Familial infantile spasms and hypsarrhythmia associated with leucodystrophy

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In an Italian family, two little girls were affected by a condition characterized by infantile spasms, hypsarrhythmia, and rapid motor deterioration, resulting in death in the second year of life. A pathological study of one of them has shown sudanophilic leucodystrophy. The occurrence of this form of epilepsy in siblings is extremely rare and its association with sudanophilic leucodystrophy has not been reported in the literature to date.

CASE REPORTS

The two sisters who form the subject of this study were born a year apart. An older brother has perfect health. No evidence was obtained of neurological or metabolic disease in any other member of the family.

The elder of the affected children was delivered spontaneously, the result of an uncomplicated full-term pregnancy. The neonatal period appeared normal, as was psychomotor development up to 9 months of age, when the baby was able to sit alone, and showed a normal interest in her surroundings.

Flexion spasms first appeared at 9 months in attacks lasting about 15 to 20 minutes, followed by crying. These fits were initially present only on waking. They were predominantly in flexion but occasionally also in extension. An E.E.G. during spontaneous sleep showed intense epileptic activity on all leads with spikes, polyspikes, and slow waves mixed in a disorderly way (Fig. 1a). On waking, paroxysmal bursts of slow and sharp activity were seen (Fig. 1b). The generalized bursts of dysrhythmia on waking were often simultaneous with the myoclonic jerks. The records were considered compatible with hypsarrhythmia.

At this stage the child was less responsive, moved less than before, and showed generalized hypotonus. The FeCl₃ urine test for phenylpyruvic acid was negative. In the following months myoclonic fits became more intense and more frequent and were observed at various times during the day. At the same time, the psychomotor deterioration was progressively more evident, to the point at which the child was almost entirely motionless and unresponsive.

The E.E.G. was repeated when the baby was 15 months old, with similar results. She died at 18 months of age in status epilepticus and hyperthermia. There was no post-mortem examination.

The second affected child was born two weeks post-mature. The neonatal period was apparently normal. During the first year of life, the parents noticed a delay in development and at 11 months she was unable to sit alone and responded very little to stimuli. At this age, flexion spasms appeared first, being more frequent on waking, and after two weeks from the beginning of these symptoms, she was seen in the Neurological Outpatient Department. There she showed very little spontaneous activity, responded but slightly to various stimuli, and appeared to be mentally handicapped. However, there were no specific signs of neurological deficit. The FeCl₃ urine test for phenylpyruvic acid was negative. An E.E.G. gave evidence of hypsarrhythmia (Fig. 2).

Treatment with phenobarbital was begun, but after a month there was no improvement in the clinical condition and in the subsequent E.E.G. Treatment with A.C.T.H. was started, but after the first 25 units had been given, a high fever suddenly developed, with status epilepticus, and the child died two days after admission to hospital at the age of 13 months.

PATHOLOGY

Post-mortem examination of the second affected child revealed a brain of normal size and weight (940 g.), the convolutions appearing to be normal also. On cutting, the brain appeared oedematous: there was a slight greyish discoloration of the white matter in the cerebral hemispheres, especially in the frontal and occipital poles.

No significant changes were found in the remainder of the post-mortem examination.

HISTOLOGY

FRONTAL POLE The white matter was pale in myelin preparations and with the Holzer stain there was fibrillar gliosis (Fig. 3). There was slight loss of nerve cells in the superficial cortical layers, with a little marginal gliosis beneath the pial surface in some places. In frozen sections many microglial cells were filled with sudanophilic droplets (Fig. 4) and some blood vessels were cuffed with
FIG. 1a. E.E.G. of case 1. Records in this and in Fig. 2 were taken with a time constant of 0.3 sec. at 3 cm./sec. with a gain of 7 μV/min.

FIG. 1b.

FIG. 2. E.E.G. of case 2.
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myelin preparations and there was well-marked fibrillar gliosis with some vacuolation. In Ammon's horn there was severe loss of cells in the Sommer sector and in the end-plate with ischaemic necrosis of the remaining neurones.

