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MITOCHONDRIAL CYTOPATHIES

PATHOLOGY OF MITOCHONDRIAL ENCEPHALOMYOPATHIES

The role of the muscle biopsy, histochemistry, electronmicroscopy, measurement of respiratory chain enzymes, and genetic studies in the diagnosis of mitochondrial cytopathies (MC) is reviewed by researchers at the University of Calgary and Alberta Children's Hospital, Canada. The quadriceps femoris is generally the best muscle for a biopsy to confirm a MC. Histochemical stains essential for suspected MC include the oxidative enzymatic stains succinate dehydrogenase (SDH; Complex II) and cytochrome-c-oxidase (COX; Complex IV). Absent SDH in all fibers correlates with a severe Complex II defect; whereas absent COX in all fibers is indicative of a severe Complex IV defect. Biochemical tests are used for demonstration of Respiratory Complexes III or V. Microscopic features of MC typically include ragged-red fibers that indicate a defect of respiratory complexes I and IV; increased lipid within myofibers is indicative of Kearns-Sayre syndrome, progressive external ophthalmoplegia (PEO), and some genetic forms of Leigh encephalopathy. Glycogen may be excessive in subsarcolemmal zones of ragged-red fibers, but is a nonspecific finding. Genetic studies screen for common point mutations in mtDNA that are expressed in both striated muscles and the CNS. The indications for a mitochondrial work-up include: 1) clinical evidence of MC (eg. unexplained ophthalmoplegia, persistent lactic acidosis); 2) family history of MC and unexplained neurological or neuromuscular symptoms; or 3) histochemical findings in the muscle biopsy that suggest a MC (eg. scattered myofibers with absent COX and strong SDH activities or ragged-red fibers). Punch biopsy of the skin is an alternative to muscle biopsy, and the smooth muscle of the pili erecti muscles and axoplasm of cutaneous nerves have mitochondria suitable for ultrastructural exam.

Clinically, MC may present in the neonate as Leigh encephalopathy or mitochondrial depletion syndrome, with multisystemic failure and persistent lactic acidosis. Clinical suspicion of neonatal MC is raised by unexplained metabolic disease in the absence of

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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