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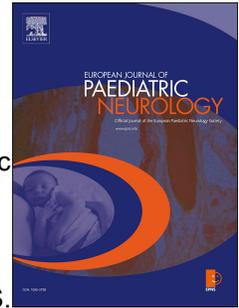
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Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with *CDKL5*-related epilepsy

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# Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with *CDKL5*-related epilepsy

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**Running title:** long-term efficacy of AED and ketogenic diet in CDKL5

**Key words:** AED, ketogenic diet, CDKL5, long-term efficacy

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Uncommon abbreviations:

*CDKL5* = X-linked cyclin-dependent kinase-like 5 gene

*MeCP2* = methyl-cytosine phosphate guanine-binding protein2

**Abstract:**

**Objective:** Mutations in the *CDKL5* gene cause an early-onset epileptic encephalopathy. To date, little is known about effective antiepileptic treatment in this disorder.

**Method:** Accordingly, the aim of this retrospective study was to explore the role of different antiepileptic drugs (AEDs) and the ketogenic diet (KD) in the treatment of this rare genetic disorder. We evaluated the efficacy in 39 patients with *CDKL5* mutations at 3, 6 and 12 months after the introduction of each treatment. One patient was lost to follow-up after 6 and 12 months.

**Results:** The responder rate (> 50% reduction in seizure frequency) to at least one AED or KD was 69% (27/39) after 3 months, 45% (17/38) after 6 months and 24% (9/38) after 12 months. The highest rate of seizure reduction after 3 months was reported for FBM (3/3), VGB (8/25), CLB (4/17), VPA (7/34), steroids (5/26), LTG (5/23) and ZNS (2/11). Twelve patients (31%) experienced a seizure aggravation to at least one AED. Most patients showed some but only initial response to various AEDs with different modes of actions.

**Significance:** Considering both age-related and spontaneous fluctuation in seizure frequency and the unknown impact of many AEDs or KD on cognition, our data may help defining realistic treatment goals and avoiding overtreatment in patients with *CDKL5* mutations. There is a strong need to develop new treatment strategies for patients with this rare mutation.

**Key words:** AED, ketogenic diet, *CDKL5*, long-term efficacy

### Introduction:

Mutations in the X-linked cyclin-dependent kinase-like 5 gene (*CDKL5*) cause an early-onset epileptic encephalopathy with severe neurological impairment. *CDKL5* mutations are almost exclusively found in females<sup>1-4</sup>. Clinical features are seizures starting before the first 4 months of life, secondary microcephaly, poor development of motor, cognitive and speech abilities and, often, hand stereotypies<sup>5</sup>. In the first weeks of life children seem to be normal. Even before the onset of the epilepsy, patients often show feeding problems, poor eye contact and delayed developmental milestones. The phenotypic spectrum in males often is at the severe end of the spectrum. In milder forms children learn to walk and the course of the epilepsy is less severe, with the possibility of achieving seizure control in some patients<sup>2</sup>. Because of previously reported clinical similarities to patients with *MECP2* mutations, patients with *CDKL5* mutations are often described as an “atypical” or “variant” Rett syndrome. The *CDKL5* disorder is an independent clinical entity associated with early-onset encephalopathy<sup>2-3</sup>. In severe forms most of the distinctive clinical features of Rett syndrome are lacking<sup>2,4-8</sup>.

In contrast to typical Rett syndrome with epileptic seizures unlikely starting before the age of three years, in patients with *CDKL5* mutations seizures usually start between the first day and 4 months, often as infantile spasms<sup>1; 9-10</sup>. Melani et al. described a peculiar seizure pattern with prolonged generalized tonic-clonic seizures, consisting of a tonic part with vibratory contractions lasting 2-4 minutes, followed by a clonic phase with a series of spasms and later repetitive distal myoclonic jerks<sup>11</sup>

Half of the children with *CDKL5* mutations older than 3 years may show seizure remission, the remaining continue to experience from intractable spasms, multifocal and myoclonic seizures<sup>9-10</sup>.

To date, little is known if any type of treatment might more likely change the seizure frequency in patients with *CDKL5* encephalopathy. The purpose of this retrospective multicenter study was therefore to describe the efficacy of AEDs and KD in patients with *CDKL5* mutations.

#### Patients and Methods:

Twenty-one centers in Europe and the United States contributed their experience on drug treatment of patients with *CDKL5* mutations. Using an electronic questionnaire, anonymized data were reported. Inclusion criteria for our patients were epilepsy together with an identified *CDKL5* mutation and a follow-up of the first AED for at least 3 months.

