

A Case of Leigh's Disease with Initial Manifestation of Dystonia

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A case of Leigh's disease (subacute necrotizing encephalomyelopathy) is reported with such noteworthy features as early onset, dystonia, paraparesis the presence of low attenuation areas in both basal ganglias on computerized tomography of the brain and the presence of a high signal intensity in both basal ganglias in T² weighted image by MR. The electron microscopic findings of muscle biopsy are suggestive of pleoconial mitochondrial myopathy.

Key Words: Leigh's Disease, subacute necrotizing encephalomyelopathy, dystonia, pleoconial mitochondrial myopathy

Leigh's disease (subacute necrotizing encephalomyelopathy) is a familial degenerative disorder of infancy and early childhood. This disease is a progressive poliodystrophy primarily affecting the neurons of the brainstem, thalamus, basal ganglia and cerebellum. Leigh first described it in 1951, in a 7-month-old boy who died after a 6 week illness in which he had anorexia, deafness, optic atrophy, spasticity and Babinski signs. We report here a 28-month-old Korean boy with Leigh's disease. This case reveals dystonia as the initial symptom of Leigh's disease.

CASE REPORT

A 28-month-old male patient was admitted because of gait disturbance and dystonic posture which started 4 months before admission. This dystonic posture consisted of flexion of the left hand and plantar flexion of the right foot on walking (Fig. 1). Also, he complained of mild dysarthria, occasional nausea and vomiting. One month prior to the admission, he walked with

shaky steps, but he was able to walk one or two steps. On admission, he showed progressive paraparesis and excessive dystonic posture, mainly in both lower extremities. He was unable to walk. He showed postural instability when he sat on a chair. There were no past significant medical illnesses, such as birth trauma, drug related sickness, CO poisoning, or delayed development. He had neonatal jaundice 1 month after birth but he was fully recovered. There were no specific family histories that resembled the patient's symptoms. He was a healthy male child with no skeletal deformity. Growth was good. He was alert. On the Denver Development Screening Test, his language, fine motor and gross motor ability all lagged behind compared to the norms for his age. There were no cranial nerve dysfunctions. Cerebellar function seemed to be relatively good. Spasticity and dorsiflexion of the left foot, flaccidity and plantar flexion of the right foot were present in the resting state. Deep tendon reflexes were normal. Babinski sign was positive in the right side. He was able to turn and sit but not walk because of paraparesis. Power of the upper extremities was normal, but that of lower extremities was grade 4. CBC, urine CBC, urine analysis, SMA12 and serum electrolytes were not significant. ANA and RF were negative. Serum CK, serum pyruvate, serum lactic acid, vitamin B₁₂ and serum folate were in the normal range. Serum copper level and serum ceruloplasmin were not significant. Chest PA revealed pneumonic consolidation. Brain CT (Computerized Tomography)

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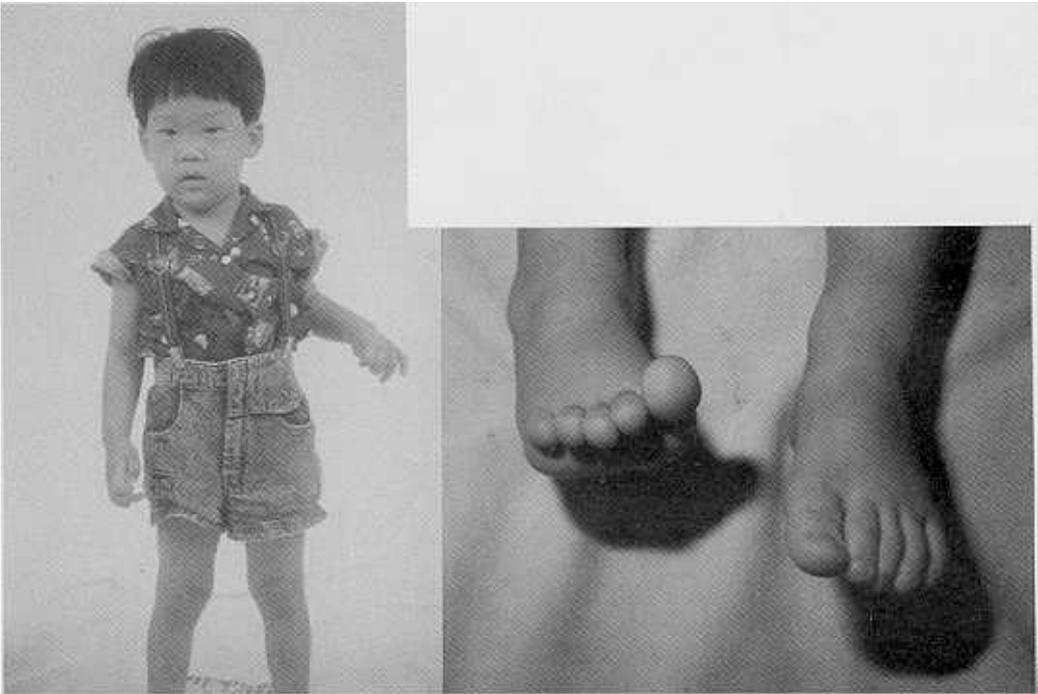


Fig. 1. The 28-month-old boy showed dystonic posture consisting of flexion of the left hand and plantar flexion of the right foot on walking.

