D-bifunctional Protein Deficiency: A Case Report of a Turkish Child

Sir,

D-bifunctional protein deficiency (D-BP) is a very rare autosomal recessive disorder of peroxisomes caused by mutation of *HSD17B4* (5q23.1) gene.[1] The *HSD17B4* product of D-BP is a multifunctional enzyme which catalyzes the second (enoyl-CoA hydratase) and third steps (3-hydroxyacyl-CoA dehydrogenase) of peroxisomal fatty acid β-oxidation.[2] D-BP has a dehydrogenase, a hydratase, and a sterol carrier protein-2 (SCP2) domains. Prototypical patients with D-BP deficiency show muscular hypotonia, poor sucking, craniofacial anomalies, hepatomegaly, and seizures beginning from the neonatal period and leading to the death of the patient by the age of 2 years.[3] To date, only a few patients with D-BP deficiency have been described in the literature.[3-6] Here, we report a Turkish girl with D-BP deficiency, who presented with drug-resistant seizures, dysmorphism, and psychomotor retardation.

Our case was a 4-year-old girl admitted to our hospital with drug-resistant seizures and severely delayed psychomotor development. At the 1st month of life, she developed tonic seizures, which were treated with phenobarbital successfully. At the age of 12 months, both tonic–clonic and focal seizures occurred once or twice a week and valproic acid and levetiracetam initiated. However, antiepileptic drugs had been revised frequently due to intractable seizures.

She was born to healthy consanguineous parents after an uncomplicated pregnancy at the 32th week of gestation via vaginal delivery. Her birth weight was 1500 g, birth length was 40 cm, and head circumference was 31 cm. She was hospitalized in a Neonatal Intensive Care Unit with hypotonia and feeding problems for 26 days. The family history was unremarkable for a neurological or an inherited metabolic disease. There was no history of a teratogenic agent exposure during pregnancy. On physical examination at admission, she had severe growth retardation, malnutrition, hypotonia, bilateral sensorineural deafness, and dysmorphic features such as broad forehead, high-arched palate, low-set ears, flat nasal bridge, and micrognathia. She could not say any meaningful words and could only sit without support. Laboratory evaluation revealed normal liver and renal function tests and thyroid hormone levels. Metabolic investigations including serum quantitative aminoacid levels and acylcarnitine profile, blood lactate and pyruvate levels and their ratio, very long-chain fatty acid (VLCFA), phytanic and pristanic acid levels, serum ammonia, and urine organic acid analysis were totally normal. The Stanford–Binet Intelligence Scale was compatible with severe psychomotor retardation. Echocardiography and abdominal ultrasonography revealed no abnormality. Cerebral magnetic resonance imaging (MRI) pointed out bilateral symmetrical hyperintense lesions in the posterior periventricular white matter [Figure 1]. Electroencephalography showed abnormal background activity and multifocal epileptic discharges. As all the metabolic investigations were normal, MRI did not indicate a specific diagnosis, the family history was suspicious for an inherited

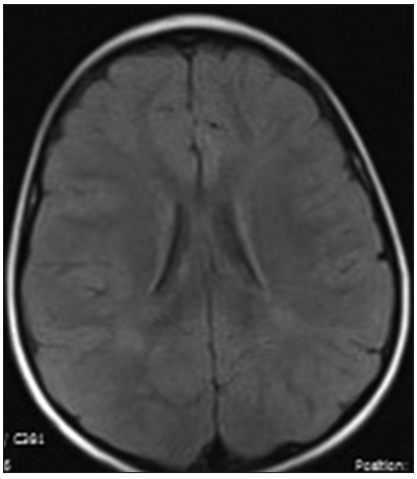

Figure 1: Cerebral magnetic resonance imaging showed bilateral symmetrical hyperintense lesions in the posterior periventricular white matter

neurometabolic disease, and hence whole-exome sequencing analysis was performed. Surprisingly, a compound heterozygous mutation c.11C>G (p.Pro4Arg) and c.1976G>A (p.Arg659His) was found in the *HSD17B4* gene. The mother was heterozygous for the mutation c.11C>G (p.Pro4Arg) and the father was heterozygous for the mutation c.1976G>A (p.Arg659His).

D-BP deficiency is a very rare inherited metabolic disease with an estimated prevalence of 1:100,000.[1] D-BP has a dehydrogenase, a hydratase, and a SCP2 domain, and the deficiencies of these enzymes lead to four different subtypes of the disease. Type I is caused by the deficiencies of both dehydrogenase and hydratase activities of the D-BP, whereas Type II and Type III are caused by the deficiencies of hydratase and dehydrogenase enzymes, respectively.[5] Recently, a new form, Type IV, is proposed to describe the mildly affected patients with compound heterozygous mutations affecting both the dehydrogenase and hydratase activities.[3-8] All the types are inherited in an autosomal recessive manner. The onset of symptoms of D-BP deficiency is usually in the neonatal period. Survival until late childhood is rare and generally it is fatal by the age of 2 years.[4] In a case series report of 126 patients with DBP deficiency diagnosed by D-BP activity measurements in fibroblasts, virtually all patients presented with neonatal hypotonia (98%) and seizures (93%) within the 1st month of life. Almost none of the patients acquired any psychomotor development, and the few patients who achieved some limited skills showed progressive loss of motor achievements. Detailed information about five patients with prolonged survival (>7.5 years) demonstrated that seizures were controlled with antiepileptic treatment in three patients and various types of seizures were poorly controlled in one patient. Only one patient had no seizures.[9] Nascimento *et al.* reported a case of D-BP deficiency with neonatal onset of seizures and hypotonia.[4] Buoni *et al*.[10] reported a case of D-BP deficiency with a peculiar epileptic phenotype defined as West syndrome with a modified hypsarrhythmic pattern and drug-resistant asymmetric spasms. Our patient was admitted to the hospital with typical clinical abnormalities described for D-BP deficiency, including neonatal hypotonia, seizures, dysmorphism, and developmental delay. Her tonic seizures showed a progression to resistant epilepsy in time. However, there were a few cases with milder clinical presentations in the literature.[7]