The retrospective study was based on parents' report of seizures as well as physician assessment of clinical description and age at onset of seizures. We retrospectively analyzed the efficacy of AED 3, 6 and 12 months after the introduction of each drug. Drug response was defined as a 50% seizure reduction. Drug response was defined as a more than 50% seizure reduction in the last 4 weeks compared to 4 weeks baseline period before starting the new AED. When a drug was discontinued, the patient was categorized as a non-responder in the following observation period. Seizure aggravation was defined as a more than 50% increase in seizure frequency. The dose of the AED and the mode and effectiveness (e.g. keton bodies) of the KD was not evaluated.

Ethical approval was obtained from the Bavarian State Medical Association ("Bayerische Landesärztekammer").

## Results:

39 patients (34 females; age: 0.6-22.4 years; mean 7.3; median: 5.8) with *CDKL5* mutations were included, 3 of them have been described in earlier publications<sup>6; 12</sup>. In one patient, who was only 7 months old, follow-up data were only available for 3 months. One additional patient died at the age of 2 years. All of them showed an epileptic encephalopathy and severe mental disability. Patients were treated with 3 to 21 (mean: 9; median: 9) different AEDs. The five most frequently used drugs were VPA (87%), LEV (79%), TPM (79%), steroids (67%) and PB (67%); 12 patients (31%) had KD (Table 1).

Thirty-four patients (87%) showed an initial response to at least one AED for several weeks, but loss of efficacy occurred in the following weeks in most. Two patients became (and still remain) seizure free: one with CBZ for 10 years, another one under a combination therapy of VGB and PB for 3 years. In the other patients seizures reoccurred after weeks to months.

The responder rate to at least one AED was 69% (27/39) after 3 months, 45% (17/38) after 6 months and 24% (9/38) after 12 months. The highest rate of seizure reduction after 3 months was reported during treatment with FBM (3/3), VGB (8/25), CLB (4/17), VPA (7/34), steroids (5/26), LTG (5/23) and ZNS (2/11). There were no significant different response rates between infantile spasms and other seizure types. The responder rate of each drug after 3, 6 and 12 months is summarized in Table 1 and Figure 1. Twelve patients (31%) experienced seizure aggravation to at least one AED. LEV (5/31), CBZ (4/15) and LTG (3/23) were described most frequently as aggravating, which often led to discontinuation of the respective AED. In case of aggravation seizure type was not specific. No severe adverse events were reported. One patient (1/1) initially responded to intravenous immunoglobulines, but showed

loss of efficacy after 2 months. 2/12 had a significant reduction of seizures under KD for more than 6 months, one of them for more than one year.

### Discussion:

The major finding of this study was that most patients with *CDKL5* mutations exhibited some and only temporary response to various AEDs with different modes of actions.

Patients with *CDKL5* mutations usually have a difficult-to-treat epileptic encephalopathy. So far there is no disease-specific antiepileptic drug regime with long-term efficacy in patients with *CDKL5* mutations available. It is an important information for parents that their child will most likely not become completely seizure-free. The aim of treatment should therefore be an at least slight reduction of seizures as well as an improvement of quality of life by teaching and supporting parents and offering further ways of treatment.

The highest, but above all still very low, responder rate after 12 months was reported with VPA (9%), whereas there was a very low number of patients responded to PHT, FBM, CBR and CLN (n=1). This antiepileptic drug is also reported as the most effective one in patients with typical Rett syndrome<sup>13</sup>, although the responder rate is much lower in patients with *CDKL5* mutations.

One patient in our study remained seizure-free under CBZ for more than 10 years. This exceptional patient is also included in the study of Jähn et al.<sup>12</sup>.

On the other hand, we observed four patients with an aggravation to CBZ. Chen et al. suggested an independent function of *CDKL5* and *MECP2*, which might be

responsible for the differences between patients with classic Rett syndrome and *CDKL5* mutations. Additionally, seizure remission could also be part of the spontaneous course of the child's epilepsy<sup>14</sup>. In other studies<sup>9-10</sup> half of the children with *CDKL5* mutations older than 3 years experienced spontaneous seizure remission for a longer period of time, which might be the cause for the disappearance of seizures in the other patient at the age of 4 years under PB and VGB. Therefore, the reason for the positive response to CBZ in one patient and to PB and VGB in the other patient remains unclear. The low rate of patients in our study becoming seizure free (2/39; 5 %) might be explained by the selection bias, that all of our patients were recruited from tertiary epilepsy centers.

