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Effectiveness of antiepileptic therapy in patients with *PCDH19* mutations

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ABSTRACT

Purpose: *PCDH19* mutations cause epilepsy and mental retardation limited to females (EFMR) or Dravet-like syndromes. Especially in the first years of life, epilepsy is known to be highly pharmacoresistant. The aim of our study was to evaluate the effectiveness of antiepileptic therapy in patients with *PCDH19* mutations.
Methods: We report a retrospective multicenter study of antiepileptic therapy in 58 female patients with *PCDH19* mutations and epilepsy aged 2–27 years (mean age 10.6 years).
Results: The most effective drugs after 3 months were clobazam and bromide, with a responder rate of 68% and 67%, respectively, where response was defined as seizure reduction of at least 50%. Defining

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long-term response as the proportion of responders after 12 months of treatment with a given drug in relation to the number of patients treated for at least 3 months, the most effective drugs after 12 months were again bromide and clobazam, with a long-term response of 50% and 43%, respectively. Seventy-four percent of the patients became seizure-free for at least 3 months, 47% for at least one year.
Significance: The most effective drugs in patients with *PCDH19* mutations were bromide and clobazam. Although epilepsy in *PCDH19* mutations is often pharmacoresistant, three quarters of the patients became seizure-free for at least 3 months and half of them for at least one year. However, assessing the effectiveness of the drugs is difficult because a possible age-dependent spontaneous seizure remission must be considered.

1. Introduction

Mutations in the *PCDH19* gene were originally identified by Dibbens et al. in patients with epilepsy and mental retardation limited to females (or Epilepsy, Female-restricted, with Mental Retardation, EFMR; OMIM# 300088) [8]. The clinical features of EFMR are highly variable. Early onset of seizures (6–36 months) and precipitation during fever are characteristic [5,7,11,13]. Seizures are focal or generalized, including tonic-clonic, myoclonic, atonic or absence seizures [10,12]. They often occur in clusters or as prolonged ictal episode, occasionally leading to status epilepticus. In the course of the disease, seizure cessation is common [6]. Early development is usually normal and often accompanied by regression at the time of seizure onset or later, with a varying degree of intellectual disability [10,12]. Behavioral problems are frequently part of the clinical picture and can manifest as autistic, obsessive or aggressive features [7,17].

The clinical spectrum associated with *PCDH19* mutations can overlap with Dravet syndrome, which is typically associated with *SCN1A* mutations [1,6]. In both syndromes, psychomotor development is generally normal before the onset of seizures, secondary progressive appearance of mental and motor delay and language regression is observed. In both syndromes, seizures are usually triggered by fever, and the association with generalized tonic-clonic and focal seizures is rather typical [2,7].

Treatment of EFMR is difficult. Especially during the first years of life, seizures appear to be highly resistant to antiepileptic drugs, while their frequency and their pharmacoresistance tend to decrease during the course of the disease [7,13]. Currently, there is limited data on treatment of these patients [10], especially, there is hardly any data on the results of treatment with a particular drug for more than 6 months, and still there is no clear consensus on how to treat these patients.

Therefore, the aim of our study was to evaluate the effectiveness of antiepileptic therapy in patients with *PCDH19* mutations including the data after one year of treatment.

2. Methods

We recruited patients with proven *PCDH19* mutations from 25 centers in 12 countries for this retrospective descriptive multicenter study by sending questionnaires to collaborating centers, where patients have been cared for regularly and received an individualized treatment. The clinical information was collected retrospectively and anonymized, using a questionnaire, which was filled out by the treating physicians, based on parents reports. Ethical approval was obtained from the Bavarian Ethic Commission.

In the questionnaire, both previous and current antiepileptic treatments were recorded and the effectiveness of the used antiepileptic drugs was assessed 3 and 12 months after the initiation of the respective medication. The influence on seizure activity was evaluated as response, non-response or aggravation, with response being defined as a seizure reduction of at least 50% after 3 or 12 months.

Response was further subdivided in seizure reduction of $\geq$50%, $\geq$75%, and 100%, with seizure reduction being defined as per cent decrease in seizure frequency. The drugs were evaluated only if they had been taken for at least 3 months in sufficiently high doses. Only drugs used in a minimum of five patients were included in the comparison of the effectiveness of the different drugs.

Furthermore, onset of epilepsy, types and duration of seizures, and provocation factors were recorded, as well as cognitive and motor development, behavioral disturbances and EEG and MRI findings, if available. Regarding duration of seizures we asked for clusters of seizure and status epilepticus, defined as a seizure lasting more than 20 min. The old definition [3] was chosen because of the retrospective design of the study.

