Letter to the Editor

A new mutation in the SEPSECS gene related to pontocerebellar hypoplasia type 2D

Hipoplasia pontocerebelosa tipo 2D: una nueva mutación en el gen SEPSECS

Dear Editor:

Pontocerebellar hypoplasias (PCH) are a heterogeneous group of autosomal recessive disorders characterized by hypoplasia of the ventral pons and cerebellum, with variable cerebral involvement and severe psychomotor retardation. Up to now ten different subtypes have been reported.

The patient is an only child of no consanguineous Moroccan healthy parents. Her prenatal ultrasound was normal, and birth was at term via uncomplicated vaginal delivery. Birth weight was 3200 g (42nd), head circumference 34 cm (27th), length 53 cm (97th).

At 18-month-old, she was admitted to our hospital to be studied due to psychomotor delay, quadriplegia and microcephaly. Clinical examination revealed inability to sedestation, standing with support, spastic quadriplegia with hyperreflexia and microcephaly.

First Brain Magnetic Resonance Imaging (MRI) performed at 14 months old was normal (Fig. 1A).

Study of metabolic diseases was normal and included: thyroid function, full blood count, lipids, hepatic profile, iron metabolism, vitamin B12, folic acid, carnitine profile, homocysteine, lysosomal enzymes, beta-hydroxybutyrate, amino acids, carbohydrate-deficient transferrin, long-chain and very long-chain fatty acids, copper and ceruloplasmin, ammonium, lactate and biotinidase activity and urine organic acids. Serology of cytomegalovirus was negative. Ophthalmological, abdominal ultrasound, cardiological examination, electromyography and nerve conduction studies were normal. Karyotype and arrayCGH found no alterations.

At 28-month-old, botulinum toxin injections were initiated in lower limbs to treat spasticity. A second brain MRI performed at 4-year-old revealed hypoplastic cerebellar vermis and hemispheres showing “butterfly-like” pattern of progressive pontocerebellar atrophy (Fig. 1B).

The exome sequencing revealed a homozygous splicing mutation (c.114+3A>G) in exon 1 of the *SEPSECS* gene. Mutations in *SEPSECS* gene have been described as the main cause of pontocerebellar hypoplasia type 2D (PCH2D). The mutation in our patient has not been described in the literature yet and it is not included in ExAC database. The silico splicing analysis conducted predicts a deleterious mutation because it affects splicing. This mutation was identified in both parents in heterozygosis. RNA-m was extracted from blood cells. The study on cDNA sample does not observe alteration in the splicing as a consequence of the variant c.114+3A>G in the intron 1 of the *SEPSECS* gene. Nevertheless, it is necessary to

Fig. 1. Brain MRI, axial and sagittal plane. (A) 14 months. (B) 4 years. Hypoplastic cerebellar vermis and hemispheres, “butterfly-like” pattern.

consider the possibility of the existence of alternative splicing in other tissues (such as brain tissue).

Currently, at the age of four years neurological examination reveals spastic quadriplegia, convergent strabismus and microcephaly. She keeps visual contact, is able to say 12 words but is unable to speak meaningful sentences. She has dysphagia for liquids. No seizures.

Pathological recessive *SEPSECS* mutations have been reported in previous studies as etiology in pontocerebellar hypoplasia type 2D, progressive cerebellocerebral atrophy and encephalopathy.¹

Clinical spectrum associated to *SEPSECS* defects may include spasticity, hypertonia, microcephaly, cognitive development delay with ataxia. Some patients have encephalopathy, associated with seizures in approximately 50%. Repeated brain magnetic resonance imaging of affected individuals shows progressive cerebellar, vermis and cerebrum atrophy. The treatment is symptomatic and focused on complications while prognosis is guarded.

According to Iwama et al.,² *SEPSECS* mutations have been reported in a total of 13 patients with PCH type 2, progressive cerebellocerebral atrophy or encephalopathy. *SEPSECS* is located in the chromosome 4 (4p15.2) and catalyzes the final step of selenocysteine synthesis. The selenocysteine, is the only genetically encoded

amino acid in humans whose biosynthesis occurs on its cognate tRNA.³

The human selenoproteome includes 25 selenoproteins with diverse biological functions. Those proteins are connected with numerous diseases, including neuromuscular, cardiovascular or endocrine disorders, cancer and inflammatory diseases. Several studies show that selenoproteins are essential for mammalian brain development⁴ and decreased function of selenoproteins can lead to disorders including Alzheimer's, Parkinson's, Huntington's disease and epilepsy. Recently *SEPSECS* mutations have been described in patients with progressive encephalopathy associated to elevated blood and cerebrospinal fluid lactate.⁵

Previous studies have reported *SEPSECS* mutations resulting in similar clinical features that our patient, including developmental delay, spasticity and atrophy of the cerebellum, vermis and cerebrum in MRI. Although the pathogenicity of the mutation in peripheral blood has not been demonstrated, it could be consequence of an alternative splicing in other tissues.

In conclusion, it may have been identified a new mutation in the *SEPSECS* gene related with clinical and radiological features of PCH type 2 not described in the literature yet.

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