Leigh's Syndrome: A report of four cases*

LEIGH SENDROMU: DÖRT OLGU SUNUMU

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SUMMARY

Leigh's syndrome (subacute necrotizing encephalomyelopathy) is a progressive neurodegenerative disorder with onset usually in infancy or early childhood. Clinical signs include motor and/or intellectual abnormalities, nystagmus and ophthalmoparesis, ataxia and optic atrophy. Several mutations of somatic and mitochondrial DNA were identified. In this report we represent four siblings from two different families diagnosed as Leigh's syndrome with two different DNA mutations. These patients referred to the hospital with psychomotor retardation, muscle weakness, hypotonia, epileptic seizures. The disease showed fulminant progression and all of the patients were lost with signs of brainstem dysfunction. Nucleotide (nt) 8993 mutation which is the most common DNA point mutation in Leigh's syndrome was determined in the first family. A new DNA point mutation (nt 8343) was found in the second family but this new mutation was accepted nonpathogen after enzymatic studies of the mitochondrial complexes.

Key words: Leigh's syndrome, psychomotor retardation, lactic acidosis, nt 8343, nt 8993.

ÖZET

Leigh sendromu (subakut nekrotizan ansefalopati) infant ve erken çocukluk döneminde ortaya çıkan progresif bir nörodejeneratif hastalıktır. Klinik bulgular arasında motor ve/veya mental retardasyon, hipotoni, solunum anormallikleri, nistagmus ve oftalmoparezi, ataksi ve optik atrofi vardır. Hastalıkla ilgili somatik ve mitokondriyal DNA mutasyonları tanımlanmıştır. Bu yazıda Leigh sendromu tanılı, iki ayrı DNA mutasyonu gösterilmiş iki ayrı aileden dört kardeş olgu sunulmuştur. Hastalar hastaneye psikomotor retardasyon, kas zayıflığı, hipotoni ve epileptik nöbetler ile başvurdu. Hastalık tüm olgularda hızla ilerledi ve dört olgu da beyin sapı disfonksiyonu ile kaybedildi. Yapılan incelemelerle birinci ailede en sık mutasyon olan nükleotid (nt) 8993 mutasyonu ve ikinci ailede enzimatik çalışmalardan sonra nonpatojen kabul edilen yeni bir DNA nokta mutasyonu (nt 8343) saptandı.

Anahtar sözcükler: Leigh sendromu, psikomotor retardasyon, laktik asidoz, nt 8343, nt 8993.

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Leigh's syndrome (LS), described in 1951 is a neurodegenerative disorder of infancy or childhood (1). This disease usually starts in the first year of life and leads to death within months or years. Juvenile and adult onset forms have also been described (2). LS can be inherited as X-linked, autosomal recessive or ma-

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ternal trait. Defects of pyruvate dehydrogenase complex(PDHC), pyruvate carboxilase, cytochrome C oxidase(COX-complex IV), NADH-CoQ reductase (complex I) have been associated with LS. Cytochrome C oxidase deficiency is the most common biochemical defect associated with LS (3-5).

These enzymes of respiratory chain are located in the mitochondria and their deficiencies cause a disturbance in energy metabolism. A disturbance of pyruvate metabolism or a deficiency of the respiratory chain often leads to elevated lactate and pyruvate levels in serum, cerebrospinal fluid (CSF) and urine. It is a multisystem disorder. Central nervous system (CNS) involvement causes to developmental delay, psychomotor regression, ataxia, seizures, peripheral neuropathy, optic atrophy and brain stem dysfunctions. Elevated levels of lactate in blood or CSF are the most consistent laboratory finding. Symptoms usually start after a few months of normal development and the course is typically rapid. Death is frequently caused by central respiratory failure or by aspiration pneumoniae followed by sepsis (5).

CASE REPORT

Four cases with similar clinic findings referred to the hospital. They were all born normally after a full term pregnancy. Parents were healthy and unrelated. Case 1 and 2 were siblings.

Case 2 referred to the hospital when his brother's autopsy just concluded. Case 3 and 4 were also siblings. Case 3 referred to the hospital 3 years after his brother's death. Case 1 and case 3 progressed very rapidly. They needed mechanic ventilation, so magnetic resonance imaging (MRI) could not be performed. Case 2 and case 4 received supportive treatment with carnitine, coenzyme Q, thiamine and pyridoxine. Blood samples of case 2, case 4 and their mothers were sent to France for mutation analyses. The mutation analyses were done in France by Y. Malthiery and P.Reynier in Laboratoire de Biochime. Point mutation at nt T8993C which is the most common cause of LS was determined in the first family. A new DNA mutation at nt A8343G was determined in the second family, but this new mutation was accepted nonpathogen after the enzymatic studies of mitochondrial complexes. NADH-CoQ reductase (complex I), succinate dehydrogenase (complex II), cytochrome C reductase (complex III), COX (complex IV), complex I+III, and complex II+III were studied in this patient. Autopsy was performed to all of the cases. Severe widespread spongioform changes, vascular proliferation, astrocytosis and well-demarcated necrotizing lesions with prominent capillaries confirmed the diagnosis (Figure 1). Clinical and radiological findings of the cases are given in Table I.

