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Preliminary Study About A Significant and Treatable Cause of Epileptic Encephalopathy: GRIN2D Mutation

Epileptik Ensefalopatinin Önemli ve Tedavi Edilebilir Bir Nedeni Hakkında Ön Çalışma: GRIN2D Mutasyonu

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ABSTRACT

Aim: The *GRIN2D* gene mutation causes severe forms of epileptic encephalopathy. NMDAR antagonists and magnesium sulfate could be useful as adjunctive therapy to control seizures in individuals with *GRIN2D* encephalopathy. The aim of this study was to describe the clinical features and treatment options of *GRIN2D* encephalopathy.
Methods: Patients followed up with epileptic encephalopathy in our pediatric neurology clinic were investigated for genetic etiology using next-generation sequencing (NGS)-based tests. Patients with the *GRIN2D* mutation were overviewed for clinical and genetic characteristics.
Results: A total of 53 patients were screened and *GRIN2D* mutations (c.3684_3685insGA, c.3248_3254del, c.1579G>T, c.47_49del) were detected in four patients. Occipital epileptic activity was frequently detected among our patients. Three patients received memantine treatment for intractable epilepsy and remained seizure-free.
Conclusion: *GRIN2D* encephalopathy is a treatable epileptic encephalopathy, and its recognition is important in terms of outcomes. Occipital epilepsy is generally benign, but developmental and epileptic encephalopathies such as *GRIN2D* encephalopathy should be considered in the presence of concomitant developmental delay.

Keywords: developmental delay; epileptic encephalopathy; *GRIN2D*; memantine; NMDA

ÖZ

Amaç: *GRIN2D* gen mutasyonu, ağır epileptik ensefalopatiye neden olur. NMDAR antagonistleri ve magnezyum, *GRIN2D* ensefalopatili bireylerde nöbetleri kontrol etmek için faydalı bir tedavi seçeneği olabilir. Bu çalışmanın amacı *GRIN2D* ensefalopatisinin klinik özellikleri ile tedavi seçeneklerini tanımlamaktır.
Yöntemler: Çocuk nöroloji kliniğimizde epileptik ensefalopati ile izlenen hastalar genetik etiyoloji açısından yeni nesil dizileme yöntemi tabanlı testler ile incelendi. *GRIN2D* mutasyonu olan hastalar klinik ve genetik özellikler açısından değerlendirildi.
Bulgular: Toplam 53 hasta tarandı. 4 hastada *GRIN2D* mutasyonları (c.3684_3685insGA, c.3248_3254del, c.1579G>T, c.47_49del) tespit edildi. Hastalarımızda oksipital epileptik aktivite sıklıkla tespit edildi. 3 hastaya inatçı epilepsi için memantin tedavisi başlandı ve bu hastalar nöbetsiz olarak takip edilmekteler.
Sonuç: *GRIN2D* ensefalopati, tedavi edilebilir bir epileptik ensefalopatidir ve hastanın sağkalımı açısından tanınması önemlidir. Oksipital epilepsi genellikle iyi huyludur, ancak eşlik eden gelişimsel gecikme varlığında *GRIN2D* ensefalopatisi gibi gelişimsel ve epileptik ensefalopatiler akla gelmelidir.

Anahtar Sözcükler: epileptik ensefalopati, gelişme geriliği, *GRIN2D*, memantin, NMDA

