Myoclonic encephalopathy in the CDKL5 gene mutation

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Abstract

Objective: Epilepsy with mutation of the CDKL5 gene causes early seizures and is a variant of Rett syndrome (MIM (312750), which is reported typically as infantile spasms. The purpose of this study was to analyze the epileptic histories and EEGs of patients with the CDKL5 mutation.

Methods: We reviewed the epilepsy histories and electroclinical analyses of three girls aged 9.5, 7.4, and 9.4 years, each with a mutation of the CDKL5 gene.

Results: We revealed the presence of an encephalopathy that started by 1.5 months of age. At first, seizures involved tonic spasms or complex partial seizures, and were complicated by the later appearance of complex partial, tonic, and unexpectedly, myoclonic seizures. This form of epilepsy was drug resistant. Routine and prolonged video EEGs both displayed a homogeneous electroclinical pattern consisting of (a) unique background with diffuse high voltage sharp waves of 6–7 Hz, and absence of the typical rhythmic frontal-central theta activity present in Rett syndrome; (b) unique awake and sleep background, with diffuse, high voltage, continuous sharp waves with multifocal and diffuse spikes; (c) rhythmic, diffuse, 15 Hz activity accompanied clinically by tonic seizures; (d) intercritical pattern with pseudoperiodic, diffuse, sharp waves or pseudoperiodic, diffuse spike and polyspike or wave discharges; and (e) diffuse, spike, polyspike and wave discharges accompanied by massive or focal myoclonias or both.

Conclusions: Patients with the CDKL5 mutation have an early onset, epileptic encephalopathy in infancy that evolves into myoclonic seizures in childhood with a unique EEG pattern.

Significance: Recognizing this type of encephalopathy could be useful in prompting clinicians to proceed further with their diagnostic work in patients not fitting the criteria of classical Rett syndrome.

Keywords: CDKL5 gene; Myoclonic encephalopathy

1. Introduction

Rett syndrome is a severe neurodevelopmental disorder that affects females almost exclusively, and is characterised by a wide spectrum of clinical manifestations. MECP-2 mutations have been identified in about 80% of patients with classic Rett syndrome, in about 50% of patients with the preserved-speech variant, and in lower percentages of patients with other variants (Miltenberger-Miltenyi and Laccone, 2003; Zappella et al., 2003). The early-seizure variant of Rett syndrome (MIM #312750) was described initially by Hanefeld in 1985 (Hanefeld, 1985) in a female patient with early seizures reported as infantile spasms. Recently, Weaving et al. (Weaving et al., 2004) reported another three patients (two females and one male) with this variant, and Scala et al. (Scala et al., 2005) reported two other female patients. A mutation in the CDKL5 gene was found in the patients reported by Weaving.
et al. (Weaving et al., 2004) and Scala et al. (Scala et al., 2005). However, the epilepsy was poorly characterized in these patients. Here, we report our evaluation of the epileptic history and the related EEG patterns of three girls, who exhibited myoclonic encephalopathy and a mutation in the CDKL5 gene.

2. Methods

Routine and prolonged video EEG recordings were obtained from the three patients over the period September 2000 to March 2005. We retrospectively reviewed the epilepsy histories and, if available, the EEGs recorded in other hospitals. We performed all EEG and long-term video EEG studies in the laboratories of our pediatric clinic in Siena, Italy. Video EEG recordings were performed using a computerized EEG system (Brain Quick System 98, Micromed s.r.l., Mogliano Veneto, TV, Italy). Scalp electrodes were positioned according to the international 10/20 system. The studies were recorded with the patients in a supine position or sitting, while awake and sleeping. The mean duration was 30 ± 12 min for the EEG recording, and 20 ± 4 h for the video EEG. One investigator (S.B.), trained electroencephalographer, analyzed all video EEG recordings using a split-screen video that allowed optimal and simultaneous visualization of the patient and EEG tracing.

2.1. Patient 1

Patient 1 was a 9.5-year-old girl with a deletion in exon 18 of the CDKL5 gene, leading to protein truncation at position 908. She was born at term with slight cyanosis, weighing 3.6 kg and with a head circumference of 34 cm (50th centile). Her neuromotor development was severely impaired from birth. At the age of 5 years, she was hypotonic and unable to hold an object in her hands. The MRI of the head, karyotype, and metabolic evaluation were normal.

