A RARE CAUSE OF AUTISM AND EPILEPSY : GRM7 GENE MUTATION

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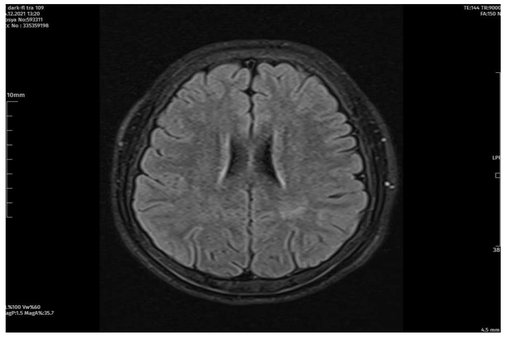
OBJECTIVE: GRM7 gene mutation is a rare autosomal recessive mutation and causes defects in glutamate receptors (1). GRM 7 gene mutation can cause developmental delay, microcephaly, resistant epilepsy, hypotonia, hyperreflexia, autism, attention deficit and hyperactivity disorder (2). Here, we present two male siblings from a non-consanguineous marriage with severe developmental delay, microcephaly , epilepsy and GRM7 gene mutation.

CASE 1: A 17-year-old male patient admitted to our hospital with generalised tonic clonic seizure. He has early-onset hypotonia progressing to spasticity and developed seizures at 1 year of age. Microcephaly, tetraparesis, intellectual disability and motor stereotypes movements such as nodding and stereotypical handshakes were present in neurologic examination. Cranial magnetic resonance imaging (MRI) demonstrated patchy T2 hyperintensities in subcortical and deep periventricular white matter (Picture 1). MR Spectroscopy was normal. Electroencephalography (EEG) examination revealed generalised epileptic discharges (Figure 1). He is on antiseizure treatment with levetiracetam, clobazam and sodium valproate, but his seizures are resistant to antiepileptic treatment.

CASE 2: A 13-year-old male patient admitted to our hospital with generalised tonic clonic seizures started at 2 years of age. He has severe intellectual disability, walkes with support, nonverbal and unable to comprehend or follow simple commands. Cranial MRI and EEG were normal. Seizure control was achieved with 30mg/kg/gün sodium valproate and the patient has been seizure free for three years.

RESULTS: Whole exome sequencing (WES) was performed in both patients and GRM7 missense homozygous mutation (c.2671G>A p.Glu891Lys) was identified.



Picture 1: Cranial MR ımaging (axial T2- FLAIR) of Case 1

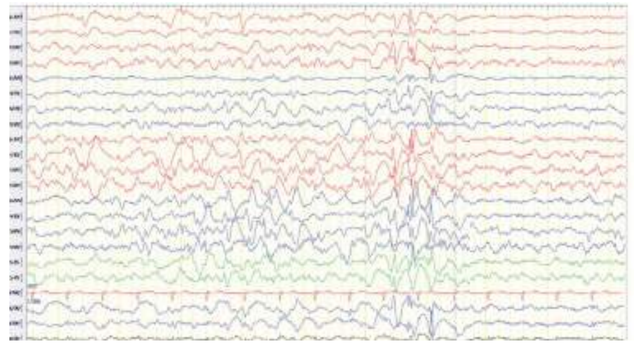


Figure 1 : EEG of Case 1

CONCLUSION: Defects in ion channels and neurotransmitter receptors are implicated in developmental delay and epileptic encephalopathy (1). Glutamate is an excitatory neurotransmitter that is implicated in the pathophysiology of epilepsy and acts via ionothropic (iGluRs) and metabotropic (mGluRs) glutamate receptors (2). Hyperexcitability of the glutamatergic pathway could lead to the severe epilepsy phenotype. Metabotropic glutamate receptor 7 (mGluR7), encoded by GRM7, is a presynaptic G-protein coupled glutamate receptor, most highly conserved mGluR, and critical for synaptic transmission (1). GRM7-related disorders are both congenital and progressive in nature. GRM7 biallelic variants can cause a severe neurological phenotype characterized by microcephaly, developmental delay, stereotypic movements (head nodding and hand clasping), epileptic encephalopathy, hypomyelination and cerebral atrophy (1).

Therefore, loss-of-expression or loss-of-function mutations in GRM7 should be considered as a potential underlying cause for patients with unexplained developmental delay, stereotypic movements and epilepsy.

References

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