

Efficacy, Tolerability, and Retention of Antiseizure Medications in *PRRT2*-Associated Infantile Epilepsy

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Abstract

Background and Objectives

Pathogenic variants in *PRRT2*, encoding for the proline-rich transmembrane protein 2, were identified as the main cause of self-limiting sporadic and familial infantile epilepsy. Reported data on treatment response to antiseizure medications (ASMs) in defined monogenic epilepsies are limited. The aim of this study was to evaluate the treatment response of ASMs in children with monogenic *PRRT2*-associated infantile epilepsy.


Methods

A multicenter, retrospective, cross-sectional cohort study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria. Inclusion criteria were occurrence of infantile seizures and genetic diagnosis of likely pathogenic/pathogenic *PRRT2* variants.

Results

Treatment response data from 52 individuals with *PRRT2*-associated infantile epilepsy with a total of 79 treatments (defined as each use of an ASM in an individual) were analyzed. Ninety-six percent (50/52) of all individuals received ASMs. Levetiracetam (LEV), oxcarbazepine (OXC), valproate (VPA), and phenobarbital (PB) were most frequently administered. Sodium channel blockers were used in 22 individuals and resulted in seizure freedom in all but 1 child, who showed a reduction of more than 50% in seizure frequency. By contrast, treatment with LEV was associated with worsening of seizure activity in 2/25 (8%) treatments and no effect in 10/25 (40%) of treatments. LEV was rated significantly less effective also compared with VPA and PB. The retention rate for LEV was significantly lower compared with all aforementioned ASMs. No severe adverse events were reported, and no discontinuation of treatment was reported because of side effects.

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 **Class of Evidence**
Criteria for rating
therapeutic and diagnostic
studies
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PRRT2-Study-Group coinvestigators are listed in the appendix at the end of the article.

Ethics Declarations: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Glossary

ASM = antiseizure medication; BFIS = self-limiting sporadic and familial infantile epilepsy; CBZ = carbamazepine; ICCA = infantile convulsions and paroxysmal choreoathetosis; ILAE = International League Against Epilepsy; OXC = oxcarbazepine; PB = phenobarbital; PKD = paroxysmal kinesigenic dyskinesia; VPA = valproate.

Discussion

In conclusion, a favorable effect of most ASMs, especially sodium channel blockers such as carbamazepine and OXC, was observed, whereas the efficacy and the retention rate of LEV was lower in *PRRT2*-associated childhood epilepsy. Tolerability in these young children was good for all ASMs reported in the cohort.

Classification of Evidence

This study provides Class IV evidence that in individuals with *PRRT2*-associated infantile epilepsy, sodium channel blockers are associated with reduced seizure frequency but levetiracetam is not.

Pathogenic variants in *PRRT2*, encoding for the proline-rich transmembrane protein 2 (OMIM*614386), are identified as the leading genetic cause of self-limiting sporadic and familial infantile epilepsy (BFIS, OMIM#605751).^{1,2} *PRRT2* has also been associated with paroxysmal kinesigenic dyskinesia (PKD, OMIM#128200)³ and the overlapping disorder of paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC, also known as ICCA [infantile convulsions and paroxysmal choreoathetosis], OMIM#602066).⁴ BFIS manifests with multiple seizure types in normally developing infants, beginning at a mean age of 6 months and usually remitting before the age of 2 years.^{5,6} Only limited data on treatment are available, and expert recommendations are derived from the allelic disorder PKD, where sodium channel blockers, e.g., carbamazepine (CBZ), have shown to be effective.^{7,8} To date, the International League Against Epilepsy (ILAE) recommendations for the management of benign infantile convulsions list carbamazepine, phenobarbital, and valproate as “possibly effective.”⁹⁻¹¹ In a recent study on 20 individuals with BFIS, oxcarbazepine (OXC) was also considered to be effective.¹² Levetiracetam is one of the most commonly used ASMs in this age group.^{9,13} In a review of 241 individuals with *PRRT2*-associated epilepsy by Ebrahimi-Fakhari et al.,^{5,14} the authors concluded that in most of the cases, a positive response to conventional anticonvulsive treatment was observed. No comprehensive comparative studies on the specific effects of antiseizure medications (ASM) on monogenic *PRRT2*-associated infantile epilepsy have been published.

