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Leigh's Disease Involving Multiple Organs

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Leigh's disease is a rare progressive neurological disorder that is characterized light microscopically by focal spongy necrosis in the brain and electron microscopically by mitochondriopathy. We report an autopsy case of Leigh's disease that showed abnormalities in the liver, kidney and skeletal muscle as well as the central nervous system. The patient was an 18-month-old girl who has carried a diagnosis of cerebral palsy ever since her birth to a 20-year-old mother. The baby was generally hypertonic and mentally retarded. She died of severe metabolic acidosis. Postmortem examination showed growth retardation, fatty liver, fatty kidney and soft brain. Brain section showed multifocal softenings in the brainstem, basal ganglia and periventricular areas. Microscopically increased capillaries with endothelial proliferation, vacuolar degeneration and mild gliosis were seen in the brain. The axons were relatively preserved. Liver and kidneys showed microvesicular fatty change. Myofiber degeneration of the skeletal muscle was also noted. Electron microscopic examination showed markedly increased mitochondria in the parenchymal cells of the brain, liver and kidney. The mitochondria showed round to ovoid ballooned appearance including electron-dense core-like structures and pseudoinclusions of glycogen granules.

Key Words: *Leigh's disease, Brain, Liver, Kidney, Mitochondrial disease, Subacute necrotizing encephalomyelopathy.*

INTRODUCTION

Leigh's disease is a rare progressive neurological disorder of infancy which resembles Wernicke's disease in the adult except for sparing of the mammillary bodies, involvement of the spinal cord, and absence of hemorrhage (Feigin et al., 1954). It is characterized by focal spongy necrosis mainly in the brainstem and basal ganglia. This disease is generally thought to be caused by an anzyme defect in the mitochondria, although there is some debate on what is the defective enzyme (Pincus et al., 1976; Sander et al., 1984; Sheu et al., 1984). The mitochondrial abnormality has been reported in some cases of Leigh's disease (Walter et al., 1986; Paulus et al., 1990). It can, however, involve the rest of the central nervous system (Vuia, 1975), myocardium (Langes et al., 1985), peripheral nerves (Crosby et al., 1974) and skeletal muscles (Jacobs et al., 1990). Therefore Leigh's disease now is considered as a kind of systemic disease by mitochondrial enzyme defect. It can involve other visceral organs but only fatty change of the liver (Vuia, 1975; Kamoshita et al., 1968) and renal tubular acidosis (Hirschman et al., 1978) were reported. We report an autopsy case of Leigh's disease that showed abnormalities in the liver, kidney and skeletal muscles as well as the central nervous system.

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CASE REPORT

An 18 months old girl was brought to the emergency room of Kangnam General Hospital because of respiratory difficulty on April 2, 1992, which had developed abruptly while oral feeding was instituted.

She was born on August 1990 to a 20 year old un-

married mother via normal full term spontaneous delivery. The birth weight was 2.45 kg. Although no specific anomaly was noted after birth, failure to thrive and poor feeding were problems, and weight gain was poor.

She was admitted for the first time at 9 months of age for the evaluation of the above problems. On admission she could not fix her gaze. No specific lesion was found in the eyes. The karyotype was 46, XX. Brain CT on September 27, 1990 showed a low density lesion in the left temporal area. The ventricle size was normal.

She was managed conservatively and discharged. Her second admission was on October 13, 1990 because of fever and irritability at age 2 months. Growth parameters were below 3 percentile. Neurological examination showed increased muscle tone in both extremities and trunk. Scissoring movement of the lower extremities was noted. Routine laboratory tests did not show any abnormality except for increased values of AST and ALT (46.9 u/l and 57.9 u/l). She was discharged after conservative treatment. On March 15, 1991 she had episodes of fever and seizure. The fever subsided a few days later without any specific therapy.

She was readmitted on April 12, 1992. She was pale and dyspneic. Oxygen was given and the dyspnea was relieved a few days later. Chest X-ray showed no abnormality. Respiration became difficult again and seizure developed after a few days. Blood gas analysis showed metabolic acidosis with anion gap of 20 mEq/l. Despite management, the metabolic acidosis and anion gap aggravated. She expired on the same day.

