

Answering reviewers

- If day is mentioned then you should also add the date of admission respectively. Was it given after the therapy stopped working?

- The dates have added.

Oxazepine was added in January 5, 2021, no seizures, but a rash appeared four weeks later and sleep increased. Oxazepine was discontinued on February 25, 2021, and the rash abated. Perampanel was added in February 26, 2021.

- If you could add generic name of drug in brackets

- perampanel

- How was the seizure controlled throughout the month of January? Can you specify detailed dates regarding the events.

- There were no seizures in January.

Oxazepine was added in January 5, 2021, but a rash appeared four weeks later and sleep increased.

- Can you mention the number of siblings, is it the first or second baby or single baby? And if there are other offspring's then what is their condition please elaborate.

- The patient was the only child in his family and neither parent had other offspring. There was no obvious family history of developmental delay or seizures.

Electroencephalography

Electroencephalography performed in July 2020 revealed an abnormal electroencephalogram: slightly more medium-high amplitude in the left and right frontal regions, a few full-conduction irregular medium-high amplitude

spikes, sharp slow waves, and a slow background rhythm. In July 2021, video electroencephalography revealed highly rhythmic patterns during most of the waking period and the entire sleep period. On the basis of irregular slow waves with full diffusion of 2–7 Hz, the patient exhibited multifocal slow waves, spiky slow waves, polyspinous slow waves, with left and right asymmetry, asynchronous anterior and posterior findings, pronounced anterior activity, and obvious sleep period (Figure. 2).

Genetic analysis

Genomic DNA was isolated from peripheral blood that had been collected from the patient and his parents. Candidate mutation sites were examined by Sanger sequencing. Complex heterozygous mutations were found in the patient's ADSL gene: the splicing mutation c.154-3C>G (present in his father; Figure. 3A–C) and the missense mutation c.71C>T (p. Pro24Leu) (present in his mother; Figure. 3D–F).

The bioinformatics softwares PSIPRED V4.0

(<http://bioinf.cs.ucl.ac.uk/psipred/>) and RaptorX

(<http://raptorx.uchicago.edu>) were used to predict the secondary and tertiary structures, respectively, of mutant and wild-type ADSL proteins. The missense mutation c.71C>T causes an amino acid change from proline to leucine (p. Pro24Leu), possibly leading to a change in polarity (Figure. 4A–F). The splicing mutation c.154-3C>G was predicted to be pathogenic, according to the SD-Score Algorithm (Figure. 5).