

## Caregiver's perception of epilepsy treatment, quality of life and comorbidities in an international cohort of CDKL5 patients

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### Abstract

**Objective:** CDKL5 is a genetic condition associated with drug-resistant epilepsy and intellectual disability. There is limited information on its natural history. We investigated the natural history, complications, and the effectiveness of current treatment strategies.

**Methods:** This study was conducted in conjunction with the CDKL5-UK Charity, with patients recruited from the USA and Europe. Online questionnaires were completed by parents/carers and included information relating to demographics, growth, development, epilepsy, comorbid conditions, and efficacy and side effects of antiepileptic treatments.

**Results:** Thirty-nine of the 44 patients were female. Median age was five years (range five months to 31 years), and all had a history of epilepsy. All patients had developmental delay, with 4/21 able to run and 4/22 able to climb. Gastrointestinal problems were reported in 31/43. Cardiac arrhythmia was seen in 11/29.

Over one-quarter of the patients had tried ten or more antiepileptic medications. Vigabatrin was reportedly the most effective AED (antiepileptic drug) in 12/23; clobazam (most effective in 6/14); sodium valproate (most effective in 5/27), and levetiracetam (most effective in 3/27). VNS (Vagal Nerve Stimulator) was reported to be effective in 9/12. One year after VNS insertion, 9/12 reported improved (QoL), and there were improvements in mood, school achievement and concentration in (9/11). The ketogenic diet was considered effective and to have improved QoL in (12/23).

**Conclusion:** Vigabatrin appears to be more effective than other AEDs. VNS and ketogenic diet are also relatively effective. Gastrointestinal and cardiovascular system complications are common. The results may help to guide management of epilepsy in CDKL5. It highlights a possible link between CDKL5 and potentially treatable life-threatening complications such as cardiac arrhythmia. More research in this area may help us develop a more systematic approach to treating these patients. HIPPOKRATIA 2017, 21(3): 130-135.

**Keywords:** CDKL5, natural history, epilepsy, vagal nerve stimulator, ketogenic diet, vigabatrin

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### Introduction

CDKL5 (Cyclin-dependent kinase-like 5) is a serine-threonine kinase which is believed to play an important role in processes such as alternative splicing, neuronal morphogenesis, and dendritic arborization, and also in energy metabolism. Mutations in the *CDKL5* gene are associated with severe X-linked infantile spasms and learning disabilities<sup>1,2</sup>. There are more than 100 cases of CDKL5 deficiency which have been reported in literature<sup>3</sup>. Most cases are in females, but there are a few male patients who have been affected by this disorder<sup>4</sup>. Small case series have shown that children with CDKL5 deficiency present with early-onset epilepsy (before five months of age), poor head growth, stereotypies, sleep disturbances and severe developmental delay<sup>5,6</sup>.

CDKL5 disorders were previously believed to be a variant of Rett syndrome<sup>7</sup>. However, there have been a

large number of patients with CDKL5 who did not meet the diagnostic criteria for early-onset seizure variant of Rett syndrome, and therefore CDKL5 disorder was suggested to be a separate entity from Rett syndrome<sup>8,9</sup>. In addition, CDKL5 expression has been found to be stable in lymphoblastoid cell lines in individuals with Rett syndrome. It has also been shown that in the brain of MECP2 (methyl CpG binding protein 2) deficient mice there is no interaction between CDKL5 and MECP2 at the level of transcription<sup>10,11</sup>.

Very little is known about the *CDKL5* gene's function<sup>12</sup>. It is believed to play an important role in proliferation and development of neuronal cells. Patients with the *CDKL5* mutation have a high level of 4-hydroxynonenal protein adducts, which is a marker of oxidative stress, as a result of mitochondrial dysfunction in their peripheral blood lymphocytes<sup>13</sup>. Other physiological deficits that

have been linked to CDKL5, such as cytokine dysregulation, impaired protective mechanisms against oxidative stress, and abnormal thyroid function. This suggests that CDKL5 deficiency can have an impact on several physiological systems, and therefore it may cause other health issues besides refractory epilepsy and developmental delay.

Unlike Rett syndrome, very little is known about the natural history and associated comorbidities in CDKL5 disorders<sup>14</sup>. The available literature is based on very small case series from individual centers. The best evidence-based approach for treating seizures in CDKL5 disorders is not known. The efficacy of the nonmedicinal approaches, such as the Vagal Nerve Stimulation (VNS) and the ketogenic diet, have not been investigated in this group of patients. In this study, we aimed to answer some of these uncertainties in a large international group of children and adults with CDKL5 disorders. We examined the natural history and associated comorbidities in CDKL5. We also investigated the efficacy of different treatment modalities for epilepsy in this group.