2.2. Patient 2

Patient 2 was a 7.4-year-old girl with a frameshift deletion at C838–847 of the CDKL5 gene. She was born at term by caesarean delivery because of fetal hypoxia. The Apgar scores were nine at the first minute and 10 at the fifth minute. Her birth weight was 3.26 kg (25th percentile), but length and head circumference were not recorded. Her neuromotor development was severely impaired from birth. At the age of 4 years, she was unable to walk, grasp, or speak, and was profoundly mentally retarded. The neuromotor delay remained unmodified up to the age of 7.4 years. MRI showed an arachnoid cyst in the left temporal region. The karyotype and metabolic evaluation were normal.

2.3. Patient 3

Patient 3 was a 9.4-year-old girl with a frameshift deletion in exon 5 of the CDKL5 gene, which caused a loss of most of the CDKL5 protein (NP 003150). She was born at term with slight cyanosis and birth weight of 3.8 kg. Her neuromotor development was severely impaired from birth. She was able to sit alone at 1.5 years of age. The MRI of the head, karyotype, and metabolic evaluation were normal.

3. Results

3.1. Patient 1

3.1.1. Epilepsy history

Seizures first started at 2 weeks of age, and consisted of abrupt flexion of the upper limbs with hypertonia, cyanosis, and fixed gaze, lasting for about five seconds. The seizures were isolated or in pairs, separated by a few minutes, with three to four episodes a day, and occurred during wakefulness or sleep. Drug therapy with valproic acid, lamotrigine, and phenobarbital was ineffective. Seizures continued at a frequency of one to three per day. From the ages of 4.9–9.4 years, the seizures continued, with additional features of abrupt awakening, crying, and hypertonia. At the age of 7 years, generalized or focal myoclonic jerks and slight tonic seizures appeared during sleep. Drug therapy, with carbamazepine (30 mg/kg per day), valproic acid (20 mg/kg per day), and phenobarbital (3 mg/kg per day) was ineffective. At the age of 9.1 years, the introduction of clonazepam (0.1 mg/kg per day) to replace phenobarbital significantly decreased the frequency of seizures from once a day to once a week.

3.1.2. Analysis of the EEG pattern

The EEGs taken from the age of 1 month and in the following few years were not available directly, but were reported as showing sporadic, focal abnormalities. The first directly available EEGs, obtained at the age of 4.9 years (not shown) and 7.8 years, disclosed two patterns: (a) background with diffuse high voltage sharp waves of 6–7 Hz, and absence of the typical rhythmic frontal-central theta activity present in Rett syndrome (Aldrich and Garofalo, 1990); and (b) awake and sleeping background, with diffuse, high-voltage, continuous sharp waves with multifocal and diffuse spikes (Fig. 1(A1) and (B1)). Video EEG taken during sleep at the age of 9.5 years unexpectedly disclosed an electroclinical pattern (Fig. 1(C1)–(E1)), consisting of (c) rhythmic, diffuse, 15 Hz activity, accompanied clinically by tonic seizures; (d) intercritical pattern with pseudoperiodic diffuse, sharp waves or pseudoperiodic, diffuse spike and polyspike or wave discharges; and (e) diffuse, spike, and polyspike and wave discharges accompanied by massive and focal myoclonias.
Fig. 1. EEGs from patients 1, 2, and 3. Note the presence of the several patterns characterizing the early myoclonic encephalopathy. (A) Background with diffuse high voltage sharp waves of 6–7 Hz, and absence of the typical rhythmic frontal-central theta activity present in classical Rett syndrome. (B) Awake and sleep background, with diffuse, high voltage, continuous sharp waves with multifocal and diffuse spikes. See text for details. (C) Rhythmic, diffuse, 15 Hz activity accompanied clinically by tonic seizures (arrows). (D) Intercritical pattern with pseudoperiodic, diffuse, sharp wave, spike and polyspike or wave discharges. (E) Diffuse spike, and polyspike and wave discharges accompanied by massive or focal myoclonias (arrows). Note: Figure 1A and 1B are EEGs; Figure 1C–1E are prolonged video EEGs. The patients’ ages at the time of recording were: for A and B, 7.8 years (patient 1), 7 years (patient 2), and 8.7 years (patient 3); for C–E, 9.5 years (patient 1), 7.4 years (patient 2), and 9.4 years (patient 3).
3.2. Patient 2

3.2.1. Epilepsy history

Seizures started on the first day of life and consisted of episodes of tonic extension of the upper and lower limbs, cyanosis and, after 15–20 s, hypotonia and sleep, with a frequency of about one per day. The seizures were unchanged at the age of 4 months, despite antiepileptic therapy with phenobarbital (5 mg/kg per day). At age 8 months, vigabatrin was introduced as an added therapy, and decreased the seizure frequency to one per week. From the age of 4.3 years, polymorphic seizures (complex partial), with tonic, focal and massive myoclonic jerks were reported. Drug therapy with valproic acid (30 mg/kg per day) and levetiracetam (45 mg/kg per day) was not effective. Clonazepam (0.1 mg/kg per day), introduced as an added therapy, decreased the frequency of seizures to one per 1.5 weeks. This seizure pattern has remained unchanged until the time of writing.

