Neurometabolic diseases. Clinical aspects

Johan Lundgren

Inborn errors of metabolism affecting the central nervous system can be defined as disorders of the mechanisms by which specific major foodstuffs are converted to energy or cellular and tissue building blocks and final products and the mechanisms by which foodstuffs and products are degraded to be excreted. These include mechanisms involving absorption and modification of vitamins and minerals; mechanisms for degrading molecules to provide energy or to be excreted; mechanisms for making acetyl-coenzyme A, nonessential amino acids, cholesterol, long-chain fatty acids, prostaglandins, and the complex lipids they lead to; mechanisms for making the proteins that are the structure of cells, inside and out, and that are the prime catalysts of cellular chemistry, enzymes; and mechanisms for neutralizing molecules that represent potential environmental toxins.

The presenting symptoms of neurometabolic disorders are caused by progressive destruction of motor, mental and perceptual functions. They include loss of function and seizures associated with earlier death often before adulthood. The symptoms are often very unspecific. Neurometabolic disorders can affect any organ system and usually affect multiple organ systems. Manifestations vary from those of acute life-threatening disease to subacute progressive degenerative disorder. Progression may be unrelenting with rapid life-threatening deterioration over hours, episodic with intermittent decompensations and asymptomatic intervals, or insidious with slow degeneration over decades.

The most common neurometabolic disorders to be considered are organic acidurias and amino acid apathies followed by neuronal ceroid lipofuscinoses, urea cycle disorders, congenital lactic acidosis, peroxisomal disorders, and, less frequently, sphingolipidoses, mucopolysaccharidoses, glycoprotein degradation disorders and fatty acid oxidation disorders.

Neuronal ceroid lipofuscinoses

The neuronal ceroid lipofuscinoses (NCLs), also known as Batten disease (Santavouri et al. Suppl Clin Neurophysiol. 2000;53:443), are a group of neurodegenerative disorders. They are considered the most common of the neurogenetic storage diseases with a prevalence of 1 in 12,500 in some populations. They are associated with variable yet progressive symptoms including seizures, dementia, visual loss, and/or cerebral atrophy. The most common lipofuscinosis is juvenile neuronal ceroid lipofuscinosis (JNCL = CLN3) or Spielmeyer-Vogt’s type. Typically onset is between ages 5 and 8 years, and usually the initial symptom is visual loss followed by dementia, ataxia, dystonia and death in the second to third decade of life. Seizures are less prominent. MRI shows moderate cerebral atrophy and retinitis pigmentosa is found on eye examination.

Peroxisomal disorders

Peroxisomal disorders are a group of genetically heterogeneous metabolic diseases that share some dysfunction of peroxisomes. The peroxisome is a cellular organelle measuring 0.5
micron in diameter that participates in important cellular functions such as beta-oxidation of very-long-chain fatty acids (VLCFA), plasmalogen production, and bile acid synthesis. Zellweger described the first case of peroxisomal disorder; this was followed in quick succession, over the next 3 years, by a number of additional case reports.

An example of a peroxisomal disorder is adrenoleukodystrophy (ALD), in which early development is entirely normal, and the first neurological manifestation occurs most commonly between ages 4 and 8 years. The early manifestations often are mistaken for hyperactivity or attention deficit disorder; however, the clearer neurological manifestations, such as impaired auditory discrimination, visual disturbances, signs of dementia, spatial disorientation, poor coordination, or seizures, supervene late and the disease then may progress rapidly. This leads to a vegetative state within 2 years and death at various intervals thereafter. Less common adolescent and adult cerebral forms occur at a later age. The use of Lorenzo's oil in the treatment of X-ALD has been controversial.

**Lysosomal storage diseases**

Lysosomal storage diseases describe a heritable group of heterogeneous human disorders characterized by the accumulation of undigested macromolecules intralysosomally, resulting in an increase in the size and number of these organelles and ultimately in cellular dysfunction and clinical abnormalities. They are generally classified by the accumulated substrate and they include sphingolipidoses, glycoproteinoses, mucolipidoses, and mucopolysaccharidoses (MPSs),

One fatal lysosomal disorder is Krabbe disease, infantile globoid-cell leukodystrophy (galactosylceramidase). Its incidence is 1:50,000. Krabbe disease manifests in infants usually in the second half of the first year with central nervous system manifestations of spasticity, irritability, motor regression, hyperesthesia - auditory, tactile, and visual, peripheral neuropathy, hyperpyrexia, failure to thrive, vomiting, gastroesophageal reflux and seizures. MRI shows high-intensity areas of demyelination in the brainstem and cerebellum. No effective medical therapy exists for Krabbe disease.