FRONTO-PARIETAL REGION The white matter was rather pale in myelin preparations and distinctly vacuolated (Fig. 6) with slight fibrillar gliosis; in frozen sections only a few microglial cells were filled with sudanophilic droplets, and some blood vessels were cuffed with phagocytes containing fat. There was no significant cell loss in the fronto-parietal cortex or in the insula.
OCCIPITAL LOBE  The external and internal sagittal layers were well myelinated but otherwise the white matter was very pale in myelin preparations, with many vacuoles and many fat-containing microglial cells. There was no significant cell loss in the cortex.

BASAL GANGLIA AND SUBTHALAMUS  No significant changes were present in the striatum and pallidum, except for some vacuoles, similar to those seen in the white matter, in the pallidum. The lateral nuclear masses of the thalamus and subthalamic body were finely vacuolated, with vacuoles much smaller than those seen in the white matter. This change was not visible in frozen sections and there was no definite nerve cell loss or gliosis. The corpus callosum, corona radiata, internal capsule, anterior commissure, and the fibre bundles in the putamen, pallidum, thalamus, and subthalamic region were well myelinated.

CEREBELLUM  A few Purkinje cells showed homogenizing changes. The granular layer was thin and the granules less densely packed than normal (Fig. 7a). No significant changes were present in the dentate nucleus or the white matter.

BRAIN-STEM AND SPINAL CORD  There were many fat-containing microglial cells in the pes pedunculi. The medullary pyramids and pyramidal tracts were poorly myelinated.


FIG. 7a. FIG. 7b.

FIG. 7. Severe atrophy of the granular layer in the cerebellar cortex (Fig. 7a). Cerebellar cortex in a child (1 year old) who died in status epilepticus (Fig. 7b). Nissl (paraffin).
spongy degeneration of the van Bogaert and Bertrand type, a condition often associated with progressive enlargement of the head and heavy brains (Banker, Robertson, and Victor, 1964; Hogan and Richardson, 1965). Similar features have also been noted in other conditions, notably maple syrup urine disease and homocystinuria (Crome, Dutton, and Ross, 1961; Silberman, Dancis, and Feigin, 1961; Chou and Waisman, 1965) and in cases of infantile spasm and hypsarrhythmia (Poser and Low, 1960). In the present cases large amounts of sudanophilic products, evidence of active demyelination, were present, a finding, which, together with a raised level of lipid and non-lipid hexosamines obtained by chemical studies, points in the direction of sudanophilic leucodystrophy.

Alzheimer's type II glial cells and spongy change prominent in the subcortex, which are essential features of van Bogaert and Bertrand disease, were not observed.

Infantile spasms have been observed in a familial case of infantile spongy degeneration (van Bogaert and Bertrand, 1949) as well as in maple syrup urine disease (Allen, 1964). This variety of epilepsy has long been regarded as a clinical syndrome and has been subdivided into two groups, symptomatic and cryptogenic. In the former, development is retarded before the onset of the spasms, and a pathological process might be recognizable; in the latter, development is apparently normal before the onset of spasms (Jeavons and Bower, 1964).

Recent neuropathological data (Bignami, Zappella, and Benedetti, 1964) have provided further evidence that this form of epilepsy can be present in a variety of infantile encephalopathies such as gross congenital malformations, tuberous sclerosis, metabolic diseases, sequelae of birth injuries, and infections of the central nervous system. In some of these cases, as well as in one of the sisters described here, development was apparently normal until the onset of the spasms.

**SUMMARY**

Two cases of infantile spasms and hypsarrhythmia occurring in siblings are reported. In one of them study of the brain revealed severe vacuolation and demyelination of the cerebral white matter, with large amounts of sudanophilic products and with raised levels of lipid hexosamines and non-lipid hexosamines. These changes were thought to be compatible with a pathological diagnosis of sudanophilic leucodystrophy.

We are grateful to Dr. R. M. Norman for his advice.
REFERENCES


Since this paper went to press the following paper has been brought to our notice:


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J Neurol Neurosurg Psychiatry 1966 29: 129-134
doi: 10.1136/jnnp.29.2.129

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