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SCIENTIFIC LETTERS

Familial EXOSC3-related pontocerebellar hypoplasia☆,☆☆

Hipoplasia pontocerebelosa tipo I familiar con mutación en *EXOSC3*

Dear Editor:

Pontocerebellar Hypoplasia (PCH) refers to a heterogeneous group of rare neurodegenerative disorders with autosomal recessive inheritance characterised by hypoplasia of cerebellum and pons associated with progressive microcephaly.[1] Ten subtypes have been identified to date (PCH1-10); of which the individual incidence is unknown and the genotype–phenotype correlation has yet to be fully determined. Pontocerebellar hypoplasia type 1 (PCH1), the most prevalent, is distinctively associated with neuronal degeneration in the anterior horn of the spinal cord, giving rise to a clinical picture compatible with spinal muscular atrophy type 1 that includes severe hypotonia and significant feeding difficulties.[2,3] In this article, we present the cases of two siblings, born to healthy nonconsanguineous parents and of Romani descent, that had PCH type 1B associated with a mutation in the *EXOSC* gene. There was no relevant family history.

Case 1

Female newborn. Pregnancy with few checkups and normal prenatal ultrasound findings. Uncomplicated term delivery with Apgar score of 7/8. The patient required resuscitation with positive pressure ventilation in the delivery room. The physical examination revealed generalised severe hypotonia with very reduced deep tendon reflexes, shallow breathing, arthrogryposis with contractures in hands and elbows, *genu recurvatum* in the right lower extremity and fracture at the epiphyseal-metaphyseal junction in the distal third of the femur. The facial phenotype was not dysmorphic, save for the features resulting from hypotonia. Anthropometric measurements at birth: weight, 2330 g (5th–10th percentile); length, 44.5 cm (<3rd percentile); head circumference, 32.5 cm (10th–25th percentile). The patient needed mechanical ventilation due to progressive respiratory failure and placement of a nasogastric tube for enteral nutrition due to inefficient sucking and swallowing. Peripheral hypotonia was suspected, leading to performance of electromyography (EMG), which revealed a clear neuropathic pattern. The karyotype was 46, XX. The results of single-gene testing of the *SMN1* gene were normal, ruling out spinal muscular atrophy type 1. The unexpected finding of hypoplasia of the pons, vermis and cerebellar hemispheres in magnetic resonance imaging (MRI) of the head, along with ventriculomegaly with normal intracranial pressure, guided the diagnosis of PCH type 1, which was subsequently confirmed by molecular testing, which identified a homozygous missense mutation in exon 1 of the *EXOSC* gene (c.92G>C). The patient died at age 4 months of complications of aspiration pneumonia.

Case 2

Male. Uncomplicated delivery at 39 weeks' gestation, with normal findings in prenatal ultrasound examinations. Apgar score of 8/9. The patient did not need resuscitation in the delivery room. Anthropometric measurements at birth: weight, 2560 g (<5th percentile); length, 46.7 cm (10th–25th percentile); head circumference, 32.5 cm (<5th percentile). The clinical presentation was similar to that of his deceased sister, requiring mechanical ventilation and enteral feeding through a nasogastric tube. The karyotype was 46, XY. Head MRI revealed hypoplasia of the pons and cerebellum, compatible with the diagnosis of PCH type 1 (Fig. 1). The patient died at age 4½ months due to cardiorespiratory failure. The findings of the postmortem histopathological examination (spinal cord and muscle) were consistent with spinal muscular atrophy, with gliosis and a reduced number of Purkinje cells in the granular layer in the cerebellum. Molecular testing detected the same homozygous mutation (c.92G>C) in the *EXOSC3* gene, confirming the clinical diagnosis. Both parents were heterozygous carriers of the mutation.

Pontocerebellar hypoplasia type 1 (OMIM# 606489) manifests in the neonatal period with severe hypotonia, absent or reduced deep tendon reflexes, contractures and very weak sucking requiring the use of nasogastric feeding to ensure adequate nutrition. It is associated with a high incidence of aspiration pneumonia, whose complications are usually the cause of early death. Table 1 summarises the

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Table 1 Diagnostic criteria for PHC type 1.

Criteria	Major	Minor
Clinical-neurologic	Hypotonia Muscle atrophy Dystonia Spasticity EMG: lower motor neuron involvement	Contractures Swallowing insufficiency Nystagmus Seizures Strabismus
Neuroradiologic	Hypoplasia and/or atrophy of the cerebellum Hypoplasia and/or atrophy of the pons Cerebellar vermis and cerebellar hemispheres equally affected	Intracerebellar cysts Ventriculomegaly

Neuropathologic	Muscle	Spinal cord	Cerebellum
	Neurogenic muscle atrophy	Degeneration and loss of motor neurons in the anterior spinal horn	Loss of Purkinje cells. Folial atrophy. Degeneration of dentate nuclei.

