Case Report

A Peroxisomal disorder with uncommon characteristics resembling epileptic encephalopathy

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ABSTRACT

Background: D-bifunctional protein (DBP) deficiency is a rare peroxisomal disorder related to fatty acid oxidation, characterized by autosomal recessive inheritance due to mutations in the HSD17B4 gene. This condition encompasses a broad spectrum of diseases, including Zellweger syndrome, an adrenoleukodystrophy-like phenotype, as well as manifestations such as ovarian dysgenesis or neurodegenerative patterns.

Case Report: We report a case of a four-year-old girl, born to consanguineous parents with one sibling death, who presented with early-onset neonatal refractory seizures, mild facial dysmorphism, global developmental delay, profound hypotonia, pigmentary retinopathy, and ovarian dysgenesis, with a normal metabolic profile. Whole exome sequencing revealed a mutation in the HSD17B4 gene, consistent with D-bifunctional protein deficiency.

Conclusion: This case highlights the clinical variability of D-bifunctional protein deficiency and underscores the importance of genetic testing for accurate diagnosis, particularly in patients with a consanguineous background and complex presentations that mimic epileptic encephalopathies.

Keywords: D-Bifunctional Protein Deficiency, Epileptic Encephalopathy, Peroxisomal disorder.

INTRODUCTION

D-bifunctional protein (DBP) deficiency is a rare peroxisomal disorder associated with fatty acid oxidation, characterized by autosomal recessive inheritance. The condition is caused by mutations in the HSD17B4 gene, leading to a deficiency in one or both enzymatic activities of the D-bifunctional protein. Clinically, it presents with a broad spectrum of diseases, as illustrated in Figure 1.

Neurologically, the condition presents in the early neonatal period with seizures, profound hypotonia, dysmorphism, and psychomotor delay, often resulting in the early demise of affected individuals within the first two years of life [1]. We present the case of a Pakistani girl exhibiting a combination of features consistent with D-bifunctional protein deficiency, including an epileptic encephalopathy phenotype and an HSD17B4 variant genotype.

CASE REPORT

This is the case of a 4-year-old Pakistani girl who presented to us at Children's Hospital, Lahore in January 2023. She was born to consanguineous

parents, with a sibling who had passed away at the age of 2 years due to similar complaints. Her birth history was unremarkable. She was delivered via cesarean section at 39+6 weeks, with APGAR scores of 7 and 8 at 1 and 5 minutes, respectively.The patient developed neonatal seizures on the third day of life, characterized by multifocal to generalized tonic-clonic seizures occurring multiple times per day. Initially, the seizures were refractory to treatment, requiring antiepileptic polytherapy with levetiracetam, phenobarbitone, and sodium valproate during the first two years of life. However, by her second birthday, seizure control had improved, allowing a step-down to monotherapy, which provided fair control. Her developmental milestones have been globally delayed, with no neck holding, gaze fixation, or vocalization at 4 years of age. She has a head circumference of 47 cm (10th percentile), fair complexion, and subtle dysmorphic features, including hypertelorism and a flat nasal bridge. She also exhibits generalized profound hypotonia with elicitable reflexes. Systemic examination reveals no visceromegaly, and her heart sounds are normal. Ophthalmological examination showed retinitis pigmentosa with pale discs, while audiometry results were within normal limits.

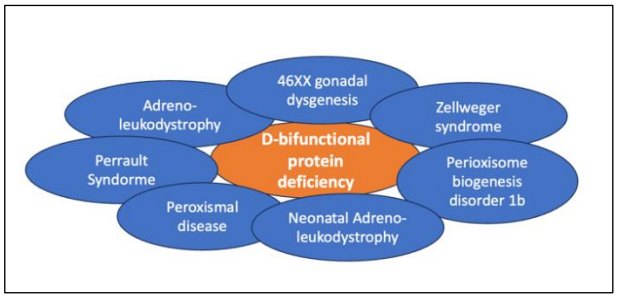

Figure 1: Disease spectrum of D-bifunctional protein deficiency

Cranial ultrasonography during the neonatal period revealed a grade 1 intraventricular hemorrhage. However, follow-up MRI of the brain showed a prominent ventricular system, indicative of brain atrophy (Figure 2). Electroencephalography (EEG) demonstrated multifocal epileptiform discharges with attenuation (Figure 3).

