Mitochondrial Myopathy of Cerebro-Hepato-Renal (Zellweger) Syndrome

Harvey B. Sarnat, Geoffrey Machin, Husam Z. Darwish, and Steven Z. Rubin

SUMMARY: The muscles of four infants with cerebro-hepato-renal (Zellweger) syndrome were studied during life and/or at necropsy. A mitochondrial myopathy was demonstrated, similar to mitochondrial alterations demonstrated in liver and brain in this disease. Muscle fibers with red-staining subsarcolemmal aggregates were identified with Gomori trichome stain in two cases. Subsarcolemmal and intermyofibrillar zones of increased concentrations of NADH-TR, SDH, and cytochrome-c-oxidase activity were demonstrated histochemically in all four cases. Degenerative and cytoarchitectural changes in muscle fibers were not found. Ultrastructural studies showed large aggregates of mitochondria and increased lipid in the subsarcolemmal and intermyofibrillar spaces. Degenerative changes in mitochondria and lipid also were demonstrated, but paracrystalline inclusions were not seen. The distribution of these changes was not uniform between patients or between different muscles in the same patient. The diaphragm was affected more severely than proximal or distal muscles of the extremities. Direct involvement of muscle mitochondria in this disease may interfere with energy metabolism and contribute to the clinical findings of hypotonia, weakness, and respiratory insufficiency. The muscle biopsy with histochemistry and electron microscopy may be used as a diagnostic adjunct in suspected cases, but the variation encountered dictates caution in the interpretation of negative findings.

RÉSUMÉ: Nous avons étudié les muscles de 4 patients souffrant du symdrome cérébro-hépato-rénal de Zellweger soit durang la vie, soit à l'autopsie. Nous avons démontré une myopathie mitochondriale semblable aux altérations mitochondriales trouvées dans le foie et le cerveau dans cette maladie. Dans deux cas les colorations au trichrome de Gomori ont identifié des agrégats de sous-sarcolemme de couleur rouge. Chez les 4 cas nous avons démontré par histochimie des zones sous-sarcolemmes et intermyofibrillaires de concentration élevée de l'activité NADH-TR, SDH et cytochrome-c-oxidase. Nous n'avons pas trouvé de modifications dégéneratives ou cytoarchitecturales dans les fibres musculaires. Les études en microscopie électronique ont montré des gros agrégats de mitochondries et une augmentation de la concentration des lipides dans les espaces sous-sarcolemme et intermyofibrillaires. Il existe des changements dégénératifs dans les mitochondries et les lipides mais sans inclusions paracrystallines. La distribution de ces modifications n'était pas uniforme d'un patient à l'autre ou d'un muscle à l'autre chez le même patient. Le diaphragme semblait plus sévèrement touché que les muscles promimaux ou distaux. Cette attentie des mitochondries explique probablement les symptômes d'hypotonie, faiblesse et insuffisance respiratoire. Cette approche diagnostique peut donc être utile, mais il faut interpréter avec prudence tout résultat négatif.

The cerebro-hepato-renal syndrome of Zellweger is an autosomal recessive disease characterized by typical facies, intrahepatic biliary dysgenesis and hepatic failure, multiple renal cortical cysts, and intrauterine growth retardation (Bowen et al., 1964; Passarge and McAdams, 1967; Jan et al., 1970; Patton et al., 1972; Danks et al., 1975). Neuropathologic findings consist of incomplete neuronal migrations in brainstem and cerebral cortex resulting in heterotopias and abnormal gyral formation, and delayed or arrested myelination of subcortical white matter and long tracts of the central nervous system (Volpe and Adams, 1972; Agamanolis et al., 1976; Della Giustina et al., 1981).

Infants with this disease have generalized muscular hypotonia and weakness, respiratory difficulties, and a poor suck. Most die in early infancy. A mitochondrial disorder is recognized both morphologically and biochemically in the brain and liver (Goldfischer et al., 1973; Lott et al., 1979; Trijbels et al., 1981), but lesions in striated muscle have not been fully defined. The hypotonia, weakness, and hyporeflexia have usually been attributed to neuropathy, central nervous system involvement, and systematic illness.

The following report describes a mitochondrial disorder demonstrated by histochemical and ultrastructural findings in striated muscle obtained by surgical biopsy and/or necropsy in four infants with cerebro-hepato-renal syndrome.

CASE REPORTS

Case 1: A 2360 gram girl was born at 37-weeks gestation. She had dysmorphic features suggestive of cerebro-hepato-renal syndrome, generalized hypotonia, weakness, and hyporeflexia. The liver was enlarged. Recurrent hypoglycemia occurred. The infant lived 4½ months, with a course characterized by chronic mild cholestatic jaundice, poor suck, failure to thrive, respiratory infections, acidosis, persistent weakness, and seizures. Renal function was normal, although ultrasonography of the kidneys suggested cystic changes. Chromosomes were normal. Studies of amino acids, urinary reducing substances, and thyroid function were normal. The cause of death was respiratory insufficiency and cor pulmonale.