Seizure aggravation was frequently (31%) reported to at least one AED. Any AED can have a paradoxical effect of exacerbating seizures in any type of epilepsy. In other epileptic encephalopathies some AEDs can lead to an exacerbation of epilepsy. E.g., in patients with Dravet syndrome, CBZ and LTG in particular are known to aggravate seizures<sup>2; 15; 16</sup>. This might be explained by the fact that both drugs are sodium channel blockers and Dravet syndrome is frequently caused by sodium channel (*SCN1A*) mutations. In this cohort, LEV (5/31), CBZ (4/15) and LTG (3/23) led to aggravation. Our data did not allow to predict if certain AEDs with a distinct mode of action are more likely to aggravate seizures in patients with *CDKL5* mutations.

No severe adverse events were reported, but detailed information regarding tolerability was not obtained in our study.

None of patients who achieved a significant reduction of seizures exhibited improvement of cognitive functions. This underlines the epileptic encephalopathy as part of the syndrome and not the epilepsy as the cause of the severe mental

impairment<sup>17</sup>. We prefer to consider the epilepsy in patients with *CDKL5* mutations as a genetic epilepsy with encephalopathy versus an epileptic encephalopathy (defined by cognitive involvement due to ictal and/or interictal activities. Because of age-related and spontaneous fluctuations in seizure frequency and types, overall benefit of different AEDs remains unclear.

There are some limitations of our study, mainly because of its retrospective character, selection bias due to recruitment of all patients from tertiary epilepsy centers and a lack of a standardized protocol. Nevertheless, our data might be important for clinicians facing the challenge to treat children with infantile-onset refractory epilepsy of unknown origin, regarding the following aspects:

1. So far, the detection of a *CDKL5* mutation does not allow to offer a specific concept to preferred AED. Nevertheless, it is important to make the genetic diagnosis for proper genetic counseling.
2. Due to long-term efficacy of all AEDs in our patients with *CDKL5* mutations was low and seizure-freedom exceptional, there is a danger to overtreat these patients. On the other hand, even a slight seizure reduction for a short period of time might improve patient's as well as parents' quality of life. Realistic treatment goals have to be defined in collaboration with the parents.
3. Multicenter clinical long-term observations including prospective assessment of side effects for a better benefit-risk ratio analysis might help clinicians to define treatment strategies in patients with this rare and refractory epileptic encephalopathy.

In conclusion, we found the long-term efficacy of multiple AEDs and KD in patients with *CDKL5* mutation to be low. Nevertheless, our data may help to define realistic treatment goals in collaboration with the parents focusing not only on epilepsy-specific variables such as seizure frequency and epilepsy severity but on the overall health-related quality of life. There is a strong need to develop new treatment strategies for patients with this rare mutation.

Disclosure:

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.

