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SCIENTIFIC LETTER

Genotype of a severe D-bifunctional protein deficiency
Genotipo de curso grave en un déficit de proteína D-bifuncional

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Among peroxisomal disorders,[1] D-bifunctional protein deficiency (D-BPD), caused by a recessive mutation in the *HSD17B4* gene, leads to a very infrequent neurodegenerative disease (1/100,000 live births), frequently with neonatal onset.[2,3] The severity of this disease, first described in 1989,[4] depends on the residual enzymatic activity, with type I being the most severe and type III being the least severe.[5,6] We present the clinical, biochemical, genetic, and radiological phenotype of a neonate delivered after uneventful vaginal birth at 40 weeks of gestation, who was admitted due to hypoglycaemia, hypotonia, and feeding difficulties. On the second day of hospitalisation, he developed short-lasting multifocal clonic seizures. His parents were consanguineous (first cousins), and had two other healthy sons and two daughters who had died in the neonatal period and at 6 months, respectively, with hypotonia and seizures of unknown aetiology.

Phenotypic characteristics included mild retrognathia, low-set ears, slightly increased space between nipples, and bilateral cryptorchidism. The patient presented hepatomegaly, with the liver having an elastic consistency and being approximately 3 cm larger than normal (size increased during hospitalisation), and palpable splenic edge. Neurological examination revealed normoreactive pupils, lack of visual tracking, generalised hypotonia and scarce spontaneous movements, and general areflexia without clonus. The results of the echocardiography and abdominal ultrasound were normal, with the exception of the presence of ectopic testes, proximal to the inguinal canal. No retinal or anterior segment abnormalities were observed. A brain and cervical spinal MRI scan performed 18 days after birth showed a slight alteration to the supratentorial white matter, consisting of a diffuse, symmetrical lesion predominantly affecting the occipital and temporal lobes; no cerebellar white matter involvement or neuronal migration disorder was observed (Fig. 1). Electromyography and electroneurography findings were normal.

The laboratory analysis revealed cholestasis and elevated gamma-glutamyl transferase (735 IU/L), with no other aminotransferases presenting elevated levels. Morning cortisol level was decreased, with increased adrenocorticotropic hormone level (Table 1) and hyponatraemia, requiring hydrocortisone replacement therapy. Levels of very-long-chain fatty acids, phytanic acid, and pipecolic acid were pathologically elevated. Polyunsaturated acid, arachidonic acid, and docosahexaenoic acid levels were slightly elevated, but erythrocyte count was normal. Primary biliary acid and trihydroxycholestanoic acid levels were also elevated. Erythrocyte plasmalogens were slightly decreased (Table 1).

The patient presented several focal seizures, with electroencephalography revealing a burst–suppression pattern with episodes of spikes, sharp waves, and theta wave bursts at different locations; these findings are compatible with Ohtahara syndrome. After several combinations of