Muscle biopsy (postmortem): Specimens of the quadriceps femoris, deltoid, extensor digitorum longus of the forearm, and diaphragm were secured within two hours after death.
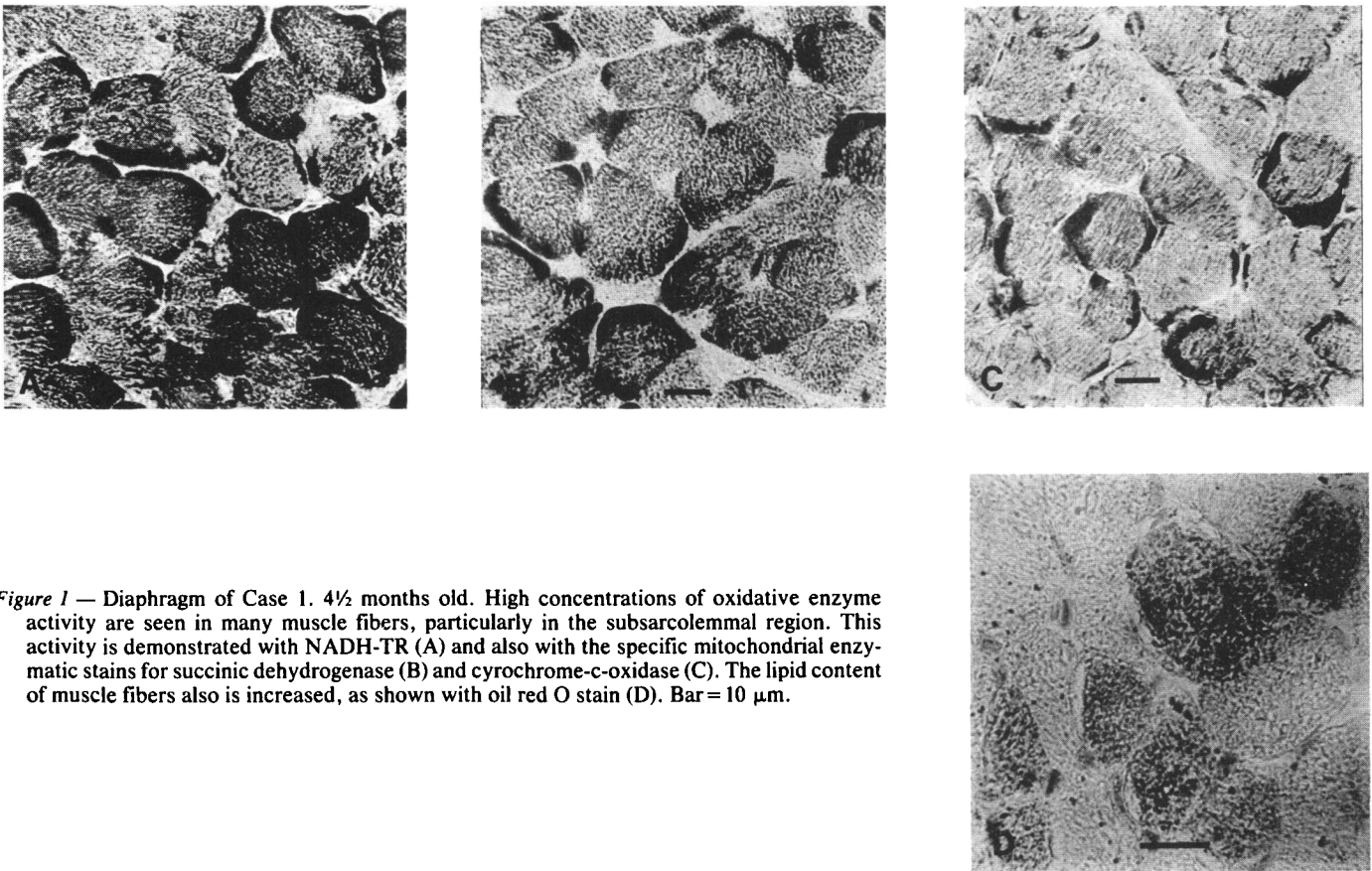
Figure 1 — Diaphragm of Case 1. 4½ months old. High concentrations of oxidative enzyme activity are seen in many muscle fibers, particularly in the subsarcolemmal region. This activity is demonstrated with NADH-TR (A) and also with the specific mitochondrial enzymatic stains for succinic dehydrogenase (B) and cyrochrome-c-oxidase (C). The lipid content of muscle fibers also is increased, as shown with oil red O stain (D). Bar = 10 μm.

The three muscles of the extremities studied showed no histologic alterations. Increased concentrations of unevenly distributed NADH-TR and SDH activities were demonstrated histochemically in the subsarcolemmal and intermyofibrillar spaces of some type I myofibers. The diaphragm, by contrast, exhibited many atrophic and hypertrophic fibers with red staining subsarcolemmal accumulations shown with the modified Gomori trichrome method. These zones stained intensely with NADH-TR, SDH, and cytochrome-c-oxidase stains (Figs. 1A, B, C), but not with PAS or phosphorylase stains. About 20 percent of diaphragmatic muscle fibers contained increased amounts of neutral lipid demonstrated by oil red O stain (Fig. 1D). Fiber types were in normal proportions and distribution, determined by ATPase stains preincubated at alkaline and acid pH ranges. Acridine orange fluorescent stain was normal.