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INTRODUCTION

Glutamate is the main excitatory neurotransmitter of the central nervous system (CNS). Glutamate takes an important part in many basic neuronal functions and CNS processes, such as learning, memory, and synaptic plasticity. [1] N-methyl- D-aspartate receptors (NMDAR) are voltage-dependent ionotropic glutamate receptors and tetrameric assemblies containing GluN1 and GluN2 subunits. Four independent genes (*GRIN2A, GRIN2B, GRIN2C,* and *GRIN2D*) encode GluN2A-D subunits.[2] NMDAR activity is crucial for neurodevelopment, synaptogenesis, general cognition, spatial learning, locomotion, and memory formation. NMDAR mutations (*GRIN1* [MIM: 138249], *GRIN2A* [MIM: 138253], *GRIN2B* [MIM: 138252], *GRIN2C* [MIM: 138254], and *GRIN2D* [MIM: 602717]) are associated with variable neurologic diseases, including schizophrenia, intellectual disabilities, autism, epilepsy, and attention-deficit/hyperactivity disorder.[3] Epileptic encephalopathies manifest with intractable seizures and neurodevelopmental disabilities and have monogenic disorders as part of the various etiologies. Children with epileptic encephalopathy have a shortened life expectancy, and most patients experience little to no relief from seizures with anti-epileptic drug (AED) treatment. In light of technological advances, genetic analysis has provided for establishing the precise genetic etiology in individuals.[4] Validation of genetic etiologies and specific disease mechanisms make personalized therapeutic regimens possible. Genetic variations of the autosomal dominant inherited *GRIN2D* gene mutation cause severe forms of epileptic encephalopathy, which manifest early during infantile or adolescent development. NMDAR mutations cause greatly increased current flow through mutant-GluN2A-containing NMDARs, leading to the excessive excitatory drive, thereby inducing seizure activity and/or excitotoxicity.[5] Memantine is a noncompetitive antagonist of the NMDA-type glutamate receptor. It interacts with the Mg+2 binding site of the channel to prevent excessive activation while sparing normal function.[6] NMDAR antagonists and magnesium sulfate might be useful adjunctive therapy to control seizures in individuals with *GRIN2D* encephalopathy.[4] Here, we report distinct clinical, genomic, and therapeutic features of four patients with *GRIN2D* encephalopathy with different variants of the *GRIN2D* gene.

METHODS

Patients who were followed up with epileptic encephalopathy in the pediatric neurology clinic of Antalya Training and Research Hospital and had a genetic diagnosis were retrospectively screened. The genetic diagnosis was made by investigating the most common actionable genes of epileptic encephalopathy using next-generation sequencing (NGS)-based tests (Table 1).[7] Each variant was evaluated according to the American College of Medical Genetics and Genomics (ACMG) criteria. [8] The information about genetic examinations of the patients was given in details in the cases section.

Epileptic encephalopathy is defined as an electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy by the International League Against Epilepsy (ILAE) Commission on Classification and Terminology.[9]

The aim of this study was to describe the clinical features and treatment options of *GRIN2D* encephalopathy. Electroencephalography (EEG), magnetic resonance imaging (MRI), and metabolic screening tests were performed for all patients with *GRIN2D* mutations. Only the clinical and genetic characteristics of patients with *GRIN2D* encephalopathy were reviewed and presented in this study. Written informed consent was obtained from all parents of the children, which was approved by Antalya Research and Training Hospital Ethics Committee (Date: 04.03.2021 number: 1/44).

RESULTS

Patients:

A total of 53 patients with epileptic encephalopathy were screened using NGS-based tests. A genetic mutation associated with epileptic encephalopathy was detected in 33 patients (62,2%). Novel variants in *GRIN2D* were detected in four patients (7,5%) and none of these variants was reported in the literature before. By using the ACMG criteria, we classified *GRIN2D* variants as pathogenic or likely pathogenic. The clinical and genetic

characteristics and treatment regimens of patients with *GRIN2D* encephalopathy which is rare and treatable are presented as case reports below.

Case 1

The first patient was a 3-year-old girl, who presented to our clinic with status epilepticus at age 2.5 years. She was previously followed with intractable epilepsy, global developmental delay, and static encephalopathy. Her prenatal period was uneventful, and she was born at term as the first child from nonconsanguineous parents. She had no previous neurologic medical history in her family. She had migratory focal clonic seizures in the first week of life. Later, hypotonia and eye flutter accompanied the seizures. Phenobarbital, levetiracetam, and topiramate were given for the seizures, respectively. She was unresponsive to treatment, had status epilepticus, and was admitted to the pediatric intensive care unit (PICU) at age 3 months. Her seizures were managed with midazolam and thiopental infusions. Carbamazepine and clonazepam were added to treatment instead of phenobarbital. She was admitted to the PICU three more times for status epilepticus until the age of 2 years. Valproic acid, lamotrigine, sulthiame, and clobazam were also added to treatment but she was unresponsive.

A physical examination revealed normal deep tendon reflexes, strabismus, bilateral ocular flutter, truncal ataxia, and mild hypotonia. She had no dysmorphic features or pathologic reflexes. She was able to hold her head at the age of 8 months and sit unsupported at the age of 14 months. She could not walk or talk.

