Short report

Necrotising haemorrhagic encephalomyelopathy in an adult: ? Leigh's disease

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Summary A 21 year old male, well-nourished and non-alcoholic, died after five weeks illness. He
had suffered epileptic fits, bilateral internuclear ophthalmoplegia, bulbar and pontine paralysis,
tetraparesia, ataxia and dystonia. A CT brain scan showed low density lesions of the striatum
bilaterally. Post-mortem studies revealed pathological anomalies compatible with Leigh's disease,
although the presence of haemorrhages and involvement of the mamillary bodies could also suggest
Wernicke's encephalopathy.

Leigh's disease is unusual in the adult. Eighteen cases
with pathological verification have been published.1-11 It is even questionable whether some of
the cases, such as patient 2 of Feigin and Goebel,1 patient 1 of Kalimo et al8 and all those of Feigin and
Budzilovich5 were really suffering from Leigh's dis-
ease. Among the cases with a reasonably certain diag-
nosis, the symptoms began in adult life in only five,2 3 6 10 11 so that the remaining cases may be juve-
nile forms with prolonged survival.10 We present the
clinical, radiological and pathological study of a patient
with Leigh's disease in whom the five weeks course of the disease took place in adult life.

Case report
The patient was a 21 year old male, neither alcoholic nor
undernourished, the third of the healthy children of non-
consanguineous parents. He was admitted to hospital
because of a progressive illness of three weeks duration,
consisting of epileptic fits, diplopia, dysarthria, dysphagia
and weakness of the left limbs. Neurological examination
revealed pale optic discs, bilateral internuclear ophthal-
moplegia, dysarthria, bilateral facial, lingual and palata-
pharyngeal paresis, and motor deficit (4/5) of all four limbs,
more pronounced on the left. Tendon jerks were brisk, the
cutaneous-abdominal reflexes were present and Babinski's sign
was elicited bilaterally. There was hypotonia, ataxia and
action dystonia of distal distribution in all four limbs.
Repeated blood tests for copper, ceruloplasmin, aminoacids,
ph, lactate and pyruvate levels were normal. An electro-
retinogram showed reduced amplitude and very prolonged
latencies. Cortical somatosensory evoked potentials and
motor and sensory nerve conduction velocities were normal.
A CT brain scan and a right carotid angiogram were normal.
The only abnormality found in the CSF was a protein content
of 7 g/l. Repeated subsequent CT scans revealed
bilateral low density of the caudate nucleus, putamen and
thalamus, with no enhancement (fig 1). The level of con-
sciousness gradually deteriorated until he was in coma,
showing a slight reaction to pain. The pupils were fixed and
medium in size. Oculocephalic, oculovestibular and corneal
reflexes were abolished. Tendon jerks, cutaneous-abdominal
and plantar reflexes also disappeared. Respiration became
irregular. The patient died of cardiorespiratory failure two
weeks after admission. He was treated with phenobarbitone
(150 mg/day) and i.v. thiamine (1200 mg/day).
The necropsy was carried out immediately after death. No
macroscopic or microscopic abnormalities were found out-
side the nervous system. The brain weighed 1530 g. Macro-
scopically, there was bilateral uncinate herniation, more pro-
nounced on the left side. The cortex presented diffuse
haemorrhages of patchy distribution. There were bilateral
necrotic cavities in the caudate nucleus and putamen (fig 2)
The thalamic nuclei were dark grey. Haemorrhages were
observed around the aqueduct of Sylvius, below the floor of
the fourth ventricle and in some cerebellar folia. Micro-
scopically, there were diffuse lesions in the cerebral cortex
with spongiosis, proliferation of fine-walled capillaries and
recent perivascular haemorrhages (fig 3a). The neurons were
mostly preserved; only a few were shrunken and pycnotic. In
the hippocampus, the cortex showed neuronal loss and glio-