Electron microscopy of all muscles revealed that many muscle fibers had increased accumulations of mitochondria and lipid droplets in the subsarcolemmal region and in the intermyofibrillar sarcoplasm (Figs. 2, 3). They were particularly abundant adjacent to sarcolemmal nuclei (Fig. 4). Most mitochondria had normal ultrastructure, but some exhibited myelin figures, swelling, or other degenerative changes (Fig. 5). Paracrystalline inclusions were not seen. The amount of glycogen was normal. The sarcotubular system was not altered. Peroxisomes could not be demonstrated. Degenerative changes in myofibrils and Z-band streaming were not observed.

Postmortem Findings: The following abnormalities were demonstrated: multiple renal cortical cysts, hepatic enlargement with fatty change, pancreatic islet cell hyperplasia, anomalous origin of left vertebral artery from aortic arch, interstitial desquamative pneumonitis; pachgyria and heterotopias of the cerebral cortex.

Case 2: A term male infant weighing 3250 grams required intubation at birth, after an uncomplicated pregnancy and delivery. His dysmorphic appearance was consistent with cerebro-hepato-renal disease. The liver and spleen were enlarged, and he developed jaundice at 24 hours of age. Generalized muscular hypotonia and weakness were present and tendon reflexes were diminished. He was lethargic and developed seizures, controlled with phenobarbital. He remained deeply icteric throughout his life, with predominantly conjugated hyperbilirubinemia. Plasma and urine amino acid chromatography was normal and no reducing substances were found in the urine. Chromosomes had a normal karyotype. Ultrasonography suggested that polycystic kidneys, and renal tubular acidosis had developed. He required feeding by gavage and had frequent respiratory tract infections. He died at 29 days of age. A stillborn term infant had been delivered by the mother a year earlier.

Muscle biopsy: A quadriceps femoris muscle biopsy was performed at 3 weeks of age. Perimysial connective tissue was mildly increased. More than half of random muscle fibers were less than 12.5 μm in cross-sectional diameter (normal mean for age 15 μm). A few fibers had central nuclei. Abnormal inclusions or subsarcolemmal aggregates were not demonstrated with the modified Gomori trichrome stain. Histochemical stains revealed equal numbers of types I and II muscle fibers in a mosaic distribution. NADH-TR and SDH stains showed smudging of diformazan deposits and increased concentrations of activity in irregular zones mostly adjacent to the sarcolemma in type I fibers (Fig. 6A). Cytochrome-c-oxidase activity was present.

Figure 2 — Quadriceps femoris muscle of Case 1. Large accumulations of intact mitochondria are seen in the intermyofibrillar spaces, but many contain small, electron-dense granules that may be condensed lipoproteins (small arrowheads). Lipid droplets are only mildly increased (large arrowheads). EM. Bar = 1 μm.
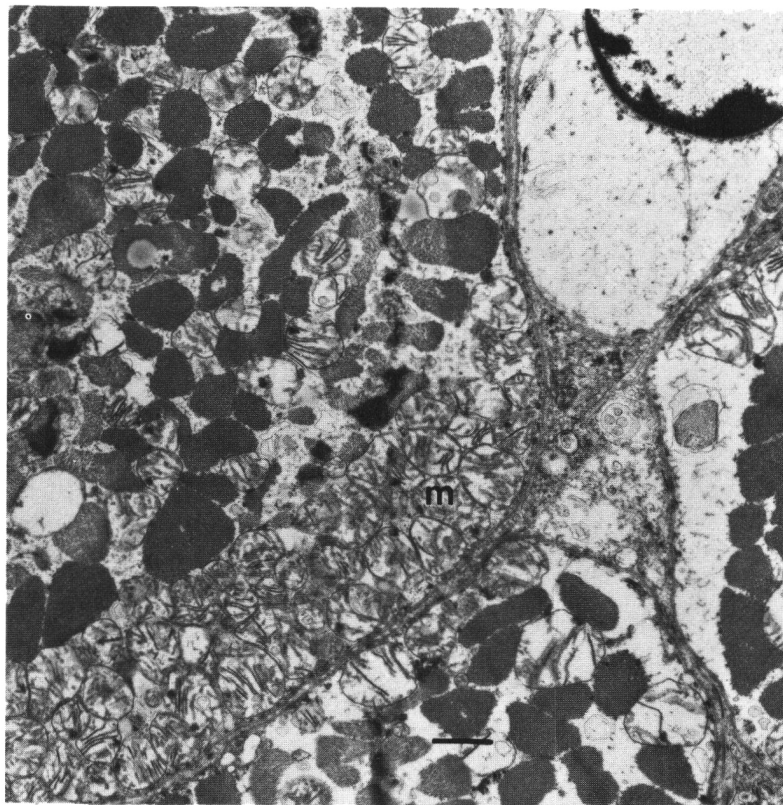