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

ACCEPTED MANUSCRIPT

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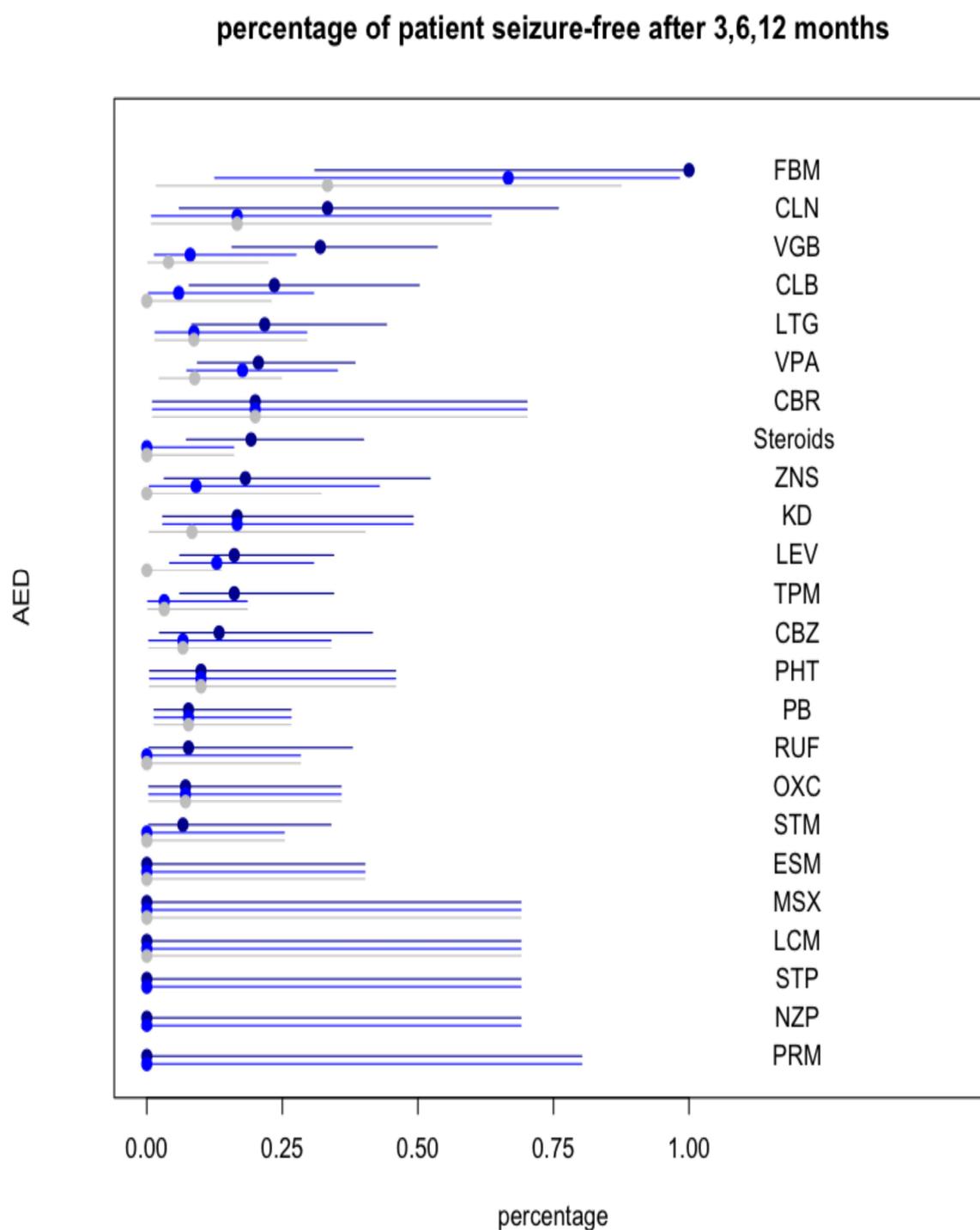
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<b>AED</b>	<b>n</b>	<b>Responder rate after 3 months</b>	<b>Responder rate after 6 months</b>	<b>Responder rate after 12 months</b>
VPA	34	7 (21%)	6 (18%)	3 (9%)
LEV	31	5 (16%)	4 (13%)	0
TPM	31	5 (16%)	1 (3%)	1 (3%)
Steroids / ACTH	26	5 (19%)	0	0
PB	26	2 (8%)	2 (8%)	2 (8%)
VGB	25	8 (32%)	2 (8%)	1 (4%)
LTG	23	5 (22%)	2 (9%)	2 (9%)
LTG	23	5 (22%)	2 (9%)	2 (9%)
CLB	17	4 (24%)	1 (6%)	0
RUF	13	1 (8%)	0	0
CBZ	15	2 (13%)	1 (7%)	1 (7%)
OXC	14	1 (7%)	1 (7%)	1 (7%)
ZNS	11	2 (18%)	1 (9%)	0
PHT	10	1 (10%)	1 (10%)	1 (10%)
ESM	8	0	0	0
CLN	6	2 (33%)	1 (17%)	1 (17%)
BR	5	1 (20%)	1 (20%)	1 (20%)
MSX	3	0	0	0
FBM	3	3 (100%)	2 (67%)	1 (33%)
LCM	3	0	0	0
STP	3	0	0	0
PRM	2	0	0	0
Ketogenic diet	12	2 (17%)	2 (17%)	1 (8%)

**Table 1: Responder rate of AED's after 3, 6 and 12 months**

LEV: Levetiracetam; VPA: Valproic Acid; TPM: Topiramate; PB: Phenobarbital; VGB: Vigabatrin; LTG: Lamotrigin; CLB: Clobazam; RUF: Rufinamide; CBZ: Carbamazepine; STM: Sultiame; ZNS: Zonisamide; PHT: Phenytoine; ESM: Ethosuximide; CLN: Clonazepam; BR: Bromide; MSX: Mesuximide; FBM: Felbamate; LCM: Lacosamide; STP: Stiripentol; PRM: Primidone



**Figure 1.** Response rate of the antiepileptic drugs investigated in the current study, sorted by average response rate. The dots correspond to the average response rate in a given AED, the colors indicate 3 months (dark blue), 6 months (light blue) and 12 months (grey) follow-up. The lines indicate the 95% confidence interval of the response rate.

## Highlights:

- so far little knowledge about effective antiepileptic treatment in CDKL5 patients
- retrospective study in 39 CDKL5 patients: effect of AEDs/ ketogenic diet (KD)
- responder rate to one AED or KD: 69% (3 months), 45% (6 months); 24% (12 months)
- twelve patients (31%) experienced a seizure aggravation to at least one AED
- our data may help defining realistic treatment goals and avoiding overtreatment