# LEIGH SYNDROME: CLINICAL AND PARACLINICAL STUDY

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***Abstract-*** ***During two years study about Mitochondrial diseases (Sep 1999- Agu 2001), 15 cases of Leigh syndrome (LS) were diagnosed, that consisted of 11 boys and 4 girls aged between 6 to 156 (mean: 40.5) months. Most of the patients (46.7 %) became symptomatic between 1-5 years of age. Triggering factors were reported in 66.6 % of the patients and 40% of them became symptomatic after infections. The most frequent presenting symptoms of the patients were somnolence and lethargy (40 %), developmental regression (20%) and seizure (13.3%). The most common neurologic findings were developmental regression or arrest (93.3%), seizure (93.3%), abnormal tone (86.7%) and abnormal movements (53.3%). Blood lactate increased in 93.3% and blood ammonia elevated in 26.7% of the cases. Symmetric striatal necrosis (100%) and caudate nucleus involvement (73.3% ) were the most frequent neuro imaging findings of the patients.***
***Acta Medica Iranica, 40(4); 236-240: 2002***

***Key Words:*** ***Leigh syndrome, mitochondrial disease, seizure, dystonia, encephalopathy, lethargy, blood ammonia, blood lactate***

## INTRODUCTION

Leigh in 1951 at autopsy of a 7 months old boy who developed progressive somnolence, blindness, deafness and spasticity found focal symmetric necrotic lesions in scattered areas of the brain and spinal cord. (1,2) This clinicopathologic association was named subacute necrotizing encephalopathy (SNE) or Leigh Syndrome (LS). LS is a progressive neurodegenerative disorder with onset usually in infancy or early childhood and a characteristic neuropathology.

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This syndrome comprises a heterogenous group of mitochondrial diseases and clinical manifestations are extremely variable. LS is the most common mitochondrial syndrome (3). Clinicaly three different syndromes can be distinguished: 1) The neonatal form that presents with disorders of sucking, swallowing and respiration (ondine curse). 2) The classic infantile form that presents under two years of age, with psychomotor slowing, encephalopathy and seizure (3-5). A juvenile form of disease have been described with insidious onset of predominant extrapyramidal manifestations. Elevation of blood and cerebrospinal fluid (CSF) lactate and pyruvate are the main biochemical findings of LS. Symmetric hyper intense lesions of basal ganglia and brain stem on T2-weighted brain MRI, is highly suggestive of LS (4). Different enzyme deficiencies have been found, including pyruvate carboxylase (6), pyruvate dehydrogenase complex, biotinidase, complex I, II, IV and V of respiratory chain (7,8). Spontaneous, mendelian and maternal inheritance pattern have been reported (4,6). Whereas LS remains strictly a neuropathologic diagnosis, the characteristic clinical feature, typical radiologic findings and frequent findings of elevated blood or CSF lactate allows a diagnosis to be made antemortem in most patients (8,9).

## MATERIALS AND METHODS

Fifteen cases with highly suspected diagnosis of LS were evaluated between Sep 1999 to Aug 2001 at the pediatric neurology clinic of Mofid Children's hospital. These patients were selected out of 62 cases of mitochondrial disorders. Paraclinical investigations consisted of blood lactate and ammonia, blood gas, blood and urine amino acid chromatography, urine sugar chromatography and cranial neuroimaging. Some investigations were impossible to accompish in all patients such as CPK and CSF protein measurement and muscle biopsy for Ragged Red-Fiber (RRF) detection. The diagnosis of LS was based on acceptable clinical presentations with raised blood lactate level and presence of pathognomonic

symmetric bilateral basal ganglia necrosis in neuroimaging (10). LS diagnosis was ruled out when other metabolic disorders such as organic acidemia were documented. Data analysis were done with SPSS (version10).

## RESULTS

The patients consisted of 15 children, 11 boys (73.7 %) and 4 girls (26.7 %), aged between 6 to 156 months. Mean age was 40.5 months. Table 1 shows the onset age of clinical manifestations. 11 cases (73.3%) had first cousin parents. Family history of all patients was unremarkable. Triggering factors reported in 10 patients (66.6%) included infections (6 cases), circumcission (2 cases), trauma (1 case) and vaccination (1 case). The most frequent presenting symptoms of patients were somnolence and lethargy ( 6 cases ), developmental regression (3 cases) and seizure ( 2 cases). Table 2 and 3 shows the clinical and paraclinical findings of the patients. Blood amino acid-chromatography and urine sugar chromatography were normal in all patients. Urine amino acid-chromatography documented mild aminoaciduria in only one case and the others were normal. CPK measurement became possible in 6 patients that was elevated in 2 of them. CSF protein was normal in all of the 9 patients, that underwent lumbar puncture. Muscle biopsy was done in 3 cases and RRF was not reported. Brain CT Scan in 2 cases and brain MRI in 13 cases were the neuroimaging studies of our patients. One of the patients underwent MR Spectroscopy in Russia. Genetic study became possible in only one patient which was negative for point mutation of 8993.