Source: Eggens et al.[4]

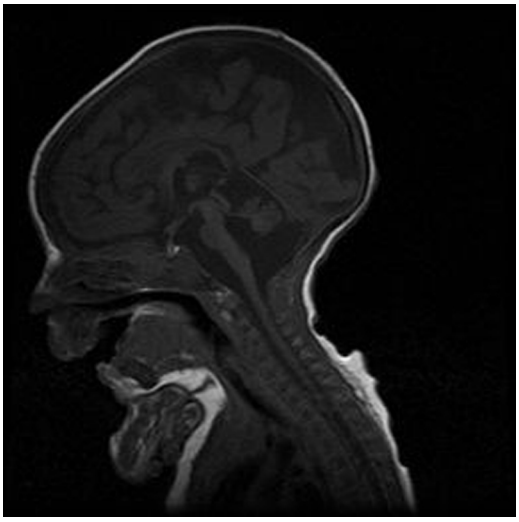

Figure 1 Brain MRI.

clinical criteria for the diagnosis of PCH type 1. The prognosis is highly uncertain, and symptomatic treatment and support measures are the only options currently available. Survival varies, with ranging from infancy to adolescence,[4] and there are no biological or genetic markers that allow reliable prognostication. Most sporadic cases of PCH had initially been associated with mutations in various genes (*TSEN54*, *RARS2* and *VRK*) until the identification of the *EXOSC3*[5] gene, of which mutations have been detected in 50% of the cases studied. The *EXOSC3* gene encodes a component of the human exosome, a protein complex involved in RNA processing. Its discovery provided evidence than changes in the exosome can cause disease in humans.[5] The c.92G>C mutation in the *EXOSC3* gene has been identified in some cases of PCH1 reported in the literature, especially in the Czech Romani population, and associated with the most severe form of disease.[6]

We ought to mention that the *EXOSC3* gene is not included in many of the gene panels designed for the assessment of PCH, which should be taken into account in the investigation of these patients given the large size of the Romani population in Spain.

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Use of levetiracetam in neonatal seizures☆

Uso de levetiracetam en crisis convulsivas neonatales

Dear Editor:

Neonatal seizures (NSs) occur in 1.5 per 1000 live births, with a higher incidence in preterm newborns. They usually result from asphyxia, haemorrhage, brain malformations, metabolic disturbances, inborn errors of metabolism or infection.[1] The challenges posed by its diagnosis and the decision of which children to treat are compounded by the growing evidence on the deleterious effects of the drugs approved for this purpose: phenobarbital and phenytoin. Both achieve seizure reduction in at least 50% of cases, and have been associated with neuronal apoptosis in animal models. For this reason, other drugs that have fewer apparent side effects are increasingly being used off-label. Levetiracetam (LEV) was approved by the Food and Drug Administration in 2012[2] for the treatment of partial-onset seizures in children aged 1 month and older.

We reviewed the use of LEV in newborns admitted to our unit between January 2011 and May 2016. Table 1 summarises the characteristics of these patients. Twenty-three newborns were treated. Their weights ranged between 1610 and 4100 g, and 17.4% had been born preterm. Table 2 presents data on the types of seizures, diagnostic tests and outcomes.

Levetiracetam was used as the first-line agent in 17.4% of the patients, and was the second-line agent in 73.9%, in most cases after phenobarbital failure. In 15 patients (65.2%), treatment was initiated with an intravenous loading bolus at a dose of 10–50 mg/kg. A maintenance dose was used in 91.3% that ranged between 10 and 40 mg/kg/2 doses, with increases of 10 mg/kg every three to five days. Out of the 19 patients in which it was used as the second-line agent, the dose of the first-line agent could be reduced in 63.1% in the first week after initiation of LEV. In eight patients, there was no improvement in either clinical or electrical seizures in the first 24 h, but 15 patients (65.2%) did improve (with improvement understood as the cessation of seizures or a reduction in frequency of at least 50%). We did not find evidence of adverse effects in any of the patients. There was treatment limitation in four patients, which was unrelated to the use of LEV. Of the 19 remaining patients, 88.9% were discharged with a LEV regimen (77.8% as monotherapy).

The use of LEV in NSs is becoming increasingly frequent despite not having been approved, as it is the case of most anticonvulsant agents used in infants. It is more recommended by paediatric neurologists than by neonatologists.[1,2] A retrospective chart analysis[3] identified 72 newborns treated with LEV, most of them born preterm, and found no adverse effects leading to treatment discontinuation. The definition of seizure was based on clinical features only, as aEEG or EEG were not used, so the efficacy results of this study are debatable. Previous studies have included between six and thirty-eight newborns,[2] and some were exclusively on preterm neonates ($n = 12$).[4] One prospective study[5] in 38 newborns in which LEV was used as the first-line agent found clinical improvement, and the EEG taken at one week post birth in 30 of these newborns showed no evidence of side effects, although the protocol tolerated the administration of two doses of phenobarbital during LEV titration, so that phenobarbital or the natural course of the seizures may have influenced the results. There is a published case of anaphylaxis following infusion of LEV in a neonate,[6] and it is possible that children with complex clinical situations and previous management are difficult to identify. A recent study found an association between LEV and neuronal cell death in newborns with asphyxia not treated with hypothermia.[6] Given the scarcity of the evidence on newborns, the safety of this drug for the first-line treatment of NSs remains to be determined, and most current guidelines that include LEV do so as a second-line agent.

There are limitations to this review. In addition to its retrospective design, the number of cases is small, although we have not found any other Spanish publication on the subject; our unit was not equipped with video-EEG to diagnose seizures, although we used aEEG and EEG to guide the treatment. A larger sample size would help determine whether there is an association between gestational age or the aetiology of the seizures and the response to LEV.

In conclusion, LEV is increasingly being used for the treatment of NSs, usually as the second-line agent. It seems to be at least as effective as classical anticonvulsants. Since it was associated with few side effects and seems to be less harmful to the brain, LEV is a drug to consider, even in preterm newborns. Prospective studies are needed to learn the effects of this drug in the short and long term.

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