Adult form of Leigh's disease: a clinico pathological case with CT scan examination

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SUMMARY The clinical and pathological findings of a 31-year-old woman, in whom the diagnosis of Leigh's disease was made, are reported. CT scan examination with contrast enhancement showed symmetrical areas of low density, in both thalami, anterior limbs of internal capsules and corpus callosum. Longstanding chronic lesions involved the optic chiasma and the cerebral peduncles and consisted of myelin loss, status spongiosus, astrocytic gliosis and marked capillary proliferation. The neurons were spared. In the basal ganglia, internal capsules and corpus callosum, these lesions were more recent and consisted of focal necrosis, perivascular oedema and few lymphocytic perivascular cuffings.

Subacute necrotising encephalomyelopathy (Leigh's disease) rarely occurs in adults: to our knowledge only 16 pathologically studied cases have been reported and only one of these had computed tomography. This paper reports the clinical and pathological findings of an adult case in which the diagnosis of Leigh's disease was made.

Case report

A 31-year-old Chilean woman was admitted to hospital because of visual impairment and increasing stupor. The family history was difficult to obtain because the patient lived alone, did not speak French well and was stuporous. She only could say that her mother was epileptic. The patient was not alcoholic. At the age of 21 years, she had suffered from an episode of confusion which lasted one week and resolved spontaneously. Two months before death, she developed intellectual slowing, behavioural abnormalities and impairment of recent memory. One month later, she experienced transient fever, headache and nausea and over the following weeks, her mental state worsened; she had visual hallucinations, became stuporous and was admitted to the hospital. The patient could answer when questioned; she frequently yawned and made chewing movements. Neurological examination revealed ptosis of the left upper lid, bilateral paresis of the 6th nerve, a right facial palsy and a right extensor plantar response. The general examination was unremarkable. The patient seemed well nourished and showed no signs of chronic alcoholism. BP was 120/80 mmHg. CSF was normal on two occasions; two days before death, it contained 68 mg/100 ml protein, 18% γ globulin. EEG showed non specific generalised slow waves. The CT scan revealed bilateral, ill defined areas of low density in both thalami and anterior limbs of internal capsules (fig 1a, b). Parts of these lesions showed diffuse enhancement after contrast injection. Such a contrast enhancement was also seen in the splenium of the corpus callosum (fig 1c, d).

The following investigations gave normal results: blood cell count, FSR, urea nitrogen, serum glucose, Na, K, P, Ca, ceruloplasmin, antinuclear antibodies, viral antibodies, parasite antibodies. From the first day of hospitalisation, intravenous 5% then 10%, glucose infusion was administered with a vitamin supplement containing 50 mg/day of thiamine. Four days before death, she received an additional intravenous injection of 1 g/day thiamine hydrochloride. She deteriorated rapidly becoming increasingly drowsy. Chewing movements became more marked. Neurological examination revealed bilateral pinpoint non-reactive pupils, complex and variable disorders of eyes movements, bilateral facial palsy, generalised rigidity, brisk deep tendon reflexes and bilateral extensor plantar responses. One day before death, her temperature rose to 42°C without evidence of infection and she became deeply comatose. In spite of attempt to resuscitate her, she died of acute respiratory failure 10 days after admission. Post-mortem examination, 27 hours after death, revealed mild bronchopneumonia. The liver was normal.

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Neuropathological examination was performed after 20 days of 10% formalin fixation. Blocks from many regions of both cerebral hemispheres, cerebellum, brainstem and spinal cord were embedded in paraplast or in celloidin and stained with haematoxylin and eosin, Loyez stain for myelin, Bodian silver impregnation for axons combined with Luxol fast blue and by the Gordon and Sweet method for reticulin. The brain weighed 1300 g. Gross examination showed bilateral pale granular fresh necrotic lesions involving symmetrically the heads of the caudate nuclei, the internal capsules, the walls of the third ventricle and the thalami. Older greyish lesions were observed in the posterior parts of the cerebral peduncles. The optic chiasma looked atrophic and greyish. The mammillary bodies were normal macroscopically.

