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Brief Communication

New insights in phenomenology and treatment of epilepsy in CDKL5 encephalopathy

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ABSTRACT

Eight patients, seven girls and one boy, had *CDKL5* gene mutation, duplication, or deletion. Epileptic spasms started at a mean age of 3.5 months (range = 4 weeks–8 months). In five cases, tonic seizures preceded spasms at a median age of 6 weeks. In one patient who started at 8 months, spasms had a component of terror on awakening, reminding sleep terror. In two patients, electroencephalogram polygraphy of a so-called tonic seizure revealed that the tonic phase was followed by an overlooked clonic phase and then by a cluster of spasms during which each spasm was preceded by a brief clonic jerk revealed by electromyography. This sequence is rather particular and can be an early diagnostic clue. Progressive transition from this seizure type to epileptic spasms in clusters seems to result from increasing expression of the *CDKL5* gene, as the child grows older. Five patients responded to the combination of vigabatrin and zonisamide.

Mutations in the *CDKL5* gene are a main cause of developmental delay with epileptic spasms (ES) in girls [1,2]. Epilepsy exhibits a specific sequence in which ES are preceded by tonic or focal onset seizures and eventually followed by myoclonic epilepsy [3,4]. Klein et al. reported a peculiar seizure sequence of hypermotor/tonic component/spasms in cluster characterizing each ictal event [5]. Epileptic spasms in CDKL5 encephalopathy rarely respond to the usual first-line treatments, vigabatrin (VGB) and steroids, nor to zonisamide (ZNS) in monotherapy [6,7]. Our series shows that the peculiar ictal characteristics are recognizable from the first weeks and that the combination of VGB and ZNS is promising.

1. Patients and methods

1.1. Patients

We identified 14 patients with CDKL5 mutation and epileptic encephalopathy, and selected the eight patients (see Table 1) for whom clinical and therapeutic data were sufficient, i.e., those with video-electroencephalogram (EEG)/polygraphy before onset of ES and/or who received the combination of VGB and ZNS. Two patients had early video-EEGs before any treatment; for the six others, parents provided home videos. Follow-up ranged from 3.5 to 13 years. The six patients with incomplete data were not included. The study has been reviewed and approved by local research ethics committee of MediClubGeorgia Medical Center.

1.2. Phenotype

We reviewed the videos performed at home by the parents and the polygraphy video records including EEG for two patients (# 2 and 3), and bilateral deltoid electromyography (EMG) for one (#2). We focused on the age at first seizures, of ES and therapeutic combination, and age at the last seizure reported by parents.

1.3. CDKL5 gene mutation screening by Sanger sequencing

Genetic diagnosis was based on direct gene sequencing. All blood samples were obtained after receiving informed consent. This study was prospectively reviewed and approved by our local research ethics committee.

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Genomic DNA was extracted using standard procedures from the peripheral blood leukocytes of patients with severe encephalopathy. Screening of the *CDKL5* gene (patients 1–3: RefSeq: NM_003159.2) was performed by polymerase-chain reaction (PCR) using genomic DNA from the patients and their parents and direct sequencing using BigDye dideoxy terminator chemistry and an ABI3130xl genetic analyzer (Applied Biosystems). Primer sequences and positions, PCR conditions, and product size were previously described [8] and are available upon request. Sequence variants in *CDKL5* are numbered starting from the first base of the ATG codon, numbering base on reference sequence (NM_003159.2). Description of the sequence (Human Genome Variation Society, http://www.hgvs.org/mutnomen/recs.html) was done with the assistance of Alamut Visual software version 2.4.2 (Interactive Biosoftware, Rouen, France). The five other patients underwent Whole Exome Sequencing.

2. Results

Age of onset, molecular genetic findings, seizure phenotype, and course are given in the table (see Table 1).

2.1. Ictal phenomenology

Clusters of ES were first noticed between 4 weeks and 8 months (mean 3.5 months), in combination with hypsarrhythmia for six patients, and were preceded by tonic seizures between 3 and 8 months of age (median 6 weeks) in five patients.

