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D-Bifunctional Protein Deficiency in a Neonate, are We Missing?- A Case Series

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

D-bifunctional protein deficiency (D-BP) is an extremely rare autosomal recessive peroxisomal disorder caused by a mutation in the HSD17B4 (5q23.1) gene. In this case series, we report three cases in which clinical signs appeared during the neonatal period. Two cases had early seizures and hypotonia, and another case had breastfeeding jaundice with hypotonia. In our first case, we identified a unique frameshift deletion c.398delC p.Ala133Glu fs.6. One patient died in the fourth month of life, whereas the other two were followed up. We report these cases because they are part of an unusual case series. In our case series, one case presented breastfeeding jaundice, and in another case, we identified a novel mutation that will help to expand the phenotypic and genotypic spectrum of D- BP.

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1. INTRODUCTION

D-bifunctional protein is a multifunctional enzyme that catalyzes the second (enoyl-CoA hydratase) and third (3-hydroxy acyl-CoA dehydrogenase) steps of peroxisomal fatty acid-β-oxidation. The D-bifunctional protein has a dehydrogenase, a hydratase, and a sterol carrier protein-2 (SCP2) domain. A deficiency of D-bifunctional protein is a disorder that leads to neurodegeneration that begins in infancy and is associated with hypotonia and seizures. [1] During developmental regression, children develop hyperreflexia and hypertension with loss of vision and hearing and do not survive beyond 2 years. This may be accompanied by hypertelorism, a long philtrum, a high-arched palate, a large fontanel, and hepatomegaly, which may mimic Zellweger syndrome. Therefore, it is also called pseudo-Zellweger syndrome.

2. CASE PRESENTATION

2.1 Case series

Here, we are presenting 3 cases of D-bifunctional protein deficiency that we diagnosed in a span of 2 years, from 2021 to 2023, in our hospital in Niloufer, Hyderabad, India. We retrospectively collected the data. We searched large databases, and as per our reliable sources, we found some case reports and one case series. Due to the uniqueness of our case series, we are reporting.

2.1.1 Case 1

A term male baby, appropriate for gestational age (AGA), born to a gravida-two mother in second-degree consanguineous marriage via lower segment caesarean section (LSCS). The baby cried immediately after birth and was brought to the hospital at 20 days of life with reduced activity, jaundice, and loss of weight. There was no organomegaly; however, the baby's cry, tone, neonatal reflexes, and activity were decreased. There were no obvious congenital anomalies or dysmorphism, and the baby's serum bilirubin was 11.4 mg/dl, without any incompatibility. The jaundice was termed breastfeeding jaundice since it disappeared after appropriate feeding. Given the baby's neurological abnormality with good sensorium, we preferred to conduct a brain magnetic resonance imaging (MRI) and gene rather than a workup for inborn errors of metabolism (IEM). The MRI showed bilaterally increased T1 signal intensity, while in the genetic exome, the sequencing was in favour of D-bifunctional protein (D-BP) deficiency (Table 1). Creatine kinase-myocardial band (CK-MB) levels were normal for age and as such no fasciculations of the tongue were observed. The baby was lost follow-up. We counselled the parents about genetic testing but they deferred.

2.1.2 Case 2

A term male child, AGA, born to a gravida-three mother with normal, live children, in a non-consanguineous marriage. The baby was born via elective LSCS because of a previous caesarean section. He did not cry immediately after birth and was referred on day 3 of life to Niloufer Hospital on account of refractory seizures that started on day 1 of life. The seizures were controlled with levetiracetam. The baby was hypotonic, and clinical signs of craniofacial dysmorphism were present: a high forehead, low-set ears, high-arched palate, small mouth, and narrow eyelids. Both truncal tone and peripheral tone were decreased. Also, both active tone and passive tone were reduced. Given the baby's altered sensorium, he was worked up for meningitis and IEM; however, no abnormalities were detected. CK levels were also normal, and whole exome sequencing (WHS) confirmed a pathogenic variant of DBP deficiency.

2.1.3 Case 3

A term male baby, AGA, is the second in birth order from a third-degree consanguineous marriage. The baby presented at 4 months of age with reduced activity, lethargy, and global developmental delay. He did not cry immediately after birth and developed seizures on the third day of life. The baby had macrocephaly, frontal bossing, prominent philtrum, low-set ears, hypotonia, and a wide-open anterior fontanelle. The ophthalmologic examination was normal (Fig. 1). Brain MRI showed thin/absent corpus callosum, pachygyria, and polymicrogyria involving the frontal and parietal lobes, ventriculomegaly, and asymmetry. Brain-evoked response auditory (BERA) revealed a profound hearing loss in both ears.

Table 1. Clinical And laboratory profile of cases

		Case 1	**Case 2**	**Case 3**
	Age	**Neonatal period**	**Neonatal period**	**Neonatal period**
	Sex	**Male**	**Male**	**Male**
Clinical Features	Jaundice	+	-	-
	Tone	decreased	decreased	decreased
	Dull activity	+	+	+
	Seizures	-	+	+
	Dysmorphic features	-	high forehead, low set ears, high arched palate, small mouth, narrow eyelids	macrocephaly, frontal bossing, prominant philtrum,low set ears
Vlcfa	C26(0.33 - 1.33µmol/L)	0.77	0.88	6.62
	C26:22(<0.030)	0.002	0.01	0.02
	C24:C22(0.32 - 1.07)	0.4	0.7	2.0
	Pristanic acid (<3 µmol/L)	0.9	NP	NP
	Phytanic acid (<16 µmol/L)	5.3	-NP	NP
Laboratory Investigations	MRI	bilateral increased T1 signal intnsity, possibly related to hyperbilirubinemia	myelination in appropriate for age No structural abnormality MRS: non specific	Thin /absent corpus callosum, pachygyrus, polymicrogyris involving frontal and parietal lobes,ventriculomegaly and asymmetry
Genetic Sequencing	Gene	HSD17B4	HSD17B4	HSD17B4
	Location	exon 7	intron 20 and Exon 20	exon 19
	Inheritence	homozygous /autosomal recessive	compound heterozygous	homozygous
	Variant change	c.398delC p.Ala133Glu fs.6	c.1767+1G>A c.1732T>C	c.1591C>T