PATHOLOGICAL FINDINGS

The general appearance was unremarkable. The liver weighed 277g and right and left kidneys weighed 26.1g and 27.3g, respectively. The liver showed mild fatty change. The kidneys were grossly unremarkable. The brain weighed 676 gm after formalin fixation. The external surface was grossly unremarkable. Brain section showed multifocal symmetrical softenings in the basal ganglia, brainstem and periventricular area (Fig. 1). Microscopically the most characteristic feature was noted in the brain. Multiple vacuolation of the neuropils with marked capillary proliferation and mild gliosis were seen in the brainstem, basal ganglia, and periventricular area. However, axons were relatively preserved in the lesions (Fig. 2). The olivary nuclei and brainstem motor nuclei and tegmental plate were particularly involved by this process. The caudate nucleus,

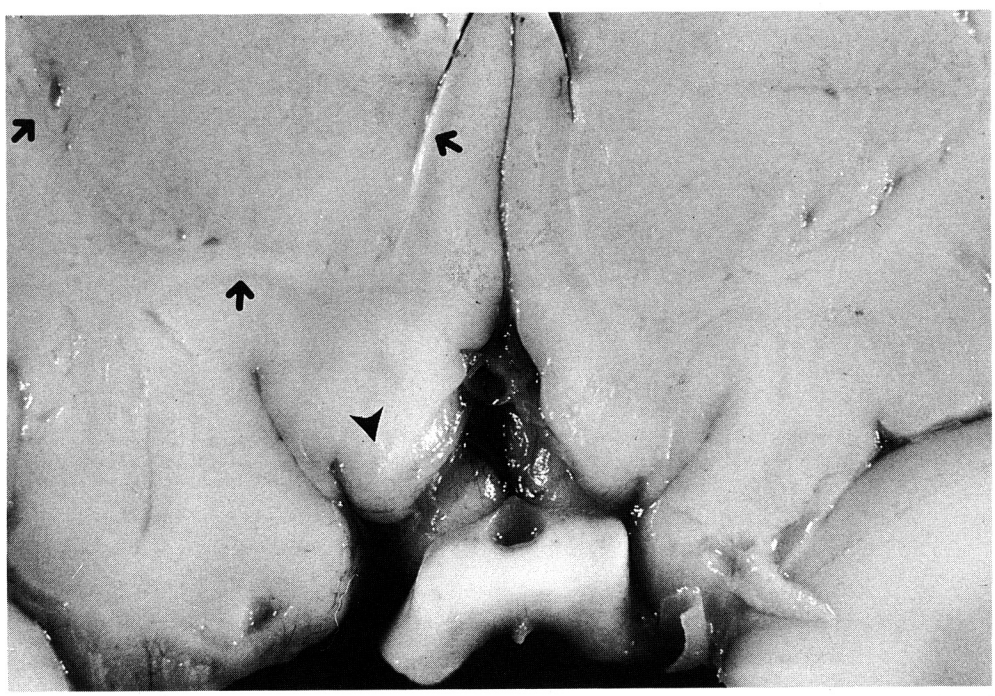

Fig. 1. Brain. The cut section shows symmetric gray discoloration and softenning in the basal ganglia and white matter around it (arrowhead). The mammillary is intact, grossly (arrow).