For the two patients with video-EEG/polygraphy recording of the first seizure type, it disclosed a very particular electroclinical sequence (Videos 1, 2). Within a minute following awakening, generalized tonic contraction associated with EEG flattening lasting 15 s (Fig. 1a,b) was followed by right side clonic jerks (1–2 Hz) associated with spike waves (Fig. 1c), then a switch to a cluster of spasms consisting of a slower, bilateral contraction with a slow wave on EEG, during which a left temporal discharge occurred (Fig. 1d,e).

Furthermore, polygraphy for patient 2, shows that during the cluster of ES, each spasm was preceded by a clonic jerk recorded on EMG (Fig. 2) (Video 1) [9]. For one patient starting seizures at 8 months (#4), ES were associated with a behavior suggesting night terror.

Thus, at the age of first, so-called tonic seizures, spasms as part of these seizures had been overlooked clinically and were a discovery of video-EEG polygraphy.

2.2. Course and effect of treatment

Conventional antiepileptic treatment strategy of infantile spasms had been given, namely vigabatrin monotherapy followed by steroid for all patients, topiramate and zonisamide monotherapies for 2 patients, and the ketogenic diet for one, with no or insufficient effect. The eight patients received the combination of VGB and ZNS at recommended doses. Five patients who started the combination at respectively 4.5 months and at 2, 3.5, 7, and 11 years experienced an over 90% decrease in seizure frequency or became seizure-free. For three patients who started the combination at respectively 3, 3, and 4 years, it did not modify the seizure frequency. Seizures tended to change over the months following onset, losing the tonic and the clonic phases, leaving the patient with clusters of spasms, easily recognizable from a mean age of 3.5 months (range = 4 weeks–8 months).

At the end of follow-up, patient 2 who had started at 4.5 months the combination of VGB and ZNS, had clearly better development, and she could sit and grasp objects. The patient who started with ES and a behavior of night terror at the age of eight months but never exhibited hypsarrhythmia, could also walk and had good contact at the age of 4 years. All other patients had severe developmental delay, hand stereotypes, hypotonia, and could not walk independently. They had autistic features with poor interest in the surrounding and poor eye contact. They had no pyramidal signs and no dysmorphia. The only boy with *CDKL5* duplication had the worst outcome with up to 100 tonic seizures a day.

Interictal EEG showed hypsarrhythmia for all patients (first recorded between 4 and 20 weeks of age), except patient 2 who was treated before the appearance of hypsarrhythmia, and patient 4 who started with ES at the age of eight months. Vigabatrin or ZNS alone had failed to control seizures, but their combination controlled them in 5 of 8 patients.

Table 1
Patients data.

Patient/sex	Molecular genetics	Age at first seizure noticed by parents/ seizure sequence	Age at first documented spasms/ EEG before treatment	Age starting VGB/ZSM combination and doses in mg/kg/d	Age at last visit
1 F	c.119C>T (p.Ala40Val)	7 weeks/ Tonic, followed by atonic, then clonic	20 weeks/ Hypsarrhythmia	11 years VGB 100 ZNS 5	13 years, Rare seizures, on ZNS monotherapy
2 F	c.1733-1737dup	6 weeks/ Tonic, followed by focal clonic synchronous, followed by ES	11 weeks/ Hypsarrhythmia	4.5 months VGB 70 ZNS 6	4 years No seizures
3 F	c.578A>T (p.Asp193Val)	4 weeks/ Tonic, then focal clonic, then bilateral asynchronous	10 weeks/ No hypsarrhythmia	3.5 years VGB 125 ZNS 10	5.5 years 90% seizure decrease Rare ES but myoclonic jerks persist
4 F	c.1153C>T p.Gln385Ter	8 months/ tonic contraction followed by hypotonia, then a cluster of ES	8 months/ No hypsarrhythmia	4 years VGB 40 ZNS 6	4.5 years Seizures persist
5 M	c.495dupT p.Ala166Fs	4 weeks/ ES erratic myoclonus tonic seizures	4 weeks/ Hypsarrhythmia	3 years VGB 54 ZNS 5.4	5 years ES persist
6 F	c.464G>A p.Gly155Asp	4 months/ ES	4 months/ Hypsarrhythmia	7 years VGB 40 ZNS 4	10 years ES disappeared
7 F	c.2673_2682del GGAACCCGCA	6 weeks/ tonic seizures	3 months/ Hypsarrhythmia	2 years VGB 100 ZNS 5	3.5 years ES decreased by 90%
8 F	c.400C>T, p.Arg134Tre	3 weeks/ tonic–clonic seizures	4 months/ Hypsarrhythmia	3 years VGB 36 ZNS 5.4	4 years No effect