PRRT2 is predominantly expressed in presynaptic membranes of excitatory neurons in the cerebral cortex, basal ganglia, cerebellum, and hippocampus.^{1,3,15,16} Within neuronal networks, loss of *PRRT2* leads to an increase of spontaneous and evoked activity and increased excitability of neurons.¹⁷⁻²⁰ *PRRT2* interacts with several neuronal proteins, regulating Ca²⁺-mediated synchronous neurotransmitter release, directly affecting intrinsic neuronal excitability by

negative modulation of Na⁺ channels, and modifying synaptic plasticity during brain development.^{21,22} The aim of this study was to evaluate treatment response of antiseizure medications in children with monogenic *PRRT2*-associated infantile epilepsy.

Methods

This retrospective, observational, cross-sectional analysis was conducted according to “Strengthening the Reporting of Observational Studies in Epidemiology” criteria.²³ Data were collected within the German Network for Rare Neurologic Disorders in Childhood (“Erhebung Seltener Neurologischer Erkrankungen im Kindesalter”) and from collaborating geneticists in Denmark.²⁴ The genetic diagnosis was established as part of the diagnostic workup. The cohort analyzed in this study overlaps with individuals from a study on the phenotypic spectrum of individuals with *PRRT2*-associated disease, where detailed clinical and sequence variation information is described.⁶ To analyze treatment effects in *PRRT2*-associated infantile epilepsy, we collected systematic data on epilepsy treatment in 52 cases (40 cases with previously reported clinical characteristics and 12 novel individuals). Only individuals with likely pathogenic or pathogenic variants according to the American College of Medical Genetics and Genomics criteria were included.²⁵ Clinical data were collected using a web-based survey answered by the treating child neurologist. The survey included detailed questions on the type of treatment, dosage, response, and adverse events. Because of the retrospective, observational, cross-sectional design of the study, it did not influence the choice of treatment by pediatric neurologists. The medications administered represent a common practice for the treatment of childhood focal and generalized epilepsy. Levetiracetam is one of the most commonly used ASMs in this age group.^{9,13}

Quantitative variables are described by sample size, mean or median, and SD. Statistical comparison between the mean

Table 1 Characteristics of 52 Children With Infantile Epilepsy and Genetic Variation of *PRRT2*

Age at	No. of patients	Mean	Minimum	Maximum	SD
Inclusion (y)	52	5.9	0.7	26	6.3
First-reported seizure (mo)	52	5.3	1	15	2.2
Diagnosis of BFIS (mo)	51	5.9	1	15	2.4
Seizure freedom (mo)	51	11.3	4	30	6.3
Genetic diagnosis (mo)	49	37.9	3	216	55.3

Abbreviation: BFIS = self-limiting sporadic and familial infantile epilepsy.

values was performed with the Welch 2-sample *t* test. Frequencies of descriptive variables are illustrated with number, sample size, and percentages. Statistical comparison of frequencies was performed with the 2-tailed Fisher exact test. *p* < 0.05 was considered statistically significant. The *p* values resulting from the statistical analyses have a purely descriptive character. A treatment was defined as each single use of an ASM in an individual. The treatment effect was rated by the treating child neurologist based on medical notes and seizure diaries on a 5-step ordinal scale (worsening, no effect, less than 50% seizure reduction, more than 50% seizure reduction, and seizure freedom), comparing seizure frequencies before treatment and 3 months after start of the medication. If an ASM was exchanged within a shorter interval, seizure activity prior to the start of the following ASM was rated as treatment effect. In case of combination therapies, the treatment effect was attributed to the last added ASM. For statistical comparison, “effective” treatment was defined as >50% seizure reduction or seizure freedom vs “ineffective” treatment with <50% seizure reduction, no effect, or worsening of seizure frequency. To rule out confounding effects from age, the age at each start of ASMs was included in the analysis. Descriptive analysis was performed with IBM SPSS Statistics version 27.

