Successful use of perampanel in GABRA1-related myoclonic epilepsy with photosensitivity

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Pathogenic variants in gamma-aminobutyric acid type A receptor subunit alpha1 (GABRA1) is a protein coding gene that has been associated with a broad phenotypic spectrum of epilepsies. These have ranged from mild generalized forms to early-onset severe epileptic encephalopathies. Both in mild and in severe forms, tonic-clonic and myoclonic seizures with generalized spike and wave discharges and photoparoxysmal responses are common clinical manifestations. We present the case of a 14-year-old girl referred to our clinic with uncontrolled epilepsy. She was found to carry a heterozygous variant (c.335G > A) in GABRA1, already described in the literature and classified as “pathogenic” according to ACMG guidelines. The patient showed severe drug resistance with seizures often triggered by photic stimulation. The introduction of perampanel therapy led to overall reduction of the focal and generalized myoclonic seizures and complete clinical control of the light-triggered seizures.

To our knowledge this is the first report of perampanel efficacy in photosensitive epilepsy, and in particular in the presence of a GABRA1 variant. New evidence is needed to confirm our findings in this case.

Introduction

Gamma-aminobutyric acid type A (GABA-A) receptors are key mediators of inhibitory synaptic transmission in the central nervous system. They are pentameric chloride channels assembled using 5 of 19 possible subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π and ρ1–3).

Pathogenic variants in the gamma-aminobutyric acid type A receptor subunit alpha1 is a protein coding gene that has been associated with a broad phenotypic spectrum ranging from mild generalized epilepsies to early-onset severe epileptic encephalopathies. Both in mild and in severe forms, tonic-clonic and myoclonic seizures, associated with generalized spike-and-wave discharges (GSWs) and photoparoxysmal responses, are common clinical manifestations.

Perampanel (PER) is a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor antagonist with a broad spectrum of efficacy in the treatment of epilepsy. PER is approved in the European Union (EU) and United States of America (USA) for use, as an adjunctive agent, in the treatment of primary generalized tonic-clonic seizures and focal-onset seizures (with or without secondary generalization) in patients aged >12 years. In the USA, PER is also approved as an adjunctive therapy or as monotherapy for focal seizures in patients aged ≥4 years.

Case report

A 14-year-old girl was referred to our clinic with drug-resistant epilepsy. She had been born full term to healthy nonconsanguineous parents after an uneventful pregnancy. A family history of epilepsy and autism was reported.

After a normal postnatal course and normal early psychomotor development, at 11 months of age she started to show developmental delay. She currently displays a stable, moderate level of intellectual disability coinciding with seizure onset.
She initially presented focal motor seizures and sporadic focal to bilateral tonic-clonic seizures, often triggered by fever. Interictal EEG showed normal background activity with focal central-parietal discharges, mainly left sided, and sporadic GSWs. Valproate (VPA) was initiated (maximum dose 30 mg/day) leading to seizure control and significant reduction in epileptiform EEG abnormalities.

Her brain MRI was normal and CGH array was performed that showed no pathological findings. At the age of 6, due to seizure relapse, levetiracetam (LEV) was added to the treatment.

Following the discovery of ovarian cysts, VPA was discontinued and the patient relapsed; the new episodes consisted of myoclonic jerks and focal motor clonic seizures involving the right upper limb, with head deviation to the right and impaired awareness; they lasted 15–20 min and were followed by post-ictal confusion and headache. Gradual disruption of EEG organization appeared, characterized by generalized spike and polyspike-wave complexes associated with myoclonic jerks.

Different antiseizure medications (ASMs) were progressively introduced; eventually, even three-drug therapy with lamotrigine (LTG), zonisamide (ZNS) and lacosamide (LCS) failed to improve the seizures.

When the patient was 14, a targeted next-generation sequencing (NGS) of 221 intellectual disability-related genes was performed. A de novo heterozygous c.967G > A (p.Val323Met, NM_001127644.2) missense variant in SLC2A1, classified as "likely pathogenic" according to the American College of Medical Genetics and Genomics guidelines, was documented. The same mutation was found in the mother, who is currently asymptomatic. GLUT1 deficiency syndrome was excluded on the basis of the patient's normal CSF-to-blood glucose ratio (0.68). At a later date, because of her continued drug resistance, a ketogenic diet was nevertheless initiated; this proved ineffective and was discontinued after 6 months.

