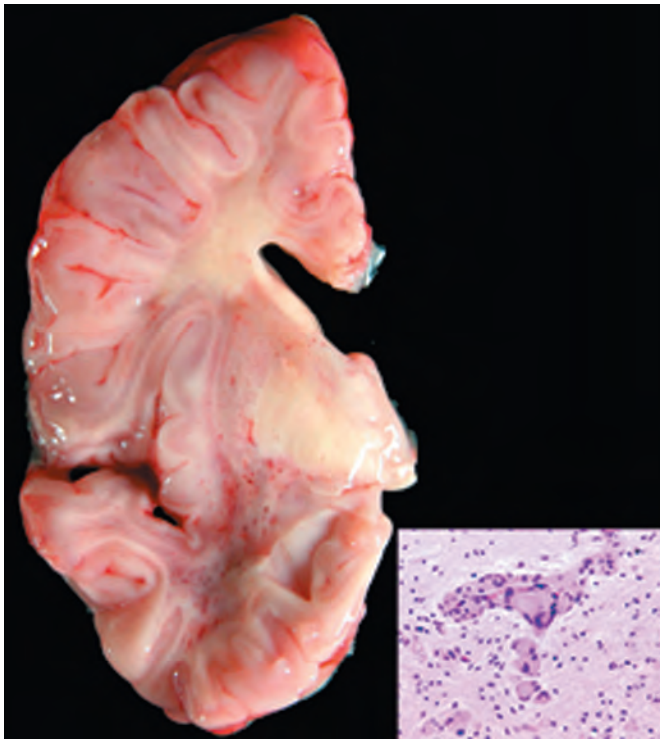

Figure 28-44 Krabbe disease. Much of the white matter is gray/yellow because of the loss of myelin. *Inset*, "Globoid" cells are the hallmark of the disease.

white matter. The membrane-bound vacuoles contain complex crystalloid structures composed of sulfatides; when bound to certain dyes such as toluidine blue, sulfatides shift the absorbance spectrum of the dye, a property called *metachromasia*. Similar metachromatic material can be detected in peripheral nerves and in the urine, the latter being a sensitive method of establishing the diagnosis.

- **Adrenoleukodystrophy** is an X-linked recessive disease associated with mutations in a member of the ATP-binding cassette transporter family of proteins (ABCD1), which is involved in the transport of molecules into the peroxisome. In the typical form of the disease, young males present with behavioral changes and adrenal insufficiency. The disease is characterized by the inability to catabolize very-long-chain fatty acids (VLCFAs) within peroxisomes, resulting in elevated levels of VLCFAs in serum. The symptoms result from a progressive loss of myelin in the CNS and peripheral nerves, as well as adrenal insufficiency. In the white matter, there is loss of myelin accompanied by gliosis and extensive lymphocytic infiltration. Atrophy of the adrenal cortex is present, and VLCFA accumulation can be seen in remaining cells. An allelic disorder presents in adults (both male and female) as a slowly progressive predominantly peripheral nerve disorder known as *adrenomyeloneuropathy*; the symptoms in female carriers are usually more mild. Some of the disorders of peroxisomal biogenesis also manifest as a leukodystrophies, particularly Zellweger spectrum disorder.

A wide range of other forms of leukodystrophy occurs, some with defects in lipid metabolism. Several other mechanisms of selective injury to white matter have been identified, including mutations in genes that encode proteins required for myelin formation (*Pelizaeus-Merzbacher disease*) or intermediate filament proteins such as GFAP (*Alexander disease*), and genes for various subunits of translation initiation factor eIF2B (*vanishing white matter leukoencephalopathy*).

Mitochondrial Encephalomyopathies

Disorders of energy generation can cause a range of neurologic disease, often in association with abnormalities in other tissues. While many of the inherited disorders of mitochondrial oxidative phosphorylation present as muscle diseases (Chapter 27), the critical dependence of neurons on oxidative phosphorylation for generation of ATP is reflected in the frequent involvement of the CNS in these disorders.

The mitochondrial genome, which is entirely inherited from the mother, encodes only 13 proteins, 22 tRNAs, and two rRNAs. The remainder of the proteins involved in mitochondrial function are encoded by the nuclear genome, including those involved in oxidative phosphorylation, mitochondrial metabolism and structure, as well as mitochondrial biogenesis, fission and fusion and replication of mitochondrial DNA. Thus, some mitochondrial disorders show maternal transmission because the affected genes lie in the mitochondrial genome, but many others do not. There is a complex genotype-phenotype relationship in these disorders: the same mutation may manifest as different phenotypes, and the same phenotype may result from one of several mutations.

An additional critical aspect to understanding mitochondrial diseases is *heteroplasmy*, which describes the condition in which cells have a mixture of normal and abnormal mitochondria (typically in the setting of a mitochondrial genome mutation). The expression of the disease may differ from cell to cell depending on the ratio of cells carrying the normal and mutant mitochondria. In general, mitochondrial disorders in the CNS selectively target neurons and gray matter; the disruption of energy generation is often reflected in elevated tissue lactate levels, which can be demonstrated by spectroscopic imaging methods. At the histologic level, there can be loss of staining for enzymatic activity of cytochrome C oxidase.

- **Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)** is characterized by recurrent episodes of acute neurologic dysfunction, cognitive changes, and evidence of muscle involvement with weakness and lactic acidosis. The stroke-like episodes are often associated with reversible deficits that do not correspond to specific vascular territories. Pathologically, areas of infarction are observed, sometimes with vascular proliferation and focal calcification. Studies have shown that both neurons and vascular smooth muscle cells have altered expression of cytochrome c oxidase, suggesting that the underlying pathogenesis is driven both by the metabolic changes in neurons as well as the ability of the cerebral vasculature to respond. The most common mutation observed in MELAS is in the gene encoding mitochondrial tRNA-leucine (MTTL1).