Standard Protocol Approvals, Registrations, and Patient Consents

The study adheres to the principles set out in the Declaration of Helsinki. All individuals or guardians gave their informed consent for data acquisition, sharing, and genetic testing. The study was approved by the ethics committee of the University of Heidelberg (S-318/2018).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

The cohort of individuals with *PRRT2*-associated infantile epilepsy analyzed in this study consisted of 52 cases. All individuals presented with an infantile seizure disorder in line with a clinical diagnosis of BFIS. Clinical characteristics from all included individuals are summarized in Table 1. Sixteen were male (30.8%) and 36 were female (69.2%) individuals. The mean age at inclusion into the study was 5.9 years (SD 6.3).

Molecular Analysis

The median diagnostic delay from onset of infantile seizures to genetic diagnosis was 7 months (SD 75.6). Forty-nine individuals carried monoallelic variants, with the frameshift variant c.649dupC; p.Arg217Profs*8 most frequently identified. Three individuals presented with biallelic homozygous (1) or compound heterozygous (2) variants. 33/52 (63%) variants were of familial origin, 6/52 (12%) de novo, and in 13 cases, no data on inheritance were available. A summary of the spectrum of sequence variations is listed in eTable 1 (links. lww.com/NXG/A542).

Epilepsy

Most individuals developed clusters of seizures with a maximum seizure frequency of at least 2 seizures per day in 23/52 (44%) of cases and of more than 5 seizures per day in 8/52 (15%) of cases. The mean duration of active seizures was 5.7 months (SD 6.8). In single patients, seizures recurred later in life (2/52). Generalized-onset bilateral tonic-clonic or tonic seizures were reported in 31/52 (60%) individuals, focal motor and focal impaired awareness seizures in 11/52 (21%) of individuals, whereas 10/52 (19%) individuals displayed both focal and generalized seizures. One patient developed a convulsive status epilepticus at the age of 9 months.

Development

Prior to onset of seizures, all children developed normally. Despite the high seizure burden, cognitive and motor development was described as normal in 50/52 (96%) individuals during the course of disease. A mild delay of motor milestones and a mild language delay was described in single individuals. A girl with continuous spikes and waves during sleep developed a mild-moderate intellectual disability during childhood.

Treatment

Ninety-six percent (50/52) of all individuals received ASMs. The use of additional rescue medications (diazepam and midazolam) was reported in 27/52 (52%) of all individuals during the course of the epilepsy. A total of 79 treatments were prescribed in the 52 children, and 9 different ASMs were used. Number of treatments, mean dosage, age at start of treatment, treatment effect of first ASM and overall treatment effects, and the proportion of changes to other ASM are summarized in Table 2. The mean delay to start of treatment was 1.1 months (SD 1.8). A total of 24/52 (46%) individuals

Table 2 Summary of Antiseizure Medications

Anti-seizure medication	LEV	OXC	VPA	PB	CBZ	STM	AZA	VGB	BRV
No. of treatments	25	15	12	11	7	5	2	1	1
Mean dose (mg/kg/d)	48.7	22.2	27.9	4.8	12.2	7.7	6.6	100	6
Mean age at start of treatment (mo) (SD)	5.9 (2.37)	7.3 (2.0)	6.7 (3.3)	5.3 (2.6)	8.3 (5.4)	12.5 (4.4)	5.5	6	7
“Effective” treatment as first ASM (yes/total)	17% 4/23	100% 4/4	100% 6/6	100% 9/9	100% 4/4	50% 1/2	100% 2/2	NA	NA
Retention rate of first ASM	17% 4/23	100% 4/4	67% 4/6	78% 7/9	100% 4/4	50% 1/2	100% 2/2	NA 0/0	NA 0/0
Overall effective treatment (yes/total)	24% 6/25	100% 15/15	84% 10/12	100% 11/11	100% 7/7	60% 3/5	100% 2/2	NA 1/1	NA 0/1
Overall proportion of replacement with another ASM (change/total)	19/25	0/15	6/12	2/11	1/7 ^a	2/5	0/2	0/1	1/1

Abbreviations: ASM = antiseizure medication; AZA = acetazolamide; BRV = brivaracetam; CBZ = carbamazepine; LEV = levetiracetam; OXC = oxcarbazepine; PB = phenobarbital; STM = sultiame; VGB = vigabatrin; VPA = valproate.

