A Rare Cause of Developmental Epileptic Encephalopathy: D-Bifunctional Protein Deficiency with a Novel Pathogenic Variant

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INTRODUCTION

- D-bifunctional protein deficiency (D-BP) is an autosomal recessive peroxisomal fatty acid oxidation disorder
- Presents with; severe developmental delay, hypotonia and refractory neonatal seizures [1]
- The clinical picture is indistinguishable from Zellweger spectrum disease

CASE REPORT

A two-month-old a female infant; born at 35th weeks of gestation from consanguineous parents admitted with recurrent neonatal seizures

- Examination; generalized hypotonia, severe developmental delay, and facial dysmorphism (long face, broad forehead, micrognathia, flat nasal bridge) **(Fig.1)**
- Laboratory; biochemistry and first-step metabolic screening were normal
- Brain MRI; normal
- Plasma VLCFA; high levels of C26:0-cerotic acid and pristanic acid
- EEG; multifocal epileptic discharges and frequent electroclinic seizures on video-EEG monitoring **(Fig.2)**
- Epileptic encephalopathy NGS panel: **novel homozygous pathogenic variant in *HSD17B4* gene** c.1011delT (p.Y337*fs*1) (a premature stop codon) consistent with D-BP (OMIM#261515)
- Parental segregation study revealed heterozygous carrier state for parents **(Fig.3)**

Figure 1. Facial dysmorphism

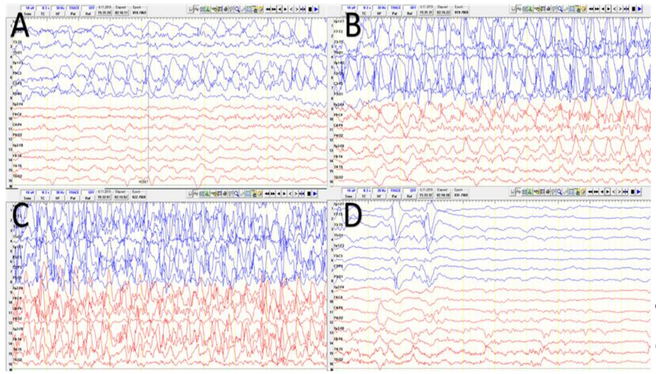

Figure 2. A: An electrographic seizure pattern with sharp-slow wave discharges originating from left central regions (C3), B: spread of discharges to right hemisphere (C4), C: radiating to both hemispheres, D: termination of electrographic activity with background slowing and suppression

DISCUSSION

- Single-enzyme deficiency with biochemical and clinical features resembling Zellweger syndrome.
- Severe developmental delay, hypotonia, seizures in the early months of life, and death by two years of age [2].
- Watkins et al. reported the first case of D-BP in a newborn, who had severe hypotonia and refractory seizures [3].
- EEG characteristics of D-BP was reported in two infants with multifocal spikes in the interictal EEG [4].
- A recent clinical and biochemical review of over 100 patients DBP has documented a similar clinical phenotype [5].

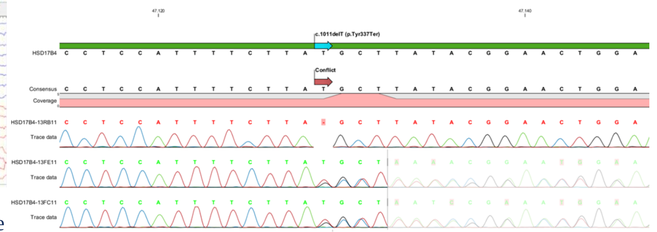

Figure 3. Parental segregation study

CONCLUSIONS

- Next generation genetic studies should be the next step for differential diagnosis of DEE once initial investigations are completed.
- Next generation genetic studies are highly relevant in precision diagnosis when used in proper clinical context.
- Entering an era of novel therapies targeting the cause of seizures rather than seizures themselves.
- Precise diagnosis not only facilitates to inform families better about prognosis but also is the first step towards precision medicine whenever available.

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