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Cranial ultrasound findings in aspartoacylase deficiency (Canavan disease)

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Abstract. Canavan disease (CD) is a rare leukodystrophy which is lethal in infancy or early childhood. The underlying biochemical abnormality in CD is a hereditary deficiency of *N*-aspartoacylase transmitted in an autosomal recessive fashion. We report on the ultrasound (US), CT, and MRI findings of three unrelated boys with biochemically confirmed CD. At 6 and 9 months of age, two CD patients with rapid neurological deterioration showed markedly enhanced acoustic attenuation of the white matter with the exception of the corpus callosum, giving the appearance of a reversed pattern of echogenicity of cortical gray and subcortical white matter. While gyri and sulci had an almost normal US appearance, the periventricular gray matter featured prominently with increased echogenicity. In contrast another CD patient with a more protracted course had ventricular enlargement when examined by US at 5 and 9 months but no alteration in white matter echogenicity. MRI showed impaired myelinization in all three patients with Canavan disease.

Aspartoacylase deficiency – Canavan disease [1] or Van Bogaert-Bertrand disease [2] – is a rare lethal neurodegenerative disorder inherited in an autosomal recessive fashion. Its clinical course is characterized by progressive macrocephaly without internal hydrocephalus and unrelenting neurological deterioration. Symptoms, which start in early infancy in most cases (infantile CD), progress to blindness, spasticity, and ultimately decerebrate rigidity. Until 1989, confirmation of a diagnosis of Canavan disease (CD) suspected on clinical grounds required histopathological examination of brain tissue. This has been replaced by measurement of urinary excretion of *N*-acetyl aspartic acid (N-AA), which is increased in CD [3], and aspartoacylase activity assayed in cultured fibroblasts, which is absent or very low in CD [4, 5]. The presence of aspartoacylase activity in cultured amniotic cells and chorionic villi affords a tool for prenatal diagnosis of CD. Increased N-AA signals, concomitant with low or absent choline signals, have been found in proton magnetic resonance spectroscopy of CD children [6, 7]. Leukodystrophics signs can be consistently demonstrated on CT and MRI brain scans, while atropic changes appear to vary [7–9]. In the following report we present the ultrasound (US) findings of three boys diagnosed with infantile CD in our institution between 1988 and 1992.

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Case reports

Patient A presented at 2 months of age with truncal hypotonia and irritability. He did not pay attention to visual stimuli but smiled when talked to. He did not acquire further skills, while progressive enlargement of his head was noticed during the following months. At 18 months he had extreme macrocephaly, lack of emotional responses and spontaneous movements, and pronounced spasticity of all limbs, and required feeding by nasogastric tube.

In patient B, poor head control, poor vision, and mild macrocephaly were first noticed at 5 months of age. At 8 months his head control improved, and subsequently he started to grasp with both hands, crawl, and babble, and even sat if placed. However, developmental arrest ensued at 15 months of age, followed by progressive neurological deterioration.

Lack of head control and slight macrocephaly were first noticed in patient C at 3 months of age. At 6 months macrocephaly was more pronounced, accompanied by limb spasticity and poor vision.

Details of the history of patients A and B have been reported previously [10]. All three boys showed markedly elevated urinary N-AA levels, with apparent correlation to the speed of clinical deterioration. In the two boys in whom aspartoacylase activity was assayed in fibroblasts, a profound reduction could be demonstrated.

Imaging

In patient A, US imaging with a 5-MHz sector transducer was performed at 2 and 9 months of age and showed high white matter echogenicity, with the exception of the corpus callosum. Echogenicity increased over time. High echogenicity was also noted for the basal ganglia and the thalamus, both of which had a swollen appearance. A first CT scan at 2 months of age showed bilateral hypodense areas in the basal ganglia; another CT scan at 18 months featured dif-