^a Exchange for OXC in a seizure-free individual due to suspected side effects. Effective treatment was defined as > 50% seizure reduction or seizure freedom vs ineffective treatment with < 50% seizure reduction, no effect, or worsening of seizure frequency.

received more than 1 ASM and 6/52 (12%) more than 2 in the course of the disease (Figure 1). By the time of study inclusion, 12/52 (23%) individuals still received ASM treatment (the median age of individuals with ongoing treatment: 27 months, SD 15.8). In 23/52 (44%) cases, the treatment was stopped, at a mean age of 26.4 (SD 15.1) months. In 17 cases, the information was missing.

Efficacy

Of all single treatments with ASMs, 55/79 (69%) were evaluated as “effective.” Of all cases, 25/52 (32%) were free of seizures within 1 month from the start of the first treatment. Compared with levetiracetam (LEV), the overall efficacy of treatment was rated higher for OXC ($p < 0.0001$), phenobarbital (PB) ($p < 0.0001$), CBZ ($p = 0.0005$), and valproate (VPA) ($p = 0.0011$) (Table 2, Figure 2, and eFigure 1, links. lww.com/NXG/A542). The isolated effect of the primarily used ASM also showed a clear difference between LEV and sodium channel blockers (OXC & CBZ, $p < 0.0001$), PB ($p < 0.0001$), and VPA ($p = 0.0004$). Sodium channel blockers were used in 22 individuals and resulted in seizure freedom in all but 1 child, who showed a reduction of more than 50% in seizure frequency. The use of LEV resulted in worsening of seizure activity in 2/25 (8%) individuals and no effect in 10/25 (40%) of treatments. To address a possible dose-dependent effect of LEV, we divided the LEV group into a low-dose subgroup and a high-dose subgroup based on the mean dose and compared the reported treatment effects: There was no difference between the 2 subgroups ($p = 0.617$). The mean age at the start of treatment did not differ significantly between LEV and OXC (6.08 months, SD 2.45 vs 7.4 months, SD 2.1, $p = 0.19$) (Figure 3). Since 2015, LEV was the most commonly used ASM in the cohort. It was started frequently as the first ASM (92%, 23/25), whereas OXC was

started as the first ASM in 4/15 (27%) of treatments and was more often prescribed as the second or third choice (Figure 1).