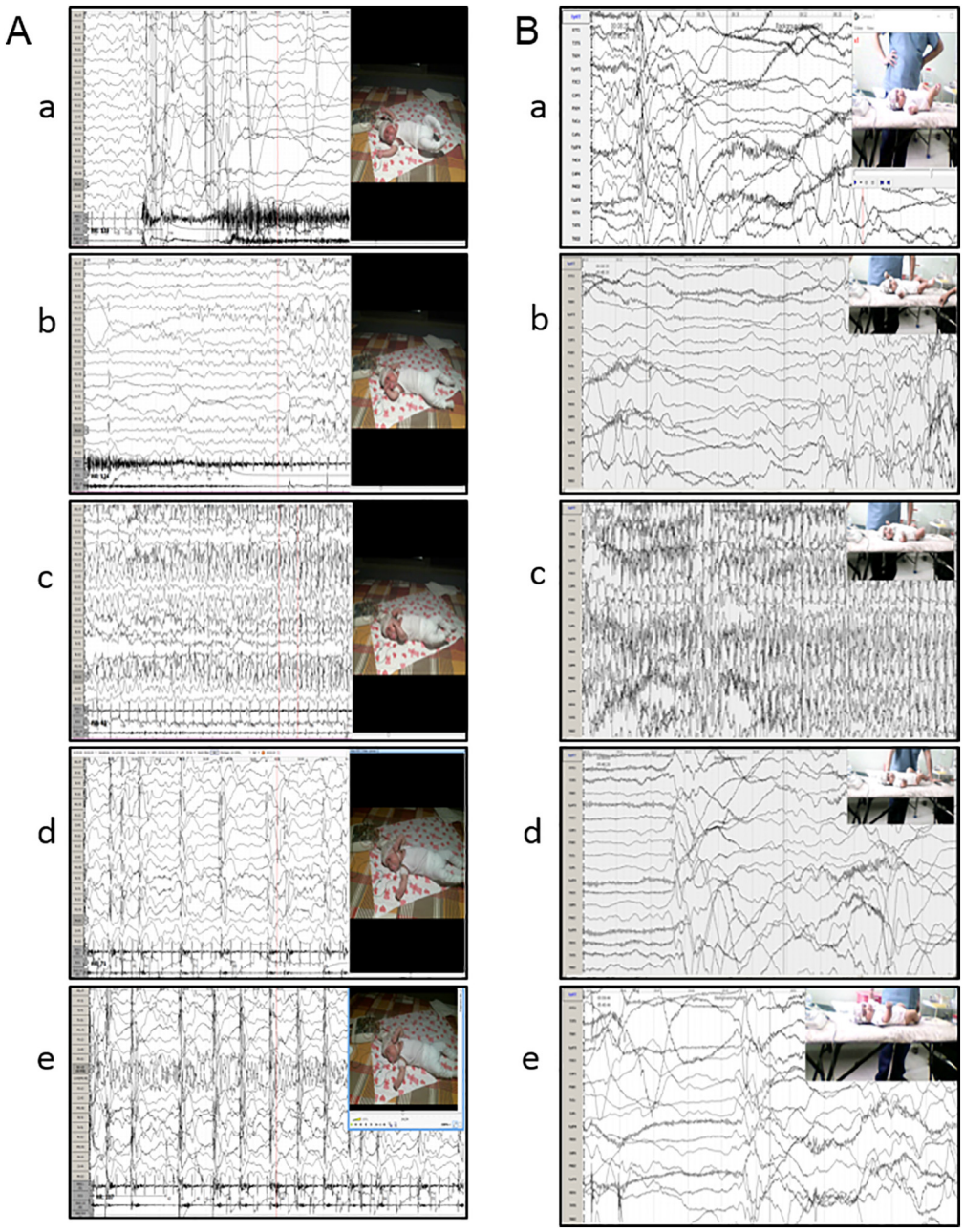

Fig. 1. Comparative video/EEG recording of patient 2 (column A) at the age 2 months 21 days, and patient 3 (column B) at the age 2 months 8 days shows very similar aspect. Amplitude 10 μV/mm, Speed 30 mm/s. Note that the left deltoid EMG also records the artifacts of ECG. a: asymmetric tonic phase lasting 10 to 20 s with flattening of the EEG. b: end of tonic phase and beginning of clonic phase. c: asymmetrical clonic phase with asymmetrical spike waves of decreasing frequency lasting 30 to 60 s. d: transition to spasms. In patient 2, spasms are more or less periodic, at 0.5–1/s; the EMG shows brief jerks preceding each spasm expressed with the usual lozangic shape characteristic of epileptic spasms. e: Left temporal discharge during the cluster of spasms in patient 2; three spasms with high amplitude slow waves can be seen for patient 3. The recorded seizures lasted respectively 2 min 25 s for patient 2 and 3 min 25 s for patient 3.

For two of them spasms control was associated with major EEG improvement.

3. Discussion

A previously unreported seizure phenomenology in two patients with *CDKL5* mutation, masked by early tonic seizures, was disclosed by polygraphy, providing an early diagnostic clue. On the other hand, the response to the combination of VGB with ZNS is encouraging, whatever the age. Seizures disappeared in the patient treated soon after onset of epilepsy (at 4.5 months), but also in a child who started this combination after 7 years of age.

When seizures are recorded with polygraphy including deltoid electromyogram, repeat and very mild muscle contractions can be noticed from the very first record, when only tonic events have been noticed clinically. Therefore, the pattern of ES seems to appear very early in life, in the course of first tonic seizures, being extremely mild at first, then with growing intensity and evolving to recognizable clusters of ES as hypsarrhythmia appears. It seems therefore that spasms are present from the very beginning of epilepsy. One patient (#4) without hypsarrhythmia exhibited cluster of ES with behavior of fear difficult to distinguish from night terror, which could be considered as hypermotor component reported by Klein et al. [5]. Spine lesions in pyramidal neuron, not only abnormal *N*-methyl-D-aspartic acid (NMDA) neurotransmission underlying the

