GRIN2A-Related Severe Epileptic Encephalopathy Treated with Memantine: An Example of Precision Medicine

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Abstract

Epileptic spasm (ES) is one of the seizure types which is difficult to treat. Next-generation sequencing has facilitated rapid gene discovery that is linked to ES and *GRIN2A* being one of them. Genotype-driven precision medicine is on the horizon and is a targeted treatment approach toward the precise molecular cause of the disease. *GRIN2A* gene encodes for a subunit of N-methyl-D-aspartate (NMDA) receptor and it has been suggested from in vitro studies and few case reports that memantine, a NMDA receptor antagonist, was shown to reduce seizures in patients with *GRIN2A* mutations. Here, we describe a patient with a novel *GRIN2A* mutation and severe drug-resistant ES who became seizure free with memantine.

Keywords

► GRIN2A
► precision medicine
► memantine

Introduction

West syndrome is an epileptic encephalopathy of infancy that manifests as epileptic spasms (ES), hypsarrhythmia, and psychomotor retardation.[1] The worldwide incidence is estimated to be 0.25 to 0.42 per 1,000 live births per year.[2] It can be caused by a variety of different etiologies that can have a significant impact on the management and overall outcome. Genetic diagnoses are frequent, with a rapidly growing list of genes linked to ES including *GRIN2A, TSC1, TSC2, FOXG1, STBXBP1, ALG13, PNPO, ADSL, PHACTR1,* and *TIMM50*.[3] Not all patients with mutations in these genes develop ES, and extensive research is ongoing to find acceptable explanations.

Precision medicine could become a new paradigm for the prevention and treatment of disease based on individual variability in genes, environment, and lifestyle for each person.[4] Understanding of basic differences between patients leads to repurposing of drugs or even development of new therapeutics.[4] Precision medicine has grown lately in conjunction with the wide availability of genetic technologies especially the next-generation sequencing.[5] We describe a patient with *GRIN2A* mutation and West syndrome whose ES is controlled with memantine.

Case Presentation

This is a 3-year-old boy who was born to third-degree consanguineous parents. He was a product of normal vaginal delivery at term with unremarkable perinatal and neonatal periods. In the first few months of life, he was noted to be developmentally delayed. At the age of 6 months, he started to have frequent asymmetric flexor spasm with head and eye deviation to the right side. He later developed myoclonic jerks involving upper limbs. He was treated with vigabatrin (VGB) (140 mg/kg/day) and high dose prednisone (8 mg/kg/day) without any benefit. The patient's body weight was 10 kg. Topiramate (TPM), phenobarbital (PHB), clonazepam (CLZ), and levetiracetam (LEV) were also tried without any benefit. CLZ was later replaced by clobazam (CLB) due to

increased oral secretions that improved after replacement, but there was no benefit in seizure control. LEV was discontinued due to inefficacy and TPM was discontinued due to nephrocalcinosis. Lacosamide (LAC) was added, and the patient was also started on classic ketogenic diet (KGD) with some benefit. The patient continued to have ES.

He has a maternal aunt with seizures and a paternal cousin with a speech delay. No significant family history otherwise. Developmentally he regressed since his seizures started. He did not have any dysmorphic features or neurocutaneous stigmata. He was not able to follow or fixate. There was axial and appendicular severe hypotonia with hyperreflexia and upgoing plantar reflex bilaterally. He was able to move all his extremities but had fisting of his hands. He had severe laryngomalacia that is improving with time. Rest of the systemic examination was unremarkable.

Basic metabolic workups including plasma amino acids, urine organic acids, acylcarnitine profile in plasma and urine, serum ammonia, serum lactate, and pyruvate were all within normal limits. Neurotransmitter levels in cerebrospinal fluid were done to rule out pyridoxine deficiency and were also unremarkable. Brain magnetic resonance imaging showed diffuse volume loss, and magnetic resonance spectroscopy was unremarkable. Electroencephalogram (EEG) showed modified hypsarrhythmia with a burst suppression pattern. Next-generation sequencing epilepsy panel was done at the CGC Genetics laboratory that showed heterozygous c.1083G > A (p. Leu361 =) variant in GRIN2A, which is a novel mutation not described in the literature or population databases. The same mutation was found in his mother who is reportedly healthy.

Based on the genetic results of this GRIN2A mutation, we started the patient on 0.15 mg/kg/day of memantine and very slowly titrated it up to 1 mg/kg/day. Upon reaching the goal dose, the patient's seizures significantly reduced, and he is now seizure free for more than 10 months except once when he had his habitual 1-hour long cluster of ES when he was admitted in the pediatric intensive care unit for respiratory syncytial virus pneumonia. The patient presented with subjective fever, ES, and respiratory distress. He was compliant with all his medications including memantine prior to the admission. During this admission, patient was admitted to general pediatric service and memantine was inadvertently not continued during the admission for 6 days, but the seizures did not recur. The exacerbation of ES was thought to be due to a viral illness.

Since he was seizure free, PHB was weaned successfully, and currently he is on a weaning schedule for VGB. He continues to be on KGD and is tolerating it well. Currently, he is following and fixating and recognizes parents but is nonverbal and unable to roll over or fully support his neck.