Drug Retention

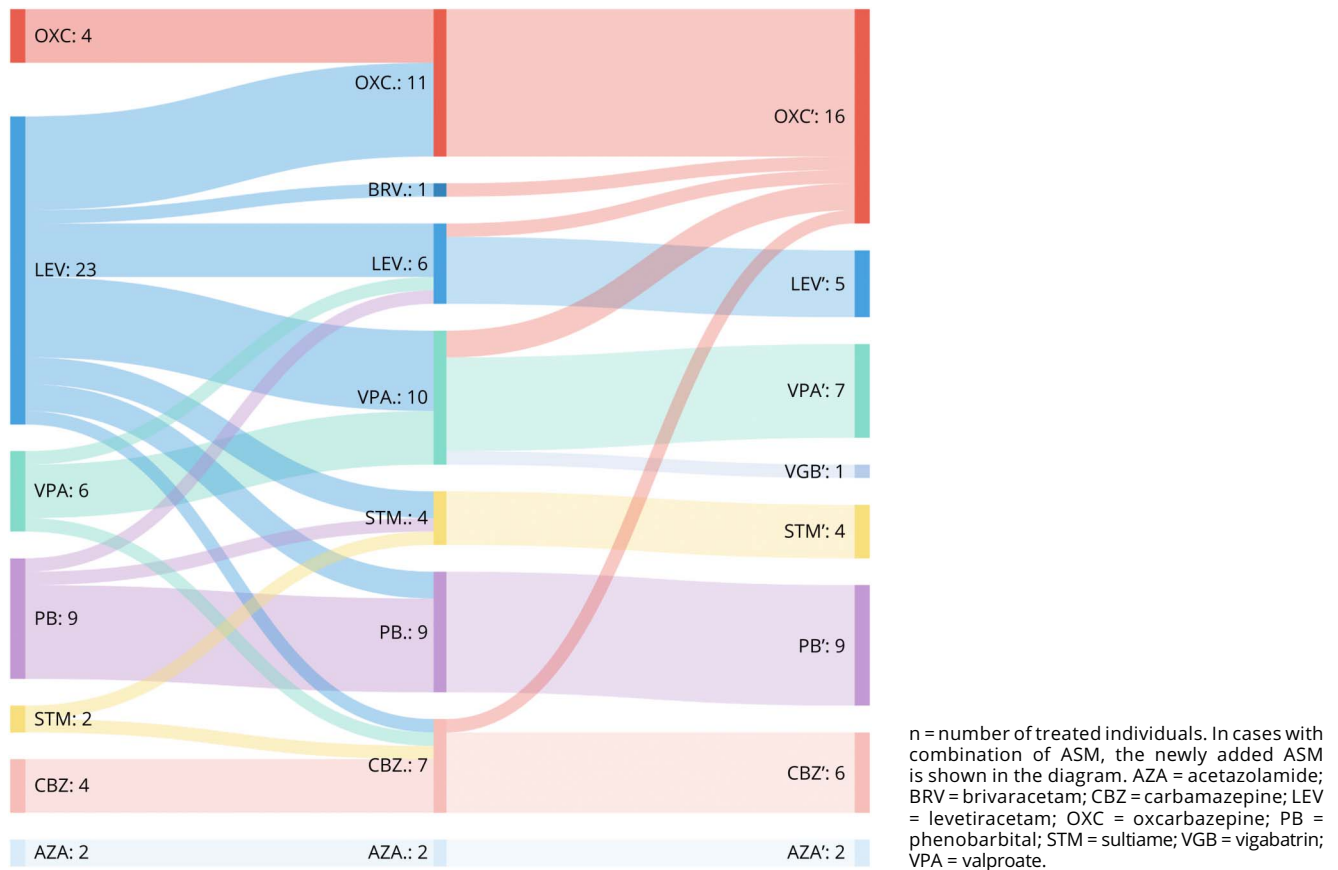
Retention of the first ASM was high for sodium channel blockers (8/8, 100%) and PB (7/9, 78%). VPA was maintained in 4/6 initial treatments (67%). The retention rate for the initial treatment with LEV was 17% (4/19). Overall, retention to treatment with LEV was significantly different from that to OXC ($p < 0.0001$), PB ($p = 0.0024$), and CBZ ($p = 0.0057$).

Genetic confirmation of a variant in *PRRT2* was reported to have affected further treatment decisions in 17/49 individuals (35%). Child neurologists reported that the genetic diagnosis justified less aggressive treatment approaches (5), led to a treatment with sodium channel blockers (6), early tapering of therapy (1), or no treatment at all (1). In 4 cases, no further specifications were given. Because the genetic diagnosis was performed after the onset of seizures, it did not affect the initial choice of medication.

The initial choice of treatment was also not influenced by concomitant movement disorders. Only 2 of 52 children had concomitant movement disorders in infancy. In all children, infantile seizures were the first symptom. One child developed dystonic episodes 1 month after the onset of seizures, although he was treated with sulthiame. Both the seizures and the dystonic movements were then controlled with oxcarbazepine.

Another girl showed benign myoclonus in infancy at 10 months of age, 6 months after the onset of seizures. Neither manifestation was controlled with levetiracetam, followed

Figure 1 Sankey Diagram of Treatment Changes From First-Line to Third-Line Therapy



by valproate therapy. After identification of the pathogenic variant c.649dupC in *PRRT2*, treatment was successfully switched to oxcarbazepine.

Tolerability

No severe adverse events were reported, and no discontinuation of treatment was reported due to side effects. VPA was associated with more aggressive behavior in 1 individual and with increased tiredness in another. Sultiame was associated with restlessness and sleep disorder in 1 individual. CBZ was suspected to underly anemia and neutropenia in 1 patient, which was later diagnosed as autoimmune neutropenia. brivaracetam was associated with increased tiredness in 1 individual.

Classification of Evidence

Retrospective, noncontrolled, cross-sectional Study (Class of Evidence IV) to evaluate the treatment response to different ASMs in individuals with *PRRT2*-associated infantile seizures. Relevant outcomes were seizure frequency and retention to treatment.