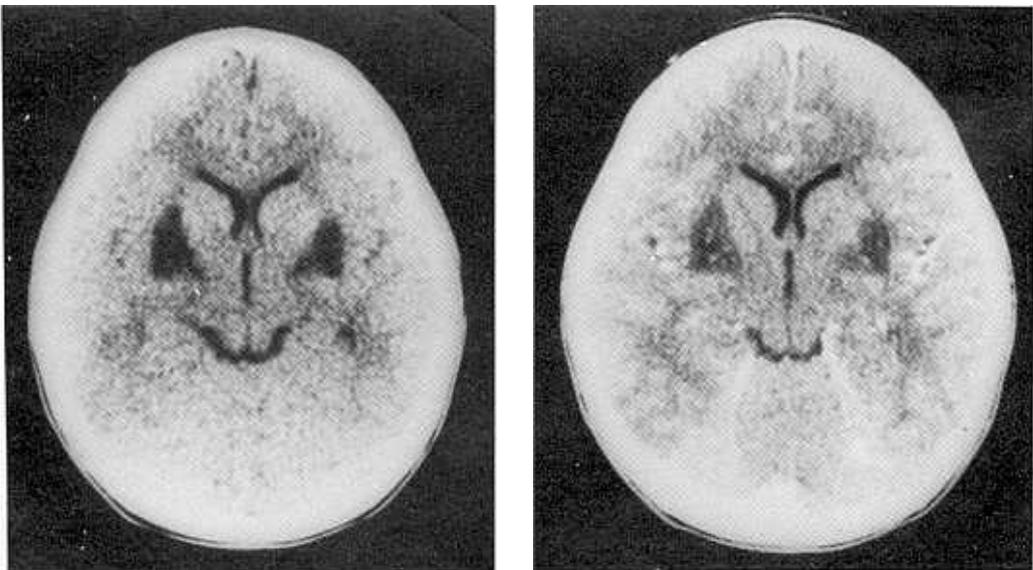


Fig. 2. Brain CT showed bilateral putaminal low densities.

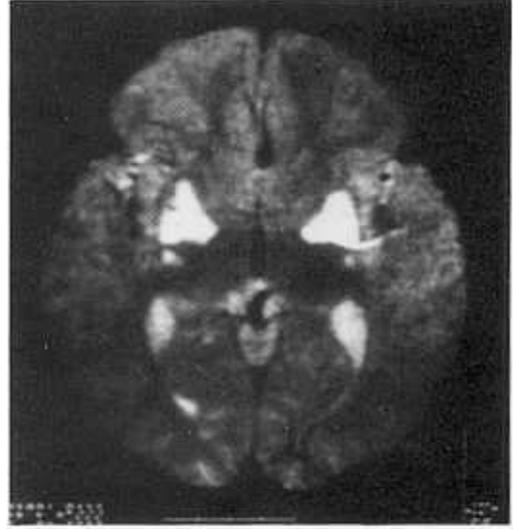


Fig. 3. Brain MR scan revealed a high signal intensity of both basal ganglia in T² weighted image.

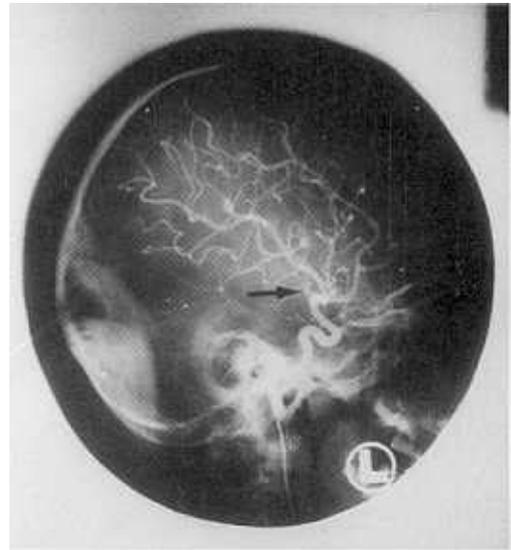


Fig. 4. Cerebral angiogram showed bilateral hypertrophy of basal perforating arteries.

showed bilateral putaminal low densities (Fig. 2). The brain MR (Magnetic Resonance) scan revealed, in T² weighted image, an unusual high signal intensity of both basal ganglia (Fig. 3).