**Table 1.** Age of clinical presentations in 15 cases of Leigh syndrome

| Age | Frequency | Percent |
|---|---|---|
| 0-6 months | 4 | 26.7 |
| 7-12 months | 2 | 13.3 |
| 1-5 years | 7 | 46.7 |
| 5-10 years | 1 | 6.7 |
| > 10 years | 1 | 6.7 |

No significant correlations were found between age of clinical presentations and triggering factor (p= 0.797), presence of abnormal movements (p= 0.813), impairment of consciousness (p= 0.292) and visual impairment (p=0.147).

**Table 2.** Clinical findings of 15 cases of Leigh syndrome

| Findings | Frequency | Percent |
|---|---|---|
| Developmental regression | 14 | 93.3 |
| Seizure | 14 | 93.3 |
| Abnormal tone | 13 | 86.7 |
| Abnormal movements | 8 | 53.3 |
| Impairment of consciousness | 8 | 53.3 |
| FTT | 8 | 53.3 |
| Visual problem | 7 | 46.6 |
| Microcephaly | 5 | 33.3 |
| Hearing loss | 2 | 13.3 |
| Myopathy | 2 | 13.3 |
| Respiratory disturbances | 2 | 13.3 |

**Table 3.** Paraclinical findings in 15 cases of Leigh syndrome

| Findings | Frequency | Percent |
|---|---|---|
| Blood lactate elevation | 14 | 93.3 |
| Blood ammonia elevation | 4 | 26.7 |
| Acidosis | 1 | 6.7 |
| Symmetric striatal necrosis | 15 | 100 |
| Caudate nucleus involvement | 11 | 73.3 |
| Brain atrophy | 6 | 40 |
| White matter involvement | 3 | 20 |
| Structural brain anomaly | 2 | 13.3 |
| Brain stem involvement | 2 | 13.3 |

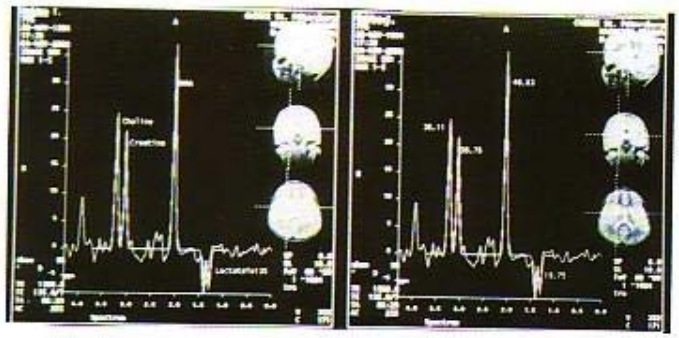

**Fig. 1.** MR spectroscopy of the basal ganglia shows abnormal peak of lactate (serum lactate of this patient was normal)