Discussion

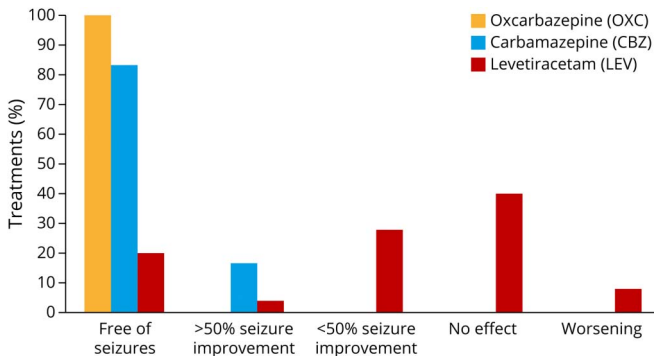
In this study, we analyzed the efficacy, retention, and tolerability of anti-seizure medications in a large multicenter cohort

of 52 individuals with *PRRT2*-associated infantile seizures. Our study has several important findings: considering the retention rates and the evaluated efficacy of the treatments, not only sodium channel blockers (OXC and CBZ) in particular, but also PB and VPA, showed favorable effects in infants with *PRRT2*-associated epilepsy and had a good safety profile in this vulnerable age group. LEV, which is frequently used in neonatal and infantile epilepsies, was rated less effective for seizure control and had a lower drug retention rate.

In line with published data, age at onset, frequency of seizures, duration of seizure activity, semiology of seizures, and molecular distribution of variants in our cohort is representative for *PRRT2*-associated self-limiting sporadic and familial infantile epilepsy.⁵ One individual presented with status epilepticus, an exceptional feature in *PRRT2*-associated epilepsy at the age of 9 months,²⁶ but the course of BFIS and treatment response did not deviate from the rest of the cohort.

Development before and in the course of the disease was unremarkable in almost all individuals (50/52), independent of the high seizure frequency over several months. Besides the positive developmental and epilepsy outcome, quality of life and psychosocial well-being of families with infants with seizures is generally reduced.²⁷ Despite subsequent remission,

Figure 2 Treatment Effect of Sodium Channel Blockers and Levetiracetam

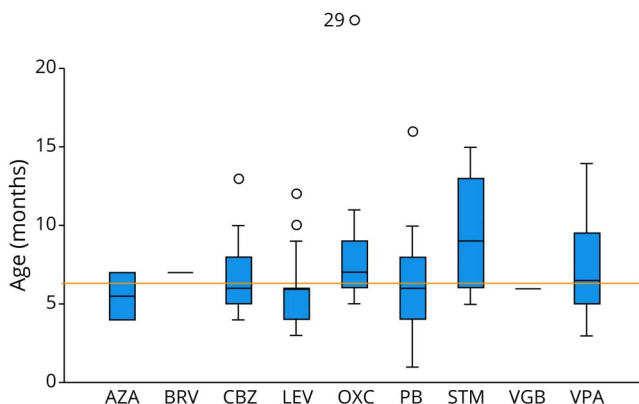


seizure freedom through effective antiepileptic treatment is of great importance in this vulnerable group.

Ebrahimi et al.⁵ provided a comprehensive review on a historic cohort of 602 published individuals with *PRRT2*-associated BFIS and reported no superior ASMs. With long-term remission in virtually all children, the overall response to treatment reported for *PRRT2*-associated BFIS was excellent.⁵ It is important that the ASMs used for infantile seizures have changed recently. While before 2015, only 1 individual with LEV treatment was reported in all studies, LEV was now the most commonly used ASM in our cohort.