At that time, the patient was experiencing multiple daily focal myoclonic seizures of variable duration, involving the upper limbs, and occurring in clusters or in isolation; clobazam was sometimes needed to stop them. Furthermore, two to three times a week, she was also presenting generalized myoclonic seizures characterized by head myoclonic jerks, followed by limb and trunk myoclonic jerks, leading to falls, as well as generalized myoclonic- tonic-clonic seizures characterized by head and limb myoclonic jerks, sometimes with head deviation, followed by the tonic-clonic phase with falls. In both cases, seizures lasted 1–2 min.

In the same year, she also experienced photic stimulation-triggered myoclonic seizures, mainly involving the trunk and upper limbs, and sometimes causing falls. (Fig. 1). These seizures did not respond to ASMs (LTG, ZNS and LCS). To reduce them we also prescribed Z1 lenses, which have been found to be remarkably effective in controlling photoparoxysmal responses in a very large number of photosensitive epilepsy patients, irrespective of their type of epilepsy or ASM regimen. The mechanisms of action of these special blue lenses include polarization, reduction of luminance, and filtering of red light [1].

ZNS was stopped and topiramate (TPM) was added to the therapy; the focal, the generalized myoclonic, and the generalized myoclonic-tonic-clonic seizures decreased slightly, but those provoked by light (both natural and artificial) gradually worsened, making the girl unable to participate in outdoor activities or go swimming (even wearing Z1 lenses), in the latter case due to the light reflecting off the water.

At this point, further NGS screening, this time using an epilepsy multigene panel, detected a de novo heterozygous missense variant in GABRA1, i.e. c.335G > A (p.Arg112Gln, NM_001127644.2), classified as "pathogenic" according to American College of Medical Genetics and Genomics guidelines. This variant has already been described in the literature in association with a similar phenotype. The c.967G > A variant in SLC2A1 was again detected. No variants of unknown significance were identified.

LCS was discontinued and PER was added to the therapy with TPM and LTG.

The EEG recordings subsequently improved, showing better organization and reduced slow activity. The GSWs decreased, while photic stimulation, even without Z1 lenses, ceased to elicit EEG photoparoxysmal responses, or did so without clinical manifestations (Fig. 2).

Overall, seizure frequency also diminished and today, after one year of treatment, this improvement persists. The frequency of generalized myoclonic seizures and generalized myoclonic-tonic-clonic seizures, from more than once a week, has now stabilized at one every two to three months. Isolated focal myoclonic seizures occur exclusively prior to menstruation.

Discussion

Mutations in GABRA1 have a wide phenotypic spectrum, including benign forms of unspecified epilepsy, juvenile myoclonic epilepsy, photosensitive idiopathic generalized epilepsy, and generalized epilepsy with febrile seizures plus, but also moderately severe phenotypes such as myoclonic-astatic epilepsy and mild epileptic encephalopathy, associated with mild-moderate developmental delay, and severe forms of developmental and epileptic encephalopathies such as Dravet-like syndromes, variably associated with severe developmental delay, behavioral problems, and autistic features. Seizures are prominent and include febrile seizures, absence, focal, focal to bilateral tonic-clonic, tonic, tonic-clonic, atonic and myoclonic-atonic seizures, and convulsive status epilepticus; the most frequent seizures are tonic-clonic and myoclonic, and in half of patients generalized photoparoxysmal responses on EEG occur during intermittent photic stimulation [2].

Our patient's phenotype, characterized by psychomotor delay and seizures of different types, including myoclonic epilepsy, and light-triggered seizures, has already been described in patients with GABRA1 mutations.

In particular, five patients with the same mutation as our case (p.Arg112Gln) are reported in the literature [2,3]. Seizure onset occurred at between 7 months and 11 months of age, with febrile, focal clonic, and tonic-clonic seizures. Over time, other seizure types also appeared (absences, tonic, atonic, clonic, myoclonic, and even status epilepticus in one patient). One patient showed normal development, and one a speech and language delay; moderate developmental delay was reported in the others. EEG was normal in two patients, whereas GSWs, focal discharges, and symmetrical theta waves were documented in the others. Brain MRI was normal in three patients, whereas one showed a Chiari I malformation, and the other a calcified subependymal nodule in the left lateral ventricle.