Lesions clearly seen in sections stained for myelin, looked ill defined; they did not correspond to a vascular territory and involved the upper part of the optic chiasma, the head of both caudate nuclei, the septum pellucidum, the anterior limbs of both internal capsules, the anterior parts of both thalami (fig 2a), the splenium of the corpus callosum, the superior and inferior colliculi and the peri-aqueductal region (fig 2b). A small focus of myelin loss was observed in the inferior part of the corpus callosum in its middle third. The cerebral cortex, centrum semi-ovale, the mammillary bodies, the anterior parts of the cerebral peduncles, pons, medulla, cerebellum and spinal cord were unaffected.

Microscopical examination showed two types of lesion. The first consisted of longstanding chronic changes involving

**Fig 1**  CT scan examination. (a, b) plain scan: ill defined low dense areas in both thalami and anterior limbs of internal capsules. (c, d) same levels after contrast injection: enhancement in both thalami and in the splenium of the corpus callosum.
the optic chiasm and the cerebral peduncles. They consisted of ill-defined areas of myelin loss, status spongiosus, astrocytic gliosis and marked capillary proliferation with endothelial hyperplasia. The neurons when present, for example in the third nerve nuclei and in the periaqueductal grey matter, (fig 3a) were generally preserved but many showed the changes of central chromatolysis. Axons were relatively spared. The other type of lesion was more recent and involved the basal ganglia, internal capsules, walls of the third ventricle and the corpus callosum. These lesions consisted of focal necrosis associated with perivascular oedema; many lipid phagocytes were present and few vessels were cuff by lymphocytes. However, the neurons were relatively spared. Capillary proliferation was marked. No haemorrhages were seen (fig 3b).

Discussion

Since the initial description by Leigh, more than a hundred cases of subacute necrotising encephalomyelopathy have been reported (for review, see David et al). Since the clinical picture and biochemical findings may vary, the diagnosis is based on the neuropathology. Biochemical studies have shown an abnormality of the metabolism of thiamine, though this is not linked to a single inherited molecular deficit. Four different metabolic disturbances have been proposed as the cause of this disease: (1) pyruvate carboxylase deficiency, (2) the presence of a factor which inhibits thiamine

Fig 2  (a) Coronal section of the basal ganglia through the mammillary bodies. Loyez stain × 1: Necrotic, ill defined area involving both thalamus and internals capsules. Myelin loss is also present in the fornix and the inferior aspect of the corpus callosum. The mammillary bodies are spared. (b) Horizontal section of the cerebral peduncles. Loyez stain × 1: myelin loss in the inferior colliculi and periaqueductal grey matter.

Fig 3  (a) Tegmentum of the cerebral peduncle at the level of the third cranial nerve, nucleus. Haematoxylin and eosin × 16: spongiosis, gliosis and vascular proliferation. The neurons are spared or demonstrate central chromatolysis. (b) Thalamus haematoxylin and eosin × 16: necrosis with numerous lipid phagocytes, capillary proliferation with perivascular lymphocytes. Absence of haemorrhages.
pyrophosphate ATP phosphotransferase, (3) pyruvate decarboxylase deficiency and (4) cytochrome oxidase deficiency (see Ohtake et al\textsuperscript{12}).