Figure 3 — Diaphragm of Case. 1. Large numbers of closely packed mitochondria (m) are seen in the subsarcolemmal region. Myofibrils appear normal. EM. Bar = 1 μm.
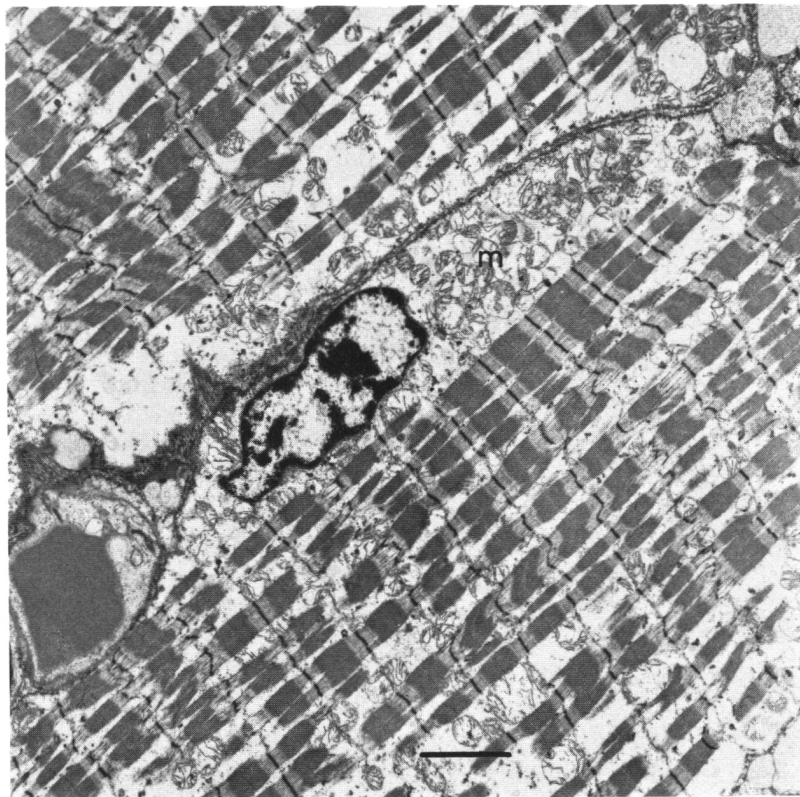
Figure 4 — Diaphragm of Case 1. Longitudinal section of muscle shows well formed sarcomeres and subsarcolemmal aggregates of mitochondria (m) adjacent to nucleus. EM. Bar = 5 μm.
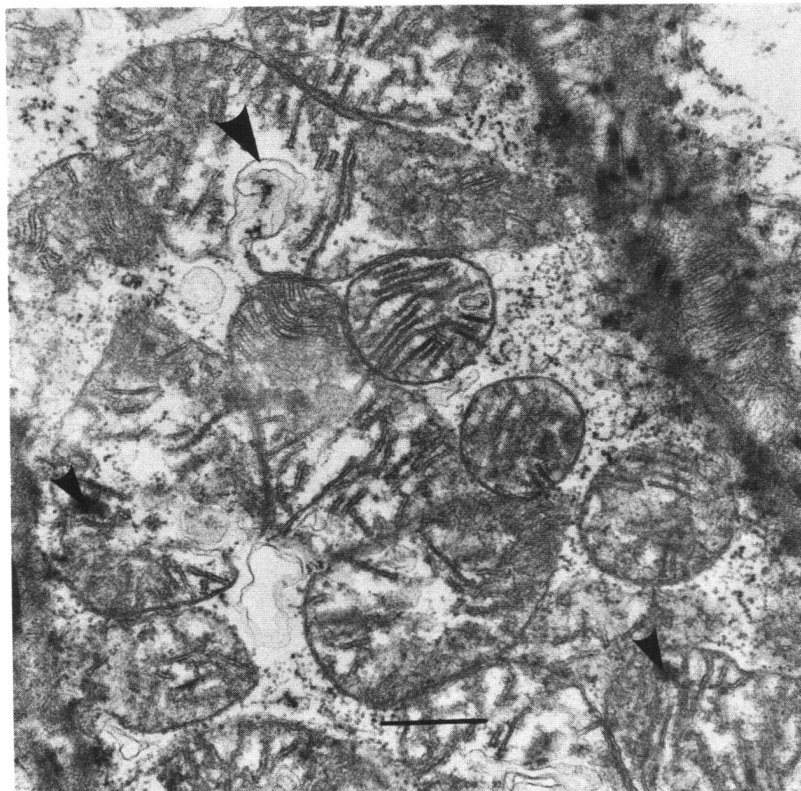