(NP:Not Performed)

Fig. 1. Case 3 showing Hypotonic posture of upper limbs and mouth

3. DISCUSSION

Very long-chain fatty acid (VLCFA) disorders fall within the broader group of peroxisomal diseases, and D-bifunctional protein (DBP) deficiency is an uncommon single peroxisomal enzyme abnormality that causes symptoms comparable to those in Zellweger syndrome. DBP deficiency is caused by mutations in the HSD17B4 (5q23.1) (Hydroxysteroid 17-Beta Dehydrogenase) gene, which codes for 17-estradiol dehydrogenase, an enzyme involved in the oxidation of VLCFAs and branched-chain fatty acids including pristanic acid and bile acid intermediates. This mutation results in VLCFA, pristanic acid, dihydroxycholestanoic acid, and trihydroxycholestanoic acid accumulation. The abnormal metabolites affect fetal neuronal myelination, differentiation, and migration, causing postnatal visual problems and deafness [2]. Affected children often have severe neurologic involvement, including hypotonia, seizures, and developmental milestone failure. Although they are born at term without growth restriction, they often have polymicrogyria, heterotopic neurons, periventricular white matter abnormalities as well and corpus callosum thinning.

The DBP is a multifunctional enzyme consisting of three domains: the N-terminal short-chain alcohol dehydrogenase domain, which is encoded by exons 1–12 of the HSD17B4 gene; the central 2-enoyl-CoA hydratase domain, which is encoded by exons 12–21; and the C-terminal sterol carrier protein 2-like domain (SCP-2 L), which is encoded by exons 21–24 [3].

DBP deficiency is known to be caused by recessive mutations in the HSD17B4 gene, and is classified into three subtypes based on the functional component involved. The type 1 subgroup involves deficiencies in both the 2-enoyl-CoA hydratase and the 3-hydroxy acyl-CoA dehydrogenase functional subunits, and affected individuals have the most severe phenotype with early onset of symptoms and early death (2 years of age). An isolated subunit deficiency causes type II and III illness (hydratase and dehydrogenase, respectively), with a less severe phenotype and longer longevity (>10 years) [4]. Genotypic and phenotypic spectrums are very variable in this disease. For instance, in our cases, intermediate metabolites increased in one case, and dysmorphism was not present in one case. Profound hearing loss was present in one case.

Nearly all of the 126 patients in a case series study on DBP deficiency manifested with newborn hypotonia (98%) and seizures (93%), as in our case series. A lack of DBP may have caused hypotonia, which may have delayed the baby's cry at birth [5]. Therefore, DBP disorder should be considered in the differential diagnosis of every patient with hypotonia, depression of neonatal reflexes, and developmental delay, especially if accompanied by polymicrogyria, seizures, sensorineural hearing loss, or adrenal insufficiency, regardless of their VLCFA profile. In a case report from China, a 1-day-old male neonate from a non-consanguineous marriage presented with "shortness of breath and hypotonia for 1 day, convulsions for 8 hours" [6]. The baby presented with varus of both feet and left cryptorchidism, including other associated dysmorphism. A case report from Turkey mentioned a 4-year-old girl presenting with refractory seizures and developmental delay [1].

K Nakano reported a case of DBP deficiency with fetal chylous ascites as well as claw hands and hammer toes [7], while Werner KM reported the case of a baby girl who presented with persistent hypoglycemia [8]. Cristel C reported two cases of dysmorphism and primary adrenal insufficiency [9]. Kui Chen reported that HSD17B4 is a gene that contributes to Perrault syndrome, with cerebellar impairment and special manifestations; however, it is crucial to differentiate this from DBP deficiency and hereditary ataxia [10]. Veronica Arora presented a case series of four children with biochemical abnormalities and cerebellar involvement [2].

Ferdinandusse et al. (2006) reported the mutational spectrum of DBP deficiency based on molecular analysis in 110 patients. They found that the effect of the amount of residual DBP activity correlates with the severity of the phenotype. Thus, the data indicated that a genotype–phenotype correlation exists for DBP deficiency [4].

Respiratory failure and aspiration are the most common causes of death in DBP deficiency, and death generally occurs before 1 year of age, although survival to at least 3 years of age is possible [8]. For instance, Takashi Matsukawa reported a case that survived for up to 27 years [11]. Nutrition, placement of a feeding tube, fat-soluble vitamin supplementation, and supportive care constitute the management approach for DBP deficiency.

4. CONCLUSION

Although a rare neurometabolic disorder, deficiency of D BP should be considered in the differential diagnosis of refractory seizures, neonatal hypotonia, and dysmorphic features. Hypotonia is a cause of birth asphyxia and birth asphyxia with HIE leads to hypotonia. As a neonatologist, we should be anxious to determine the primary pathology. This will allow early diagnosis, which is important for diagnosing a fatal disease such as D-bifunctional protein deficiency. A complete neurological examination of the newborn is very important.

CONSENT

As per international standard, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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