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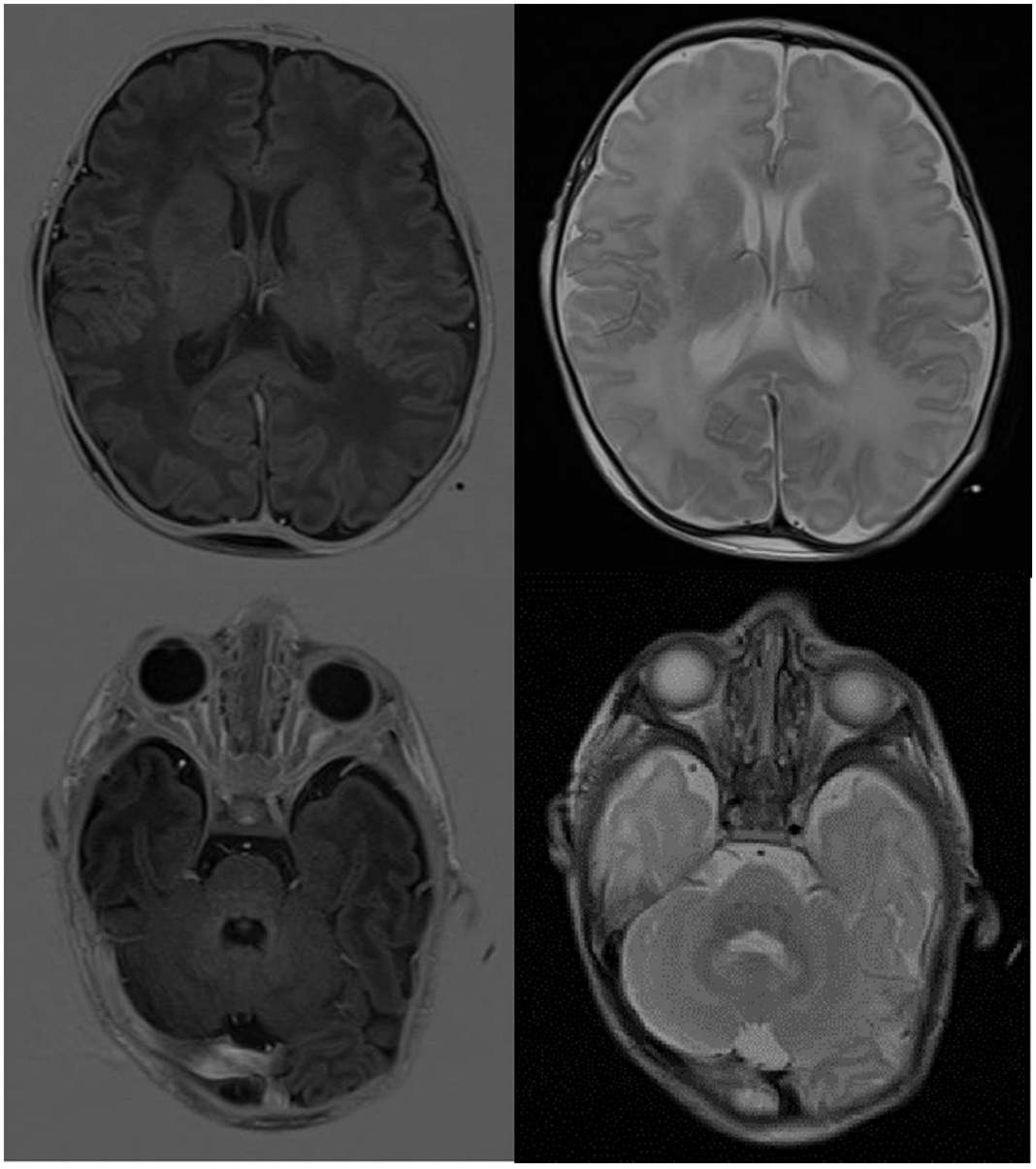

Fig. 1 MRI at 18 days of life. Upper left: axial T1-weighted sequence at the level of the basal ganglia showing a subtle diffuse pattern of white matter involvement. Upper right: axial T2-weighted sequence at the same level with diffuse white matter involvement. Both images show white matter heterogeneity, predominantly in occipital and frontal regions. A subependymal cyst is also visible in the left ventricle of the caudal-thalamic area. Lower left: axial T1-weighted sequence at the level of the inferior cerebellar peduncles (normal myelination pattern). Lower right: axial T2-weighted sequence at the level of the inferior cerebellar peduncles (normal myelination pattern).

antiepileptic drugs, seizures were eventually controlled with oxcarbazepine and valproic acid.

A targeted molecular panel revealed a homozygous pathogenic mutation (c.1369A > T [p.Asn457Tyr]) in the *HSD17B4* gene.

Seizure control and physiotherapy achieved a degree of improvement, increasing alertness and mobility and improving swallowing and sucking ability, and we were able to remove the nasogastric tube 2 months after the patient was born.