3. Results

We included 58 female patients with *PCDH19* mutations, the clinical features are shown in Table 1. At least initially, 52% of the patients showed a normal interictal EEG, and in 34% the EEG remained normal during the follow-up. In patients who underwent MRI of the brain (n = 48), normal findings were seen in 81%, a focal cortical dysplasia (FCD) was diagnosed in 4% and suspected in 10%. The remaining patients had abnormal MRI findings independently of any FCD (1× hippocampal sclerosis, 1× arachnoid cyst).

Most patients were cognitively impaired, had motor disabilities or behavioral disturbances (see Table 2). The majority of the children initially showed no abnormalities in development (86%), and the onset of developmental delay most often coincided with the seizure onset (82%; data not available for 15 patients). Five girls had a normal motor, cognitive, and behavioral development throughout the course of the disease (age at end of observation was 4 to 11 years).

Table 1
Clinical features of the included 58 patients.

Age	10.6 years (2–27 years)
Age at seizure onset	11.2 months (3–78 months)
Different seizure types	2.5 (1–6)
Generalized tonic clonic seizures	81%
At least 2 different seizures types	74%
Clusters of seizures	93%
at least one status epilepticus	45%
Provocation factors for seizures	
Fever	76%
Afebrile infections	41%
Vaccinations	14%
Emotional stress	12%
Hot bathing	2%
Motor activity	None
Photostimulation	None

Table 2
Motor, cognitive and behavioral development of patients with reported disturbances (multiple entries possible).

		Number of patients (%)
Motor development	Normal motoric development	33 (57%)
	Hypotonia	8 (14%)
	Ataxia	18 (31%)
Cognitive development	Normal cognitive development	10 (17%)
	Learning disability (IQ 70–85)	18 (31%)
	Mental disability (IQ <70)	30 (52%)
Behavior	Normal behavior	19 (33%)
	Hyperactive	12 (21%)
	Aggressive	18 (31%)
	Aggressive traits	6 (10%)
	Autistic	22 (38%)
	Autistic traits	5 (9%)
	Obsessive	1 (2%)

Antiepileptic drugs administered for at least 3 months were bromide (BR), carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), ethosuximide (ESM), gabapentin (GBP), lacosamide (LCM), levetiracetam (LEV), lamotrigine (LTG), lorazepam (LZP), nitrazepam (NZP), oxcarbazepine (OXC), phenobarbital (PB), perampanel (PER), pregabalin (PGB), phenytoin (PHT), rufinamide (RFN), sulthiame (STM), stiripentol (STP), topiramate (TPM), vigabatrin (VGB), valproate (VPA) and zonisamide (ZNS). On average, the patients received 5.5 different antiepileptic drugs (range 1–12), most patients (98%; data not available for 14 patients) received at least temporarily a combination of two or more drugs. In addition, some patients received steroids, a ketogenic diet (KD) or a vagus nerve stimulation (VNS). The frequency and effectiveness of antiepileptic drugs administered for at least 3 months are summarized in Table 3 and Fig. 1. The frequency and effectiveness of antiepileptic drugs administered for at least 12 months are summarized in Table 4 and Fig. 2. Long-term response was defined as the proportion of responders after 12 months in relation to the number of patients treated for at least 3 months.

Forty-three patients (74%) became seizure-free for at least 3 months. Twenty-six patients (45%) achieved long-term seizure freedom, 24 of them (41%) for more than one year, 22 of the latter continued to receive drugs, 13 of them as polytherapy. Two patients (3%) became seizure-free for more than 10 years, both of them still receiving polytherapy. Remission occurred at the age of 8 months to 17.3 years (mean: 7.3 years), with 46% of the patients being younger than 5 years. In patients who became seizure-free in the long term, the average duration of active seizures was 10.7 years, with a range from 1 month to 11.8 years.

4. Discussion

In this retrospective study, we investigated the effectiveness of antiepileptic drugs used in patients with *PCDH19* mutations and their clinical course. The clinical evolution of most of our patients corresponded well with the one reported previously [7,9,14]. Seizure onset occurred mostly in the typical range of 6-36 months. Notably, there was a relatively large proportion (17%) of girls with an earlier onset down to 3 months, and one girl with a relatively late seizure onset at 78 months. In accordance with reports from other groups, we found many patients with cognitive impairment and behavioral disturbances [7,9,10]. But at least five girls (9%) showed an unremarkable development with respect to motor function, cognition and behavior. Obviously, the clinical spectrum of *PCDH19* mutations is wider than usually described. Therefore, *PCDH19* mutations are presumably still underdiagnosed as possible cause of epilepsy. They should also be considered in girls with an onset of epilepsy significantly beyond the typical range and with an otherwise unremarkable development.

