

hypoxia or ischemia. Diagnosis is confirmed by muscle biopsy and quantitative analysis of respiratory chain enzymes. Many CNS and muscle diseases that are not primary MC may involve mitochondrial alterations; these include Pompe disease, spinal muscular atrophy, infantile spinocerebellar ataxia, polymyositis, Zellweger syndrome, neoplastic cells, and toxic- and drug-induced disorders. Antiepileptic drugs, especially valproate, may impair placental mitochondrial function in pregnant women. (Sarnat HB, Marin-Garcia J. Pathology of mitochondrial encephalomyopathies. **Can J Neurol Sci** 2005;32:152-166). (Reprints: Harvey B Sarnat MD FRCPC, Alberta Children's Hospital, Pediatric Neurology and Neuropathology, 1820 Richmond Rd SW, Calgary, Alberta T2T 5C7, Canada).

COMMENT. The diagnosis of mitochondrial cytopathy (MC) depends on a classical clinical presentation or phenotype, laboratory findings, and identification of ragged red muscle fibers in tissue biopsy. Mitochondrial DNA may be required for diagnostic confirmation in atypical cases.

HEPATOCEREBRAL MITOCHONDRIAL DNA DEPLETION

Two novel homozygous mutations, G352A and C269T, are documented in the gene for deoxyguanosine kinase (DGK) in 3 children with hepatocerebral mitochondrial DNA depletion syndrome reported from Columbia University College of Physicians and Surgeons, New York; University of Pisa, Italy; University of Toronto, Canada; and University of Melbourne, Australia. All 3 patients developed liver failure and metabolic acidosis in early infancy, one also had cerebral atrophy and nystagmus, a second had microcephaly, hypotonia, and nystagmus, and a third, optic dysplasia with nystagmus and muscle involvement. DGK mutations resulted in truncated polypeptides. In patient 3, who developed multisystem disease, liver transplantation did not prevent brain dysfunction. Systemic involvement portends poor long-term prognosis. (Mancuso M, Ferraris S, Pancrudo J et al. New DGK gene mutations in the hepatocerebral form of mitochondrial DNA depletion syndrome. **Arch Neurol** May 2005;62:745-747). (Respond: Salvatore DiMauro MD, Room 4-420, Columbia University College of Physicians and Surgeons, 630 W 168th St, New York, NY 10032).

COMMENT. Mitochondrial DNA depletion syndrome can affect one, particularly muscle or liver, or multiple organs, and the liver is most frequently affected in DGK gene mutations. Primary mtDNA depletion syndrome is transmitted as an autosomal recessive trait.

THIAMINE-RESPONSIVE CONGENITAL LACTIC ACIDOSIS WITHOUT MC

Six infants with thiamine-responsive congenital lactic acidosis (CLA), normal pyruvate dehydrogenase complex activity, and no evidence of mitochondrial encephalomyopathy, are reported from Tottori University, Yonago; National Children's Medical Center, Tokyo, and other centers in Japan. Histochemical investigation of muscle from 3 patients showed no ragged red fibers and normal cytochrome C oxidase activity. Two

patients were typical of Leigh syndrome, with symmetrical basal ganglia lesions on neuroimaging. Three patients were siblings born to consanguineous parents, with similar clinical manifestations of cardiomyopathy in infancy. One patient was diagnosed in the neonatal period, and high-dose thiamine therapy (17-35 mg/kg day) was begun before the occurrence of acute neurologic deficit; at age 2, the brain MRI was normal and at age 4, her development was normal. Although rare, thiamine-responsive CLA should be recognized early by prompt measurement of lactate and pyruvate levels. The monitoring of lactate and pyruvate is helpful in determining the most effective dose of thiamine. (Toyoshima M, Oka A, Egi Y et al. Thiamine-responsive congenital lactic acidosis: clinical and biochemical studies. **Pediatr Neurol** August 2005;33:98-104). (Respond: Dr Toyoshima, Department of Pediatrics, Tottori Prefectural Central Hospital, 730 Ezu, Tottori 680-0901, Japan).

COMMENT. Congenital lactic acidosis (CLA) usually leads to metabolic decompensation or neurologic deterioration, such as Leigh syndrome or mitochondrial encephalopathy. In rare cases, early diagnosis and treatment with large doses of thiamine may result in amelioration of symptoms, normal lactate and pyruvate levels, and normal development.

DEGENERATIVE AND DEMYELINATING DISEASES

PROGNOSIS OF X-LINKED ADRENOLEUKODYSTROPHY

The natural history of X-linked adrenoleukodystrophy (ALD) was determined by questionnaire survey in a nation-wide retrospective study of 145 patients at Gifu University School of Medicine, and the Ministry of Health, Labor and Welfare, Japan. The various forms of ALD included childhood cerebral in 46 patients, adrenomyeloneuropathy [AMN] (39), adult cerebral (33), adolescent (14), and olivo-ponto-cerebellar [OPC] (13). Initial symptoms were different in the various forms: in the childhood cerebral form, these were intellectual and visual disturbances; gait and sensory disturbances characterized the AMN form; psychic and gait disorders in the adult cerebral form; visual and gait symptoms in the adolescent form; and gait disturbance in the OPC form. Age of onset influenced rate of progression: rapid in the under age 8 years, and more slowly in the over 8 year group. Half the patients with AMN and OPC had developed cerebral symptoms at 10 years after onset. (Suzuki Y, Takemoto Y, Shimozaawa N et al. Natural history of X-linked adrenoleukodystrophy in Japan. **Brain Dev** August 2005;27:353-357). (Respond: Dr Yasuyuki Suzuki, Medical Education Development Center, Gifu University School of Medicine, Yanagido 1-1, Gifu 501-1194, Japan).

COMMENT. X-linked adrenoleukodystrophy is a neurodegenerative disease with demyelination, adrenal insufficiency and accumulation of very-long chain saturated fatty acids. The childhood cerebral form of ALD accounts for 32% of cases in Japan, and the AMN form (27%) is the second most common phenotype. ALD occurs in 1:30,000 and 1:50,000 boys in Japan, compared to 1:20,000 to 1:200,000 in other countries (Bezman and Moser, 1998). Based on the above study, ALD should be classified according to age of onset as well as the clinical phenotype, in evaluating success of treatment. A rapid rate of progression is expected in younger patients, and those with ataxia would be expected to develop cerebral symptoms later.