At the age of 6 months, the patient returned to our consultation; he presented few weekly seizures, was able to feed by mouth, and did not require ventilatory support. However, he presented severe global hypotonia (no head control), areflexia, lack of visual tracking, and limited interaction with the environment. The patient died at the age of 12 months.

Our patient presented hypotonia with areflexia, Ohtahara syndrome, and adrenal insufficiency; clinical phenotype and laboratory findings are compatible with D-BPD. Of these patients, 68% present facial dysmorphism,[5] which is similar to but milder than that observed in Zelweger spectrum disorders.

An MRI study revealed diffuse supratentorial leukoencephalopathy with no involvement of the cerebellar peduncles, which differs from typical progression. At onset, the

Table 1 Blood analysis values.

	Result	Reference values
Cortisol	1.1 μg/dL	5–25 μg/dL
ACTH	211 pg/mL	6–76 pg/mL
Sodium	0.4–129 mEq/L	135–145 mEq/L
C22:0	37 μmol/L	50 ± 16 μmol/L
C24:0	76 μmol/L	38 ± 14 μmol/L
C26:0	6.22 μmol/L	0.55 ± 0.17 μmol/L
C24:0/C22:0	2.04 μmol/L	0.77 ± 0.12 μmol/L
C26:0/C22:0	0.167 μmol/L	0.012 ± 0.004 μmol/L
Pristanic acid	0.52 μmol/L	0.41 ± 0.25 μmol/L
Phytanic acid	7.86 μmol/L	3.40 ± 1.60 μmol/L
Pipecolic acid	3.42 μmol/L	1.22 ± 0.59 μmol/L
Polyunsaturated fatty acids		
Arachidonic acid	218 μmol/L	493 ± 144 μmol/L
Docosahexaenoic acid	67 μmol/L	135 ± 41 μmol/L
Bile acids		
Glycolic acid	11 μmol/L	<4 μmol/L
Taurocholic acid	12 μmol/L	<3 μmol/L
Glycochenodeoxycholic acid	11 μmol/L	<0.2 μmol/L
Taurochenodeoxycholic acid	4 μmol/L	<4 μmol/L
Trihydroxycholestanoic acid	1 μmol/L	Not detectable
Erythrocyte plasmalogens		
C16:0	0.03 μmol/L	0.077 ± 0.035 μmol/L
C18:0	0.066 μmol/L	0.12 ± 0.054 μmol/L

hilum of the dentate nucleus and the superior cerebellar peduncles are usually affected. The parietal–temporal white matter is subsequently affected, with no involvement of U-fibres.[7,8]

A type-IV D-BPD has been proposed, characterised by less severe phenotypic and biochemical features and longer survival.[6] Clinically, it corresponds to Perrault syndrome, characterised by sensorineural hearing loss, ovarian dysgenesis in female patients, and occasionally such neurological alterations as cerebellar ataxia and progressive intellectual disability. This deficiency is attributed to missense mutations affecting both hydratase and dehydrogenase activity.[9] Although all reported cases of juvenile D-BPD present compound missense mutations, mutations are also described in patients with neonatal onset, presenting phenotypic variability.[10]

A total of 83 *HSD17B4* mutations have been described.[9] It has been suggested that these entities present a clinical overlap, potentially resulting in underdiagnosis of D-BPD.[11] The mutation we report affects the enoyl-CoA hydratase domain, causing type-II D-BPD,[2,3] with a population allele frequency estimated at 0.0000159.[12,13] Most patients with type-I and type-II D-BPD die before the age of 2 years, as in the case of our patient and probably also his two sisters.

Treatment includes supportive and hormone replacement therapy. The literature includes reports of cases achieving slight symptom improvement with docosahexaenoic acid supplementation, but no increase in life expectancy or quality of life.[8]

Ethics approval

We declare that we followed our centre's protocols on the publication of patient data, and all participants signed the informed consent form.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.10.008.

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