Microcephaly, seizures and neurodevelopmental delay associated with PNKP mutation: case report

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Keywords: PNKP, microcephaly, seizures, neurodevelopmental delay

A variety of early-onset epileptic encephalopathies associating recurrent clinical seizures with microcephaly and neurodevelopment delay are caused by inherited defects in DNA repair. One of the most severe epileptic syndromes of early childhood is associated with SCN1A mutations, also known as Dravet syndrome. The PNKP gene is involved in the repair of single and double stranded DNA breaks which play an important role in neuronal development and neurodegeneration.

We present a one year old with an early-onset of focal epileptic seizures which started at the age of 6 months. Clinically, he presented microcephaly, neurodevelopmental delay and intermittent convergent strabismus. The frequency of the seizures was 1/month and their duration varied from 16 to 50 minutes, without a response to intrarectal Diazepam. Until this day he presented 7 focal epileptic seizures corresponding to EEG abnormalities found.

The cerebral MRI showed subcortical demyelination and signs of bilateral hippocampal atrophy. We used whole exome sequencing (WES) to identify homozygosity for a frameshift c.1253_1269dup p.(Thr424Glyfs*49) mutation in PNKP. The patient responded best to antiepileptic treatment with Levetiracetam and Nitrazepam which also showed an improvement in EEG abnormalities.

Mutations in this autosomal recessive gene were previously related to syndromes characterized by infantile epileptic encephalopathy or ataxia-oculomotor apraxia (AOA) type 4. Our patient's phenotype resembled other cases described in the literature, but also associated AOA which is less described, therefore distinguishing our case. The report validates the importance of DNA testing in differential diagnosis of early-onset epileptic encephalopathies, antiepileptic drug response and prognostic.