile, late infantile, and adult forms.

Clinical manifestations. For purposes of this paper, the term Tay-Sachs disease refers to the congenital disorder that occurs primarily but not exclusively in Jewish families from Eastern Europe. The disease is characterized by weakness beginning at about six months of age, progressive mental and motor deterioration, blindness, paralysis, dementia, seizures, and death usually by three years of age. The "cherry-red spot" in the macula of the eye is the clinical sign most frequently associated with Tay-Sachs disease.

Pathologically, there is a ballooning of nerve cells throughout the nervous system due to accumulation of lipid material. By electron microscopy, cytoplasmic nerve cell lipid bodies are visible. The lipid that accumulates is ganglioside GM₂ and the specific enzymatic defect responsible for the widespread deposition of this lipid is the absence of hexosaminidase A. The diagnosis of Tay-Sachs disease requires the identification of the accumulated lipid material and documentation of the specific enzymatic defect.

Genetics. The inheritance of Tay-Sachs disease follows laws of Mendelian genetics. The transmission appears to be autosomal recessive, since both parents of patients are clinically normal, sex ratios are equal, and both parents have enzyme levels that are intermediate between those of patients and normal controls. Thus a child who inherits one recessive gene from only one parent is a carrier or has the trait, but is clinically completely normal. Only a child who inherits two Tay-Sachs genes, one from each parent, will have the fatal disease.

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two carriers marry, there is a 25% chance with each pregnancy that the child will have the disease and a 50% chance that the child, like the parents, will be a carrier. There is also a 25% chance that the child will be totally free of the disease as well as of the carrier state. If a carrier marries a noncarrier, none of the children can have the fatal disease, but half the children will be carriers.

Concerning the gene frequency, it has been estimated that one in 30 Ashkenazi Jews and one in 300 non-Jews is a carrier of the Tay-Sachs gene. If a Jew (one in 30 risk) marries another Jew (one in 30 risk), the chance that both husband and wife are carriers is one in 900. Therefore, one in 900 Jewish couples is at risk for having children with Tay-Sachs disease. For such a couple, each pregnancy has a 25% chance of producing a child with the fatal disease. Hence, the incidence of Tay-Sachs disease in the Jewish population (assuming there is no intermarriage with non-Jews) is one in 3600 births. The disease is 100 times less common in non-Jews. In view of the high rates of intermarriage between Jews and non-Jews in the United States, the incidence of Tay-Sachs births is probably much less than one in 3600. One expert has calculated that 30 children with Tay-Sachs disease are born annually in North America. There is also a debate in the medical literature as to whether the incidence of Tay-Sachs disease is increasing or not.

**Detection of carriers.** Since hexosaminidase A is deficient in all tissues of patients with Tay-Sachs disease, and since carriers, on the average, have 50% of normal hexosaminidase A activity, the assay for this enzyme can be performed on serum, fibroblasts, or other easily available tissue including leukocytes and tears. The test exploits the different thermal stabilities of the two hexosaminidases: hexosaminidase A is heat labile, whereas hexosaminidase B remains unchanged by heat at 50°C. This serum heat inactivation test is currently in use in many medical centers, some of which employ semiautomated methodology. Electrophoretic separation of the two hexosaminidases can also be achieved.

**Amniocentesis and prenatal diagnosis.** Intrauterine diagnosis of Tay-Sachs disease in an unborn fetus is now possible by a procedure called transabdominal amniocentesis, in which a small quantity of amniotic fluid, which bathes the developing embryo, is removed from the mother’s uterus. The fetal cells in this fluid are grown in the laboratory and tested for the presence or absence of hexosaminidase A. Amniotic fluid itself or uncultured cells can also be used for enzyme assay. The incidence of unfavorable side effects of amniocentesis to mother or fetus is low and accidents of major significance are unusual.

There are pitfalls in the prenatal diagnosis of even major chromosomal abnormalities by amniocentesis. Specifically, in regard to Tay-Sachs disease antenatal diagnosis is not always correct. Uncultured amniotic fluid cells may have decreased hexosaminidase A activity even in normal fetuses. Furthermore, some members of families in which Tay-Sachs has appeared have no detectable enzyme activity but seem to be healthy. In such families, the absence of the enzyme in amniotic fluid cells or cultures may be uninterpretable. In spite of these and other technological problems, the results of amniocentesis in