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Case report

# Leigh syndrome and partial deficit of cytochrome c oxidase associated with epilepsia partialis continua

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Epilepsia partialis continua (EPC) has previously been reported in only two patients with Leigh syndrome (LS). We report here a subject in whom LS and partial deficit of cytochrome c oxidase (COX) were associated with EPC. Epilepsy in this subject appeared when neurologic impairment was clearly evident and MRI showed cortical lesions typically associated with congenital lactic acidosis.

Keywords: Leigh syndrome; COX partial deficit; Epilepsia partialis continua

## **1. INTRODUCTION**

Leigh syndrome (LS) or subacute necrotizing encephalopathy is characterized by specific neuropathological features and heterogeneous clinical, biochemical, and molecular abnormalities [1].

In the infantile form with onset during the first two years of life, patients present lactic acidosis, hypotonia and psychomotor regression, dysphagia, ataxia, dystonic movements, ophthalmoplegia, respiratory difficulties and, in a later stage, spasticity. The course of LS generally is progressive and fatal [1].

Defects of some mitochondrial enzymes, pyruvate dehydrogenase complex (PDHC), cytochrome c oxidase (COX or complex IV), NADH-Co Q reductase (complex I), and pyruvate carboxylase (PC), have been associated with LS [2]. In other cases, without PDHC, COX, complex I or PC defect, a T > Gpoint mutation at nt 8993 in the ATPase 6 gene of the mitochondrial DNA was demonstrated [3].

Seizures occur in some cases of LS and are mostly of partial or myoclonic type [3-12]. Colamaria et al. [13] reported two children affected by congenital lactic acidosis, myoclonic dystonia and epilepsia partialis continua (EPC).

In this paper, we report a new patient in whom LS and partial deficit of COX were associated with EPC.

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### 2. CASE REPORT

The patient is a 5-year-3-month-old male born at term from consanguineous parents, by cesarean section; birth weight was 3800 g (> 90th centile), no particular problems are reported to have occurred perinatally. Two brothers are normal and the family history does not show the presence of any neurological disease.

At 3 months of age, the infant started to smile and was able to follow objects with the eyes; at 4 months satisfactory head control was achieved.

At the age of 6 months the infant was hypotonic and showed difficulties in grasping objects with the right hand. Dystonic movements involving the right limbs were also evident. The neurologic examination showed marked axial hypotonia and hyperactive deep tendon reflexes. Lactic acid, in blood samples, was 36 mg/dl (normal values < 30 mg/dl), the ratio between lactic and pyruvic acids (L/P = 45) was increased. Cerebral CT scan showed a mild enlargement of Sylvian and subarachnoid sulci, prevalently in the frontal areas, and two clear-cut, symmetrical and markedly hypodense areas in the lenticular nuclei.

From the age of 6 months until now, a worsening of the neurological state has been observed and the child has progressively lost the ability to control his head, to maintain a sitting position, to crawl, and to roll. Dysphagia for solid food is present; verbal language is absent. The four limbs show spastic hypertonia, with hyperactive tendon reflexes, bilateral ankle clonus and positive Babinski sign.

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At the ophthalmological examination, strabismus and a normal fundus are evident.

At 1 year and 6 months of age a blood gas analysis was performed; this showed a metabolic acidosis (pH 7.22; bicarbonate 8 mmol/l; base excess -13; pCO<sub>2</sub> 30).

At the age of 3 years and 4 months, the child started to present myoclonic jerks, almost continuous, of the chin; subsequently, they involved the right and the left limbs, respectively. Ictal episodes started a few weeks after the myoclonic jerks and were characterized by loss of consciousness, deviation of the head and the eyes towards the right, limb hypertonia and asymmetric postural flexion of the upper limbs. The polygraphic recording of seizures showed only a flattening of traces. The frequency of these seizures (several per day) and the severity of myoclonic jerks were not modified by antiepileptic drug therapy with valproic acid, vigabatrin, carbamazepine, phenobarbital, and lamotrigine which were taken in various combinations.

The different EEGs recorded before the onset of myoclonic jerks and seizures did not show paroxysmal abnormalities. Poly-graphic recording performed at the age of 4 years and 7 months, however, showed the presence during wakefulness of almost continuous myoclonic jerks involving frontal and temporal leads, together with the EMG traces from the right buccinator muscle and from the extensor muscles of both forearms. The background

activity was slow; however, there was no interictal paroxysmal activity probably because of the myoclonic muscle artifacts (Fig. 1). During drowsiness, a marked decrease in myoclonic potentials and the occurrence of paroxysmal discharges, consisting of quasi-rhythmic rapid spikes and polyspikes at a frequency of approximately 1/s, in the left frontal-central areas, were observed. Each paroxysmal potential was correlated with a brief myoclonic contraction recorded by the EMG of extensor muscles of the right forearm (Fig. 2). The brainstem auditory evoked potentials showed a prolonged central conduction time.