Many of our patients showed features comparable to those of Dravet syndrome, even though they do not necessarily present with all the criteria for the clinical diagnosis. Like in children with *SCN1A* mutations, seizures were partly triggered by emotional stress, vaccinations or bathing, although the main provocation

Table 3
Effectiveness of AED after 3 months of use. Total number of patients treated with each antiepileptic drug and number of patients in whom these drugs showed response, non-response (seizure reduction <50%) or aggravation. Response was further differentiated into a seizure reduction by ≥50%, ≥75% and 100% (seizure free).

	Total	Response	50–74%	75–99%	100%	Non-response	Aggravation
BR	6	4 (67%)	1 (17%)	1 (17%)	2 (33%)	2 (33%)	0
CBZ	26	7 (27%)	2 (8%)	1 (4%)	4 (15%)	16 (62%)	3 (12%)
CLB	28	19 (68%)	4 (14%)	3 (11%)	12 (43%)	9 (32%)	0
CZP	9	4 (44%)	2 (22%)	0	2 (22%)	5 (56%)	0
ESM	2	0	0	0	0	2 (2/2)	0
GBP	2	0	0	0	0	2 (2/2)	0
LCM	4	3 (3/4)	0	1 (1/4)	2 (2/4)	0	1 (1/4)
LEV	38	13 (34%)	5 (13%)	3 (8%)	5 (13%)	25 (66%)	0
LTG	24	7 (29%)	3 (13%)	1 (4%)	3 (13%)	16 (67%)	1 (4%)
LZP	1	1 (1/1)	1 (1/1)	0	0	0	0
NZP	2	0	0	0	0	2 (2/2)	0
OXC	21	4 (19%)	2 (10%)	0	2 (10%)	15 (71%)	2 (10%)
PB	28	12 (43%)	2 (7%)	4 (14%)	6 (21%)	16 (57%)	0
PER	2	1 (1/2)	0	0	1 (1/2)	1 (1/2)	0
PGB	1	0	0	0	0	1 (1/1)	0
PHT	14	1 (7%)	1 (7%)	0	0	12 (86%)	1 (7%)
RFN	6	1 (17%)	1 (17%)	0	0	4 (67%)	1 (17%)
STM	9	1 (11%)	1 (11%)	0	0	8 (89%)	0
STP	5	2 (40%)	0	1 (20%)	1 (20%)	3 (60%)	0
TPM	29	11 (38%)	2 (7%)	1 (3%)	8 (28%)	18 (62%)	0
VGB	5	1 (20%)	0	0	1 (20%)	4 (80%)	0
VPA	50	22 (44%)	5 (10%)	3 (6%)	14 (28%)	28 (56%)	0
ZNS	3	1 (1/3)	0	1 (1/3)	0	2 (2/3)	0
Steroids	3	1 (1/3)	0	0	1 (1/3)	2 (2/3)	0
KD	4	2 (2/4)	0	1 (1/4)	1 (1/4)	2 (2/4)	0
VNS	1	1 (1/1)	0	1 (1/1)	0	0	0

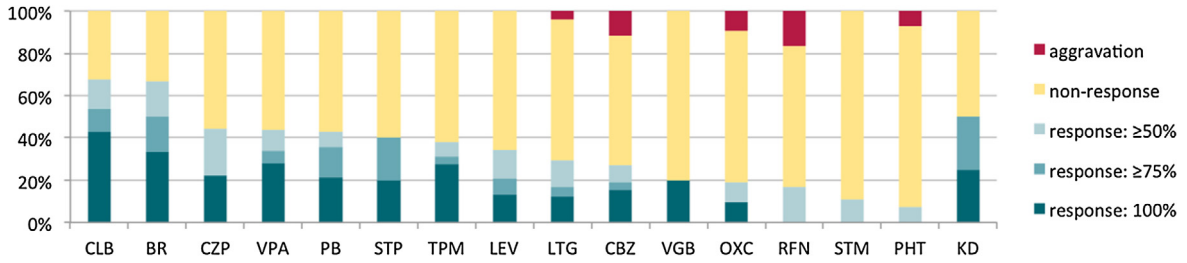

Fig. 1. Effectiveness of antiepileptic drugs after 3 months of use, differentiated in aggravation, non-response (seizure reduction <50%) and response (seizure reduction ≥50%). Response was further differentiated in seizure reduction of ≥50%, ≥75% and 100% (seizure free). Only drugs applied in at least 5 patients are shown (KD: $n = 4$).