## Methods

The CDKL5-UK Charity has a database of 44 children and adults with CDKL5. They provide support for families and carers of those diagnosed with CDKL5 and are a resource for up to date research and information on the condition. With the support of the staff and supporters at the CDKL5-UK Charity, we performed a qualitative study by providing an online questionnaire that was accessible to any parent or carer registered on the CDKL5-UK Charity database. The patients were from the USA, Europe and UK. We had no access to their medical records, and neither we, nor the charity had any communication with any of the patient's medical practitioners.

The questionnaire was not a validated set of questions. We used a practical and pragmatic approach. The questionnaire was based on case reports of CDKL5 in the literature and patients' complaints. The questionnaire asked questions relating to the children's growth parameters, areas of development - gross motor, vision and fine motor, hearing and speech, and social skills, including personal care, and observed development compared with peers. For the developmental section, we have included only those patients aged five years and above in order to minimize false negatives. For example, when we ask parents of an infant whether they are able to walk, they may say no, however, this could be due to the child's age rather than the condition.

We also asked a number of detailed questions relating to the child's epilepsy and perceived efficacy, and side effects of anti-epileptic treatments by the family, including VNS and the ketogenic diet. We did not define the word "efficacy". We asked parents and carers "What do you think is the best (the most effective) antiepileptic medication?". The assessment of AED (antiepileptic drug) response was qualitative. We also asked about child's initial presentation, diagnosis, and comorbid conditions.

Parents and carers gave consent to be contacted for this project. We were advised by University Hospitals Bristol Research and Development team that, since we were not collecting the data directly and there was no patient-identifiable information or planned medical exposure, the survey-style study design did not require specific institutional ethical approval.

## Results

### *Patient characteristics*

Parents/carers of 44 patients with CDKL5 contributed to the project. The median age of the patients was five years (range five months to 31 years). The proportion of females was 39/44. All the patients had a genetic diagnosis of CDKL5. Thirty-nine parents/carers provided genetic details. The median age at which the parents noticed there was a problem with their child was four weeks of age and median age at which the CDKL5 diagnosis was made was two years. Three of the 44 patients were initially thought to have gastroesophageal reflux, and one patient was believed to have cerebral palsy before the diagnosis of CDKL5 was made. Not all of the questions were answered by all of the parents and carers. Some parents and carers left some questions blank.

### *Epilepsy*

All the 44 patients had epilepsy, and only three patients were seizure free at the time of the survey. The patients were reported to have different types of seizures, such as generalized tonic-clonic, atonic drops, tonic, myoclonic, spasms and absence. Seizure type had remained stable in only 4/44 patients.

### *Antiepileptic medications*

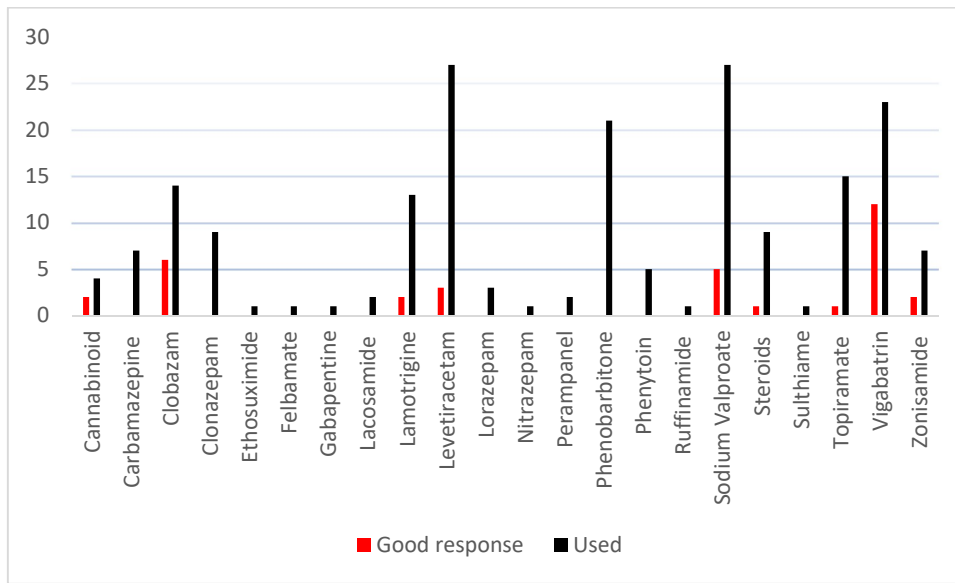
Two out of 44 patients were on no antiepileptic medications at the time of the project. Parents and carers of two patients did not answer the antiepileptic medication question. Thirteen out of 40 were on one antiepileptic drug, 16 on two, nine were on three, and two were on four antiepileptic drugs.