Discussion

We describe a case of West syndrome most likely caused by a mutation in GRIN2A. This gene is located in the short arm of chromosome 16 at 16p13.2. It is a 14-exon gene encoding for a subunit of N-methyl-D-aspartate (NMDA) receptor heterotetramers, which is composed of two NR1s and two NR2s. GRIN2A

protein is a part of NR2 complex.[6] NMDA receptors are responsible for the influx of Na^+, K^+, and Ca^{2+} to the cell after activation by glutamate. The activity of this receptor can be blocked by Mg^{2+} ions leading to regulation of its excitability.[7]

The clinical spectrum of GRIN2A-related speech disorders and epilepsy is broad and can be classified into epilepsy-aphasia syndrome and other epilepsy phenotypes that include infantile-onset epileptic encephalopathy.[3,8] West syndrome, like our case, is a type of infantile-onset epileptic encephalopathy presenting as ES.[1] Endele et al described a case of ES with a de novo c.1845C > A mutation in GRIN2A.[6]

Although GRIN2A mutations are considered autosomal dominant, family members with the exact mutation may have normal phenotype or mild form of the spectrum. This can partially be explained by presumed incomplete penetrance along with variable expression of disease.[9–11]

Drug-resistant epilepsy (DRE) continues to pose a great challenge in treating patients with epilepsy. Despite the increasing number of new fourth-generation antiepileptic medications available with different mechanism of actions like cannabidiol, eslicarbazepine, brivaracetam, and perampanel,[12–15] the overall outcome in newly diagnosed epilepsy is almost unchanged over the years,[16] and the prevalence of DRE in patients with epilepsy continues to be around 30%.[17] Epileptic encephalopathies are usually associated with DRE and seizures can be difficult to control with the available treatment options including antiepileptic drugs, KGD, and neurostimulation therapies.[18] This highlights the importance of developing novel treatment options to overcome the burden of epilepsy, and genotype-driven precision medicine brings hope. Some patients, who once thought to have untreatable diseases, are getting better care and more effective therapies. Precision medicine approach in epilepsy requires identification of the underlying causative genetic alteration, determination of resulted functional physiologic dysfunction leading to loss of physiologic control of neuronal excitability, and then to evaluate treatments that can reverse or inhibit the functional alteration.[19]

Many successful stories of precision medicine in epilepsy are found in the literature. A common example is of Glucose transporter1 (GLUT1) deficiency syndrome, where the underlying genetic mutation in solute carrier family 2 member 1 (SLC2A1) leads to improper function of GLUT-1 protein that is responsible for the entrance of glucose through blood-brain barrier and therefore leading to starvation of the brain. The established treatment of this genetic disease is KGD, leading to the replacement of glucose by ketones as the primary source of energy, which can easily cross blood–brain barrier without the need for any protein carriers and supply enough energy to reduce seizures and prevent the progress of the disease.[20] Other examples of precision medicine are summarized in ►Table 1[21–49] and ►Table 2.[50–55]

The use of memantine in treating GRIN2A-related epilepsy was suggested by in-vitro studies as well as in an encouraging case report with a great reduction in seizure frequency after the introduction of memantine.[56] Memantine is an uncompetitive NMDA receptor antagonist that binds preferentially to the NMDA receptor-operated cation channels.[57]

Table 1 Examples of precision medicine in genetic epilepsy

Gene mutation	Related conditions	Treatment	Reference
ALDH7A1	Pyridoxine-dependent epilepsy	Pyridoxine	Hunt et al[21]
DEPDC5	Familial focal epilepsy with variable foci	Everolimus (in model studies only)	Marsan et al[22] Galanopoulou et al[23]
GAMT, GATM, SLC6A8	Cerebral creatine deficiency syndromes	Creatine monohydrate	Bianchi et al[24] Salomons et al[25]
KCNJ10	EAST syndrome	Carbamazepine	Ali et al[26]
KCNQ2	Early infantile epileptic encephalopathy 7 (EIEE7)	Retigabine (in missense mutations)	Kato et al[27] Weckhuysen et al[28] Numis et al[29] Schenzer et al[30]
KCNT1	Nocturnal frontal lobe epilepsy Epilepsy of infancy with migrating focal seizures	Quinidine (in gain-of-function mutations)	Bearden et al[31] Abdelnour et al[32]
PNPO	Pyridoxal 5′-phosphate-dependent epilepsy	Pyridoxal 5′-phosphate	Mills et al[33]
PRICKLE	Progressive myoclonic epilepsy	USP9X inhibitors (laboratory study)	Paemka et al[34]
SCN1A	Dravet syndrome GEFS+ ICE-GTC seizures Intractable infantile partial seizures Myoclonic-astatic epilepsySimple febrile seizuresLennox–Gastaut syndrome Infantile spasms	Stiripentol Aggravation of seizures with sodium channel blockers	Chiron et al[35] Thanh et al[36] Wirrell et al[37] Brunklaus et al[38]
SCN2A	Early infantile epileptic Encephalopathy 11 (EIEE11) Benign familial infantile seizures	Sodium channel blockers(especially phenytoin and carbamazepine)	Nakamura et al[39] Howell et al[40]
SCN8A	Early infantile epileptic encephalopathy 13 (EIEE13)		Kong et al[41] Larsen et al[42] Boerma et al[43] Wagnon and Meisler[44]
SLC2A1	GLUT1 DS	Ketogenic diet (avoid valproic acid and phenobarbital)	Vannucci and Simpson[45] Alter et al[46] Kass et al[47]
TSC1 and TSC2	Tuberous sclerosis complex	Everolimus	Krueger et al[48] French et al[49]