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sis. In the putamen, globus pallidus, and caudate nucleus, necrotic areas were seen (fig 3b), with numerous macrophages, astrocytic gliosis, spongiosis and capillary proliferation. Outside the necrotic areas, the neurons were relatively preserved. Similar changes, without necrosis, were present in the thalamus, hypothalamic nuclei, periaqueductal gray matter (fig 3c), substantia nigra, dorsal nucleus of the vagus and hypoglossal nucleus. The mamillothalamic bodies showed severe spongiosis, vascular proliferation, shrunken neurons, some macrophages containing iron and preservation of the peripheral white matter (fig 3d). The cerebral white matter appeared moderately pale, with the nerve fibres undamaged. Haemorrhagic necrosis and vascular proliferation were present in some cerebellar folia. The cerebellar white matter and deep gray nuclei were normal. The spinal cord showed microhaemorrhages, vascular proliferation and spongiosis with preserved neurons, in the anterior and intermedio-lateral horns. The lateral and posterior columns were normal. Most of the optic nerve fibres were demyelinated. The sural nerve and the sympathetic ganglia were normal. In the skeletal muscle, there were signs of acute denervation of moderate intensity, with no mitochondrial abnormalities found in the electron microscope study.

Discussion

The clinical picture was that of a multifocal encephalomyelopathy. The findings on the CT scan made one suspect the presence of Leigh's disease because of the similarity to the abnormalities seen in infantile and juvenile forms of the disease. We excluded other entities in which low density of the striatum has also been reported, such as Wilson's disease, anoxic, ischaemic and toxic encephalopathies, hypo- glycaemia, wasp stings, and bilateral striatal necrosis of unknown cause in children. As far as we know, only three adult patients with pathologically proven Leigh's disease have been studied by means of CT brain scan. Whetsell and Plaitakis mention the existence of “edema of the mid-brain” in one of the three cases. In the case of Gray et al symmetrical areas of low density were observed in both thalami and anterior limbs of internal capsules; these and the splenium of the corpus callosum were enhanced after IV contrast. The case of Maso et al showed “enlargement of the fourth ventricle and atrophy of the cerebellum”. Bilateral thalamic low density has also been noted in infantile and juvenile forms of Leigh's disease, in viral encephalitis and exceptionally in Wernicke's encephalopathy.
Fig 3 (a) Cerebral cortex. Recent microhaemorrhages, spongiosis and moderate vascular proliferation can be seen. Haematoxylin & eosin; bar = 310 μm. (b) Necrotic cavity in the left putamen. Haematoxylin & eosin; bar = 1 cm. (c) Periaqueductal gray matter. Note necrosis, vascular proliferation and preserved neurons. Haematoxylin & eosin; bar = 1200 μm. (d) Mammillary body lesion showing spongiosis, haemorrhages and numerous preserved neurons. Haematoxylin & eosin; bar = 310 μm.

The distinction between the adult form of Leigh's disease and Wernicke's encephalopathy is based fundamentally on the topography of the lesions, which morphologically are very similar. Denis Leigh, in his initial description of the subacute necrotising encephalomyelopathy, considered the diagnostic possibility of a Wernicke's encephalopathy in an infant. In the present case, neuropathological findings are compatible with both diagnoses. The involvement of the optic nerves, gray matter of the spinal cord, substantia nigra, the necrotic cavitation of the striatum and the severe bulbar and pontine lesions, are more suggestive of Leigh's disease than of Wernicke's encephalopathy. The presence of haemorrhages and the lesion of the mammillary bodies are traditionally considered to be typical of Wernicke's encephalopathy. The presence of haemorrhages and the lesion of the mammillary bodies, the whole of neuropathological findings, in absence of alcoholism and malnutrition is more suggestive of Leigh's disease than of Wernicke's encephalopathy. Moreover, bilateral low density of the striatum has never been reported in Wernicke's encephalopathy. To our knowledge only two cases of Wernicke's encephalopathy have been reported with CT scan abnormalities other than alcoholic cerebral atrophy. In these two cases, low density, both periaqueductal and on either side of the third ventricle was observed, with normal density of the striatum.

The study of this case suggests that the topography of the lesions is not an absolute nosological criterion of differentiation between adult Leigh's disease and Wernicke's encephalopathy. The demonstration of disorders of pyruvate and thiamine metabolisms or of the respiratory chain may be necessary to elucidate the diagnostic dilemma.

We thank Dr José Obeso for helpful suggestions.
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doi: 10.1136/jnnp.50.2.224

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