Brain ultrasound in Canavan disease

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Abstract Canavan disease (*MIM* 271900) is a rare autosomal recessive leukodystrophy due to mutations in the ASPA gene (*MIM* 608034) and characterized by a clinical onset at 3–5 months of life, macrocephaly and poor head control, weak cry and suck, development regression and hypotonia. Here, we report cranial ultrasound findings at birth and at 4 months of age in a patient affected with Canavan disease. The comparison of our sonographic data with few other cases in literature allows us to suggest a characteristic pattern in Canavan disease.

Keywords Cranial ultrasound · Brain ultrasound · Canavan syndrome · Aspartoacylase deficiency · Neonatal hypotonia · Leukodystrophy

Riassunto La malattia di Canavan (*MIM* 271900), dovuta a mutazioni nel gene ASPA (*MIM* 608034), è una rara leucodistrofia a trasmissione autosomica recessiva. E' caratterizzata dalla presenza di macrocefalia e scarso controllo del capo, pianto flebile, suzione poco valida, ipotonia e regressione neuromotoria. In questo lavoro riportiamo la descrizione dell'ecografia cerebrale in un paziente affetto dalla malattia di Canavan eseguita alla nascita e all'età di 4 mesi di vita. Dal raffronto con i dati precedentemente riportanti in letteratura possiamo suggerire la presenza di un quadro ecografico a livello cerebrale caratteristico nella malattia di Canavan.

Abbreviations

CD	Canavan disease
MR	Magnetic resonance
NAA	Acetylaspartic acid
AD	Alexander disease

Introduction

Leukodystrophies are hereditary metabolic diseases, in which the underlying biochemical abnormalities lead to defect of myelination, or to demyelination [1, 2]. Canavan disease (CD, *MIM* 271900) is a rare autosomal recessive leukodystrophy characterized by a clinical onset at 3–5 months of life, macrocephaly and poor head control, weak cry and suck, development regression and hypotonia progressing to spasticity and hyperreflexia [3, 4]. CD is due to mutations in the ASPA gene (*MIM* 608034) encoding aspartoacylase enzyme that catalyzes the conversion of acetylaspartic acid (NAA) to aspartate and acetate [3, 4]. Decreased aspartoacylase activity leads to NAA concentrations increasing up to 1,000-fold, resulting in disruption of the oligodendrocyte–axon interface, astrocytes vacuolization, spongiform changes, edema and loss of myelination [5].

The diagnosis is addressed by clinical features, biochemical data by increased urinary NAA excretion and neuroimaging, mainly cerebral magnetic resonance (MR). To date, there are few data of brain sonography in leukodystrophies in general and in CD in particular [6–10].

Here, we present the US cerebral features in a CD case and sonographic changes in the first month of life.

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Fig. 1 Sonographic findings of the patient at birth. Sector transducer. Coronal (a) and lateral (b, c) view. Note increased echogenicity of the white matter, thalamus and caudate

Case presentation

The patient was a 4-month-old child born from consanguineous Egyptians parents. Details of the patient's history have been reported previously [4]. At birth, clinical evaluation was unremarkable except for a picture of macrocephaly. As the 4-year-old brother was suspected to be affected of CD, the proband underwent to brain sonography that displayed slight undefined gyri due to echogenicity of the white matter, including thalamus and caudate (Fig. 1 a, b, c), but no other abnormalities. At 4 months of age, concurrently to neurological deterioration, we performed brain US (Fig. 2) despite the technical limits described in head examination of full-term babies. Brain US disclosed alteration of echogenicity of both gray and white matter with increasing of echogenicity of white matter, characterized by a homogenous fine texture, and with high echogenicity of the pial demarcation of the low echogenic cortex. Mild ventricular dilatation and enlargement of sinocortical space were also noted.

CS was confirmed in the proband and in his brother by molecular analysis of ASPA gene [4].

Discussion

Leukodystrophies comprise a broad group of progressive, inherited disorders affecting mainly myelin. Though the diagnosis is not found in many patients with leukodystrophies, distinctive clinical and neuroimaging features unique to them can aid in diagnosis. MR is the most important

Fig. 2 Sonographic findings of the patient at 4 months of age. Sector transducer. Note a white matter hyperechogenicity characterized by a homogenous fine texture and an intense signal of pial demarcation as a marginal line. Mild ventricular dilatation and enlargement of sinocortical space were also present

neuroimaging modality for patients with leukodystrophies and it seems to be more reliable in detecting mild or moderate white matter abnormalities than cranial ultrasound [11–13]. Furthermore, diffusion-weighted MR allows the detection of major diffusion abnormalities and the identification of various edema types, of which the so-called myelin edema is particularly relevant to leukodystrophies, in particular CD [12]. However, brain sonography can provide valuable information on white matter changes and it is a bed-side procedure characterized by safety and cheapness [13]. An integrated approach may be the most appropriate and cost-effective to study neonatal and infant neurological diseases.

Changes in white matter that are a consequence of a dystrophic process are very hyperechoic and can be irregularly shaped, linear or with undulating appearance [14]. To date, in literature, only five cases of brain US investigation in CD have been reported, of which only one with a US follow-up [6–8]. The findings here reported confirm brain US features of CD: remarkable increase, intensifying over time, of the echogenicity in white matter and nucleus caudatus and thalamus, and low echogenicity of gray matter giving an apparent reversed pattern of signal. In particular, in advance stages of the disease, we described a white matter hyperechogenicity characterized by a homogenous fine texture and an intense signal of pial demarcation. These findings, that can be assessed in previous reported images [7, 8], seem to be highly characteristic of CD. By these two signs, together with a “reversal” of white and gray matter signal intensities, we suggest that brain US could be useful in discriminate CD. On the other hand, experience with sonographic analysis in leukodystrophies is limited. CD differential diagnosis should include X-linked adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy, Pelizaeus–Merzbacher disease, Alexander disease (AD), and megalencephalic leukoencephalopathy with subcortical cysts [11–14]. In Alexander disease, US disclosed the obliteration of sulci and of the normal intracerebral landmarks with a decrease in acoustic attenuation of cerebral tissue and with an alteration in white matter echogenicity characterized by a ground-glass appearance [9]. In CD, differently to AD, a dilatation of subarachnoid space was reported and no cystic lesions were found [9, 14]. Hyperechoic changes in the striatum and thalamus were found not only in CD but also in birth asphyxia and in different inborn errors of metabolism. However, birth asphyxia is characterized by periventricular leukomalacia and cystic evolution, and in inborn errors of metabolism there can be a variable association with calcifications, ventricular dilation, abnormal cortical folding, lenticulostriate vasculopathy and other anatomical abnormalities [15].

Finally, we confirm a characteristic US pattern in CD and we suggest that in patients with progressive macrocephaly and hypotonia brain ultrasonography should be the first step in diagnostic *iter* as it may be helpful to address further diagnostic, both neuroradiological and biochemical, work-up. However, as the lack of reports in literature, further investigations in sonographic evaluation in different leukodystrophies and in white matter changes are needed.

Conflict of interest B. Drera, C. Poggiani declare that they have no conflict of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). All patients provided written informed consent to enrolment in the study and to the inclusion in this article of information that could potentially lead to their identification. The study described in this article does not contain studies with animal subjects performed by any of the authors.

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