Figure 5 — Diaphragm of Case 1. Closely packed mitochondria have well preserved cristae and external membranes. Glycogen granules are seen both within and between mitochondria. Degenerative changes are seen in some mitochondrial membranes (large arrowhead), and dense intramitochondrial granules are demonstrated (small arrowheads) but no paracrystalline inclusions are seen. EM. Bar = 0.5 μm.
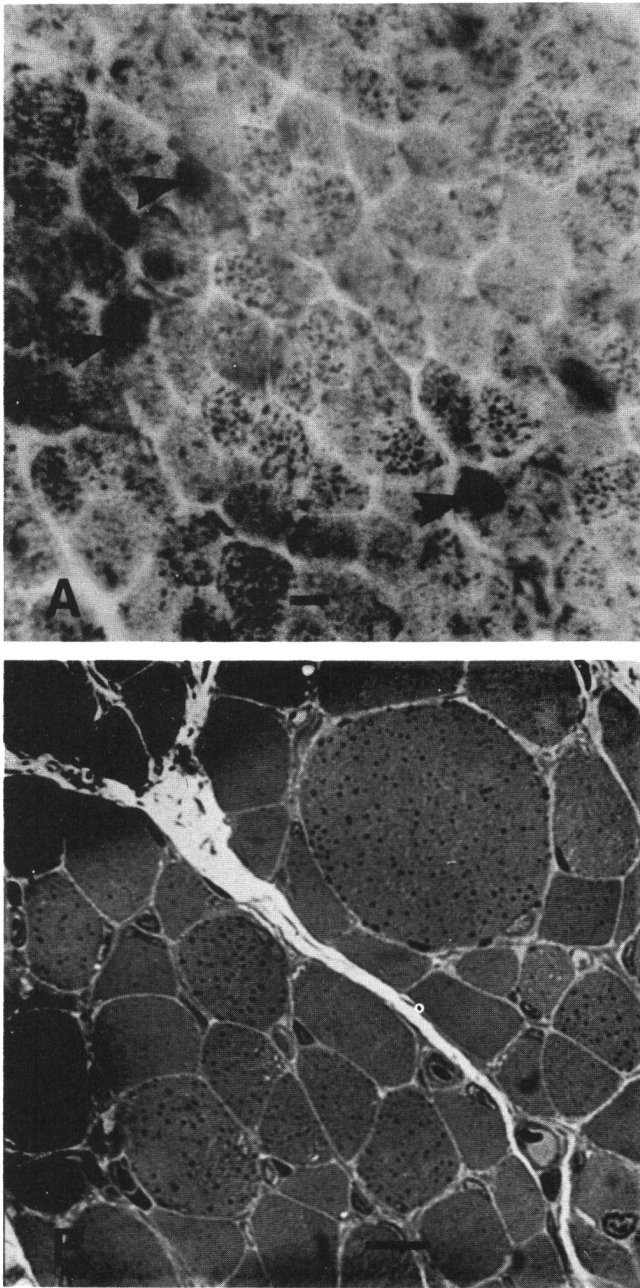
throughout the sarcoplasm of many fibers (Fig. 6B). Electron microscopy demonstrated increased mitochondria and lipid droplets in many myofibers and the two structures were so altered that they often were difficult to distinguish from each other. Many were undergoing degenerative changes, with membrane-limited vacuolar debris and myelin figures, but paracrystalline inclusions were not demonstrated. A few incompletely formed concentric cristae were identified in some mitochondria. Myofibrils were well organized, but focal loss of myofilaments was common (Fig. 7). Peroxisomes were not seen.

Postmortem Findings: The following abnormalities were demonstrated: multiple renal cortical cysts; fibrosis and iron deposition in the liver; patent ductus arteriosus and fenestrated atrial septum; aspiration pneumonitis; generalized pachygyria of the cerebral cortex.

Case 3: A 4-month infant girl was dead on arrival at hospital. Her birth weight was 2955 grams after an uneventful pregnancy and delivery. Severe generalized hypotonia, weakness, an incomplete Moro reflex, and poor suck were noted at birth. Facies characteristic of the cerebro-hepato-renal syndrome and high-arched palate were observed.
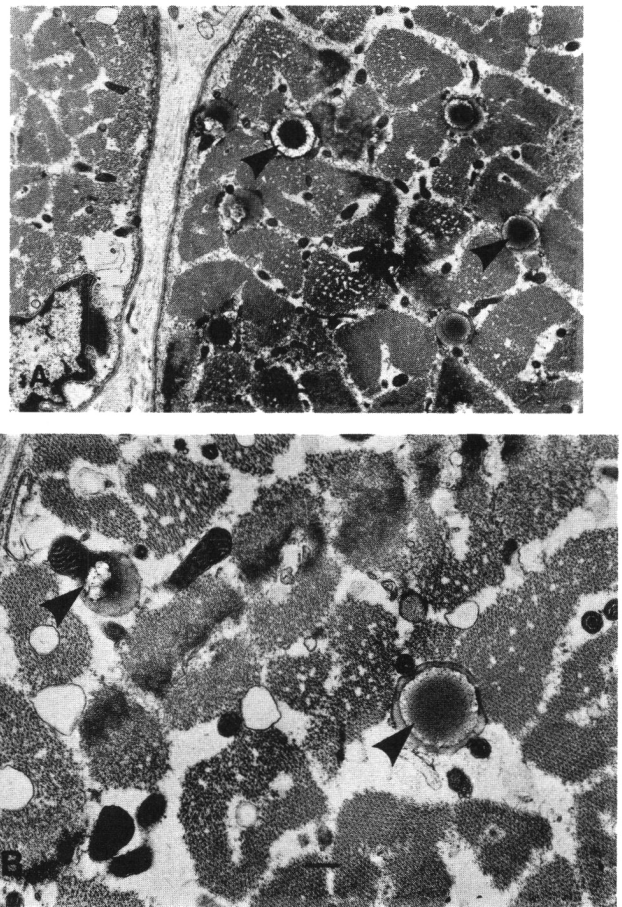