The patient's first EEG showed multifocal epileptic anomaly and remained similar until the age of 1 year. Metabolic studies: ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, lactate, pyruvate, tandem mass spectrometry, vitamin B12, and folic acid were within normal limits. Her brain MRI and MR spectroscopy were normal.

At age 2.5 years, she had status epilepticus and was admitted to the PICU, when we first evaluated her for a pediatric neurology consultation. Her recent treatment regimen was valproic acid, lamotrigine, sulthiame, and clobazam. Her seizures continued as a multifocal clonic type while she was receiving midazolam and thiopental infusions. An EEG study during status epilepticus showed ictal epileptic discharges in the bilateral parietooccipital region. Ketamine infusion was initiated, and her seizures stopped. The second EEG study after the ketamine infusion showed interictal parietooccipital epileptic activity. Clinical exome sequencing (CES) was conducted after the ketamine response. A novel, heterozygous *GRIN2D* c.3684_3685insGA variant was detected. A *GRIN2D* c.3684_3685insGA (NM_000836.4, p.Pro1229AspfsTer290T) variant was evaluated according to the ACMG criteria, and this variant was classified as pathogenic because it was a null variant (frame-shift) and in gene *GRIN2D*, for which loss-of-function is a known mechanism of disease (gnomAD Loss-of-Function Observed/ Expected = 0.0529 is less than 0.763), associated with developmental and epileptic encephalopathy 46 (PVS1 criteria), not found in gnomAD genomes (PM2 criteria), compatible with the patient's clinic (PP4 criteria). Oral memantine (0.5 mg/kg/day) and magnesium sulfate therapies were initiated. Her seizure frequency and severity reduced gradually. In the last visit, the patient was seizure-free for 4 months, could continue her daily life, and her neuromotor development was improved. The latest EEG study was normal (Figure 1). She has been able to walk and talk with simple words since the age of 33 months (Table 2).

Case 2

Patient 2 was a 4.5-year-old girl who presented with neonatal seizures. Her prenatal period was uneventful, and she was born at term as the second child from nonconsanguineous parents. She had no previous neurologic medical history in her family. Her first seizure was focal onset motor clonic type on the 16th day of life. The first EEG study was normal. She was seizure-free for 2 months after phenobarbital therapy. She had flexor spasm seizures at 3 months, and the EEG study revealed hypsarrythmia. Adrenocorticotropic hormone (ACTH) and pyridoxine treatments were initiated and levetiracetam was added to treatment later. She had neuromotor developmental delay; she was able to raise her head at age 9 months and sit unsupported at the age of 26 months. She could not walk or talk.

Table 1. List of actionable genes

Actionable genes	HGNC Approved Gene Symbol	Phenotypes #MIM number
Alpha-2B-Adrenergic Receptor	*ADRA2B*	607876
Aldehyde Dehydrogenase 7 Family, Member A1	*ALDH7A1*	266100
Folate Receptor, Alpha	*FOLR1*	613068
Guanidinoacetate Methyltransferase	*GAMT*	612736
L-Arginine:Glycine Amidinotransferase	*GATM*	612718, 134600
Potassium Channel, Voltage-gated, Kqt-Like Subfamily, Member 2	*KCNQ2*	613720, 121200
Potassium Channel, Voltage-Gated, Kqt-Like Subfamily, Member 3	*KCNQ3*	121201
Potassium Channel, Subfamily T, Member 1	*KCNT1*	614959, 615005
Methyl-Cpg-binding Protein 2	*MECP2*	300496, 300673, 300260, 300055, 312750
Pyridoxamine 5-Prime-Phosphate Oxidase	*PNPO*	610090
Polymerase, DNA, Gamma	*POLG*	203700, 613662, 607459, 157640, 258450
Proline-Rich Transmembrane Protein 2	*PRRT2*	602066, 128200, 605751
Quinoid Dihydropteridine Reductase	*QDPR*	261630
Sodium Voltage-gated Channel, Alpha Subunit 1	*SCN1A*	607208, 604403, 609634
Sodium Voltage-gated Channel, Alpha Subunit 2	*SCN2A*	613721, 618924, 607745
Sodium Voltage-gated Channel, Alpha Subunit 8	*SCN8A*	618364, 614306, 614558, 617080
Solute Carrier Family 19 (Thiamine Transporter), Member 3	*SLC19A3*	607483
Solute Carrier Family 2 (Facilitated Glucose Transporter), Member 1	*SLC2A1*	614847, 606777, 612126, 608885
Solute Carrier Family 6 (Neurotransmitter Transporter, Creatine), Member 8	*SLC6A8*	300352
Syntaxin-binding Protein 1	*STXBP1*	612164
Tsc Complex Subunit 1	*TSC1*	607341, 606690, 191100
Tsc Complex Subunit 2	*TSC2*	607341, 606690, 613254
Glutamate Receptor, Ionotropic, N-Methyl-D-Aspartate, Subunit 2A	*GRIN2A*	245570
Pyridoxal Phosphate-binding Protein	*PLPBP*	617290
Glutamate Receptor, Ionotropic, N-Methyl-D-Aspartate, Subunit 2D	*GRIN2D*	617162