The functional consequences of this mutation have been studied by Hernandez et al. (2019), who found that it likely disrupts coupling of GABA binding to channel gating, leading to altered GABA potency and to reduction of inhibitory inputs in neurons and therefore increased excitability [4].

The literature shows a variable response to ASMs in patients with GABRA1 mutations. In particular, some patients carrying the p.Arg112Gln variant, despite showing widely varying phenotypes, became seizure free on monotherapy with VPA or LEV and conversely, others developed drug resistance [2,3].

There is still no consensus on an effective drug therapy in these patients.

We considered adjunctive therapy with PER in view of the evidence of its effectiveness in children and adolescents with drug-
resistant epilepsy [5–7]. A review by Trinka et al. (2021), which included randomized controlled trials, observational cohort studies, and case reports highlights conflicting results on the effectiveness of PER on myoclonic seizures. In the largest observational cohort of patients with these seizures (N = 48 with idiopathic generalized epilepsies), a mean 65% reduction in days with myoclonic seizures was obtained one year after addition of PER, and 65% of patients achieved myoclonic seizure freedom.

Case studies including patients with progressive myoclonus epilepsies such as Unverricht-Lundborg and Lafora disease reported considerable improvements in myoclonic seizure frequency or severity [5,8–10].

When we introduced PER, our patient had already tried various different ASMs, including sodium channel blocking ASM that are known to have the potential to worsen myoclonic seizures. Although we certainly cannot exclude that these drugs may have contributed to the maintenance of myoclonic seizures in our patient, there is no doubt that she obtained a clear overall reduction in focal and generalized myoclonic seizures, as well as complete clinical control of photic stimulation-triggered seizures when PER was added to the therapy. It is worth noting that when this new ASM was introduced, the patient was under treatment with TPM and LTG, and that the dosage of these drugs has not been changed since then.

The mechanism of this response to PER, an \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, in a subject with an identified mutation that affects GABA, is not clear. A review by Hanada [11] reports that PER inhibits the early phase of synchronization, so it is possible that a reduction of hyper-synchronization underlies its broad-spectrum efficacy [11].
However, some studies seem to document more complex mechanisms; Ya-Chin Yang et al. [12], for example, report that ictogenesis depends on the AMPA receptor-dependent recruitment of pyramidal-inhibitory neuronal network oscillations, tuned by dynamic glutamatergic and GABAergic transmission, suggesting that the anticonvulsant effect of PER could stem from disruption of coordinated network activities rather than simply decreased neuronal excitability or excitatory transmission [12]. Satake et al. [12], on the other hand, reported that synaptic activation of AMPA receptors inhibited GABA release from cerebellar interneurons [13].

As regards the treatment of photosensitivity, there are reports in the literature documenting the efficacy of different ASMs, namely carisbamate, LTG, vigabatrin, LEV and VPA; furthermore, one controlled trial examining the effect of sodium valproate found it to be effective in 61% of cases [14]. Covavis has proposed a treatment algorithm [15], based on literature review [16], in which the first step is VPA monotherapy, with LEV as an alternative for patients with idiopathic generalized epilepsy and photosensitivity. LEV and VPA are also reported to be well tolerated when combined. Clobazam, LTG, ethosuximide, and topiramate are recommended as second choices.

As far as we know, the use of PER has yet to be explored in photosensitive epilepsy.

Conclusion

To our knowledge, this is the first report of PER efficacy in photosensitive epilepsy, and in particular in the presence of a GABRA1 variant.

New evidence is needed to confirm our findings in this case. While there can be no doubt that photosensitive myoclonic epilepsies are still a challenge and that new studies are needed to explore and assess new therapeutic options, it is also true that epilepsy therapy is moving towards precision medicine, and from this perspective our observations may make a valuable contribution. As yet, no PER efficacy studies have been conducted in patients with GABRA1 mutations. Bearing in mind other genetic mutations for which target therapies have been identified, we suggest that the preliminary data reported herein warrant further scientific investigation as a new therapeutic possibility.

Ethical statement

The patient was treated in compliance with the ethical principles derived from the Declaration of Helsinki and in line with Good Clinical Practice guidelines and applicable legislation. Written informed consent for publication was provided by the patient and her parents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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