This finding was highly suggestive of Leigh's disease. The EEG showed a normal sleep pattern. The EKG was normal and EMG and NCV were not significant. Cerebral angiography showed bilateral hypertrophy of the basal perforating arteries (Fig. 4). A muscle biop-

sy performed in the left vastus medialis muscle revealed generalized atrophy and occasional grouped atrophy of muscle fibers under the light microscope (Fig. 5-a). Under the electron microscope, the myofibers revealed decreased myofibrils which were replaced by unaggregated glycogen particles and amorphous material. In some fibers, there was an increased number of mitochondria which were slightly swollen but did not contain paracrystalline inclusion

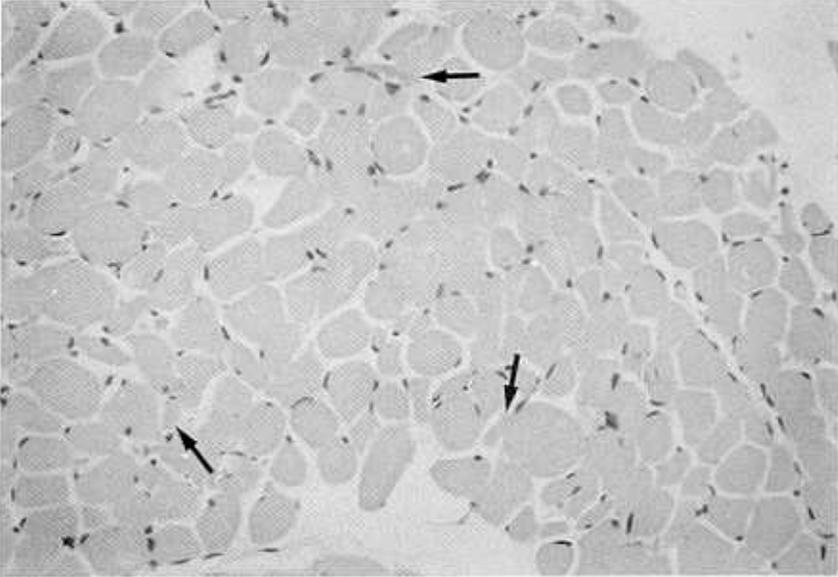


Fig. 5-a. Under light microscopy, the myofibers showed moderate variation in size, Scattered small round or relongated fibers were seen (arrows). (H & E $\times 200$).

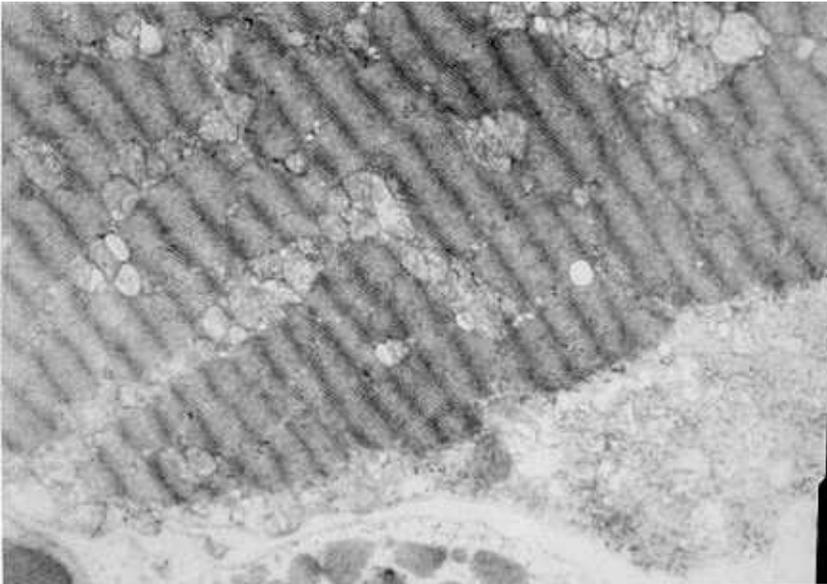


Fig. 5-b. Under electron microscopy, the myofibers showed an increased number of swollen mitochondria between myofibrils and subsarcolemmal accumulation of unaggregated glycogen particles. (Uranylacetate and lead citrate stain $\times 12,500$).

bodies. The interstitium showed deposits of amorphous material. Vacuolar changes were unremarkable

(Fig. 5-b). these findings were suggestive of pleoconial mitochondrial myopathy.