High levels of blood lactic acid (2.81-5.07 mmol/l, normal values < 1.7 mmol/l) and of L/P ratio were repeatedly detected during different admissions to hospital. Also cerebrospinal fluid lactic acid was increased (4 mmol/l). Leukocyte biotinidase, serum and erythrocyte folate, and lymphocyte methylene tetrahydrofolate reductase were normal. The histology of the quadriceps muscle biopsy was normal.

Skin fibroblast mitochondrial enzymes showed a partial deficit in COX (6.77 nmol/min/mg protein, normal range  $17.87 \pm$ 3.99). No NARP (neurogenic weakness, ataxia, retinitis pigmentosa) mutation was found by Southern blot DNA analysis.

The first cerebral MRI study, at the age of 10 months, showed alterations of the lenticular nuclei and of the cerebral peduncles (Fig. 3). The second MRI, at the age of 3 years and 4 months,

#### WAKEFULNESS



Fig. 1. EEG recording during wakefulness, a few days after the onset of myoclonic jerks, showing slow background activity and continuous myoclonic potentials (R BUCC = right buccinator muscle, R EXT = right forearm extensor muscles, L EXT = left forearm extensor muscles).

showed an enlargement of the lesions found previously extending to the frontal and parietal regions of both hemispheres, and to the paramedian parietal and mesencephalic posterior regions (Fig. 4).

# 3. DISCUSSION

The clinical characteristics of our patient and hyperintense lesions of T2-weighted MR images involving the lenticular nuclei and the brainstem are typical features of LS. Cortical lesions with different extension and localization have occasionally been reported in LS, both at neuroimaging and at autopsy studies: diffuse [5,9,14], or focal with different areas involved [3,4,10,13,15].

Thus, it seems that Leigh's original concept of the necrotizing encephalomyelopathy [16] has expanded to increased cerebral involvement in the mitochondrial encephalopathies.

A picture of continuous jerks initially localized in a limited area of the body (the chin, in our patient) becoming diffuse in subsequent evolution, associated with motor or complex partial seizures, is typical of EPC [17].

The progressive clinical evolution, the onset of myoclonic jerks in early life, the short delay between onset of myoclonias and that of seizures, and some EEG features, such as the presence of paroxysmal activity not correlated with clinical manifestations, make the epileptological picture of our patient very similar to that of EPC type II [17].

Two other patients with congenital lactic acidosis and clinical features similar to those of our patient have already been reported [13]; however, in both of them it was not possible to define the molecular abnormality. On the other hand, among the patients with LS and seizures reported so far [3-12], only two presented a COX deficit [8,10]. In one of them, poorly controlled staring spells and bilateral temporal epileptiform EEG activity were reported; in the second [10], focal seizures with left hemisphere slowing and admixed temporal-occipital spikes were found. Other progressive metabolic diseases have been reported in association with EPC: MELAS syndrome [18,19], megaloblastic anemiamethylmalonic aciduria-homocystinuria [20], and Alpers disease [21]. However, EPC was noticed in our patient, and in those described by Colamaria et al. [13], only when other signs of neurologic impairment were already clearly evident, while in Alpers disease, for example, EPC is frequently an early symptom [22].

The great etiological variability of EPC and LS does not allow a satisfactory unitary pathogenetic explanation; however, the presence of cortical lesions in addition to the subcortical abnormalities might suggest that they exert a synergic action in generating EPC [23,24]. Coexistence of subcortical lesions might cause an anatomical or functional deafferentation of the overlying cortex enhancing its excitability [25].





Fig. 2. EEG recording during drowsiness showing the occurrence of sequences of quasi-rhythmic rapid spikes and polyspikes, at approximately 1/s, on the left frontal-central regions, two of which are magnified. Each paroxysmal potential is accompanied by a brief myoclonic jerk of the right forearm extensor muscles (R EXT), (abbreviations as in Fig. 1).

Finally, our report adds LS to the list of metabolic changes associated with EPC. It seems interesting to emphasize the evident time connection between the onset of the typical symptomatology of EPC and the appearance of cortical lesions at MRI. Probably, a more systematic EEG and neuroimaging monitoring of patients with LS will make it possible to verify if EPC is frequently associated with it.