**Mitochondrial disorders**

Mitochondrial encephalomyopathies are diseases caused by defective oxidative phosphorylation (OXPHOS), and affect the nervous system and/or skeletal muscle (Oldfors and Tulinius. J Neuropathol Exp Neurol 2003;62:217; Seviano and Denato. Brain 2004;127:2153) They have emerged as a major entity among the neurometabolic diseases of childhood with an incidence of 1 in 11,000 children, and also have a high prevalence in adults. Given the complexity of mitochondrial genetics and biochemistry, the clinical manifestations of mtDNA disorders are extremely heterogenous. They range from lesions of single tissues or structures, such as the optic nerve in Leber's hereditary optic neuropathy or the cochlea in maternally inherited non-syndromic deafness, to more widespread lesions including myopathies, encephalomyopathies, cardiopathies, or complex multisystem syndromes with onset ranging from neonatal to adult life. Their neurologic presentation is nonspecific with encephalopathy, failure to thrive, seizures, ophthalmpoplegia, and sensorineural hearing loss. These disorders are progressive and are aggravated by fever and
infections. They can be caused by mutations in nDNA or mtDNA. Diagnosis requires a complex battery of clinical studies coupled with diagnostic findings on muscle biopsy (abnormal structure, histochemistry, or enzyme studies) or DNA testing. Therapy for mitochondrial disorders remains largely ineffective.

**Rett syndrome**

Rett syndrome is a progressive, usually sporadic and rarely familial, disabling neurodevelopmental disorder with onset in early childhood presenting clinically with mental retardation, behavioral changes, late movement disturbances, loss of speech and hand skills, ataxia, apraxia, irregular breathing with hyperventilation while awake, and frequent seizures. It occurs almost exclusively in females with an estimated prevalence of 1 in 10-22000 births and is considered a manifestation of defective brain maturation caused by dominant mutation of the MeCP2 gene. Although many different mutations are being studied in humans and in mice, the molecular pathogenesis of this disorder remains unclear. Electroencephalography is abnormal in the final stages of the syndrome. Neuroimaging showing brain atrophy may be required for differential diagnosis that includes neurodegenerative and metabolic disorders. Neuropathology shows decreased brain growth and reduced size of individual neurons, with thinned dendrites in some cortical layers and abnormalities in substantia nigra (decreased neuromelanin content), suggestive of deficient synaptogenic development, probably starting before birth. Neurometabolic changes include reduced levels of dopamine, serotonin, noradrenalin, choline acetyltransferase (ChAT), nerve growth factors, endorphines, glutamate, and other amino acids and their receptor levels in brain. Current treatment includes symptomatic, anticonvulsive and physiotherapy.

**MRI**

Magnetic resonance imaging (MRI) has emerged as a powerful tool in the study of normal and abnormal brain structure, function, and biochemistry. In particular, functional MRI has come into its own as a tool to study normal and abnormal brain functions such as learning, memory, and motor learning, as well as delineation of neurogenetic cognitive phenotypes. White matter microstructure can be studied using diffusion tensor imaging, which may allow abnormal white matter to be visualized prior to abnormalities on anatomic MRI. Magnetic resonance spectroscopy, a noninvasive method to study brain biochemistry, may allow for the delineation of regional metabolic changes as a result of disease progression and/or therapeutic intervention. With MRI techniques, one can investigate the relationship between structure, function, genes, and behaviour (Blaser and Feigenbaum. Neuroimaging Clin N Am 2004; 14:307; Gropman. Imaging of neurogenetic and neurometabolic disorders of childhood. Curr Neurol Neurosci Rep. 2004;4:139)

**Genetic aspects**

Genetic mutations have been presumed to be the basis of inherited disease since the time of Mendel. Even now, some diseases that have been recognized for 100-150 years have known genetic defects but the protein products are not well characterized. Many genetic diseases of the nervous system can be diagnosed accurately by DNA analysis, and the pattern of
inheritance can be demonstrated within families. The molecular tools sometimes allow us predict who is likely to develop the disease and who in the family can neither develop it nor pass it on to offspring (Wang et al., N Eng J Med 2005;57:111). With recent advances in enzyme replacement therapy and gene therapy, we may someday be able to treat or perhaps even prevent some of these disorders even if we do not know how the genetic change gives rise to the disease.

Most inborn errors of metabolism are inherited as autosomal recessive conditions. Some are due to mutations on the X chromosome and follow an X-linked recessive genetic pattern. Some mitochondrial disorders are due to proteins that are transported into mitochondria and function there, but that are coded for by ordinary nuclear DNA. These follow an autosomal recessive pattern. Many mitochondrial disorders have a unique form of inheritance with only maternal transmission. The mitochondrial DNA (which is circular, like that of a bacterium) all comes from the egg and hence from the mother. None of the mitochondria in the sperm get passed on to the zygote. In the future brain-directed gene/cell therapy may be useful in the treatment of neurological alterations in lysosomal storage diseases and other neurometabolic disorders.