The term "actionable genes" is used to indicate clinical applicability based on evidence and to describe the genes that are most effective in curing, preventing and/or delaying clinical disease. In our center, the "actionable genes" list includes genes that are statistically common and associated with specific FDA-approved drug response to help patients with epilepsy to receive appropriate treatment faster. These actionable genes were filtered out by Medical Genetics Department in our center.

Table 2. Phenotype and variant summary of GRIN2D encephalopathy patients. PVL: Periventricular leukomalacia, AEDs: antiepileptic drugs, LVT: levetiracetam, VPA: valproic acid, CBZ: carbamazepine,

Patient number	1	2	3	4
Age on-set	1 wk	16 days	4 years old	16 days
Current Age (years)/Sex	3/F	4/F	18/M	7.5/M
GRIN2D variants	*GRIN2D* c.3684_3685insGA	*GRIN2D* c.3248_3254del	*GRIN2D* c.1579G>T	*GRIN2D* c.47_49del
EEG	Parietooccipital epileptic activity	Parieto-occipital epileptic activity	Bilateral temporal epileptic activity	Bilateral temporoparietal epileptic activity
MRI	Normal	PVL	Normal	Normal
Response to AEDs	No response to other AEDs, seizure-free with memantine and MgSO4	No response to LVT and VPA, seizure-free with memantine	Mild response with CBZ, LTG, LVT and memantine	Seizure free with VPA
Age on-set	1 week	16 days	4 years	16 days
Develop-mental delay and other neurological features	Hold her head at 8 mo and sit unsupported at 14 mo. She can ataxic walk and talk with simple words since 33 mo. Occuler flutter.	Raise her head at 9 mo, sit unsupported at 26 mo. Cannot walk or talk. Poor attention to surroundings, strabismus, hypertonicity, hyperactive deep tendon reflexes.	Mild mental retardation	Delayed speech development

LTG: lamotrigine.

In a physical examination, she had poor attention to surroundings, strabismus, hypertonicity, and hyperactive deep tendon reflexes. She had no dysmorphic features or pathologic reflexes.

Metabolic studies: ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, lactate, pyruvate, tandem mass spectrometry, vitamin B12, and folic acid were within normal limits. Brain MRI revealed periventricular leukomalacia and MR spectroscopy was normal. An epilepsy panel performed by using NGS analysis revealed a novel, heterozygous *GRIN2D* c.3248_3254del variant. The *GRIN2D* c.3248_3254del (NM_000836.4, p.Gly1083GlufsTer433) variant was evaluated according to the ACMG criteria, and this variant was classified as pathogenic because the variant is a null variant (frame-shift), and in gene *GRIN2D*, for which loss-of-function is a known mechanism of disease (gnomAD Loss-of-Function Observed/ Expected = 0.0529 is less than 0.763), associated with developmental and epileptic encephalopathy 46 (PVS1 criteria), not found in gnomAD genomes (PM2 criteria), compatible with the patient's clinic (PP4 criteria). No other new therapies were initiated after the genetic analysis because her seizures had been under control with levetiracetam for 2 years, but follow-up EEG studies revealed parietooccipital epileptic activity. She had migratory focal clonic seizures and ocular flutter at the age of 3.5 years. Her seizures were prolonged and refractory, she had status epilepticus and was admitted to the PICU. Valproic acid was added to her antiepileptic treatment. An EEG study showed interictal epileptic activity in the parietooccipital region (Figure 2). On follow-up, her seizures continued as the multifocal clonic-type and ocular flutter. Memantine (0.5 mg/kg/day) was added to the treatment, seizures remained under control, and valproic acid and levetiracetam treatments were stopped gradually. She has been seizure-free for 8 months and the latest EEG was normal (Table 2).

