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Short reports

Alexander's disease: cranial ultrasound findings

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Abstract. This is thought to be the first report of the recognition by cranial ultrasound of the abnormal pattern of cerebral tissues which occurs in Alexander's disease. This finding suggests that cranial ultrasound could be a useful adjunct in the diagnosis of this cerebral leukodystrophy, particularly in those infants presenting with megalencephaly.

Alexander's disease is a progressive neurodegenerative disorder characterised by early onset of megalencephaly, psychomotor retardation, spasticity, and seizures. There is no definitive biochemical test for this condition, and diagnosis relies on brain biopsy findings [1].

Recent reports suggest that computed tomography (CT) findings of low attenuation in the deep cerebral white matter, [2] with contrast enhancing lesions in the periventricular frontal regions, caudate nuclei and thalami, [3] are specific for Alexander's disease.

We report a case of Alexander's disease in which the abnormal appearance of the cerebral tissues on cranial ultrasound led to the correct diagnosis being suggested.

Case report

AD was the third child born to non-consanguinous parents after a pregnancy complicated only by mild maternal anaemia. He was delivered by a lower segment Caesarean section at term, with a birth weight of 4.2 kg, and a head circumference of 37.5 cm which was on the 98th percentile.

At 8 months of age his head circumference was 0.2 cm greater than the 98th percentile, and delayed motor milestones were apparent. When he was first seen in the neurology department at 16 months his head circumference was 54 cm, which was 3.5 cm greater than the 98th percentile. On examination at that time he was unable to stand unsupported, with exaggerated tendon reflexes, bilateral upgoing plantar responses, and athetoid movements of the upper limbs.

Although there was no history of seizures, the EEG was abnormal, with frequent episodes of high voltage (1-2 Hz) delta activity over the central and anterior regions.

The urine screen for mucopolysaccharides, amino acids and organic acids was negative, while blood tests for GM_1 and GM_2 gangliosidoses, metachromatic leukodystrophy, Krabbe's disease and adrenoleukodystrophy were also negative.

A cranial ultrasound examination (US) had been performed at 9 months, and was repeated at 16 months of age. The initial US showed mild dilatation of the lateral ventricles, with an unusual form of rounding of their lateral angles. There was no dilatation of the subarachnoid space, and no specific abnormality of the cerebral tissues was commented on, although in retrospect the texture was abnormal and the definition of the sulci more hazy than usual (Fig. 1).

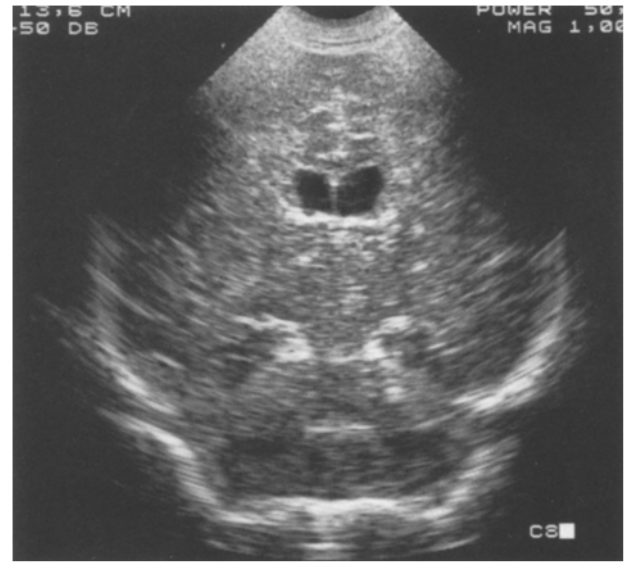

Fig. 1. Cerebral US at 9 months. Mild lateral ventricular dilatation with rounding of the lateral angles. Some loss of definition of sulci

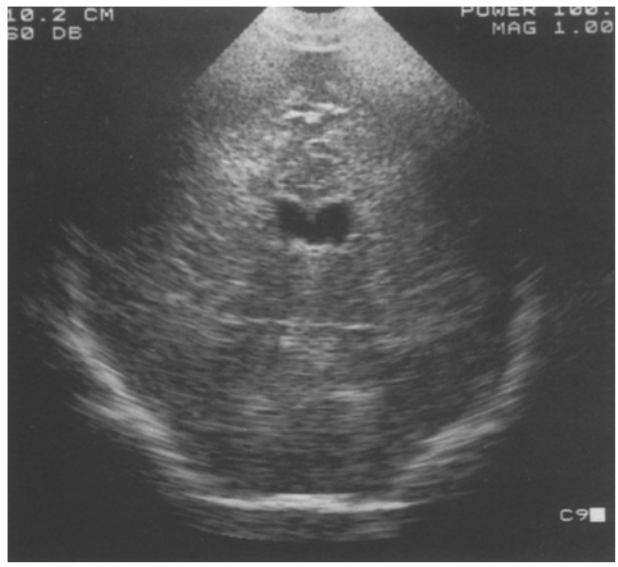

Fig. 2. Cerebral US at 16 months. Abnormal increase in brain size. Uniform appearance of cerebral tissues with loss of definition of sulci, interhemispheric fissure and anatomical landmarks

