CASE REPORT

A preterm neonate with seizures unresponsive to conventional treatment

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SUMMARY

The case of a patient who presented with neonatal seizures unresponsive to conventional antiepileptic drugs and pyridoxine is reported. The baby girl was subsequently treated with pyridoxal 5'-phosphate (PLP) on day 20 of life, and showed rapid seizure control and normal development, with only mildly abnormal liver function tests at the current age of 6 years. Sequencing of the pyridox(am)ine 5'-phosphate oxidase (PNPO) gene revealed a heterozygous insertion of a single base in exon 7. The second allele was found to be normal although the patient may carry a mutation in another gene of the vitamin B₆ pathway. Follow-up at 6 years of age showed a seizure-free young girl (on 42 mg/kg/day PLP) with normal development but mild elevation of liver function tests. A high index of suspicion for metabolic disease must be kept in mind with neonatal seizures unresponsive to conventional treatment.

BACKGROUND

Seizures in a preterm infant often disclose an intra-ventricular haemorrhage or hydrocephaly that can lead to permanent disability. Paediatricians are used to control seizures with long-term drug treatments that can have significant side effects. Occasionally, neonatal seizures are sustained by metabolic defects¹ that, when promptly recognised and treated, may have a favourable outcome.

We present clinical and iconographic evidence of one such rare case where accurate differential diagnosis and a rapid therapeutic trial prevented severe disability.

CASE PRESENTATION

A female infant was delivered at 33 and 5/7 weeks' gestation from an emergency caesarean section for fetal distress (anhydramnios and fetal tachycardia started in the third trimester). Her birth weight was 1980 g and her Apgar score was 7, 8. At 90 min of life, she developed respiratory distress, which gradually led to endotracheal intubation. Her parents are not consanguineous and are both Italian. Maternal history showed a miscarriage at 10 weeks' gestation and a male newborn delivered at 36 weeks' gestation by emergency caesarean section for fetal distress (oligohydramnios and fetal tachycardia). That baby had died on day 13 of life because of hypoxic-ischaemic encephalopathy, severe status epilepticus, sepsis and multiorgan failure.

At admission in the neonatal intensive care unit, physical examination of our patient demonstrated hepatomegaly. Her laboratory blood test showed

lactic acidosis with increased lactate dehydrogenase, creatine kinase, aspartate transaminase and cardiac troponin, while ammonia and glucose were normal.

At 5 h of life, she began to suffer from severe seizures with eyelid blinking, hypersalivation with orobuccal rhythmic movements (videos 1 and 2), jerking movements and incessant crying, as if in severe pain. Seizures rapidly progressed to a status epilepticus unresponsive to conventional antiepileptic drugs (phenobarbital, phenytoin, benzodiazepines). EEG showed severe generalised burst suppression from the second day of life (figure 1). Glycaemia and serum electrolytes continued to be normal. Blood and cerebrospinal fluid (CSF) investigations were negative for infectious disease; a

Video 1 The baby on day 1 of life demonstrating generalised tonic-clonic seizures.

Video 2 The baby on day 1 of life showing eyelid blinking and hypersalivation with orobuccal rhythmic movements.

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Figure 1 EEG tracing on day 2 of life showing severe generalised burst suppression.

brain MRI on day 3 of life showed preterm leucoencephalopathy. Detailed metabolic investigations were unremarkable except for an increase of glycine and threonine in CSF, and vanillic acid in urine. CSF lactate was normal. A therapeutic attempt was made with pyridoxine. A loading dose of 100 mg intravenous was administered followed by 18 mg/kg/die per os. After 48 h, the convulsive pattern remained clinically unchanged and pyridoxine administration was discontinued. On day 20 of life, a therapeutic breakthrough was achieved with PLP (50 mg/kg/day orally) with seizures responding dramatically to this drug. The baby stopped the frequent crying and started feeding, and conventional antiepileptic drugs could be gradually decreased and then discontinued without relapse. PLP supplementation also led to rapid normalisation of the metabolic profile and EEG tracing (figure 2). The baby was discharged home at 3 months of age and a new MRI study performed the following month showed normal features. Significant hypertransaminasemia was documented, which improved after fine tuning of PLP