Abbreviations: EAST, epilepsy ataxia sensorineural deafness tubulopathy; GEFS+, genetic epilepsy with febrile seizures plus; GLUT1 DS, glucose transporter type 1 deficiency syndrome; ICE-GTC, intractable childhood epilepsy with generalized tonic–clonic.

Table 2 Examples of precision medicine relating to adverse effects

Genetic factor	Adverse effect	Reference
CYP2C9	Risk of developing concentration-dependent neurotoxicity from PHT	Depondt et al[50]
CYP2C19	Gene-dose effect with N-clobazam	Kosaki et al[51]
HLA-B*15:02	SJS, TEN with CBZ (South Asian and Chinese)	Chung et al[52]
HLA-A*31:01	CBZ-induced hypersensitivity reactions (Japanese and European)	Ozeki et al[53] McCormack et al[54]
POLG mutations	VPA-induced hepatic failure	Stewart et al[55]

Abbreviations: CBZ, carbamazepine; PHT, phenytoin; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; VPA, valproic acid.

It is partially metabolized in the liver with no effect on CYP450 enzyme system and excreted majorly in the urine with half-life of 60 to 100 hours.[58] It is widely used in adult neurology for the management of Alzheimer's disease.[58] One reported patient with a *GRIN2A* mutation was having an average of 11 episodes per week of two types of seizure, tonic flexion of all extremities for a few seconds, and sudden myoclonic jerks. Memantine was introduced for him, and within few weeks of reaching the full dose of ∼0.5 mg/kg/day, his seizure frequency of the first type of his seizure dropped to an average of 3.3 episodes per week, while the myoclonic jerks have stopped. Moreover, inter-ictal EEG recording improved and cognitive ability remained unchanged. There was no mention of any seizure-free period.[56]

Reports in the literature have identified that synonymous single nucleotide variances (SNVs), also known as sense mutations, might not always be silent.[59] It might cause pathogenicity in some cases, mostly attributed to splicing regions alteration leading to skipping exons or inclusion of introns in the final protein product, but other explanations are suggested too, such as changes in folding energy and structure of pre-messenger ribonucleic acid.[60–62] Animal and bacteria studies have shown that some synonymous SNVs affect the efficiency of gene expression and function of the same protein. In the fruit fly, for example, the introduction of multiple sense mutations, resulting in replacement of original codons by less frequently used codons for the same amino acid, leads to a decreased level of protein carried by the modified gene, and resulted in disease phenotype in adult fruit flys.[62,63] As technologies of bioinformatics are evolving along with our understanding of genomics, it is suggested that we might be able to get more precise suspicions of pathogenicity of synonymous SNVs in the near future.[64]

Although the pathogenicity of the novel mutation in the GRIN2A was inconclusive, a trial of memantine in our patient was our last resort after the failure of the KGD, high-dose prednisone, VGB, and many other antiepileptic medications. Use of memantine in our proband showed great results, leading to a seizure-free period for more than 10 months now except one episode of seizure exacerbation during illness. This could be a promising drug for the treatment of GRIN2A-related spectrum of phenotypes, and it does enforce the previous report of efficacy of memantine in patients with GRIN2A mutations.[56,65] Pierson et al reported successful use of memantine in a patient with European and Hispanic descent who presented with early-onset epileptic encephalopathy, profound developmental delay, drug-resistant tonic and myoclonic seizures.[55] Reports in the literature indicate that theoretically not all GRIN2A mutations can be treated with memantine. Memantine is thought to be effective in mutations that lead to poor Mg^{2+} blockade of the NMDA receptor.[7] Other mutations leading to other physiologic dysfunctions of excitability control might not benefit greatly from memantine, as indicated by electrophysiologic studies done by Strehlow et al, indicating that missense mutations in transmembrane and linker domains are theoretically responsive to NMDA blockade while mutations in other sites as amino terminal domain, as in our proband, should not respond well to memantine and in contrast could be responsive to positive allosteric modulators.[66] This needs further studying to understand the underlying pathophysiology of loss-of-function and gain-of-function mutations in GRIN2A before it can be confirmed. Unfortunately, the exact physiologic defect in our patient's NMDA receptor is not known, and since we do not have the facility to do in vitro testing, we remain not sure of the exact sequela of his mutation.

We believe that cases like ours open the door for a better future of managing patients with DREs, side by side with epilepsy surgery and other evolving modalities. Further

studying of genetic causes of epilepsy with more focus on the resulting alteration in the physiology of each patient and how this alteration can be reversed is needed. Precision medicine needs our dedication and collaboration to improve the outcome of our patients in future.

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