Figure 6 — Quadriceps femoris muscle of Case 2, 1-month-old. Variation in muscle fiber diameter is seen. (A) NADH-TR stain reveals zone or 'smudges' of high enzymatic activity within many muscle fibers (arrowheads), but subsarcolemmal crescents of activity are not seen. Bar = 14 μm. Alterations in staining quality also were not seen with the modified Gomori Trichrome stain (not illustrated). (B) Plastic embedded sections of 1 μm, stained with toluidine blue, reveal scattered dense punctate deposits in the intermyofibrillar spaces, corresonding to the degenerating lipid-mitochondrial complexes demonstrated in Fig. 7. Bar = 10 μm.

Oil red O stain showed increased concentration of neutral lipid in zones corresponding to increased NADH-TR activity. Acridine orange fluorochrome stain showed no abnormally fluorescent zones in muscle fibers to suggest increased ribonucleic acid. Autofluorescence also was normal.

Epoxy resin-embedded sections of 1 μm stained with toluidine blue revealed dense punctate deposits uniformly distributed

Figure 7 — Quadriceps femoris of Case 2. Focal loss of myofilaments is seen as small 'holes' within myofibrils. Many intermyofibrillar lipid droplets and closely associated mitochondria are undergoing degenerative changes (arrowheads). Vacuolated debris replaces the internal structure. Paracrystalline inclusions and concentric arrays of cristae are not demonstrated. EM. (A) Bar = 1 μm; (B) Bar = 0.1 μm.

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Gavage feeding was required. Seizures developed at 4 days of age and were controlled with phenobarbital. The kidneys and renal collecting system were poorly visualized by intravenous pyelography. Generalized aminoaciduria was demonstrated by chromatography. The serum bilirubin was mildly elevated at one week of age, but jaundice and hepatomegaly were not present. Hypotonia and weakness persisted. She was readmitted at 5 weeks of age because of dehydration and acidosis.

Muscle biopsy (postmortem): The quadriceps femoris muscle and the diaphragm showed extensive muscle fibers with red subsarcolemmal aggregates shown by Gomori trichrome stain. These zones showed strong activity of NADH-TR and SDH. The aggregates were seen in almost all fibers identified as type I by ATPase criteria. Other cytoarchitectural alterations included internal nuclei were rare. Atrophic fibers of both types were demonstrated. Electron microscopy was unsatisfactory.

Postmortem Findings: The following abnormalities were demonstrated: multiple renal cortical cysts bilaterally, hepatomegaly with periportal fibrosis and pseudoacinar arrangement of hepatocytes, predominantly erythroid myelocytic hyperplasia of bone marrow, micropolygyria of cerebral cortex with neuronal loss, ectopia of incompletely migrated neurons in hippocampus and cerebellar cortex, and ependymal rosettes at the caudal end of the patent cerebral aqueduct.

Case 4: A 3040 gram male infant had characteristic facies of cerebro-hepato-renal syndrome. Seizures on the first day ceased after the administration of phenobarbital. He was diffusely hypotonic and required feeding by gavage. Examination at 10 days of age did not show hepatosplenomegaly or icterus. Spontaneous activity was decreased and he demonstrated no visual fixation or blink in response to light. The suck reflex was weak. Muscle tone was decreased. Stretch reflexes could not be elicited.

The infant became icteric with an increased direct bilirubin level in the first month of life. Abdominal ultrasound studies suggested abnormal renal parenchyma, but cysts were not identified.

Examination at 3 and 8 months of life revealed profound developmental arrest. The liver and spleen had become palpable enlarged. A muscle biopsy was performed at 9 months of age. He died at 11 months of age of respiratory insufficiency and aspiration of gastric contents.

Muscle biopsy: The histopathologic and histochemical findings in the quadriceps femoris muscle were similar to those described in Case 2, but less pronounced because only scattered fibers in each fascicle exhibited the 'smudges' of oxidative enzymatic activity. Subsarcolemmal red accumulations were not observed with trichrome stain. Electron microscopy revealed degenerative changes in muscle mitochondria and lipid (Fig. 8).

Postmortem Findings: The following abnormalities were demonstrated: scattered renal cortical microcysts, micronodular cirrhosis, focal micropolygyria and pachygyria of the cerebral cortex.