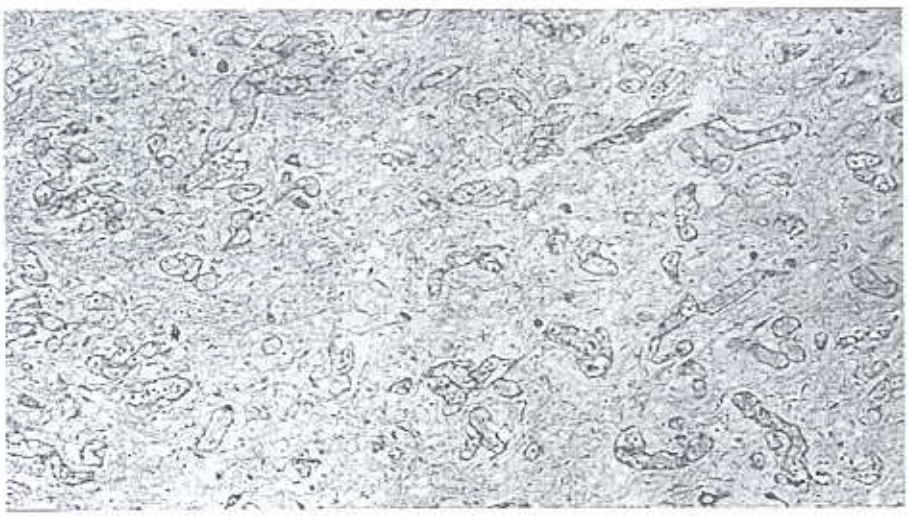

Figure 1. Advanced lesion shows capillary proliferation, disintegration of the neuropil and lipid phagocytes. H.Ex10

Table I. Clinical and radiological findings of four cases

	Case 1	Case 2	Case 3	Case 4
Age (mo)	27	4	4	3
Sex	male	female	male	female
Clinical Findings	psychomotor retardation hypotonia nistagmus optic atrophy generalized seizures irregular breathing pattern	psychomotor retardation, infantile spasm hypotonia nistagmus irregular breathing pattern	psychomotor retardation, infantile spasm spasticity nistagmus, optic atrophy irregular breathing pattern	psychomotor retardation, infantile spasm spasticity nistagmus, optic atrophy
Serum lactate	Normal	Normal	High	High
CBT	Basal ganglia involvement	Normal	Cortical atrophy	Cortical atrophy
MRI	Not done	Basal ganglia involvement (Figure 2)	Not done	Basal ganglia involvement
MRS	Not done	Not done	Not done	High lactate peak (Figure 3)
Dead time (mo)	28	9	4.5	5
Histopathology	+	+	+	+
DNA mutation	T8993C	T8993C	A8343G	A8343G

mo=months, CBT=computerized brain tomography, MRI=magnetic resonance imaging, MRS=magnetic resonance spectroscopy

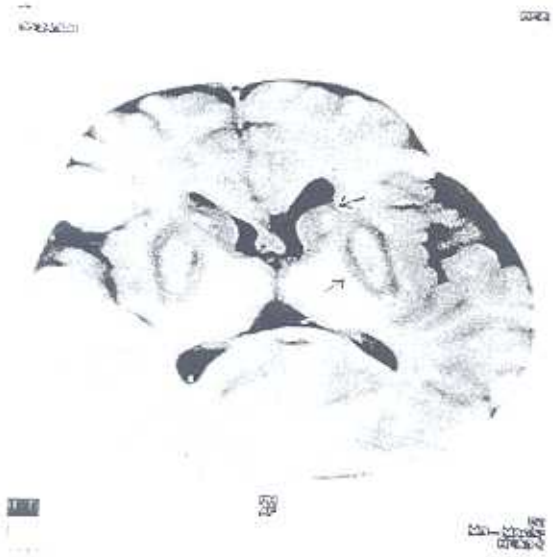

Figure 2. T1 W images of case 2 show bilaterally symmetric putamen and caudate lesions which have hemorrhage in central