Case 3

Patient 3 was an 18-year-old boy who was born at term to nonconsanguineous parents. His neonatal period was uneventful and his neuromotor development was appropriate, only his speech development was delayed. He presented for medical attention with a right focal motor clonic seizure following sudden visual loss at age 4 years. A EEG study showed bilateral occipital epileptic activity. Levetiracetam was initiated after the first seizure and oxcarbazepine was added to treatment later because of continuing multifocal clonic seizures. Multifocal clonic seizures and bilateral occipital epileptic activity remained for almost 4 years. At the age of 8 years, atonic seizures presented, and EEG studies showed bilateral temporal epileptic activity. Valproic acid, clobazam, carbamazepine, lamotrigine, rufinamide, lacosamide, sulthiame, primidone, zonisamide, topiramate were tried for treatment. Metabolic studies: ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, lactate, pyruvate, tandem mass spectrometry, vitamin B12, and folic acid were within normal limits. Brain MR and MR spectroscopy were normal. He presented to our clinic at around the age of 15 years. The only pathologic finding was mild mental retardation on physical examination. His intelligence quotient (IQ) score was 80 (IQ, Stanford Binet Intelligence Scales, 5th Edition). By that time, his seizure frequency was 4-5 times per week and the seizure types were atonic and multifocal clonic. On follow-up, his treatment was rearranged as carbamazepine, levetiracetam, and lamotrigine, and an EEG study showed bilateral frontotemporal epileptic activity. He was diagnosed as having non-Hodgkin lymphoma at the age of 16 years; therefore, he did not continue regular follow-ups for epilepsy for 1.5 years. After full remission of non-Hodgkin lymphoma, whole-exome sequencing (WES) analysis was performed and a novel, heterozygous *GRIN*2D c.1579G>T variant was detected. The *GRIN2D* c.1579G>T (NM_000836.4, p.Glu527Ter) variant was evaluated according to the ACMG criteria and classified as pathogenic because it was a null variant (frame-shift), and in gene *GRIN2D*, for which loss-of-function is a known mechanism of disease (gnomAD Loss-of-Function Observed/ Expected = 0.0529 is less than 0.763), associated with developmental and epileptic encephalopathy 46 (PVS1 criteria), not found in gnomAD genomes (PM2 criteria), compatible with the patient's clinic (PP4 criteria). Memantine (0.5 mg/kg/day) was initiated. The latest EEG study showed bilateral