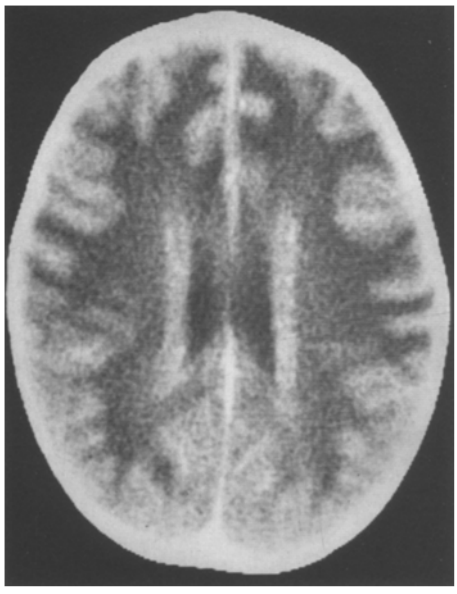

Fig. 3. CT examination at 17 months. Diffuse low density abnormality of the white matter with a rim of contrast enhancing tissue adjacent to the lateral ventricle

When the patient was re-examined at 16 months of age a skull X-ray showed mild splitting of the sutures. The US now showed obvious abnormality. There was no increase in ventricular size in spite of an abnormal increase in head circumference, suggesting that there had been abnormal increase in size of the brain. There had been a marked progression in the abnormality of the cerebral tissues during this period, indicating the progressive nature of the disorder. The sulci were now almost completely obliterated and even the interhemispheric fissure was difficult to define. The cerebral tissues appeared relatively homogeneous and of an abnormal texture, with a uniform ground-glass appearance of the white matter. The normal intra-cerebral landmarks were obliterated and there had been a decrease in acoustic attenuation of the cerebral tissues associated with these changes (Fig. 2).

A CT scan performed at 17 months of age showed a generalized diffuse low density abnormality of the white matter, with a perimeter of contrast enhancing tissue around both lateral ventricles (Fig. 3).

A brain biopsy from the right frontal lobe showed typical Rosenthal fibres, predominantly in a perivascular distribution, which is the pathologic hallmark of Alexander's disease.

Discussion

Although marked hydrocephalus has been reported in Alexander's disease [4], the major cause of the large head circumference is an increase in brain substance (megalencephaly) [1]. This can be readily confirmed by US. This case demonstrates that in addition, it is also possible to obtain information about the abnormal pattern of the brain substance. The dilated ventricles and clinical circumstances excluded cerebral oedema, and the appearances suggested a diffuse, progressive abnormality of the cerebral tissues associated with an increase in brain size. These findings in conjunction with a decrease in acoustic attenuation of the cerebral tissues suggested a diffuse infiltrating process such as a leucodystrophy, lipidosis or mucopolysaccharidosis. The low attenuation of the white matter on CT was consistent with a number of metabolic degenerative disorders including Tay-Sachs disease, GM_1 gangliosidosis, mucopolysaccharidosis or Canavan's disease, as well as Alexander's disease [5]. However only the latter two lack specific biochemical assays. Brain biopsies are still required to obtain a definitive diagnosis.

Infants with Alexander's disease may present in the first instance for cranial US because of increasing head circumference, and it is important to recognise this abnormal cerebral pattern. In the clinical context of an infant with a large head, developmental delay and no measurable biochemical abnormality, cranial US may have a useful role in suggesting the diagnosis and in identifying those infants who will ultimately require a brain biopsy.

The marked change in the ultrasonic appearance of the cerebral tissues in this case between 9 and 16 months of age occurred at the same time as an accelerated increase in head circumference from 0.2 cm above the 98th percentile, to 3.5 cm above the 98th percentile. It would appear from this case that the ultrasonic appearances are relatively nonspecific initially, but show a more abnormal pattern as brain size increases.

It also remains to be seen how the pattern of ultrasonic findings may change late in the disease, in view of the CT observations which suggest that low attenuation in leucodystrophies may be only a temporary phenomenon [3].

Further serial studies of the ultrasonic appearance in all megalencephalies of metabolic origin are needed.

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