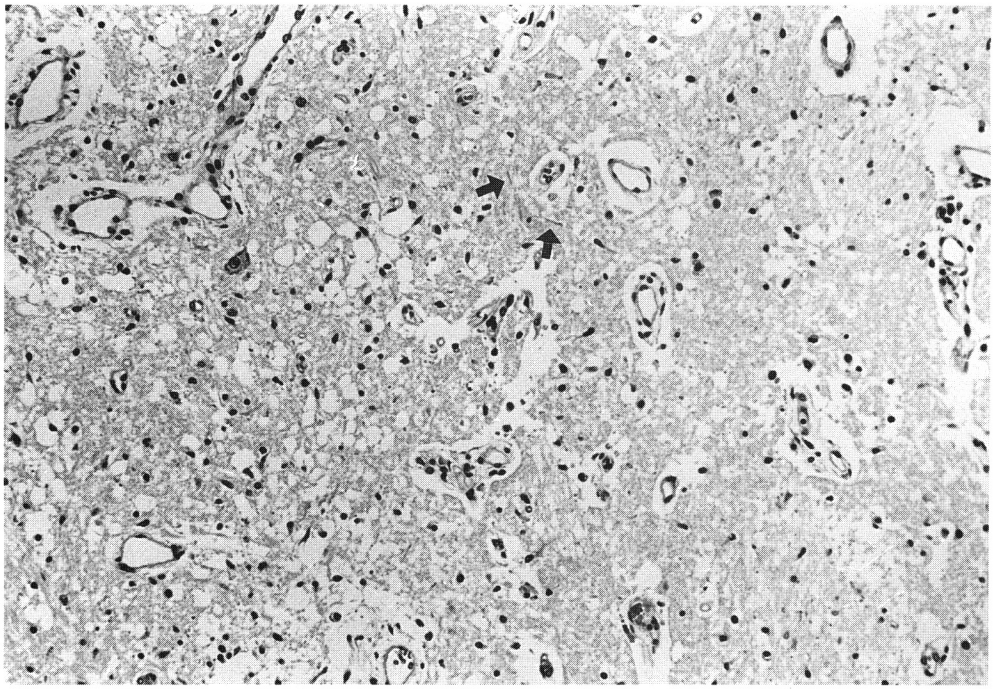

Fig. 2. Brain. The neuropils shows sponge-like vacuolations. The capillaries are increased. Relatively preserved axons are seen (arrow).

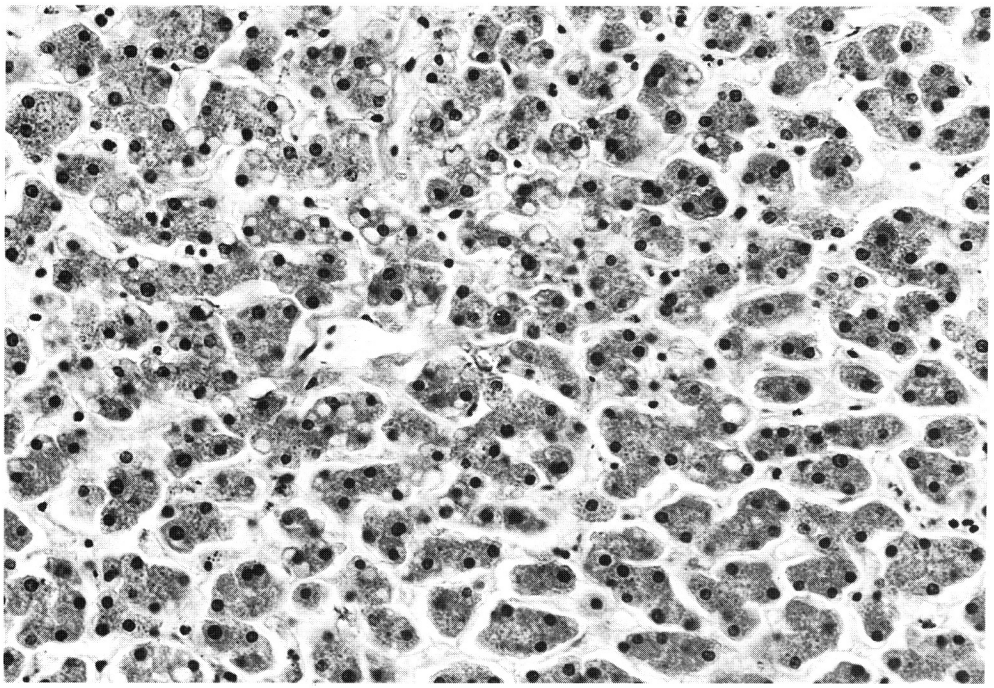

Fig. 3. The hepatocytes show a moderate to severe microvesicular fatty change and many minute granules, that are suspected to be mitochondria, are seen in the cytoplasm.