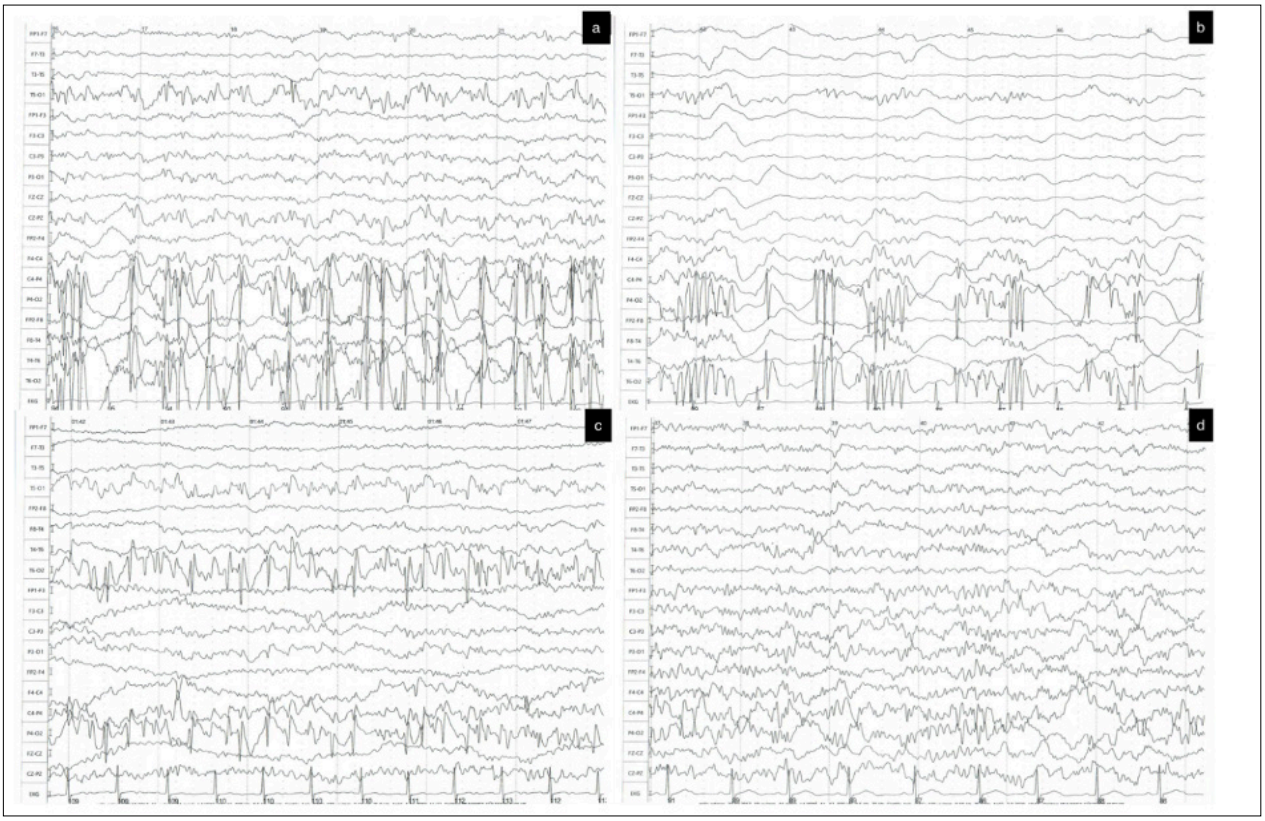

Figure 1. EEG pattern changes of patient 1: a) Convulsive status epilepticus, constant right parietooccipital epileptic activity. b)Epileptic activity after thiopental administration. c)Epileptic activity after ketamine administration. d)Normal EEG pattern after memantine treatment

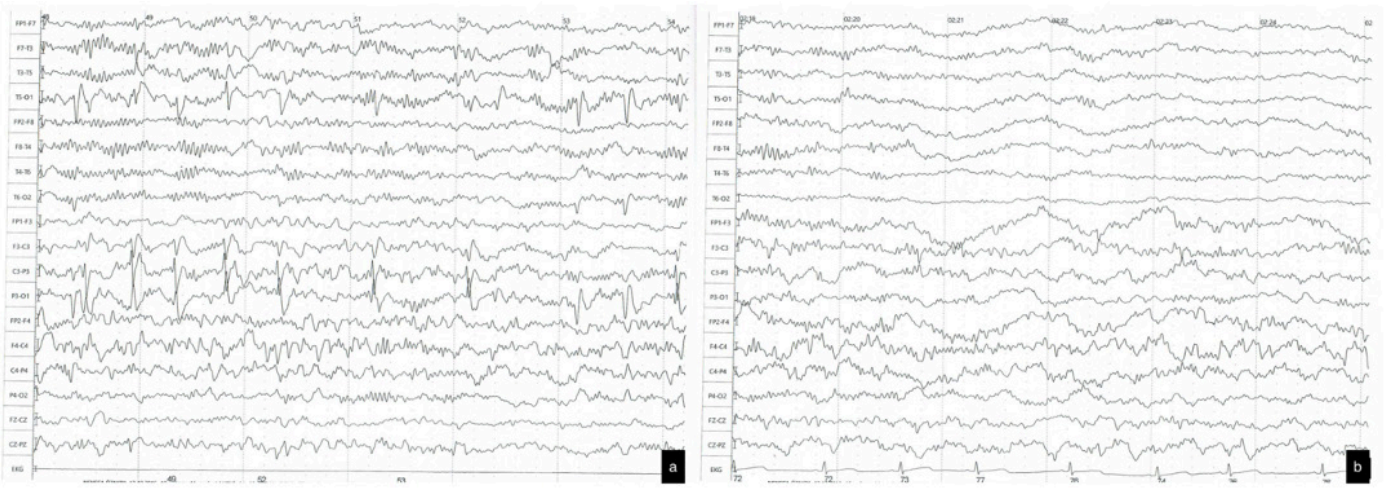

Figure 2. EEG pattern changes of patient 2: a) Intractable epilepsy left parietooccipital epileptic activity. b)Normal EEG findings after memantine treatment.