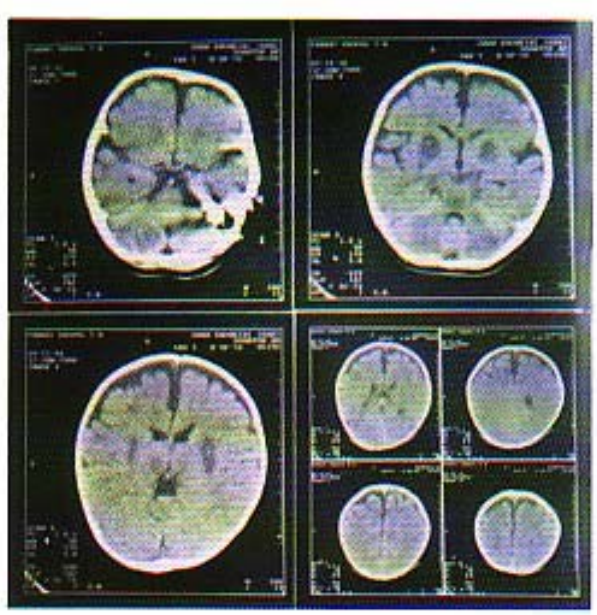

**Fig. 2.** Axial CT scan shows brain atrophy and bilateral symmetric hypodensity of the basal ganglia

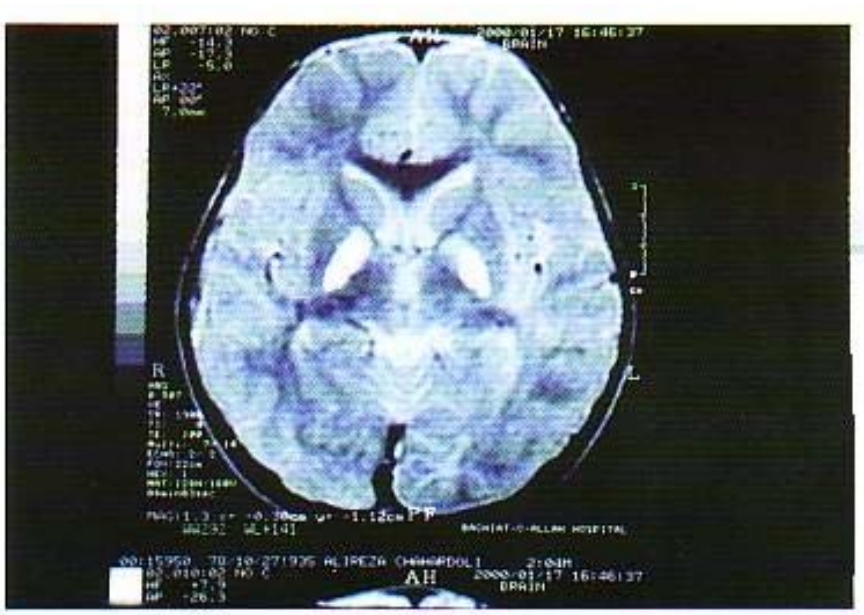

**Fig. 3.** T2 weighted brain MRI shows bilateral high signal intensity in the striatum

# DISCUSSION

We report 15 cases of LS that is remarkable. In a similar study during a two year period NissenKorn reported 5 cases of LS (6). LS affects males and females in a ratio of 3 to 2 (2). Male to female ratio in this study was 3 to 1. Forty percent of our cases became symptomatic after infections. Abrupt worsening of the patient's clinical status with infections is a common feature in LS (8). Although seizure has been reported in a few patients (10, 11, 12), we found it in 93.5% of cases. Generalized tonic or tonic-clonic seizure (46.7%) and infantile spasm (20 %) were the most common seizure types in our patients. Seventy five percent of the patients in Pincus study (11) had respiratory disturbances, where as we found it in 13.5% of our patients. Respiratory disturbances that we observed during the patient's admission were apnea and irregular respiration. Respiratory disturbances are due to brain stem involvement that may be a late problem.

Dystonia was the most common abnormal movement of our patients (40 %). Dystonia may be a predominant symptom in the juvenile form of LS (4,5). Minimum age of our patients with dystonia was 16 months. Blood lactate raised in 14 patients (93.5%). Only 1 patient had normal blood lactate but the specimen was taken when he was under treatment. Magnetic Resonance Spectroscopy (MRS) of this case showed abnormal lactate elevation in the basal ganglia (Fig. 1). It must be mentioned that normal blood lactate does not rule out the diagnosis of LS (13). Blood ammonia raised in 4 patients (26.7%). Increased blood ammonia in mitochondrial disease including LS has been reported (4,5). We found no RRF in 3 cases who underwent muscle biopsy. In a study of 18 cases of LS with respiratory chain defect, only 2 cases had RRF. (8) Absence of RRF does not exclude LS (4). CPK and CSF examinations are not diagnostic for LS, so missing data of them were not important. Cranial neuro imaging is a valuable diagnostic investigation. Symmetric bilateral basal ganglia lucencies are pathognomonic of LS, and in addition to blood lactate elevation is strongly suggestive of LS (4,14). Other neuroimaging findings of LS are involvement of cortical gray matter, cerebral white matter, dorsal pons and thalamus (15,16). Symmetric basal ganglia (striatum) lucencies were found in 100% of our patients (Fig 2,3). Table 3 shows the other neuro imaging findings of the patients. Brain anomaly was found in 2 patients that consisted of corpus callosum dysgenesis and cavum septum pallucidum. Brain anomaly was reported in LS especially due to pyruvate dehydrogenase deficiency (4,8). Clinical and neuroimaging findings of LS is similar with two newly presented entities that included putaminal necrosis (17) and acute necrotizing encephalopathy (ANE) of childhood (18). Blood lactate is normal in these two entities. In conclusion LS must be considered, in any child with encephalopathy (somnolence and lethargy), abnormal tone, abnormal movements and developmental regression. Blood lactate elevation accompanied with symmetric basal ganglia necrosis support the diagnosis of LS. Although the overal outlook of LS is poor and death is the final outcome, early diagnosis is important. Palliative therapy with coenzymes and detoxificants can prolong the life expectancy of the patients.

**Acknowledgements**

We would like to thank Dr Mohammad Yaghobi for the statistical analysis of the data, Mrs. Rasmi for her help in articles gathering and Mr. Ebadi for his photographical assistance.

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