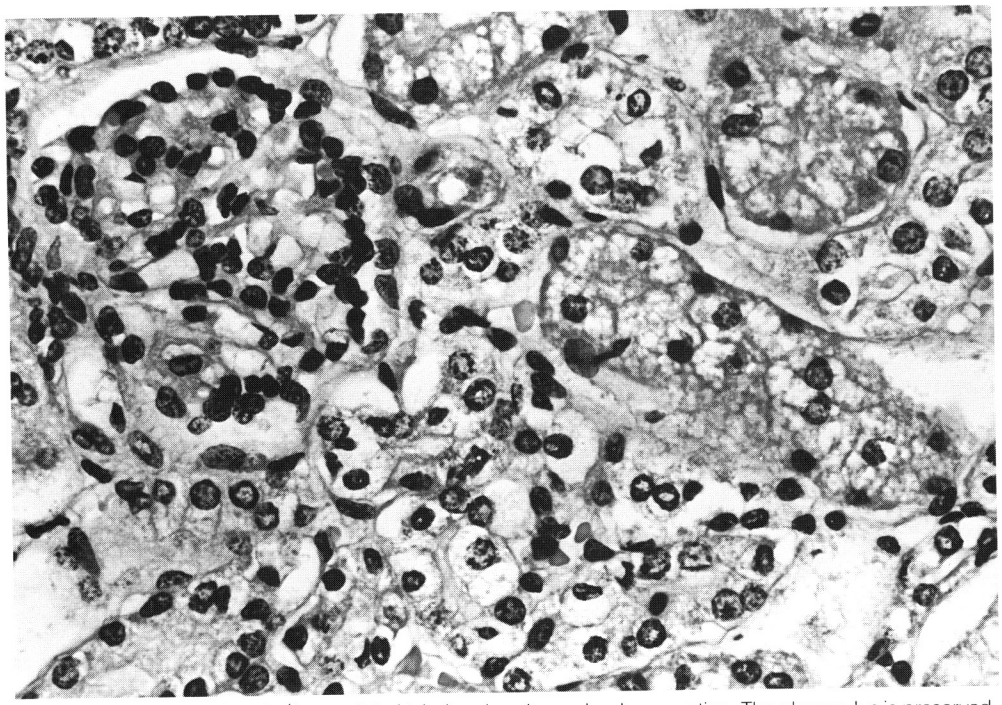

Fig. 4. Both proximal and distal convoluted tubules show lvacuolar degeneration. The glomerulus is preserved.