temporal epileptic activity. His seizure frequency was reduced to one in four or five months (Table 2).

Case 4

Patient 4 was a 7.5-year-old boy who was born at term. His prenatal period was uneventful. He was the third child of nonconsanguineous healthy parents, and his two elder brothers were healthy. Mental retardation was seen in two members of the extended family. His first seizure was multifocal clonic type and occurred on the 16th day of life. The first EEG study was normal. Phenobarbital was initiated as anticonvulsant therapy. He had a second multifocal clonic seizure at age 6 months and levetiracetam was added to his therapy. By the age of 8 months, he had the third seizure, the same as in previous seizures. Anticonvulsant therapy was rearranged as a higher dose of levetiracetam monotherapy until 1 year of age

when he experienced agitation and valproic acid monotherapy was initiated. All EEG studies were normal until age 3.5 years. He had a tonic seizure, and parietooccipital epileptic activity was detected on an EEG study for the first time.

He could sit unsupported and walk independently at the appropriate age, but his speech development was delayed. A physical examination was normal except for language skills.

Metabolic studies: ammonia, plasma, and urine amino acid analysis, long-chained fatty acid analysis, urine organic acid analysis, lactate, pyruvate, tandem mass spectrometry, vitamin B12, and folic acid were within normal limits. Brain MRI and MR spectroscopy were normal.

The patient presented to or clinic at age 4.5 years. His anticonvulsant therapy at that time was valproic acid and an EEG study showed parietooccipital epileptic activity. He had seizures once per year for 2 years. WES analysis was conducted and a novel, heterozygous *GRIN2D* c.58_60delCTG variant was detected. The *GRIN2D* (NM_000836.4, p.Leu20del) variant was evaluated according to the ACMG criteria and classified as likely pathogenic because it was located in a mutational hot spot and/or critical and well-established functional domain (e.g., the active site of an enzyme) without benign variation (PM1 criteria), not found in gnomAD genomes (PM2 criteria), protein length changes as a result of in-frame deletions/insertions in a non-repeat region or stop-loss variants (PM4 criteria), and compatible with the patient's clinic (PP4 criteria).

Follow-up EEG studies showed bilateral temporoparietal epileptic activity. Memantine was not initiated, and anticonvulsant therapy remained as valproic acid because his seizure frequency was low. His last seizure was 6 months ago. He has been receiving speech therapy rehabilitation (Table 2).

DISCUSSION

Developmental and epileptic encephalopathies (DEEs) represent a clinically and genetically heterogeneous group of age-dependent neurologic disorders characterized by the onset of refractory seizures in infancy or early childhood. Affected individuals have delayed psychomotor development or developmental regression, particularly after the onset of seizures. DEE incorporates the previous grouping of "early infantile epileptic encephalopathies (EIEE)." There are 89 described DEEs in the literature and the phenotype is also observed in other genetic disorders, including GLUT1 deficiency syndrome, glycine encephalopathy, Aicardi-Goutières syndrome, and in males with *MECP2* mutations. [10] *NMDAR* mutations are associated with DEEs; DEE27 is caused by a mutation in the *GRIN2B* gene, DEE46 is caused by a mutation in the *GRIN2D* gene.[3,4,11]

We described four patients with DEE and de novo variants in the *GRIN2D* gene. Age at onset of epileptic encephalopathy is generally before 2 years of age.[12] Camp et al. reported a median age of onset of 6.5 months for *GRIN2D* DEE.[3] Three of our patients had seizures within the first month of life and patient 3 had their first seizure rather late, at age 4 years.

