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Case Report

Hydrocephalus in pyridoxine-dependent epilepsy: New case and literature review

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Abstract

Introduction: Pyridoxine-dependent epilepsy (PDE) is a rare disorder of the lysine metabolism, characterized by a pharmacoresistant epileptic encephalopathy that usually begins in the neonatal period. However, its phenotypic spectrum is wide and not limited to seizures. We report a new case of PDE who developed hydrocephalus, along with an exhaustive review of the literature.

Case report: Our patient presented with seizures at 13 h of life. Antiepileptic drugs, vitamins and cofactors were required to achieve seizure control. Laboratory tests were congruent with PDE. She remained seizure-free until age five months, when seizures reappeared in the context of increasing head size and irritability. A cranial ultrasound showed hydrocephalus, for which she underwent ventriculoperitoneal shunting.

Discussion: Seven other patients with same features have been previously reported. Seizure onset occurred within the first 7 days in all patients. Most of the children developed hydrocephalus at 6–7 months of age. In 4 out of 7 a genetic mutation was identified, despite the accurate etiology of hydrocephalus was unknown in most of them. The case we report behaved similarly to the others previously described. We postulate that the pathogenesis of this complication could be related to the high expression of antiquitin in choroid plexus epithelium, where the cerebrospinal fluid is produced.

Conclusions: patients with PDE should be closely monitored, since they may present severe complications. We highlight the development of hydrocephalus, an uncommon but potentially life-threatening problem reported in 8 patients up to present time.

Keywords: Pyridoxine-dependent epilepsy; *ALDH7A1*; Antiquitin; Ventriculomegaly; Hydrocephalus

1. Introduction

Pyridoxine-dependent epilepsy (PDE) is an autosomal recessive inherited disorder of lysine degradation pathway characterized by a pharmacoresistant epileptic encephalopathy that can be controlled with large dosages of pyridoxine [1]. In 2006 *aldehyde dehydrogenase 7A1* (*ALDH7A1*) gene, encoding antiquitin (ATQ), was identified as the genetic basis of PDE [2]. ATQ deficiency results in accumulation of alpha-aminoadipic semialdehyde (alpha-AASA), δ1-piperideine-6-carboxylate

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(P6C), and pipecolic acid (PA), which serve as diagnostic biomarkers in urine, plasma and cerebrospinal fluid (CSF). Multiple cranial magnetic resonance imaging (cMRI) abnormalities have been described in these patients [3]. However, obstructive hydrocephalus has been infrequently reported.

We present a new patient with PDE who developed obstructive hydrocephalus during the follow-up period. A literature review on the reported PDE patients with hydrocephalus was conducted.

2. Case report

This girl was born full term to nonconsanguineous parents via caesarean section, with normal Apgar scores. Fetal ultrasounds at 30 weeks' gestation showed a left lateral ventriculomegaly, which was confirmed in fetal MRI. At 13 h of life she presented focal clonic seizures that responded to phenobarbital, phenytoin and a single dose of pyridoxine. Seizures reappeared at day 13 of life, requiring the association of valproic acid, pyridoxal phosphate, folinic acid (FA), thiamine, biotin, and cobalamin to be controlled.

The electroencephalogram showed epileptiform activity in left rolandic area. The cranial ultrasound (cUS) and cMRI confirmed an asymmetric ventriculomegaly. The latest also evidenced periventricular white matter abnormalities, corpus callosum hypoplasia and a subependymal cyst surrounding the left foramen of Monro that did not appear to be causative of ventriculomegaly. The spectroscopic study showed elevated white matter lactate. Laboratory studies showed markedly elevated urinary alpha-AASA (42.8 mmol/mol creatinine; reference range 1.39 ± 0.73), as well as plasma and CSF PA levels (4.35 μmol/L; reference range 0.01–0.14), suggesting PDE. Mutation analyses revealed homozygosity for the c.1279G > C mutation (p. Glu427Gln) in the *ALDH7A1* gene.

She was restarted on pyridoxine and remained seizure-free with normal psychomotor acquisitions until the age of five months, when she presented episodes of hypertonia, abnormal eye movements, increasing head size and excessive irritability. Head circumference was 46 cm (+3.84 SD, Spain 2009 growth charts) and cUS showed a marked triventricular hydrocephalus, mainly in lateral ventricles (Fig. 1), for which she underwent left ventriculoperitoneal shunting successfully.

Dietary lysine restriction and oral arginine supplementation began at 24 and 30 months of age respectively, as adjunct to pyridoxine (17 mg/kg/day) and FA. Antiepileptic drugs were gradually discontinued until they were stopped at the age of 3 years and 10 months. The child is currently 4 years old and presents mild developmental delay in language and fine motor domains, with normal gross motor function. She remains seizure-free so far.

3. Discussion

PDE classically presents with neonatal seizures that do not respond to pharmacologic treatment [1]. However, atypical forms may account for 1/3 of cases, including: late onset of seizures up to 3 years of age, autism, initial response to common anticonvulsants and response to extremely low doses of pyridoxine [3]. Many patients show muscle tone alterations, irritability, hyperalertness, poor feeding or vomiting [1]. Likewise, cMRI may show a variety of changes from normal to corpus callosum hypoplasia, megacisterna magna, white matter lesions, intracerebral haemorrhage or cerebellum hypoplasia [1,3]. The finding that ATQ is also a glial protein expressed during embryonic brain development provides insight into the pathogenesis of structural brain abnormalities in PDE [4]. It has been reported that early initiation of lysine-restricted diet results in mild phenotype and may improve their neurodevelopmental outcome [5].

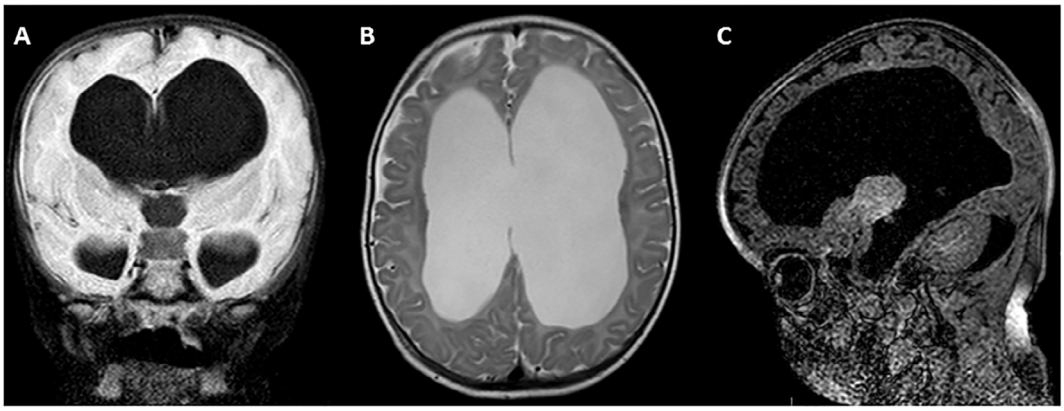

Fig. 1. Magnetic resonance imaging showing triventricular hydrocephalus. (A) FLAIR SPIR cranial weighted coronal magnetic resonance imaging (MRI) image, (B) Axial T2 weighted MRI and (C) T1-weighted fat-suppressed sagittal cranial MRI images at age 5 months showing triventricular hydrocephalus.

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