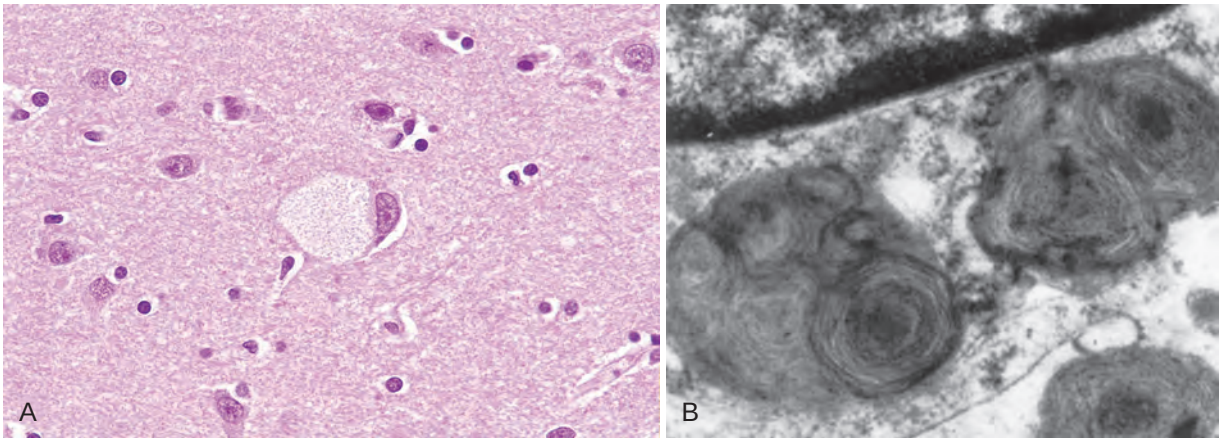

Figure 5-11 Ganglion cells in Tay-Sachs disease. **A,** Under the light microscope, a large neuron has obvious lipid vacuolation. **B,** A portion of a neuron under the electron microscope shows prominent lysosomes with whorled configurations. Part of the nucleus is shown above. (**A,** Courtesy of Dr. Arthur Weinberg, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX. **B,** Electron micrograph courtesy of Dr. Joe Rutledge, University of Texas Southwestern Medical Center, Dallas, TX.)

Clinical Features. The affected infants appear normal at birth but begin to manifest signs and symptoms at about age 6 months. There is relentless motor and mental deterioration, beginning with motor incoordination, mental obtundation leading to muscular flaccidity, blindness, and increasing dementia. Sometime during the early course of the disease, the characteristic, but not pathognomonic, cherry-red spot appears in the macula of the eye in almost all patients. Over the span of 1 or 2 years a complete vegetative state is reached, followed by death at age 2 to 3 years. More than 100 mutations have been described in the α-subunit gene; most affect protein folding. Such misfolded proteins trigger the "unfolded protein" response (Chapter 1) leading to apoptosis. These findings have given rise to the possibility of chaperone therapy of Tay-Sachs disease.

Antenatal diagnosis and carrier detection are possible by enzyme assays and DNA-based analysis. The clinical features of the two other forms of G_{M2} gangliosidosis, Sandhoff disease, resulting from β-subunit defect, and G_{M2} activator deficiency, are similar to those of Tay-Sachs disease.

Niemann-Pick Disease Types A and B

Niemann-Pick disease types A and B are two related disorders that are characterized by lysosomal accumulation of sphingomyelin due to an inherited deficiency of sphingomyelinase. Type A is a severe infantile form with extensive neurologic involvement, marked visceral accumulations of sphingomyelin, and progressive wasting and early death within the first 3 years of life. In contrast, type B disease patients have organomegaly but generally no central nervous system involvement. They usually survive into adulthood. As with Tay-Sachs disease, Niemann-Pick disease types A and B are common in Ashkenazi Jews. The gene for acid sphingomyelinase maps to chromosome 11p15.4 and is one of the imprinted genes that is preferentially expressed from the maternal chromosome as a result of epigenetic silencing of the paternal gene (discussed later). Although, this disease is typically inherited as an autosomal recessive, those heterozygotes who inherit the mutant allele from the mother can develop Nieman Pick Disease. More than 100 mutations have been found in the acid sphingomyelinase gene and there seems to be a correlation between the type of mutation, the severity of enzyme deficiency, and the phenotype.

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In the classic infantile type A variant, a missense mutation causes almost complete deficiency of sphingomyelinase. Sphingomyelin is a ubiquitous component of cellular (including organellar) membranes, and so the enzyme deficiency blocks degradation of the lipid, resulting in its progressive accumulation within lysosomes, particularly within cells of the mononuclear phagocyte system. **Affected cells become enlarged, sometimes to 90 μm in diameter, due to the distention of lysosomes with sphingomyelin and cholesterol.** Innumerable small vacuoles of relatively uniform size are created, imparting foaminess to the cytoplasm (Fig. 5-12). In frozen sections of fresh tissue, the vacuoles stain for fat. Electron microscopy confirms that the vacuoles are engorged secondary lysosomes that often contain membranous cytoplasmic bodies resembling concentric lamellated myelin figures, sometimes called "zebra" bodies.

The lipid-laden phagocytic foam cells are widely distributed in the spleen, liver, lymph nodes, bone marrow, tonsils, gastrointestinal tract, and lungs. **The involvement of the spleen generally produces massive enlargement**, sometimes to ten times its normal weight, but the hepatomegaly is usually not quite so striking. The lymph nodes are generally moderately to markedly enlarged throughout the body.

Involvement of the brain and eye deserves special mention. In the brain, the gyri are shrunken and the sulci widened. The neuronal involvement is diffuse, affecting all parts of the nervous system. **Vacuolation and ballooning of neurons** constitute the dominant histologic change, which in time leads to cell death and loss of brain substance. A **retinal cherry-red spot** similar to that seen in Tay-Sachs disease is present in about one third to one half of affected individuals.