In the biochemical workup of the child, there was borderline hyperammonemia: 139 micromol/L (normal: 18-72), few hypoglycemic episodes reported in early neonatal age. However, serum electrolytes, serum lactate, homocysteine, blood gases and anion gap were all within normal limits. Urinary gas chromatography and plasma amino acids were inconclusive. Considering dysmorphism, screening for systemic anomaly was performed and except ultrasonography of the pelvis revealing non visualized ovarian tissue, rest was within normal limits.

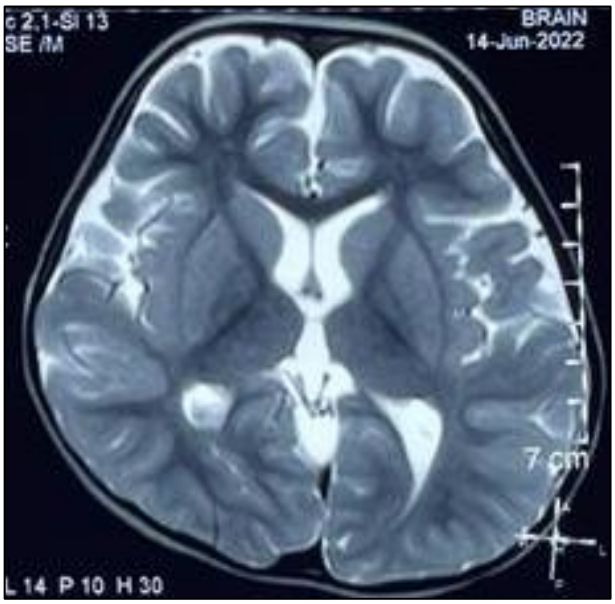

Figure 2: MRI brain axial view T2W image showing prominent ventricular and extra-ventricular spaces

Based on seizures, global developmental delay, profound hypotonia, another sibling death with same course and a normal metabolic profile, we sent her whole exome sequencing to University College London (UCL), which revealed homozygous variant for HSD17B4 consistent with Di-functional protein deficiency as mentioned in figure 4.

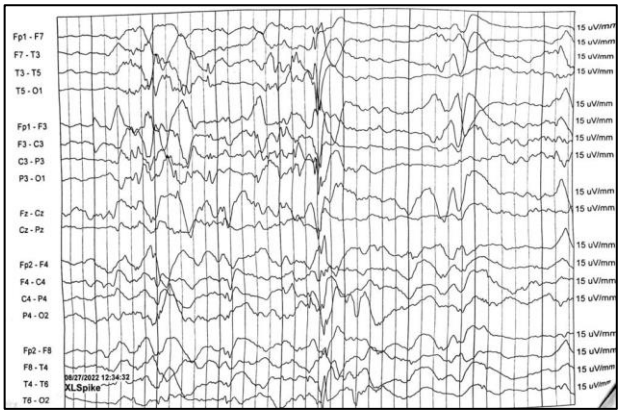

Figure 3: EEG showing multifocal discharges with attenuation

While her illness over one and a half years, the child had recurrent hospital admissions due to respiratory illnesses and recurrent seizures.

Currently, she is bed-bound, with a modified Rankin score of 5, indicating severe disability and the need for constant nursing care [2]. Genetic counseling has been provided to the family.