In this study, LEV, OXC, VPA, and PB were prescribed most frequently. Regarding the assessment of treatment effects, sodium channel blockers (OXC and CBZ) had excellent effects, and were rated as effective treatment in all respective children (22/22, 100%) with a high retention rate when used as first ASM. A specific effect on *PRRT2*-associated disease

Figure 3 Boxplot, Displaying the Mean Age at Start of ASM



Orange line: mean age at start of ASM (6.4 months). ASM = antiseizure medication; AZA = acetazolamide; CBZ = carbamazepine; LEV = levetiracetam; OXC = oxcarbazepine; PB = phenobarbital; STM = sultiame; VGB = vigabatrin; VPA = valproate.

can be assumed because *PRRT2* is a known negative modulator of sodium channels in excitatory neurons.²¹ Lack of *PRRT2* leads to hyperactivity and increased expression of voltage-dependent Na⁺ channels, as well as increased Na⁺ current amplitude in homozygous *PRRT2* knockout human and murine neurons, resulting in an overall enhancement of intrinsic excitability.^{21,22}

Comparing the treatment effects of different ASMs, we found a comparable effectiveness for sodium channel blockers and PB, but a substantial difference with LEV, which has become one of the most commonly used ASMs in the first year of life.²⁸ Treatment with LEV was frequently rated to be ineffective, and retention to treatment was low when used as the first ASM. Of interest, even worsening of seizure frequency and activation of multifocal epileptiform potentials in the electroencephalography (EEG) were reported in single cases. A change to OXC led to seizure freedom in all respective cases, an observation that has also been described in single familial cases and in a recent case series.^{12,29,30}

The presynaptic vesicle protein 2A (SV2A) is the binding site for LEV.³¹ Similar to *PRRT2*, SV2A is involved in the presynaptic vesicle release machinery. To a lesser degree, LEV also binds to the calcium sensor synaptotagmin and calcium channels, leading to reduction of Ca²⁺-mediated glutamate and gamma-aminobutyric acid release in rapidly discharging neurons.³² Absence of *PRRT2* results in opposite effects on excitatory and inhibitory synapses after short-term potentiation, with increased facilitation in excitatory transmission and increased depression in inhibitory transmission.¹⁷ LEV has been shown to cause a frequency-dependent reduction of both excitatory and inhibitory postsynaptic currents.³² The additional effect on inhibitory transmission might explain the lower effectiveness of LEV in this condition.

Considering the age-dependent course with possible initial deterioration in seizure frequency and spontaneous seizure remission over time, age at initiation and sequential use of individual ASM may confound our observations. To address this limitation, we compared the effect of the primarily used ASM and found a clear difference not only between LEV and sodium channel blockers (OXC and CBZ) but also to VPA and PB. This fact is also reflected in a lower retention rate to the initial therapy for LEV (Table 2). In addition, we compared the mean age at treatment start of each ASM, which was not significantly different for OXC, LEV, VPA, and PB (Figure 3). Still, because LEV was mostly prescribed as the first treatment, often followed by OXC (Figure 1), we cannot completely rule out a bias from this sequential use, also, because the genetic diagnosis of a *PRRT2*-associated epilepsy led to a change to sodium-channel blockers in single infants. Some of these potential biases in the evaluation of LEV can be excluded compared with PB: it was initiated very early in the course of epilepsy in most cases, it was the first ASM in almost all treatments, and there was no sequential use of LEV and PB. Still, a significant difference in perceived efficacy and retention between these 2 ASMs was found.

Ineffective ASMs were exchanged more quickly than 3 months after treatment initiation in most cases, which may have led to an underestimation of the full treatment effect. As effects of combinations of ASM were attributed to the treatment that was initiated last, effects from combinatorial and synergistic drugs may have escaped our analysis.

Given the young age at seizure onset and the unknown genetic etiology at the start of treatment, prospective controlled clinical trials are challenging, and the use of a placebo-control group seems unethical. Therefore, analysis of retrospective data is of great value. When assessing our findings, several limitations have to be considered, including the retrospective, unblinded design, the rating of efficacy by the caring pediatric neurologists with a risk of confirmation bias, and the lack of a control group. In conclusion, our data showed favorable effects of most ASM, especially sodium channel blockers, such as CBZ or OXC, but a low efficacy of LEV in *PRRT2*-associated monogenic infantile epilepsy (eFigure 1, links.lww.com/NXG/A542).

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Disclosure

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Appendix 1 (continued)

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Walid Fazeli, MD, PhD	Pediatric Neurology, Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; Institute for Molecular and Behavioral Neuroscience, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany	Drafting/revision of the article for content, including medical writing for content
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Name	Location	Contribution
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Continued

Appendix 1 (continued)

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Appendix 2 (continued)

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Appendix 2 (continued)

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