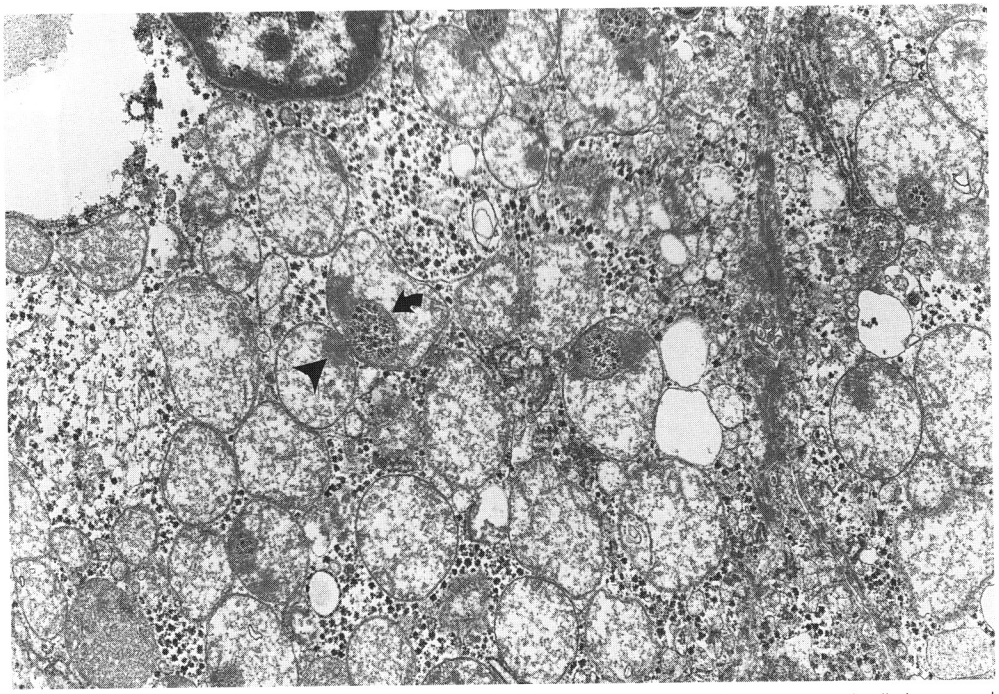

Fig. 5. Electron micrograph of the liver. The number of mitochondria in hepatocytes are markedly increased and the mitochondria show a round to ovoid ballooned appearance with the presence of electron-dense core-like structures (arrowhead) and pseudoinclusion of glycogen granules (arrow). The cristae are destroyed by autolysis (×8,000).

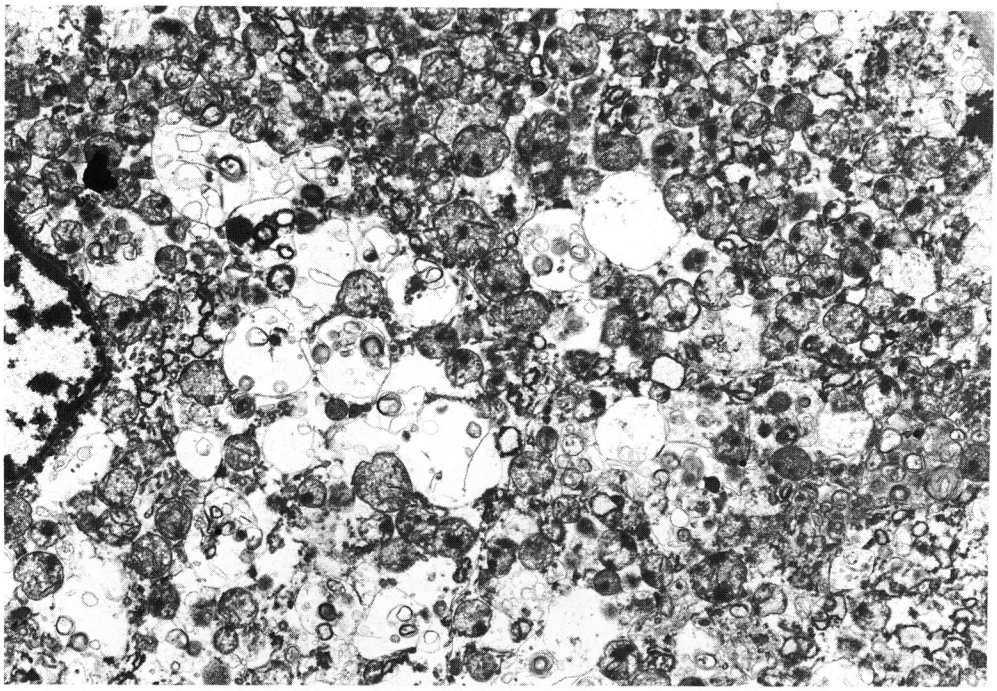

Fig.6. Electron micrograph of the kidney. The proximal convoluted tubules show a marked increase in the number of mitochondria that are ballooned to round to ovoid shape with many electron-dense core-like structures. (×4,000)

periventricular gray and thalamus were also involved. However, the mammillary bodies were spared.

The liver showed diffuse microvesicular fatty change. It was mild in some areas but other areas showed severe fatty change. There were also many brown granules in the cytoplasm. The nuclei remained in the central portion of the cells. Cholestasis was also seen. However, actual necrosis of the hepatocytes was not noted (Fig. 3). The kidneys showed vacuolar degenenative change in both proximal and distal convoluted tubules. The glomeruli were preserved (Fig. 4). Sections from the psoas muscle showed myofiber degeneration with irregular border of the myofibers. A few angulated fibers were also noted. However, inflammatory cell infiltration was not seen. Additionally, thymic involution, lymphoid depletion and extramedullary hemopoiesis in the spleen, and cortical atrophy of the adrenals were noted. The bone marrow was normocellular.