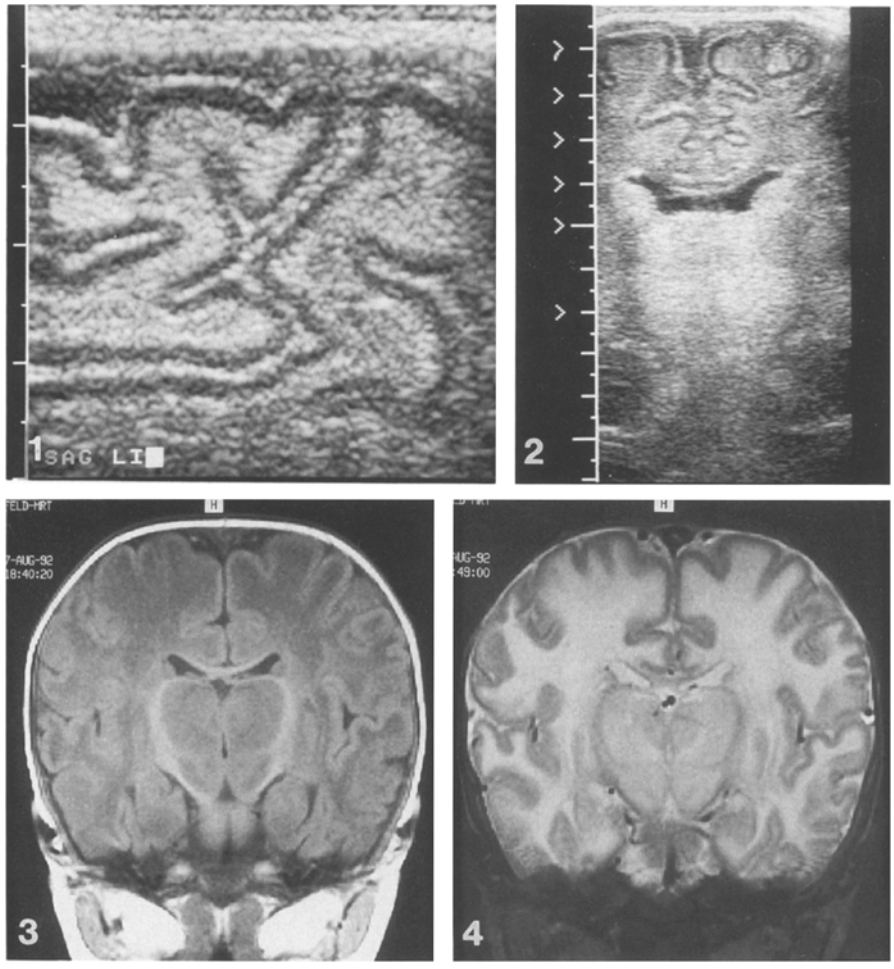

Fig. 1. High-resolution cranial US image (7-MHz linear transducer) of precentral gyri and sulci of patient C with Canavan disease at 6 months of age

Fig. 2. Cranial US image (7-MHz linear transducer) of central gray matter in patient C

Fig. 3. T1-weighted MRI san of patient C at 6 months of age (1.5 T, TR 600 ms, TE 10 ms)

Fig. 4. T2-weighted MRI scan of patient C at 6 months of age (1.5 T, TR 2500 ms, TE 80 ms)

fuse white matter hypodensity. MRI at 9 months of age showed low white matter attenuation values on T1-weighted images, giving the impression of a reversed pattern of white and gray matter signal intensities. Slightly T2-weighted images gave little difference in signal intensity of gray and white matter. Neither US, CT nor MRI showed circumscribed lesions, cortical atrophy or ventricular dilatation.

In patient B, characterized by a more protracted clinical course, 5-MHz sector US performed at 6 and 9 months of age showed slight enlargement of all ventricles, while no abnormalities of the centrum semiovale or periventricular nuclei were noted. MRI at 10 months also revealed ventricular dilatation and cortical atrophy. There was only diffuse patchy myelinization, with the notable exception of the periventricular areas. T1-weighted images showed markedly reduced contrast between cortical gray and subcortical white matter.

In patient C, US, CT, and MRI were all performed at 6 months of age. On both 5-MHz and 7-MHz US images there was a striking reversal of white and gray matter signal intensities (Fig. 1). With the exception of the corpus callosum, the white matter presented with markedly increased echogenicity and a very homogeneous fine texture. At the same time, cortical echogenicity was rather low, with a thin, highly echogenic pial demarcation from the slightly widened suabrachnoid space. Gyri and sulci appeared normal. Increased US signal intensities were also observed for the prominent-looking central gray matter areas (Fig. 2). The size of the ventricles was normal on US, CT, and MRI scans. CT scans featured diffuse white matter hypodensity and slight enlargement of the external subarachnoid space, the latter also being seen on MRI. Both T1-weighted (Fig. 3) and T2-weighted (Fig. 4) MRI scans were characterized by a salient contrast between cortical gray matter and subcortical white matter. Myelinization appeared to be restricted to the internal capsule, the corpus callosum, and the cerebellar nucleus dentatus.

Discussion

The histological hallmark of CD is widespread spongy degeneration, vacuoles 5–200 μm in diameter being most prominent in the lower cerebral cortex and the adjacent white matter. Dysmyelination starts in the subcortical arcuate fibers and progresses to the central white matter. There is no evidence of abnormal breakdown products, local inflammation, or neuronal or oligodendroglial damage. However, astrocytic swelling and proliferation, with naked nuclei and elongated mitochondria, can be observed by electron microscopy. While the chemical composition of the gray matter is virtually normal in CD, the water content of the white matter is dramatically increased [11]. As a corollary, CT in CD shows diffuse symmetrical low attenuation values of the white matter. MRI demonstrates diffuse symmetrical prolongation of both the T1 and T2 relaxation times in the white matter, causing reversal of the white matter signal intensity for T1 and T2 images. Therefore, CD white matter has a low signal intensity on CT scans and T1-weighted MRI scans, while T2-weighted MRI and apparently US yield high signal intensities.

Abnormalities suggesting a lack of myelin were seen on CT and MRI in all three patients reported here. US revealed greatly increased echogenicity of the white matter, with the notable exception of the corpus callosum in pa-

tients A and C, together with increased signal intensities of the nucleus caudatus and thalamus. However, these changes were not observed in patient B, who was characterized by a more protracteds clinical course. Unfortunately, we were unable to confirm or refute speculations that the strikingly increased white matter echogenicity seen in the two boys who showed a more rapid course of neurological deterioration would also have developed in patient B.

Clinically, CD resembles Alexander disease in its early onset progressive megencephaly and psychomotor retardation. However, N-AA levels are normal in Alexander disease and histophatological findings are dissimilar (perivascular Rosenthal fibers). CT scans in Alexander disease show generalized diffuse low-density abnormality of the white matter, while US findings are said to be characterized by hazily defined or even optically obliterated sulci and a decrease in acoustic attenuation of the cerebral tissues [12]. These findings are in marked contrast to those of the CD patients reported here. Further studies will be necessary to determine whether US does discriminate between these two diseases.

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