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## REFERENCES

- Aicardi J. Diseases of the nervous system in childhood. Oxford: MacKeith Press, 1992: 457-60.
- Robinson BH. Lactic acidemia: In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of metabolic diseases*. New York: MacGraw Hill, 1989: 869–88.
- Santorelli FM, Shanske S, Macaya A, DeVivo DC, Di Mauro S. The mutation at nt 8993 of mitochondrial DNA is a common cause of Leigh's syndrome. *Ann Neurol* 1993; 34: 827–34.
- Montpetit VJA, Andermann F, Carpenter S, Fawcett JS, Zborowska-Sluis D, Giberson HR. Subacute necrotizing encephalomyelopathy. A review and study of two families. *Brain* 1971; 94: 1–30.
- Egger J, Pincott JR, Wilson J, Erdohazi M. Cortical subacute necrotizing encephalomyelopathy. A study of two patients with mitochondrial dysfunction. *Neuropediatrics* 1984; 15: 150–8.
- Robinson BH, De Meirleir L, Glerum M, Sherwood G, Becker L. Clinical presentation of mitochondrial respiratory chain defects in NADH-coenzyme Q reductase and cytochrome oxidase: clues to pathogenesis of Leigh disease. *J Pediatr* 1987; 110: 216–22.
- Fujii T, Ito M, Okuno T, Mutoh K, Nishikomori R, Mikawa H. Complex I (reduced nicotinamide-adenine dinucleotide-coenzyme Q reductase) deficiency in two patients with probable Leigh syndrome. *J Pediatr* 1990; 116: 84–7.
- Van Coster R, Lombes A, DeVivo DC, et al. Cytochrome c oxidaseassociated Leigh syndrome: phenotypic features and pathogenetic speculations. J Neurol Sci 1991; 104: 97–111.
- Westarp ME, Holzgraefe M, Gallenkamp Thomas R, Bechinger D. Diagnosis and treatment in a case of juvenile subacute necrotizing encephalopathy Leigh without cytochrome c oxidase deficiency. *Eur Neurol* 1992; 32: 206–11.
- Keppler K, Cunniff C. Variable presentation of cytochrome c oxidase deficiency. Am J Dis Child 1992; 146: 1349–52.
- Ciafaloni E, Santorelli FM, Shanske S, et al. Maternally inherited Leigh syndrome. J Pediatr 1993; 122: 419–22.
- Yoshinaga H, Ogino T, Ohtahara S, Sakuta R, Nonaka I, Horai S. A T-to-G mutation at nucleotide pair 8993 in mitochondrial DNA in a patient with Leigh's syndrome. J Child Neurol 1993; 8: 129–33.
- Colamaria V, Franco A, Perez Jimenez A, et al. Epilessia parziale continua, acidosi lattica congenita e trattamento con dicloroacetato. *Boll Lega Ital Epil* 1993; 84: 113–5.
- Koch TK, Melvin HC, Hutchinson HT, Berg BO. Magnetic resonance imaging in subacute necrotizing encephalomyelopathy (Leigh's disease). Ann Neurol 1986; 19: 605–7.
- 15. Medina L, Chi TL, DeVivo DC, Hilal SK. MR findings in patients with subacute necrotizing encephalomyelopathy (Leigh syndrome): correlation with biochemical defect. *AJR* 1990; **11**: 379–84.

Fig. 3. T2-weighted cerebral MRI scans at the age of 10 months. A: Symmetrical hyperintense signal areas involving both lenticular nuclei, and putamen in particular, are present. B: Hyperintense signal is also found in the cerebral peduncles. C: No gross signal abnormalities are evident at the cortical level.









- Leigh D. Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatry 1951; 14: 216–21.
- Bancaud J. Kojewnikow's syndrome (epilepsia partialis continua) in children. In: Roger J, Bureau M, Dravet Ch., Dreifuss FE, Perret A, Wolf P, eds. *Epileptic syndromes in infancy, childhood, and adolescence.* 2nd edn. London: John Libbey & Co., 1992: 363-79.
- Chevrie J-J, Aicardi J, Goutières F. Epilepsy in childhood mitochondrial encephalomyopathies. In: Wolf P, Dam M, Janz D, Dreifuss FE, eds. Advances in epileptology. Vol 16. New York: Raven Press, 1987: 181-4.
- Miyazaki M, Saijo T, Mori K, et al. A case with MELAS associated with epilepsia partialis continua (in Japanese). No To Hattatsu (Tokyo) 1991; 23: 65-70.
- Colamaria V, Rubino T, Burlina AB, et al. Epilessia parziale continua e tremore similparkinsoniano in pazienti con anemia megaloblastica, omocistinuria, aciduria metilmalonica ad esordio tardo infantile. *Boll Lega Ital Epil* 1989; 66/67: 233-5.
- Holliday PL, Climie AR, Gilroy J, Mahmud MZ. Mitochondrial myopathy and encephalopathy: three cases-A deficiency of NADH-CoQ dehydrogenase? *Neurology* 1983; 33: 1619–22.
- Harding BN. Progressive neuronal degeneration of childhood with liver disease (Alpers-Huttenlocher syndrome): a personal review. J Child Neurol 1990; 5: 273–87.
- 23. Hajek M, Antonini A, Leenders KL, Wieser HG. Epilepsia partialis continua studied by PET. *Epilepsy Res* 1991; 9: 44-8.
- Colamaria V, Plouin P, Dulac O, Cesaro G, Dalla Bernardina B. Kojewnikow's epilepsia partialis continua: two cases associated with striatal necrosis. *Neurophysiol Clin* 1988; 18: 525–30.
- Schomer DL. Focal status epilepticus and epilepsia partialis continua in adults and children. *Epilepsia* 1993; 34 (Suppl. 1): S29–S36.

Fig. 4. T2-weighted cerebral MRI scans at the age of 3 years and 4 months. A: Symmetrical hyperintense signal is found, again, at the level of basal ganglia. B: Hyperintense signal at the level of the posterior areas of mesencephalon. C: The cortex shows numerous symmetrical areas of hyperintense signal involving the frontal and parietal lobes.