Electron microscopically, the common and characteristic findings were a large number of mitochondria in the cytoplasm of the neuronal cells, hepatocytes, and renal tubular epithelial cells, which showed round to ovoid balloned appearance with no definite cristae but with the presence of electron-dense core-like structure and pseudoinclusion of glycogen granules. Other organelles were seldom remained. Additionally the brain showed diffusely microcystic spaces formed at perineuronal, periglial, and perivascular areas. Vacuoles of uncertain nature and many pinocytotic vesicles were also seen in cytoplasm of neuronal cells. Fat globules were noted in hepatocytes but not neuronal cells or renal tubular epithelial cells. The glomeruli showed slightly thickened Bowmann's membrane and also abnormal mitochondria in some cells. But the tubular basement membrane was not thickened (Fig. 5, 6).

DISCUSSION

At first, Leigh's disease was considered to be a kind of nutritional deficiency, because of its histologic similarities to Wernicke's encephalopathy (Feigin et al. 1954). Although several enzyme defects such as thiamine pyrophosphate-ATP-phosphotransferase, pyruvate carboxylase, cytochrome c oxidase and pyruvate dehydrogenase were reported, none of these defects were specific enough to justify biochemically defined Leigh's disease (Walter et al., 1986).

On the other hand, ultrastructural studies showed

abnormal mitochondria in the brain (Walter et al., 1986), skeletal muscle (Crosby et al., 1974) and myocardium (Langes et al., 1985). The dominant feature was the presence of the increased numbers of enlarged mitochondria. Many showed whirled cristal membrane, and electron dense spheroid bodies. Some showed trilaminar plates and structures resembling paracrystalline formation. Since these abnormal mitochondria, however, have been described as nonspecific finding of energy metabolism deficiency, Leigh's disease could be an expression of metabolic disorder induced by energy deficiency. In our case, although many intracellular organelles were destroyed by autolysis, mitochondrial abnormality in brain and kidneys showed similar features to those of previous reports in the brain, skeletal muscle, and myocardium. In the liver, pseudoinclusion of glycogen granules in mitochondria are characteristic, but not specific, findings for Leigh's disease.

Metabolic acidosis is an important factor in the diagnosis and management of Leigh's disease and may be fatal to the patient. The main cause of metabolic acidosis was initially considered to be organic acids such as lactic acid and pyruvic acid. In 1973, Gruskin et al described two cases of renal tubular acidosis of the proximal type in Leigh's diseas and in 1978, Hirschman et al reported a case in which the cause of the metabolic acidosis was related to the increased excretion of filtered bicarbonate in one metabolic acidosis was related to the increased excretion of filtered bicarbonate in one respect, and to reduced net acid excretion secondary to a persistently low P_{CO_2} in another respect. In our case, abnormal mitochondria was seen. It is different from that in Fanconi syndrome because in Fanconi syndrome, tubular basement membrane is thickened (Woo et al., 1982)

One feature of the skeletal muscle in Leigh's disease is ragged-red fibers (Crosby et al., 1974). In our case, modified Gomori trichrome stain or electron microscopic examination of the skeletal muscle were not available. However light microscopic examination showed degenerated myofibers with irregular borders which probably represented the ragged-red fibers although autolysis was advanced.

The presence of ragged-red fibers in Leigh's diseas make difficulties in differential diagnosis from mitochondrial myopathy. The mitochondrial myopathy was initially defined by clinical symptom complex and 'ragged red fibers' in skeletal and the Leigh's disease was initially defined by clinical and pathological features similar to that of Wernicke's encephalopathy. In the mitochondrial myopathy, however, brain can be involved and characteristic pathologic features of Leigh's disease was reported in mitochondrial myopathy (Peiffer et al., 1988). The ragged red fibers are also seen in Leigh's disease. On the other hand, enzyme studies showed overlapping between Leigh's disease and mitochondrial myopathy. So the distinction between Leigh's disease and mitochondrial myopathy has become blurred and it may be more appropriate to understand Leigh's disease and mitochondrial myopathy in the category of mitochondrial encephalomyopathy or mitochondrial cytopathy. In our case, the presence of vacuolar degeneration of neuropils and capillary endothelial cell proliferation in the brain and absence of retinal degeneration, cardiac conduction defect or epileptic strokes were more compatible to Leigh's disease than the other forms of mitochondrial encephalomyopathy.

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