The lesions observed in the brain of this 31-year-old woman are very similar to those described in Leigh's infantile subacute necrotising encephalomyelopathy\textsuperscript{13} (bilateral and symmetrical necrotising or demyelinating alterations with microvascular and glial proliferation and relative preservation of the neurons, involving the optic nerves, basal ganglia and brainstem. The histopathological appearance of these alterations also resemble that of Wernicke's encephalopathy. This had led Feigin and Wolf\textsuperscript{14} first to suggest that the lesions of subacute necrotising encephalomyelopathy were related to a defect in thiamine utilisation. However, in Leigh's disease, the mammillary bodies are spared while their involvement is almost constant in Wernicke's encephalopathy. In addition, basal ganglia, optic nerves, pons, medulla and spinal cord are frequently affected in subacute necrotising encephalomyelopathy but rarely in Wernicke's encephalopathy. In contrast, thalamic lesions are more common in Wernicke's encephalopathy.\textsuperscript{15} Microscopically, haemorrhages, which are a characteristic feature of Wernicke's encephalopathy are absent in Leigh's disease. In the present case, Wernicke's encephalopathy can be reasonably excluded since there was no history of alcoholism or malnutrition and the mammillary bodies were normal.

Subacute necrotising encephalomyelopathy mainly occurs in infants and children. Some juvenile forms have been reported.\textsuperscript{2} Adult cases have been seldom described.\textsuperscript{1,7-9} Some of them have been questioned\textsuperscript{6,7} because of a history of chronic alcoholism or nutritional deficiency in some case or because of an involvement of the mammillary bodies.

Among the cases in which subacute necrotising encephalomyelopathy was a reasonably certain diagnosis who survived to adulthood, five demonstrated initial neurological symptoms in childhood which antedated the terminal illness by 15 to 33 years. These should be considered as juvenile forms. Only four cases, like ours, had an adult onset. When questioning the inherited character of the disease in the 10 cases of subacute necrotising encephalomyelopathy with an age at death over 20 years, it appears that three belong to the same family eight: in one case, increased levels of inhibitor factor were found in other members of the family;\textsuperscript{7} in two cases, the patients mothers were epileptic (ref 2, present case). The family history was clearly negative in three cases\textsuperscript{4,6,9} and in one case,\textsuperscript{4} family history was not available. This familial occurrence is roughly similar to that found in 50% of the infantile cases.\textsuperscript{16} Thus, the lack of familial history does not seem to be a criterion for separating the adult form of subacute necrotising encephalomyelopathy ("Leigh's syndrome") from the infantile form ("Leigh's disease") as proposed by Siipe.\textsuperscript{4}

Since so few cases have been reported, the clinical picture of adult subacute necrotising encephalomyelopathy is not yet well established. It seems therefore difficult to make the diagnosis of Leigh's disease in adults on clinical grounds only. Some symptoms however are more frequently observed: visual impairment which may be the only sign for several years, psychiatric symptoms, autonomic and sleep disturbances and epileptic seizures. The course of the illness is often characterised by an insidious onset followed by a quiescent period and a subacute or acute termination; a remitting or relapsing course mimicking multiple sclerosis is not rare.\textsuperscript{6,8}

A femoral arteriogram performed in one case\textsuperscript{7} showed hyperaemia of the pons and medulla without mass effect.

CT scan in infantile subacute necrotising encephalomyelopathy\textsuperscript{17-20} has shown bilateral hypodense areas in the middle of the putamen. In one adult case\textsuperscript{7} computed tomograms were interpreted as showing oedema of the midbrain. In our case, bilateral and symmetrical hypodensities with contrast enhancement were seen in both thalami, adjacent internal capsules and corpus callosum. Such a contrast enhancement has never been previously reported in Leigh's disease. It probably corresponds to the alteration of the blood-brain barrier and/or to the capillary proliferation which was also found microscopically in the thalamus.

In contrast to what is observed in Wernicke's encephalopathy, thalamic lesions are said to be rare in Leigh's disease. Nevertheless, they were observed in six out of 10 cases of adult subacute necrotising encephalomyelopathy,\textsuperscript{2,3,6,7} and in the present case the thalamus was severely involved. In addition, the thalamic lesions were somewhat different from those observed in the optic pathways and midbrain. They looked more acute and showed marked necrosis, oedema and lymphocytic perivascular cuffs.

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References

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