Early studies of *NMDAR* genes were about schizophrenia and autism spectrum disorder. In 2011, Tarabeux et al. showed neuropsychiatric disease's relation to *GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIN2D* families.[1] Camp et al. found that 31% of patients displayed autistic-like features and behaviors accompanying epilepsy.[3] None of our patients had autistic-like features or behaviors. Developmental delay and intellectual disability are part of the clinical characteristics, but affected individuals show varying severity, as in our patients; patient 3 was independent in his daily life, but patient 2 was bedbound.

In epileptic encephalopathies, particularly spasm, and tonic, clonic, myoclonic, atonic, atypical absence seizures can be seen in infancy. Over time, changes can be seen between these seizure types.[10,13] Multifocal clonic seizures and spasms are prominent in *GRIN2D* encephalopathy.[3] Multifocal clonic seizures were more common in our patients. With age, as in other epileptic encephalopathies, our patients also developed atonic, tonic, and atypical absence seizures. In *GRIN2D* encephalopathy, unlike other epileptic encephalopathies, ocular flutter, tongue movement, and body tremor, which occur out of

seizures and increase during seizures, have been reported.[3]

Hypsarrhythmia and multifocal epileptiform abnormalities are prominent EEG patterns for epileptic encephalopathies in infancy. EEG patterns can change into multifocal/focal epileptiform abnormalities, Lennox-Gastaut syndrome, and epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) over time.[13,14] A limited case series about *GRIN2D* encephalopathy revealed a multifocal epileptiform abnormality, hypsarrhythmia, focal spike-wave activity, and paroxysmal fast activity patterns on EEG.[3] One of our patients had a multifocal epileptiform abnormality and one had a hypsarrhythmia pattern in infancy. Different from the literature, two patients had normal EEG patterns in infancy. Patients 1 and 2 developed bilateral parietooccipital epileptiform activity and patient 3 developed bilateral occipital epileptiform activity later in life. Occipital epileptiform activity is mainly seen in childhood epilepsy with occipital paroxysm (CEOP) and CEOP is classified as benign childhood epilepsy. Li et al. reported a poor prognosis of occipital epileptiform activity in *GRIN2D* encephalopathy.[4] Although cerebral atrophy, cerebellar atrophy, and cortical atrophy were frequently mentioned in previous studies, no specific MRI findings were reported in *GRIN2D* mutation.[3,15]

Specific treatment options are available for some of the genetic epileptic encephalopathies; pyridoxine dependent epilepsy (PDE) caused by an *ALDH7A1* genetic defect (PDE-*ALDH7A1*), Menkes disease, pyridox(am)ine-5-phosphate oxidase (PNPO) deficiency, cobalamin G deficiency, severe methylenetetrahydrofolate reductase (MTHFR) deficiency, glucose transporter 1 (GLUT1) deficiency, glycine encephalopathy, and pyruvate dehydrogenase complex (PDHC) deficiency, uridine responsive CAD deficiency, cerebral folate deficiency, creatinine deficiency syndrome, DEND syndrome, serine biosynthesis defect, biotinidase deficiency, nonketotic hyperglycinemia, KCNQ2 encephalopathy, KCNT1-related epilepsy, and BH4 deficiency (Table 1).[16–18] Memantine is prominently used in cognitive impairments such as Alzheimer's disease.[19] With its effect on NMDARs, studies have been conducted for the use of memantine as an AED in GRIN mutations.[4–6,20] Memantine was used in patient 1 with refractory status, patient 2 with intractable seizures, and patient 3 with frequent seizures. Both patients 1 and 2 remained seizure-free, and the seizure frequency of patient 3 was reduced.

Limitations of the study

Our study has several limitations, mainly related to the study population size. The number of patients meeting the inclusion criteria was small because it was a single center study. In our opinion, it would be more effective to identify new variants and define the phenotype-genotype characteristics of these variants in a multi-center study.

CONCLUSION

Occipital epilepsy is usually benign, but with developmental delay, epileptic encephalopathy must be considered. Genetic studies are important for epileptic encephalopathy because specific therapies for targeted gene mutations are available for some epileptic encephalopathies. Genotype-phenotype correlation studies are necessary to gain more information about the subject.

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Ethics Committee Approval: Antalya Research and Training Hospital Ethics Committee (Date: 04.03.2021 number: 1/44).

Peer-review: Externally and internally peer reviewed.

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