Table 4
Effectiveness of AED after 12 months of use. Total number of patients treated with each antiepileptic drug and number of patients in whom these drugs showed response (seizure reduction ≥50%) or non-response (seizure reduction <50%). No cases with aggravation were observed. Response was further differentiated into a seizure reduction by ≥50%, ≥75% and 100% (seizure free). Long-term response was defined as the proportion of responders after 12 months in relation to the number of patients treated for at least 3 months.

	Total	Response	50–74%	75–99%	100%	Non-response	Long-term response
BR	4	3 (3/4)	2 (2/4)	0	1 (1/4)	1 (1/4)	50% (3/6)
CBZ	5	3 (60%)	2 (40%)	0	1 (20%)	2 (40%)	12% (3/26)
CLB	15	12 (80%)	3 (20%)	5 (33%)	4 (27%)	3 (20%)	43% (12/28)
CZP	2	2 (2/2)	1 (1/1)	0	1 (1/1)	0	22% (2/9)
ESM	0	0	0	0	0	0	0 (0/2)
GBP	0	0	0	0	0	0	0 (0/2)
LCM	1	1 (1/1)	0	0	1 (1/1)	0	1 (1/4)
LEV	14	8 (57%)	2 (14%)	3 (21%)	3 (21%)	6 (43%)	21% (8/38)
LTG	7	3 (43%)	0	2 (29%)	1 (14%)	4 (57%)	13% (3/24)
LZP	1	1 (1/1)	1 (1/1)	0	0	0	1/1
NZP	1	0	0	0	0	1 (1/1)	0 (0/2)
OXC	4	1 (1/4)	1 (1/4)	0	0	3 (3/4)	5% (1/21)
PB	13	6 (46%)	2 (15%)	1 (8%)	3 (23%)	7 (54%)	21% (6/28)
PER	1	1 (1/1)	0	0	1 (1/1)	0	1/2
PGB	0	0	0	0	0	0	0 (0/1)
PHT	2	1 (1/2)	1 (1/2)	0	0	1 (1/2)	7% (1/14)
RFN	1	0	0	0	0	1 (1/1)	0 (0/6)
STM	2	0	0	0	0	2 (2/2)	0 (0/9)
STP	2	1 (1/2)	0	1 (1/2)	0	1 (1/2)	20% (1/5)
TPM	12	8 (67%)	2 (17%)	2 (17%)	4 (33%)	4 (33%)	28% (8/29)
VGB	2	0	0	0	0	2 (2/2)	0 (0/5)
VPA	28	17 (61%)	3 (11%)	4 (14%)	10 (36%)	11 (39%)	34% (17/50)
ZNS	1	1 (1/1)	1 (1/1)	0	0	0	1/3
Steroids	0	0	0	0	0	0	0 (0/3)
KD	1	1 (1/1)	1 (1/1)	0	0	0	1/4
VNS	1	1 (1/1)	0	1 (1/1)	0	0	1/1

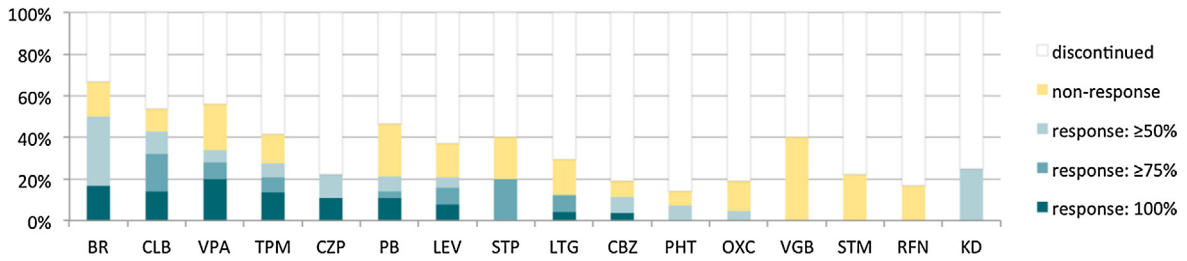

Fig. 2. Effectiveness of antiepileptic drugs after 12 months of use, differentiated in non-response (seizure reduction <50%) and response (seizure reduction ≥50%). Response was further differentiated in seizure reduction of ≥50%, ≥75% and 100% (seizure free). Long-term response was defined as the proportion of responders after 12 months in relation to the number of patients treated for at least 3 months. Only drugs applied for 3 months in at least 5 patients are shown (KD: $n = 1$).

factors were fever and infections. Differences mainly concern the cognitive development, the seizure provocation and the behavior, as patients with *PCDH19* mutations show less cognitive impairment and fewer provocation factors for seizure initiation, but present more often with behavioral problems. A characteristic feature is the occurrence of seizure clusters with relatively long seizure-free intervals. Accordingly, Dravet syndrome was clinically diagnosed in one-third of our patients. *PCDH19* mutations must therefore be taken into account for patients with Dravet symptoms.