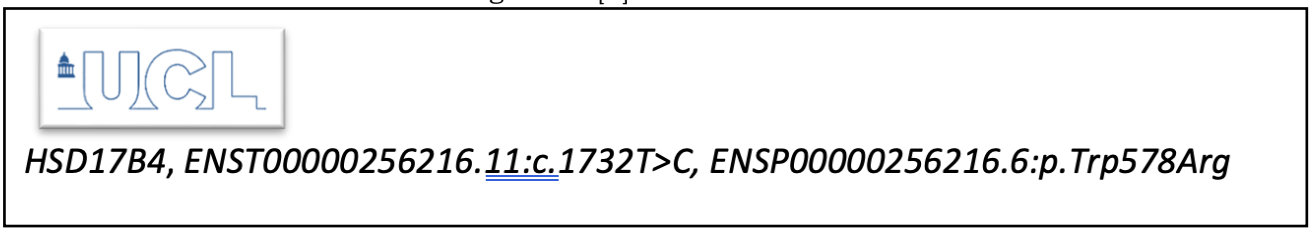

Figure 4: Result of Whole Exome Sequencing

DISCUSSION

The HSD17B4 mutation is a very rare peroxisomal disorder that presents a diverse spectrum of clinical manifestations due to the underlying defect. The neurological course of the disease involves the early onset of seizures in the neonatal period, accompanied by profound psychomotor delay, hypotonia, and craniofacial dysmorphism, with the majority of affected individuals not surviving past their second birthday [3]. Y.E. Landau et al. described four children with variable clinical phenotypes, ranging from neonatal seizures (clonic, tonic, flexor spasms) and hypotonia—similar to our index case—to sensorineural hearing loss in infancy, developmental regression, nystagmus, and the development of peripheral neuropathy by 4 years of age [4]. Yang et al. reported a 15-day-old neonate with seizures, feeding issues, and hypotonia. EEG showed a burst suppression pattern, and there was a reduced brainstem auditory response consistent with hearing loss [5].Our index case also had neonatal-onset seizures and hypotonia; however, there was no hearing impairment, and the EEG displayed a multifocal epileptiform discharge pattern, highlighting the variability in electrophysiological findings.

Chen Si et al. reported a neonate with cosmetic malformations, severe hypotonia, and seizures, accompanied by abnormal brainstem auditory evoked potentials and temporal pigmented spots on the optic disc in the right eye [6].Our index case also presented with pigmentary retinopathy. Mutations in the HSD17B4 gene are known to be associated with ovarian dysgenesis, hearing loss, and ataxia, collectively referred to as Perrault syndrome [7]. Kart et al. and Chen K et al. documented two individuals each with sensorineural hearing loss, skeletal anomalies, ovarian dysgenesis, and neurological symptoms, including late-onset ataxia, in separate studies [8,9].Our patient exhibited ovarian dysgenesis like these cases but did not display other features of Perrault syndrome, suggesting the amalgam of features indicative of DBP deficiency in our index case.

Primary adrenal insufficiency is also part of the spectrum of DBP deficiency. It was identified in one patient described by Y.E. Landau and in two siblings reported by Chapel-Crespo et al [10]. This insufficiency emerged around 2–3 years of age, marked by the onset of electrolyte imbalance. Subsequent testing with ACTH and cortisol confirmed adrenal insufficiency. However, in our index case, serum sodium and potassium levels remained normal throughout these four years, with no hyperpigmentation of the skin. Nonetheless, this highlights the importance of screening for adrenal insufficiency in these patients.

To date, there have been no reported cases of D-bifunctional protein deficiency with neurological manifestations resulting from HSD17B4 mutation in Pakistan. Given the variable clinical features of the DBP deficiency, one should contemplate it as a potential differential diagnosis when there is unexplained hypotonia, developmental delay, hearing loss, visual impairment and seizures. While very long-chain fatty acid (VLCFA) levels can provide diagnostic insights, their availability may be limited. Therefore, it is advisable to expand our clinical perspective in such cases.

CONCLUSION

HSD17B4 mutation leading to D-bifunctional protein deficiency remains a rare peroxisomal disorder, with no case reported from our country till date. Clinical perspective should be expanded in cases with unexplained hypotonia, developmental delay, hearing loss, visual impairment and seizures.

Consent to Publication: Author(s) declared taking informed written consent for the publication of clinical photographs/material (if any used), from the legal guardian of the patient with an understanding that every effort will be made to conceal the identity of the patient, however it cannot be guaranteed.

Authors Contribution: The authors confirm contribution to the paper as follows: **MZR**: Conception and design, data analysis, drafting of manuscript, **OHB**: Data collection, review of manuscript, **TS:** Supervision, critical revision, final approval, **JRA**: Literature review, drafting manuscript, editing.

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