dosage. Molecular analysis in the infant revealed a heterozygous insertion of a single base in exon 7 of the PNPO gene, which was inherited from the baby's father. It was not possible to identify a second mutation even after analysis of complementary DNA generated from the patient's fibroblast messenger RNA. Three years later, the parents had another baby girl who was treated with PLP antenatally. While genetic analysis was ongoing, the drug was cautiously tapered down without the onset of seizures. Genetic analysis of PNPO revealed that this third child was unaffected.

OUTCOME AND FOLLOW-UP

At the present age of 6 years, our patient has normal psychomotor development and head circumference. She is on a PLP regimen of 42 mg/kg divided in six doses per day. She had seizures twice, once when her mother forgot to give her a night dose and again when she had gastroenteritis with reduced enteral absorption. In both cases, seizures stopped on the

Figure 2 Normalisation of the EEG shortly after the introduction of pyridoxal 5'-phosphate supplements.

prompt administration of PLP. Her aminotransferases, alkaline phosphatases and γ -glutamyl transferase levels remain mildly elevated.

DISCUSSION

We report the case of a baby girl whose seizures from birth came under control after supplementation of a specific metabolite. Although rare, seizures of metabolic origin should be suspected when suggestive clinical elements are present. In this case, an early miscarriage and the loss of a previous neonate with similar symptoms raised a red flag. Curiously, for the second baby, the mother reported increased intrauterine activity, so when the infant was about to be delivered this phenomenon was actually documented in the final ultrasound scan. The complete refractoriness to conventional antiepileptic drugs is another element that should drive an accurate differential diagnosis. We recently published a series of 15 patients with PNPO gene mutations, 5 of them presenting with neonatal-onset seizures.² The outcome ranged from normal development to global delay. This reflects a complex genotype–phenotype interaction that may involve prematurity and age at the time of the therapeutic trial. Other additional factors that are likely to influence treatment response and outcome include riboflavin status and how well the fetus has been supplied with vitamin B₆ by the mother. Previous reports² have linked PLP supplementation to the risk of permanent hepatic injury. In the clinical report by Sudarsanam *et al.*,³ the liver biopsy showed early cirrhosis, which was attributed to the PLP therapy. The PLP dose was in fact reduced to 60 mg/kg/day and although the liver function tests improved, they did not normalise, showing persistent evidence of hepatic fibrosis and portal hypertension. It is uncertain whether the cause of this toxicity is directly due to the high-dose PLP or to degradation products of PLP that may form by photochemical reactions. We believe that liver injury is a possible complication for our case, whose liver function tests remain above normal limits. In conclusion, a neonate with apparently intractable seizures should alert the clinician of a

possible underlying metabolic disorder. Within these conditions, PNPO deficiency should be considered and a PLP/pyridoxine supplementation trial promptly instituted before ordering-specific DNA testing. Close monitoring of liver function tests is mandatory. Despite this caveat, the final outcome may be as rewarding as a normally developing child.

Learning points

- ▶ Seizures in a preterm infant often reveal a condition that is invalidating for life.
- ▶ Rarely, the seizures can be sustained by metabolic derangements that can be fully reversed.
- ▶ A high index of suspicion for metabolic disease must be borne in mind when confronted with intractable neonatal seizures.
- ▶ A clear interventional protocol must be instituted for a neonate with seizures unresponsive to conventional treatment.

Contributors FR was in charge of neonatal care and the diagnostic approach, and drafted the manuscript. PM and PTC were fundamental in the diagnostic process providing both clinical expertise and genetic testing. EDG provided the follow-up clinical care of the patient and revised the manuscript.

Competing interests None declared.

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