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

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ABSTRACT

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.

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INTRODUCTION

- Early-onset epileptic encephalopathies are severe disorders characterised by recurrent clinical seizures and neuro-developmental delay during the neonatal or early infantile periods.
- They include: Ohtahara syndrome, early myoclonic epileptic encephalopathy, West syndrome, **Dravet syndrome**, and other diseases. [1]
- PNKP gene has been associated with 3 distinct phenotypes (Fig.1):
  - **microcephaly, seizures, and developmental delay (MCSZ)** [2-5]
  - **ataxia with oculomotor apraxia type 4 (AOA4);** [6]
  - motor and axonal polyneuropathy resembling Charcot-Marie-Tooth disease. (CMT-like) [2]

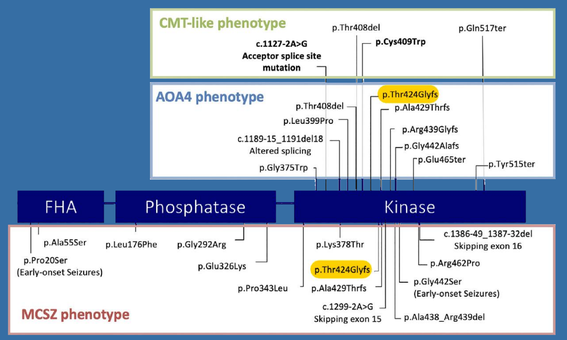

Figure 1. PNKP mutations associated with particular phenotype [2]

CASE PRESENTATION

We present a 1 year and 1 month old male with:

- **8 focal seizures with onset at the age of 6 months**, lasting for 16 up to 50 minutes, without response to intrarectal Diazepam
- Seizure frequency: **1-2/month**
- Mild neurodevelopmental delay
- No family history of diseases
- Normal prenatal and postnatal development until seizure onset
- Seizure free from August 2020

History:

- March 2020 - **seizure onset: 6 months**
- Treatment with intravenous Phenytoin and Carbamazepine after 3 focal epileptic seizures
- June 2020 - **Cerebral MRI: microcephaly, subcortical demyelination and signs of hippocampal atrophy**
  - valproic acid initiated alongside Carbamazepine
- August 2020 – first admission in pour clinic – treatment with Levetiracetam and Nitrazepam initiated, progressively removing Carbamazepine

- 13 months:
- Physical evaluation: W=9000g (p 19%), normal
- **Neurological examination: HC=43cm (p<3%), microcephaly, intermittent convergent strabismus, can maintain orthostatic posture only with support, developmental delay ~10 months.**
- Blood samples – normal
- EEG (Fig.2) during sleep – symmetrical sleep spindels with greater amplitude on the right side entangled with synchronous or asynchronous sharp wave discharges
- Oftalmological evaluation – mild hyperopic astigmatism

- **Whole genome sequencing (WES) – homozygous frameshift c.1253_1269dup p.(Thr424Glyfs*49) mutation in PNKP gene associated with autosomal recesive microcephaly, seizures, and neurodevelopmental delay**

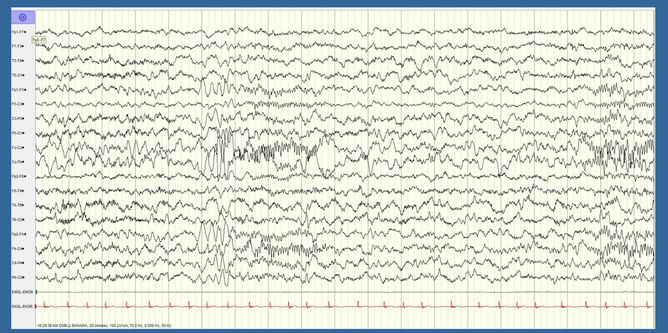

Figure 2. EEG trace during sleep depicting ample sharp wave discharges in the F-C derivations predominently on the right side (Archive of the "Dr. V. Gomoiu" Children's Hospital, pediatric neurology department)

DISCUSSION

- Final diagnosis: PNKP mutation MCSZ phenotype genetic syndrome characterised by microcephaly, focal epilepsy and mild neurodevelopmental delay
- Possible association of AOA4 phenotype
- Differential diagnosis with Dravet syndrome (SCN1A) – most frequent early-onset epileptic encephalopathy, drug resistant epilepsy
- Seizure control with antiepileptic drug therapy with Levetiracetam and Nitrazepam

CONCLUSIONS

- PNKP mutations were previously related to syndromes characterized by infantile epileptic encephalopathy or ataxia-oculomotor apraxia (AOA) type 4. [2-6]
- Our patient's phenotype resembled other cases described in the literature, but also associated signs of possible AOA4 phenotype which is rarely 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.
- Family genetic counseling needed

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