Biochemically, D-BP deficiency is characterized by increased plasma levels of VLCFA, di- and trihydroxycholestanoic acid, and pristanic acid.[2] Soorani-Lunsing *et al*.[11] reported a milder case of D-BP deficiency with normal levels of VLCFAs. Although the clinic is severe, VLCFA levels were normal in our case.

Common neuroimaging findings seen in D-BP deficiency are delayed myelination and demyelination of white matter, germinolytic cysts, and polymicrogyria of cerebral cortex. Interestingly, Mizumoto *et al*.[7] reported a patient without any abnormal finding on cerebral MRI. We demonstrated bilateral symmetrical hyperintense lesions in the posterior periventricular white matter in cerebral MRI.

In conclusion, although it is a rare neurometabolic disease, D-BP deficiency should be in the differential diagnosis of resistant epilepsy, neonatal hypotonia, and developmental delay. The interesting feature of our case was the normal levels of VLCFA despite the severe neurological involvement.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Faruk Incecik, Neslihan O. Mungan[1]

Departments of Pediatric Neurology and [1]Pediatric Metabolism, Cukurova University Faculty of Medicine, Adana, Turkey

Address for correspondence: Dr. Faruk Incecik, Toros Mah., Baris Manço Bul. 78178 Sok., Yesilpark Evleri, Kat: 7, No: 13, Çukurova, Adana, Turkey.
E-mail: fincecik@yahoo.com

References

1. Online Mendelian Inheritance in Man (OMIM). Available from: http://www.ncbi.nlm.nih.gov./Omim/CenterforMedicalGenetics,JohnsHopkinsUniversity,Baltimore,MD,andthenationalCentreforBiotechnologyInformation,NationalLibraryofMedicine,Bethesda,MD:MIM#*60186017-@BETA-HYDROXYSTEROIDDEHYDROGENASEIV; HSD17B4.
2. Suzuki Y, Jiang LL, Souri M, Miyazawa S, Fukuda S, Zhang Z, *et al.* D-3-hydroxyacyl-coA dehydratase/D-3-hydroxyacyl-coA dehydrogenase bifunctional protein deficiency: A newly identified peroxisomal disorder. Am J Hum Genet 1997;61:1153-62.
3. McMillan HJ, Worthylake T, Schwartzentruber J, Gottlieb CC, Lawrence SE, Mackenzie A, *et al.* Specific combination of compound heterozygous mutations in 17β-hydroxysteroid dehydrogenase type 4 (HSD17B4) defines a new subtype of D-bifunctional protein deficiency. Orphanet J Rare Dis 2012;7:90.
4. Nascimento J, Mota C, Lacerda L, Pacheco S, Chorão R, Martins E, *et al.* D-bifunctional protein deficiency: A cause of neonatal onset seizures and hypotonia. Pediatr Neurol 2015;52:539-43.
5. Ghirri P, Vuerich M, Ferdinandusse S, Waterham HR, Guzzetta A, Bianchi MC, *et al.* A case of D-bifunctional protein deficiency: Clinical, biochemical and molecular investigations. Pediatr Int 2011;53:583-7.
6. Matsukawa T, Koshi KM, Mitsui J, Bannai T, Kawabe M, Ishiura H, *et al.* Slowly progressive d-bifunctional protein deficiency with survival to adulthood diagnosed by whole-exome sequencing. J Neurol Sci 2017;372:6-10.
7. Mizumoto H, Akashi R, Hikita N, Kumakura A, Yoshida Y, Honda A, *et al.* Mild case of D-bifunctional protein deficiency associated with novel gene mutations. Pediatr Int 2012;54:303-4.
8. Amor DJ, Marsh AP, Storey E, Tankard R, Gillies G, Delatycki MB, *et al.* Heterozygous mutations in *HSD17B4* cause Juvenile peroxisomal D-bifunctional protein deficiency. Neurol Genet 2016;2:e114.

9. Ferdinandusse S, Ylianttila MS, Gloerich J, Koski MK, Oostheim W, Waterham HR, *et al.* Mutational spectrum of D-bifunctional protein deficiency and structure-based genotype-phenotype analysis. Am J Hum Genet 2006;78:112-24.
10. Buoni S, Zannolli R, Waterham H, Wanders R, Fois A. D-bifunctional protein deficiency associated with drug resistant infantile spasms. Brain Dev 2007;29:51-4.
11. Soorani-Lunsing RJ, van Spronsen FJ, Stolte-Dijkstra I, Wanders RJ, Ferdinandusse S, Waterham HR, *et al.* Normal very-long-chain fatty acids in peroxisomal D-bifunctional protein deficiency: A diagnostic pitfall. J Inherit Metab Dis 2005;28:1172-4.

DOI: 10.4103/aian.AIAN_273_18