There were 40/42 patients who had tried two or more antiepileptic medications and reported continuing poor seizure control. Twenty-six of the 42 patients had tried five or more antiepileptic medications, and 14/42 of the patients had tried eight or more antiepileptic medications.

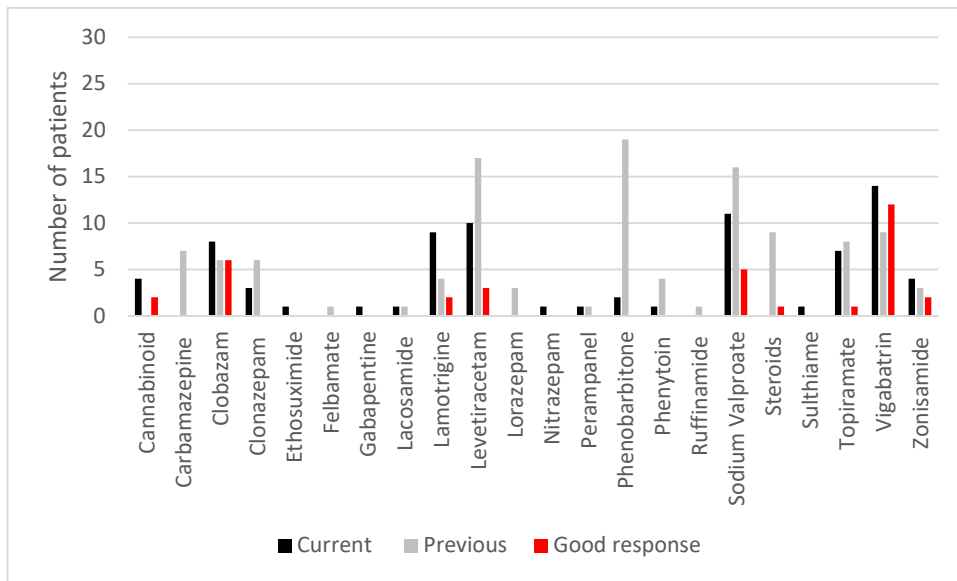
Levetiracetam had been used by 27 patients, of whom three reported a good response. Other notable AEDs reported to show a good response in some cases were: sodium valproate [5/27], vigabatrin [12/23], topiramate (1/15), clobazam (6/14), lamotrigine (2/13), clonazepam (0/9), and steroids (1/9) (Figure 1, Figure 2). Twenty-one patients had been treated with phenobarbital, but this was not reported to have a good response in any of the patients.

### *VNS*

Twelve patients had a VNS for seizure control. The median age at VNS insertion was 4.5 years. We asked



**Figure 1:** Regarding the 44 patients with CDKL5 who participated in this study, this bar chart shows the number of patients who have used an antiepileptic medication (black bars) and the number of patients whose parents and carers reported a good response (red bars).



**Figure 2:** Regarding the 44 patients with CDKL5 who participated in this study, this bar chart shows the number of patients who were on an antiepileptic medication at the time of the study (black bars), those who had previously been on an antiepileptic medication (grey bars), and the number of patients whose parents and carers reported a good response (red bars).

the parents and carers if there were any other changes made at the same time that the VNS was inserted (such as medication changes). Parents and carers of six out of 12 patients responded yes to this question. Two out of six explained their answer. One patient started puberty, and the other one had their lamotrigine dose reduced, and vigabatrin stopped. VNS was reported to be effective in 9/12. After one year of VNS insertion, two patients were on fewer maintenance antiepileptic medications, nine patients remained on the same regular medications, and in one case we obtained incomplete information. In regards

to rescue medications, two patients required fewer rescue medications, eight patients required a similar number of rescue medications, and in two cases there was incomplete information.

One year after VNS insertion, 9/12 patients were reported to have an improved quality of life, one a worsening in the quality of life, and one was reported to have no change. Nine out of ten of the parents and carers of patients who had VNS would recommend VNS to another family with a child with CDKL5 disorder. Nine patients (9/11) reported mood improvement, better concentration

and school performance and two (2/11) reported no mood change or change in concentration or school performance in response to VNS. Six patients (6/11) reported improvement in sleep while the other five (5/11) reported no improvement in sleep. The reported adverse effects were coughing in two patients, hoarseness of voice in one, and slowness in bowel motility in one patient.