DISCUSSION

The clinical diagnosis of Leigh's disease is difficult. The symptoms are variable and there are no specific biochemical findings. The early onset of SNE (subacute necrotizing encephalomyelopathy) with presenting symptoms of dystonia and paraparesis is noteworthy. David and associates reported a dystonic manifestation in 2 out of 50 cases in 1970. Campistol and associates (1986) found 8 cases with dystonia out of 78 cases before the age of two. The CT and MRI scan findings of this case are particularly suggestive of SNE. Hall and Gardner Medwin (1978) first reported 4 cases with a symmetrical, low density area in the basal ganglia on CT of the brain. Rutledge and his colleagues (1987) reported 4 cases of confirmed SNE with progressive dystonia which showed an increased signal in the neostriatum, predominantly the putamen in T² weighted image by MR. Leigh's disease or SNE was first described in 1951 by Denis Leigh.

Leigh's disease (subacute necrotizing encephalomyelopathy) is a progressive poliodystrophy, primarily affecting the neurons of the brainstem, thalamus, basal ganglia, mid brain and cerebellum (David 1976). This syndrome is transmitted as an autosomal recessive or X-linked trait. The pathology is similar to Wernicke's encephalopathy, but the mammillary bodies are spared (Feigin 1954; David 1976). On the gross examination, cerebral hemispheres may disclose small irregular areas of gray discolorization in the putamen. The microscopic feature is spongy degeneration of the neuropil which may vary in severity from slight loosening to frank necrosis, affecting gray and white matter indiscriminately without respecting anatomical boundaries and accompanied by florid proliferation of small vessels and capillaries and intense astrocytic reaction (Dayan 1970).

Leigh's disease is a syndrome caused by a number of metabolic abnormalities in energy metabolism. Lactic acidosis is frequently detectable during some phases of the illness. The metabolism described is associated with energy metabolism, including the pyruvate dehydrogenase complex (Ketzschman 1987), the cytochrome pathway, and oxidative phosphorylation outside the cytochrome pathway (Van Erven 1985). The most common abnormality appears to be cytochrome c oxidase deficiency (DiMauro 1987). Cytochrome c oxidase deficiency has been identified in brain, skeletal muscle, kidney, cardiac muscle, liver and cultured fibroblasts. Pyruvate decarboxylase deficiency has been reported in a number of patients and

is likely the underlying cause of a significant number of cases of SNE (Shy 1966).

Patients with SNE usually present during the first 2 years of life with variable clinical pictures of retarded motor and intellectual development, feeding and swallowing difficulty, vomiting, weakness, external ophthalmoplegia, visual loss, seizures, ataxia, dystonia, and peripheral neuropathy (Campistol 1986; Miyanachi 1985; Murphy 1974). Symptoms are made worse by intercurrent infection or ingestion of a heavy carbohydrate meal. Lactic acidosis may or may not be present. The children may become acutely ill and have respiratory distress. Most die after 6 months or more, a few die within 2 weeks, and one-fourth have transient spontaneous remission (Miyanachi 1985). Blood concentrations of lactate and pyruvate are usually elevated and rise even higher at the time of clinical exacerbation.

Magnetic resonance imaging appears to be superior to computerized tomography in identifying lesions of SNE. Abnormalities are frequently found in the putamen and basal ganglia and medullary olive (Shy 1954; Ji 1981; Hall 1978). Carl A. Ceyer *et al.* (1988) reported four cases with dystonia. These cases demonstrated symmetrical areas of a high signal intensity in T² weighted image by MR in the basal ganglia, predominantly the putamen. Positron emission tomography has demonstrated reduced glucose utilization in the caudate and putamen in a boy with cytochrome c deficiency (Yanai 1978). T.W. Crosby *et al.* (1974) reported a 6-year-old male patient with Leigh's disease on muscle biopsy, modified trichome stain showed 5% of ragged red fiber. There were characteristic electron microscopic findings showing that the dominant feature was the presence of enlarged (up to 3 μ) mitochondria, usually in the subsarcolemmal clusters. Many contained rectangular paracrystalline arrays compartmentalized within cristalline membranes, which were identifiable at the terminals. On cross-section, enlarged mitochondria often showed concentrically whorled membranous cristae (Crosby 1981).

This syndrome is differentiated from infantile beriberi, dystonia musculorum deformans, Hallervorden-spatz disease, Parkinsonism, GM1 gangliosidosis 1 & 2, Moyamoya disease, CO intoxication, methanol intoxication, status marmoratus and Wilson's disease (Sun 1988; Louis 1979; McCandless 1977; Rutledge 1987; Sami 1981).

Therapy of SNE with thiamine and thiamine derivatives may be accompanied by improvement for a short time, only to have the patient suffer a relapse (Pincus 1973). Glutamine (McCandless 1977) and

dichloroacetate (DEVivo 1979) have been used in treatment, but unfortunately, no therapy has been of consistent or significant value. Our patient was treated with madopar and thiamine supplement which are considered to be the factors contributing to his improvement.

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