DISCUSSION

Primary mitochondrial myopathies are now well recognized as diseases interfering with energy metabolism in muscle and causing weakness. The Kearns-Sayre syndrome ('opthalmoplegia plus'; oculocraniosomatic neuromuscular disease) is the best defined and most common of this group, affecting children and adults (Olson et al., 1972; Behrenberg et al., 1977; Di Mauro,
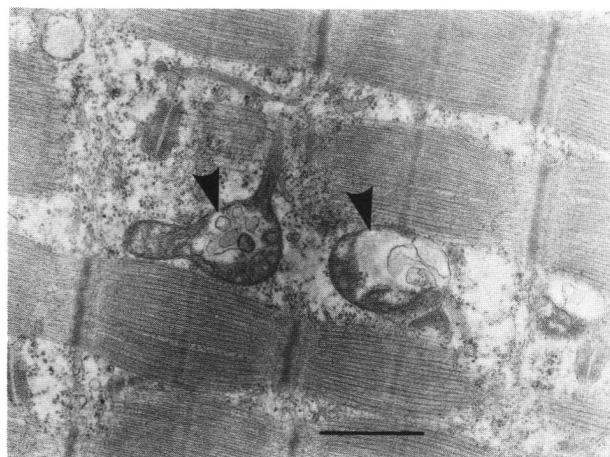

Figure 8 — Quadriceps femoris muscle of Case 4. Degenerative changes are seen in mitochondria (arrowheads), but myofibrils remain intact. EM. Bar = 1μm.

1980; Tassin et al., 1980). The hypermetabolic syndrome of Luft et al., (1962) was the first mitochondrial myopathy described, but is rare. Most mitochondrial myopathies are genetically determined diseases. Autosomal dominant and autosomal recessive forms are recognized (Tassin et al., 1980; Walter et al., 1981). In addition to this group of diseases, other hereditary diseases of mitochondria affect liver, brain, and also striated muscle as one component of the systematic metabolic disorder. Examples include Menkes' disease (kinky hair syndrome; trichopolidystrophy) (Ghatac et al., 1972; French et al., 1972) and Leigh's subacute necrotizing encephalopathy (Crosby and Chou, 1974; Willems et al., 1977). Our studies indicate the hepato-cerebral-renal syndrome of Zellweger should be added to this category.

The metabolic defects in the cerebro-hepato-renal syndrome include defects in the metabolism of pipecolic acid (Trijbels et al., 1981) and of bile acids, and in the mitochondrial respiratory chain (Goldfischer et al., 1973; Lott et al., 1979; Mathis et al., 1980; Trijbels et al., 1981). In addition, a deficiency of peroxisomes has been demonstrated in hepatic cells, proximal renal tubules, and in skeletal and cardiac muscle (Goldfischer et al., 1973; Pfeifer and Sandhage, 1979; Trijbels et al., 1981), and the pipecolic acid deficiency is probably related to the proxisomal defect (Trijbels et al., 1981). Peroxisomal deficiency may also be important in the pathogenesis of the disturbance in the mitochondrial respiratory chain because these subcellular structures contain oxidase and peroxidase enzymes. Peroxisomes are rarely demonstrated by electron microscopy in normal muscle, and none were found in our cases of cerebro-hepato-renal syndrome.

Cytochrome-c-oxidase is an enzyme of the electron transport or respiratory chain located on the inner mitochondrial membrane. It has been previously documented to have deficient histochemical activity in muscle in some mitochondrial myopathies (DiMauro et al., 1980; Nemni et al., 1981), and is inactivated in mitochondria containing paracrystalline inclusions (Bonilla et al., 1975). The enzyme also is deficient in Leigh's necrotizing encephalopathy (Willems et al., 1977). In other mitochondrial myopathies, a deficiency of reducible cytochrome-b is demonstrated (Morgan-Hughes et al., 1977; Land et al., 1981). A quantitative biochemical study of cyto-
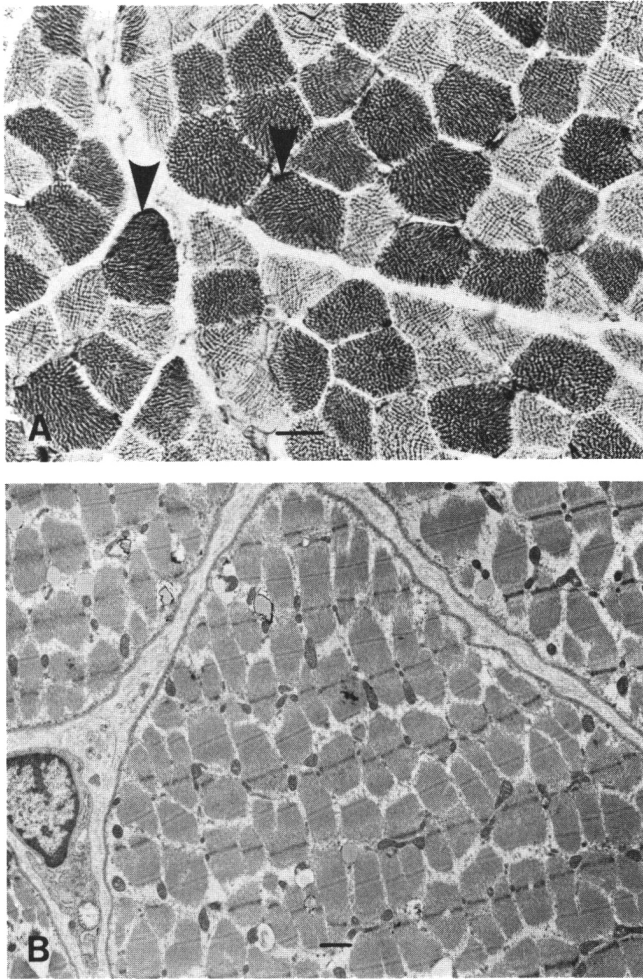
Figure 9 — Normal diaphragm of a 4-month-old infant without neuro-muscular disease or Zellweger syndrome. Increased amounts of oxidative enzymatic activity or of mitochondria are not normally found relative to other muscles. A few scattered fibers have thin subsarcolemmal crescents of increased activity (arrowheads), but they also normally are demonstrated in other muscles. (A) NADH-TR. Bar = 10 μm. (B) EM. Compare with Figures, 1, 3, 4, and 5. Bar = 1μm.

