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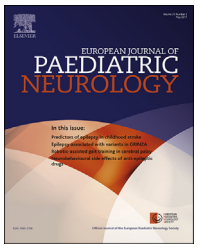

Original article

Epilepsy in patients with *GRIN2A* alterations: Genetics, neurodevelopment, epileptic phenotype and response to anticonvulsive drugs

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Abbreviations: ABPE, Atypical Benign Partial Epilepsy of childhood; ACMG, American College of Medical Genetics; AED, antiepileptic drugs; BECTS, benign focal epilepsy with centrotemporal spikes; CLB, clobazam; CSWS, Continuous Spike Waves during Slow Wave Sleep; EE, epileptic encephalopathy; EEG, electroencephalogramm; ESES, electrical status epilepticus during slow wave sleep; ExAC, Exom Aggregation Consortium; IFE, idiopathic focal epilepsy; LEV, levetiracetam; LKS, Landau Kleffner Syndrome; TPM, topiramate; STM, sultiame; VPA, valproic acid.

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ABSTRACT

Objective: To delineate the genetic, neurodevelopmental and epileptic spectrum associated with *GRIN2A* alterations with emphasis on epilepsy treatment.
Methods: Retrospective study of 19 patients (7 females; age: 1–38 years; mean 10.1 years) with epilepsy and *GRIN2A* alteration. Genetic variants were classified according to the guidelines and recommendations of the American College of Medical Genetics (ACMG). Clinical findings including epilepsy classification, treatment, EEG findings, early childhood development and neurodevelopmental outcome were collected with an electronic questionnaire.
Results: 7 out of 19 patients fulfilled the ACMG-criteria of carrying "pathogenic" or "likely pathogenic variants", in twelve patients the alterations were classified as variants of unknown significance. The spectrum of pathogenic/likely pathogenic mutations was as follows: nonsense n = 3, missense n = 2, duplications/deletions n = 1 and splice site n = 1. First seizures occurred at a mean age of 2.4 years with heterogeneous seizure types. Patients were treated with a mean of 5.6 AED. 4/5 patients with VPA had an improved seizure frequency (n = 3 with a truncation: n = 1 missense). 3/5 patients with STM reported an improvement of seizures (n = 2 truncation, n = 1 splicing). 3/5 CLB patients showed an improvement (n = 2: truncation; n = 1 splicing). Steroids were reported to have a positive effect on seizure frequency in 3/5 patients (n = 1 each truncation, splicing or deletion).
Conclusions: Our data indicate that children with epilepsy due to pathogenic *GRIN2A* mutations present with different clinical phenotypes and a spectrum of seizure types in the context of a pharmacoresistant epilepsy providing information for clinicians treating children with this form of genetically determined epileptic syndrome.

1. Introduction

Glutamate is the most relevant excitatory neurotransmitter within the central nervous system (CNS) and mediates its action via three different receptor types, AMPA-, Kainate- and N-Methyl-D Aspartate-(NMDA-)receptors.[1] Disturbance of NMDA receptors can occur by either genetic disruption of receptor-coding genes or antibodies directed against receptor peptides. Both conditions lead to significant human disease such as epilepsy, developmental delay and autoimmune encephalitis.[2–4] NMDA receptors are di-heteromeric ionotropic complexes consisting of two obligatory GluN1 subunits and two additional GluN2 or other subunits. Four different GluN2 receptor subtypes exist (GluN2A-D). These subtypes determine the functional diversity of the receptor as they reveal different expression patterns during brain development and maturation.[5,6] In addition, they show different spatial expression in the brain. GluN2A expression in rats is not detectable at birth, but it is present at P14 (corresponding to the first year of life in a human) and is mostly abundant in the adult rat. Thus, GluN2A is believed to be the most relevant GluN2 subunit from childhood to adulthood. GluN2A consist of an extracellular N-terminal (NTD) and a ligand-binding domain (LBD), three transmembrane domains (M1, 3 and 4), a re-entry loop (M2) and an intracellular C-terminal domain (CTD). The NTD harbors a Zn^{2+} binding site, which is involved in Zn^{2+} mediated inhibition of the receptor. The ligand-binding domain mediates glycine binding in GluN1 receptor subtypes and glutamate binding in GluN2 receptor subtypes, the transmembrane domains M1 to M4 build the ion channel pore. The intracellular C-terminal domain is the most divergent region among GluN2 subtypes and mediates intracellular signals. GluN2A is encoded by the gene *GRIN2A* on human chromosome 16.[7] *GRIN2A* consists of 14 exons and encodes the 1464 amino acid GluN2A subunit of the GluN2 receptor complex.

Mutations within the *GRIN2A* gene may cause benign focal epilepsy with centrotemporal spikes (BECTS).[2] In addition, *GRIN2A* gene mutations are more likely to occur in epilepsy subtypes which are believed to be a more severe variant of BECTS as Continuous Spike Waves during Slow Wave Sleep (CSWS), Landau Kleffner Syndrome (LKS) and Atypical Benign Partial Epilepsy (ABPE) of childhood.[8] The latter ones are usually difficult to treat epilepsy syndromes. Attempts have been made to use the NMDA-receptor inhibitor memantine in a patient with a mutation leading *in vitro* to a gain of function of the channel.[9,10]

In the present investigation, we studied seven patients with childhood-onset epilepsy with pathogenic alterations