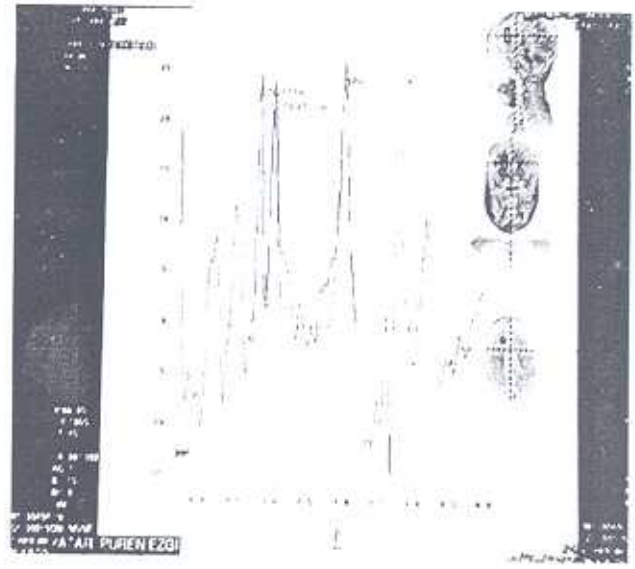

Figure 3. MR spectroscopy of case 4 shows high lactate peak

DISCUSSION

All of our cases were the infantile form of LS ultimately fatal. The early diagnosis of the disease was very important, especially for genetic counselling. All of them were referred to the hospital with psychomotor retardation and irregular breathing pattern. They had infantile spasms except case 1. In LS, a disturbance of pyruvate metabolism or a deficiency of the respiratory chain often leads to elevated lactate and pyruvate levels in serum, CSF and urine. However normal levels have also been described. Lactic acidosis was reported in 92% of patients in literature (6). The serum lactate levels were elevated in our cases 3 and 4.

Neuropathologic findings confirmed the diagnosis of LS. The capillary proliferation and necrotizing lesions in brain tissue are characteristic for LS (2,7). In one study authors found that heart, liver and kidney involvement was also possible besides CNS. Hypertrophic cardiomyopathy, microvesicular degeneration of renal tubular epithelial cells and hepatic involvement are frequently seen (7). Hypertrophic cardiomyopathy was determined in case 4.

Neuroradiological findings are consistent with basal ganglia involvement showing cystic cavitations and increased signal intensity on T2 weighted images (8). Our cases except case 1 had similar findings. We observed progressive deterioration of radiological findings in case 4. Although her first MRI showed only cortical atrophy, second MRI which was obtained two months later displayed symmetric hyperintensity in basal ganglia. Brain magnetic resonance spectroscopy (MRS) is useful for describing the elevated lactate in involved areas. MRS was only obtained from case 4 in whom elevated lactate peaks were established. Takahashi et al performed proton MRS to study the metabolic changes in the brain of a patient with LS (9). They showed that there was an elevation of brain lactate in patient's spectra although lactate and pyruvate levels in both blood and CSF had normalized with sodium dichloroacetate therapy. The clinical and MRI findings were related to the changes in spectroscopically determined brain metabolites. The results of this study indicated that the brain metabolites observed on proton-MRS are useful indicators of response to the therapy and prognosis in LS.

Molecular genetic study is very important in neurometabolic diseases. "nt 8993 mutation" which was determined in case 1,2 and their mother is responsible for some neurological disorders with a maternal inheritence pattern, including LS. This point mutation leads to an aminoacid change from leucine to arginine in ATPase subunit 6, thus causing failure in ATP synthesis (10). Four mt DNA point mutations have been described in LS, at nt 8993 T to G, nt 8993 T to C, nt 8344 A to G and nt 3243 A to G (6). Mutations of SURF-1 a gene located on chromosome 9q34 have been identified in patients with LS, associated with deficiency of cytochrome C oxidase(COX). Mutations of SURF-1 were detected in 75% of the COX defective cases in one study (11).

Santorelli et al performed a moleculer study of 50 patients with proven LS. They found that 12 patients belonging to 10 unrelated pedigrees carried the T>G mutation at nt 8993 of mt DNA (6). Rahman et al investigated the etiology of LS in 67 Australian cases, 35 with a firm diagnosis and 32 with some atypical features (12). Biochemical DNA defects were determined in 80% of tightly defined group and 41% of the Leigh-like group. Eleven patients had mitochondrial DNA point mutations nt 8993 T to G, nt 8993 T to C or nt 8344 A to G. 29 patients had enzyme defects, ie;13 respiratory chain complex I, 9 complex IV and 7 PDHC.

The relation between clinical severity and percentage of mutation is not clear in mitochondrial encephalomyopathies. Holt et al reported a good correlation between the percentage of mutant genomes and clinical fenotype (13). They determined 97% mutant genome in severe congenital encephalopathy, but 6-34% mutant genome in 5 relatives without symptoms. Tatuch et al reported over 95% mutant genome in different tissues in a child with LS, but 39% abnormal mt DNA in blood and 71% in fibroblasts of the non-symptomatic mother (14).

The most common mutation was determined in two of our cases. A new mutation was detected in the other two cases, but this new point mutation was accepted nonpathogen after the enzymatic studies of the mitochondrial complexes.

As a result; we must confirm our clinical, neuroradiological and pathological diagnosis with the support of moleculer genetic studies in fulminant progressive neurometabolic diseases.

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