#### *Ketogenic diet*

Twenty-six patients received a ketogenic diet for seizure control. The median duration of the diet was two years. The median age of the patients at the time of the diet introduction was 22 months. Three (3/26) patients had their antiepileptic medications reduced during the ketogenic diet therapy. There were no other changes during the diet therapy. The ketogenic diet was reported to be effective in twelve (12/23) of the patients. Side effects as a result of the diet were reported in 18/26 of the patients, including constipation, vomiting, and lack of energy. After one year of introducing the ketogenic diet, five patients (5/14) were on fewer antiepileptic medications, and the remaining nine (9/14) were on the same medications. Six patients (6/18) were requiring fewer rescue medications, eleven (11/18) were requiring the same amount of medications, and the remaining were requiring more medications. Improvement in the quality of their life was reported in half of the patients (10/19), and 20/25 of the parents and carers would recommend the ketogenic diet to another family with a child with CDKL5 disorder.

#### *Gastrointestinal tract*

Gastrointestinal tract problems were reported in 31/43 of the patients. Thirteen out of 27 had constipation, six patients (6/27) were suffering from gastroesophageal reflux, and 15/37 were believed to be air swallows (bloater). Eleven patients (11/36) had a feeding tube for feeding. Four out of 33 of them developed a volvulus.

#### *Cardiovascular system*

Nineteen patients (19/29) were investigated with electrocardiography (ECG) and echocardiogram (echo). Arrhythmia was found in 11/29 of them.

#### *Developmental milestones*

When we asked the parents and carers if the patients were able to feed themselves, we were informed that 5/22 were able to feed themselves. Six out of 22 were able to walk, and four (4/22) could walk independently. Four out of 22 patients were able to climb up and downstairs and four (4/21) were able to run. Hearing issues were reported in two patients (2/22) and vision problems in seventeen (17/22). Four patients (4/22) were reported to be able to talk.

### **Discussion**

This is the first study to investigate the natural history, associated comorbidities, and treatment of CDKL5 in a large cohort of children and adults with CDKL5.

All the 44 patients had a history of epilepsy. All patients had developmental delay from moderate to severe. Some were able to run, climb, and feed themselves. Most of the patients had vision problems. Abnormal heart rhythm was reported in eleven patients (11/29). Gastrointestinal tract problems were reported in two-thirds of the patients. Vigabatrin was reported to be the most effective antiepileptic medication. Both VNS and ketogenic diet were reported to be effective and to have a significant impact on the patient's quality of life, mood, school, concentration, and sleep. Over ¼ of the patients had tried eight or more antiepileptic medications. There were five male patients with CDKL5 in this cohort.

Compared with other drugs used, vigabatrin was reported to be the most effective. Fourteen patients were currently on vigabatrin at the time of data collection. This was the most commonly used drug, and vigabatrin 12/23 reported a positive response. One could argue that because a large number of patients are currently on vigabatrin, they may recall the effect more accurately, and hence produce a bias towards vigabatrin. Had more patients been currently on other drugs, the parents and carers may have reported more positively about them. As shown in Figure 1 and Figure 2, we have split the periods into current and previous to examine this potential bias. The next most common currently used medications were sodium valproate and levetiracetam. Twenty seven patients were on sodium valproate with 5/27 reporting positively, and 27 were on levetiracetam, with 3/27 reporting positively.

The percentage difference between these drugs shows that vigabatrin reported effectiveness was not subject to positive bias. From further analysis of the data, we have noted that vigabatrin was effective for all types of seizures. The median age of the patients who were on vigabatrin was 5.5 years. This shows that vigabatrin has not only been given for infantile spasms in this group. We do not have an explanation as to why vigabatrin was reported to be the most effective drug. However, it could be due to its effect on gamma-Aminobutyric acid (GABA). Vigabatrin inhibits the GABA-degrading enzyme, GABA transaminase, resulting in a widespread increase in GABA concentrations in the brain. The increase in GABA functions as a brake on the excitatory processes that can initiate seizure activity<sup>7</sup>. Most of the other antiepileptic drugs work through other mechanisms such as a reduction in Na<sup>+</sup> and Ca<sup>++</sup> channel activities, and reduction in glutamate transmission, which are all mainly through dendrites. It is believed that CDKL5 can affect dendritic growth and arborization through rearrangement of the cytoskeleton. It co-localises with F-actin and interacts with Rac-1, a Rho GTPase, which promotes the formation and/or maturation of spines by remodeling the actin cytoskeleton<sup>15</sup>. It may be, that because these patients have impaired dendritic growth, vigabatrin is more effective than other AEDs.