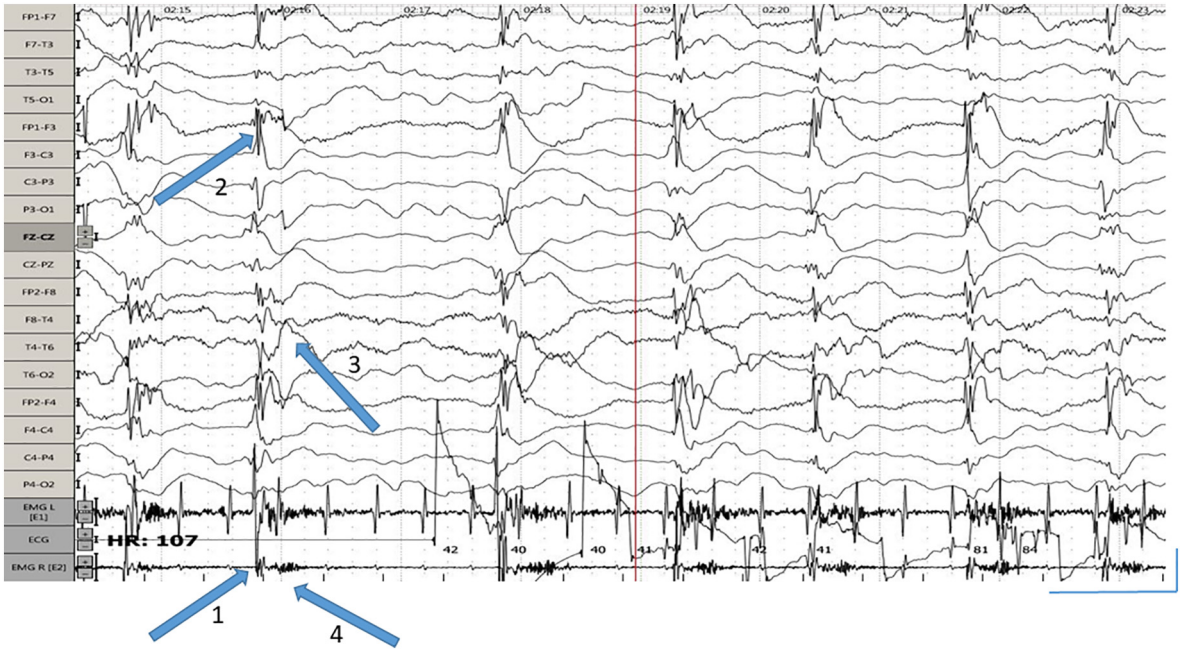

Fig. 2. In patient 2: Magnification (amplitude 50 μ/mm, speed 30 mm/s) of the polygraphic aspect of spasms showing the following sequence: a right sided jerk (1) (see video 1), then bilateral polyspikes (2) starting 25 ms later and lasting 50 ms, then the spasm (3), and then a high amplitude slow wave (4).

mechanism of ES, could account for the very early appearance of ES in *CDKL5* encephalopathy [10,11].

Polygraphy of patient 2 shows, as also illustrated by Melani et al. [12 – Fig. 2, patient 2, b], that each spasm consists of a complex and more or less periodic sequence: a brief clonic jerk precedes bilateral polyspikes, and then the spasm, followed by a long lasting high amplitude slow wave. Very early recording, before 3 months of age, could explain such a sequence, not seen when infants are recorded at the usual age of occurrence of ES. By three months of age, pyramidal tracts are fully myelinated, whereas myelination of the corpus callosum has not yet started [13]. This could explain that the upper limb clonic jerk occurs unilaterally before bilateral spikes followed by the spasms.

This new seizure sequence that we report, based on the analysis of the records of 2 patients, consisting of tonic phase, then clonic phase, then spasms should encourage searching for *CDKL5* mutation and permit starting early a promising therapeutic combination. It is noteworthy that home video may miss one or several phases of this sequence and some parents report different videos corresponding to different phases of the same seizure type.

Very few studies report the effect of conventional drug treatment of patients with *CDKL5* mutation: Müller and coworkers stressed that less than one-third experience an over 50% reduction in ES frequency, and there is rapid loss of efficacy after a few months [6]. We speculate that efficacy of the VGB and ZNS combination could be due to an action on both components of the corticostriatal loop: VGB acting on the striatum and ZNS on excessive NMDA transmission which generates ES [10]. Vigabatrin is registered only for infantile spasms, because of retinal toxicity. However, any chance to prevent intractable epilepsy with major cognitive sequelae is certainly a good reason to consider giving VGB before the full pattern of ES is built up, particularly since it has been reported that in tuberous sclerosis giving VGB before the onset of ES improves both epilepsy and cognitive outcomes [14,15]. It is therefore legitimate to start with VGB and ZNS once polygraphy discloses peculiar seizure sequence indicating to CDKL5 encephalopathy that could contribute to improve psychomotor development. However, further prospective study would be required to validate these promising findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.02.013.

Declarations of interest

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