chrome-c-oxidase in a homogenate of skeletal muscle from one patient with cerebro-hepato-renal disease showed 11.6 μmol/mg protein/min. compared with a range of 21-45.5 μmol/mg/min. in muscle from six control patients. A similar reduction of activity was found in liver and brain from this patient (Trijbels et al., 1981). However, the severe disturbance in the respiratory chain was not believed to be due to cytochrome-c-oxidase deficiency because of a residual activity of as much as 60 percent of the lowest value in the normal range. Our histochemical stains of cytochrome-c-oxidase demonstrated activity of this enzyme.

The greater involvement of the diaphragm than of muscles of the extremities in Case 1 provides an explanation for the onset of progressive respiratory failure and cor pulmonale leading to death. Caution must be exercised in the interpretation of findings in the diaphragm, however, because this muscle may normally contain some muscle fibers with more lipid content than found in muscles of the extremities (Odusate et al., 1981). Normal infant diaphragm contains a few scattered muscle fibers with thin subsarcolemmal crescents of oxidative enzymatic

activity (Fig. 9A), but not nearly as extensive as was found in our cases of cerebro-hepato-renal syndrome. Mitochondria also are not increased or aggregated in the normal infant diaphragm (Fig. 9B).

The mitochondrial alterations in number and morphology in cerebro-hepato-renal syndrome are not associated with other evidence of myopathy or muscle fiber necrosis, but the associated deficiency in intracellular respiration (i.e. oxidative phosphorylation) and interference with energy metabolism may greatly diminish muscular function, expressed clinically as weakness and hypotonia. Whether carnitine deficiency occurs in cerebro-hepato-renal syndrome is not yet known, but it could be systemic due to hepatic involvement, or muscular in type.

This 'mitochondrial myopathy' is similar to other diseases of the same nature, muscle being only one of many involved organ systems. The mitochondrial myopathy of cerebro-hepato-renal syndrome could be termed 'pleoconial', but the distinction from 'megaconial' in the early literature on diseases of muscle mitochondria is no longer usually made because numerous and enlarged mitochondria often coexist. The ultrastructural degenerative changes in the mitochondria and lipid droplets are similar to those previously described in other mitochondrial myopathies (Stadhouders, 1981). Chronic lipid storage in muscle fibers from any cause including chronic starvation may lead to regressive changes in the droplets of fat (Fig. 10).
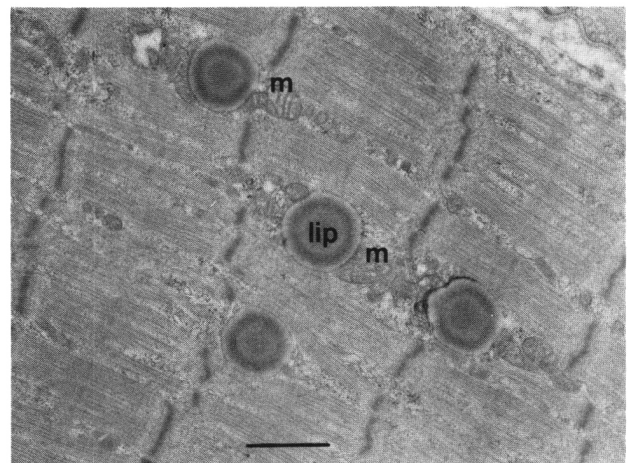

Figure 10 — Quadriceps femoris biopsy of 6-month-old infant with chronic starvation due to short bowel syndrome shows large droplets of unutilized lipid (lip) associated with normal mitochondria (m). The concentric zones of variable density within lipid is a chronic or regressive feature. Compare with Figure 7. Bar = 1 μm.

The lack of intense orange fluorescence of muscle fibers stained with acridine orange and examined under ultraviolet light further confirms that neuropathy and denervation of muscle are not part of this disease, and that regeneration of muscle does not occur.

The muscle biopsy may be useful diagnostically in suspected cases of cerebro-hepato-renal disease, but the histopathologic and histochemical findings may not be uniform in all muscles, nor between individual patients. An apparently normal or minimally altered muscle biopsy examined histologically does not necessarily exclude this diagnosis. Histochemistry and electron microscopy greatly increase the chances of demonstrating mitochondrial abnormalities.

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