Most of the patients parents/carers reported visual problems including cortical blindness. It is difficult to know whether this is part of CDKL5 or if it is due to their

developmental delay and learning disabilities, or other causes such as drug side effects. However, CDKL5 animal models have shown that lack of CDKL5 disrupts the organization of excitatory and inhibitory synapses and parvalbumin interneurons in the primary visual cortex.

It is interesting to note that arrhythmia was reported in eleven patients (11/29). Only nineteen patients (19/29) had cardiac investigations such as echo and ECG. It is possible that we might find more arrhythmias in this group, had more patients had been investigated. We cannot be certain whether these patients had cardiac arrhythmia due to CDKL5 or other unknown reasons. However, we know that the CDKL5 gene is expressed in other organs such as the heart, and this makes a biological link possible<sup>16</sup>.

Gastrointestinal problems were reported in most of the patients, including constipation, gastroesophageal reflux, air swallowing, and volvulus. Constipation was reported in thirteen patients (13/27). It is difficult to be certain whether constipation is part of the condition or it is related to other causes. The prevalence of constipation in children with learning disabilities is 26-50 %<sup>17</sup>. Constipation is also prevalent in adults with learning disabilities, and it is believed to be around 70 %<sup>18</sup>. This is probably because more people with learning disabilities are on antiepileptic medications, which can cause constipation. They are also often physically restricted and less mobile. Some genetic and neurological disorders such as Down's syndrome and cerebral palsy are believed to be strongly associated with constipation<sup>19,20</sup>. Animal studies have shown that the CDKL5 gene is expressed in various organs such as the liver, lung, testis, kidney, and spleen<sup>18</sup>. It is possible that this gene is also expressed in the bowel, as we have reported such a large number of patients in this cohort with gastrointestinal tract problems.

There are limitations regarding the current study. This study relies on parental and carer's ability to accurately and fairly recall events that occurred in the past. Therefore, subsequent events may affect the person's perspective on previous events, and thus the outcomes recorded from this study. It is important with these rare and complex conditions that an overall picture of a patients' care journey is taken into account, including the perceived effectiveness of the different treatments, and this is what we have recorded in this study. The perceived impact by patients and their parents/carers may be as important as any actual physical symptoms from the different treatments. Alongside this, we have not taken into account the length of each trial of treatment, or the order of the treatments, which may influence the effectiveness of each treatment. However, we can build up a consensus on each treatment and its impact. It is difficult with conditions such as CDKL5 to build up a clear picture of the condition and patient outcomes due to the relatively small number of patients and the range in complexity of the condition. Utilizing databases such as the CDKL5 charity to access a number of patients and to record their parent's/carers' views, is important, but not without its limitations. It may

introduce selection bias into our sampling. Double and false entries are another possibility. We noted that one family entered their answers three times. This was easy to recognize as the answers were similar for all three entries. We kept one entry and removed the other two. We cannot be certain that any other family did not enter false or misleading information. However, we know from experience that most families who support a loved one with a severe and rare condition are keen and willing to help health professionals. The assessment of AED response was qualitative. We did not offer the parents/carers a range or scale to choose from to determine the response to each drug or intervention. We chose a practical and pragmatic approach to make the questionnaire more attractive and easy for parents to complete. We did not use a standardized or validated quality of life questionnaire to investigate the effect of VNS and ketogenic diet on the patient's quality of life. We would not have been able to perform a self-reported quality of life assessment, as none of the patients would have been able to respond for themselves due to their developmental delay and learning disabilities. The aim of the study was to assess the parent's/carers' perception of these interventions.

## Conclusion

Vigabatrin appears to be more effective than other AEDs. VNS and ketogenic diet are also reported to be relatively effective. Gastrointestinal and cardiovascular system problems are common. All patients had developmental delay of varying severity. The results may help guide management of epilepsy in CDKL5. It highlights a possible link between CDKL5 and potentially treatable life-threatening complications such as arrhythmia. Over ¼ of the patients had tried eight or more antiepileptic medications. More research in this area may help us develop a more systematic approach to treating these patients, and hopefully reduce the element of trial and error when it comes to treating their epilepsy.

## Conflicts of Interests

Nothing to report

## Acknowledgement

The questionnaire used in this study can be found in the link: <https://www.curecdkl5.org/living-with-cdkl5-research/cdkl5-disorder-case-study-questionnaire/>

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