Genetic Metabolic Diseases

Disruption of metabolic processes in neurons and glia, particularly those involved in synthetic or degradation pathways that are specific to the nervous system, results in diseases that typically present early in life and progress. Some of these disorders manifest in the immediate post-natal period, while others emerge later in development. Overall, forms of these diseases with earlier onset tend to have more rapid and aggressive clinical courses.

Current classification systems are based on the cells or compartment affected (neuronal or white matter), subcellular organelle affected (e.g., lysosome, peroxisome, or mitochondrion), or metabolic pathway affected (e.g., sphingolipidoses or glycogenoses). The classification that follows is based largely on the cellular compartments that are primarily affected, since this correlates well with clinical symptoms and radiologic imaging.

- *Neuronal storage diseases* are predominantly autosomal recessive disorders caused by the deficiency of a specific enzyme involved in the catabolism of sphingolipids (including the gangliosides), mucopolysaccharides, or mucolipids. They are often characterized by the accumulation of the missing enzyme's substrate within the lysosomes of neurons, leading to neuronal death. Cortical neuronal involvement leads to loss of cognitive function and may also cause seizures.
- *Leukodystrophies* are mostly autosomal recessive disorders caused by mutations in genes encoding enzymes involved in myelin synthesis or catabolism. Some of these disorders involve lysosomal enzymes, while others affect peroxisomal enzymes. There is typically diffuse involvement of white matter leading to deterioration in motor skills, spasticity, hypotonia, or ataxia.
- *Mitochondrial encephalomyopathies* are a group of disorders of oxidative phosphorylation, often affecting multiple tissues including skeletal muscle (Chapter 27). When they involve brain, gray matter is more severely affected than white matter, as would be expected because of the greater metabolic requirements of neurons. These disorders may be caused by mutations in the mitochondrial or the nuclear genomes.

Neuronal Storage Diseases

These disorders are characterized by the accumulation of storage material within neurons, typically followed by death of the neurons. The neurologic manifestations that are result from this neuronal dysfunction or death are most often seizures as well as generalized loss of neurologic function. While many of these disorders are associated with deficits of specific enzymes that result in accumulation of substrate, others appear to be caused by defects in protein or lipid trafficking within neurons. This is a large class of disorders, with genetic heterogeneity even for clinically homogeneous entities. Current molecular methods allow whole exome and genome sequencing, which are leading to changes in the classification of these disorders. Several examples of these diseases, such as Tay-Sachs and Niemann-Pick diseases and mucopolysaccharidoses, are described in Chapter 5. Ceroid lipofuscinoses are rare disorders in which lipid pigments accumulate in neurons, and the resulting neuronal dysfunction leads to a combination of blindness, cognitive and motor deterioration and seizures.

Leukodystrophies

These disorders are caused by mutations of genes whose products are involved in the generation, turnover, or maintenance of myelin. Normal brain function depends as much on the connections between neurons as it does on the integrity of the neurons themselves and therefore the progressive and cumulative damage to myelinated fibers that appears in the leukodystrophies has devastating consequences. Several clinical features separate leukodystrophies from demyelinating diseases: the leukodystrophies typically present with an insidious and progressive loss of cerebral function, often at younger ages, and are associated with diffuse and symmetric changes on imaging studies. While many of the leukodystrophies are caused by single enzyme defects resulting in altered metabolism of myelin-associated lipids, a variety of other genetic alterations can lead to white matter diseases. The following examples are representative of this spectrum of disorders.

- **Krabbe disease** is an autosomal recessive leukodystrophy resulting from a *deficiency of galactocerebroside β-galactosidase* (galactosylceramidase), the enzyme required for the catabolism of galactocerebroside to ceramide and galactose. As a consequence of the impaired catabolism of galactocerebroside in the brain, an alternative catabolic pathway shunts galactocerebroside to galactosylsphingosine; elevated levels of this compound are cytotoxic. The clinical course is rapidly progressive, with onset of symptoms (dominated by motor signs such as stiffness and weakness) often between the ages of 3 and 6 months. Survival beyond 2 years of age is uncommon. The brain shows loss of myelin and oligodendrocytes in the CNS and a similar process in peripheral nerves (Fig. 28-44). Neurons and axons are relatively spared. A unique and diagnostic feature of Krabbe disease is the aggregation of engorged macrophages *(globoid cells)* in the brain parenchyma and around blood vessels (Fig. 28-44, *inset*). Hematopoietic stem cell transplantation, which allows repopulation of the CNS with enzymatically competent microglia, has been shown to be of benefit, particularly when performed before the neurologic deficits appear (this is also true of metachromatic leukodystrophy).
- **Metachromatic leukodystrophy** is an autosomal recessive disease that results from a deficiency of the *lysosomal enzyme arylsulfatase A*. This enzyme, present in a variety of tissues, cleaves the sulfate from sulfate-containing lipids (sulfatides) as the first step in their degradation. Enzyme deficiency therefore leads to an accumulation of the sulfatides, especially cerebroside sulfate. These sulfatides have a range of biological actions that can contribute to white matter injury, including inhibiting differentiation of oligodendrocytes and eliciting a proinflammatory response from microglia and astrocytes. The most striking histologic finding is demyelination with resulting gliosis. Macrophages with vacuolated cytoplasm are scattered throughout the