In our patients, the most effective drugs after 3 months turned out to be CLB and BR, the following drugs were significant less effective. Aggravations were rarely observed in our patients. They were only seen in connection with sodium channel blockers, although CBZ and LTG showed a relatively good effectiveness. Compared to the 3 months treatment baseline, the most effective

drug after 12 months of treatment was BR, followed by CLB and VPA. Remarkably, the typical loss of effectiveness of CLB after several months did not occur in our patients, although sometimes a decrease in effectiveness was observed [15].

A precise assessment of the effectiveness of antiepileptic drugs in patients with *PCDH19* mutations is difficult. On the one hand, our study is retrospective, based on parental reports, consequently involving unavoidable uncertainty. Most patients received at least temporarily a combination of several drugs, which makes it difficult to differentiate between the effects of the separate drugs. The number of patients is limited, more than half of the drugs have been used in less than 10 patients. On the other hand, seizures in patients with *PCDH19* mutations usually occur in clusters, often triggered by febrile infections, with seizure-free intervals of several months, and it is difficult to distinguish the effect of the drugs from the natural course. An age-dependent and spontaneous seizure remission must also be considered. After a period of intense seizure activity at the beginning, there is a frequent reduction in seizure frequency in most patients [7]. Such an evolution was particularly impressive in one of our patients with initially up to 40 seizures per day and a spontaneous progressive seizure decrease up to seizure freedom, so that the drugs could be completely tapered off without recurrence of seizures at 2 years of follow-up.

Notably, although epilepsy in *PCDH19* mutations is known to be pharmacoresistant, around three-quarters of our patients were seizure-free for at least 3 months. Nearly half of them became seizure-free for more than one year, and two even for over 10 years. Almost all of them were still on medication, although it was not clear whether the drugs were required because withdrawal was not attempted. Due to the initial seizure history, it is understandable that families may not want to take the risk of a renewed deterioration by tapering off the drugs.

There are hardly any reports on medication for epilepsies associated with *PCDH19* mutations. Higurashi et al. [10] reported a good seizure control especially with PHT, BR and CLB. The difference in effectiveness of PHT in this study compared to ours is remarkable, possibly due to the small number of cases in both studies. It is also noteworthy that in our patients aggravations occurred only in connection with sodium channel blockers, whereas Higurashi et al. reported also aggravations in connection with TPM and VPA [9]. Therapeutic consensus as described for patients with *SCN1A* mutations are not yet in sight. On balance, GABAergic drugs such as BR, CLB and VPA seem promising, analogous to their therapeutic response in Dravet syndrome [4,16]. Higurashi et al. reported that the profile of drugs showing higher efficacy in patients with *PCDH19* mutations was similar to that observed in Dravet syndrome, with the exception of phenytoin [10]. In a single case report, STP showed a good effect in combination with CLB and VPA, a well-established therapy in Dravet syndrome [18]. So maybe therapy concepts used for the Dravet syndrome with *SCN1A* mutations could also be successfully applied in patients with *PCDH19* mutations. However, sodium channel blockers caused significantly less aggravations here, but were often effective.

Remarkably, there was a relatively high proportion of abnormal MRI findings, with focal cortical dysplasia being diagnosed or suspected in several patients. While mechanisms of epileptogenesis in *PCDH19* mutations are still unclear, the role of protocadherin-19 during brain development suggests that *PCDH19* mutations lead to structural malformations [13]. This would fit well with the observed effectiveness of sodium channel blockers, with few aggravations, but not with the typical course characterized by spontaneous seizure reduction.

Further studies are needed to gain a better understanding of the mechanism of epileptogenesis in *PCDH19* mutations and to develop effective therapeutic strategies. Randomized controlled studies are desirable, but they are hardly feasible due to the low patient numbers. We have therefore chosen the retrospective approach in order to achieve first results. Retrospective studies like ours may help to get an outline of effectiveness of drugs in EFMR and to develop controlled studies, knowing that the assessment of drug efficacy will always remain biased by the favorable spontaneous course. Like with any other patient with epileptic seizures, to taper the medication after a prolonged seizure-free period seems safe in these patients and should always be taken into account.

Conflict of interest

None of the authors has any conflict of interest to disclose. 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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