3.2.2. Analysis of the EEG pattern

The first EEG, obtained at the age of 4 months, disclosed only the presence of sporadic sharp waves in the left hemispheres. At age of 1.2 years, a video EEG showed multifocal spikes more evident in the temporal and posterior regions. At the age of 4.3 years, further video EEG (not shown) disclosed complex partial and tonic polymorphic seizures, and focal and massive myoclonic jerks. The first directly available EEG, at the age of 7 years disclosed the similar background (Fig. 1(A2) and (B2)) observed in patient 1. At the age of 7.4 years, a video EEG taken during sleep disclosed the similar electroclinical pattern (Fig.1(C2)–(E2)) observed in patient 1.

3.3. Patient 3

3.3.1. Epilepsy history

Seizures first started at the age of 1.5 months and consisted of abrupt awakening, fixed gaze, tremor of the left lower limb, and difficulty in breathing lasting 15–20 s, followed by crying and sleepiness. Seizures continued at a frequency of one to three per day. At the age of 5 months, therapy with carbamazepine (40 mg/kg per day) decreased the episodes to 2 or 3 per month. Up to 2 years of age, the episodes continued to appear only during sleep, but increased in number, with daily onset and usually two or three episodes during sleep, separated by a gap of 3 h, with the added feature of tonic extension of the limbs. Drug therapy with phenobarbital (6 mg/kg per day) and vigabatrin (80 mg/kg per day) was ineffective. At the age of 8.5 years, administration of valproic acid (30 mg/kg per day) decreased the frequency of seizures to one per month. Seizures appeared only during sleep, and were characterized by crying and a scared gaze, followed by rhythmic tonic extension of the limbs and tremors lasting 5–10 min. Focal myoclonic jerks were also reported.

3.3.2. Analysis of the EEG pattern.

The first EEG, at 1.5 months of age, disclosed asymmetric hemispheric activity, which was less in the right side than in the left side and consisted of sporadic diffuse sharp waves, both while awake and asleep. At the age of 4 months, a video EEG (not available) showed abrupt, isolated, generalized jerks with bioelectrical activity associated with diffuse spikes. The interictal EEG showed the presence of sporadic multifocal and diffuse sharp waves, which were more evident in the left hemisphere. The same EEG abnormalities were reported later. The first directly available EEG, at the age of 8.7 years, disclosed the similar background (Fig. 1(A3) and (B3)) observed in patient 1 and 2. A prolonged video EEG taken during sleep at the age of 9.4 years disclosed the similar electroclinical pattern (Fig. 1(C3)–(E3)) observed in patient 1 and 2.

4. Discussion

Encephalopathy is defined as a condition in which the epileptiform abnormalities themselves are believed to contribute to a progressive disturbance in cerebral function (Engel, 2001). Encephalopathy is always accompanied by a typical EEG pattern. To date, eight forms have been recognized (Engel, 2001), two of which have the earliest onset: an early myoclonic encephalopathy (EME) (Aicardi and Goutières, 1978) and Ohtahara syndrome (OS) (Ohtahara et al., 1976). These forms share the presence of a ‘suppression burst’ on the EEG (Ohtahara et al., 1997), which in EME reappears after a transient atypical hypsarrhythmia (Aldrich and Garofalo, 1990), and in OS precedes atypical hypsarrhythmia, and, in some cases, is followed by diffuse slow spike waves (Ohtahara et al., 1976). The main clinical features of EME are the presence of fragmentary myoclonus and frequent partial seizures, and of OS, the presence of tonic spasms with or without clustering and rare myoclonus episodes (Ohtahara et al., 1997). In both of these early onset encephalopathies, seizures are intractable and many patients die in the early stage of the disease, sometimes in the first year (Ohtahara et al., 1976).

We found a homogeneous electroclinical entity in three young patients with mutation of the CDKL5 gene. We have defined this as myoclonic encephalopathy, which differs from any other forms described previously. The seizures appeared early, by 1.5 months of age, in the three patients. Interestingly, despite the early appearance of the seizures (tonic spasms or complex partial seizures) in the first year, the EEGs did not disclose any epileptic encephalopathy pattern. Later seizures were complicated and included the appearance of further myoclonic, complex partial and tonic seizures and a same EEG patterns emerged (for reference, please, see Fig. 1). Previous reports have described the presence of infantile spasms at the onset of an early epileptic encephalopathy in patients with the CDKL5 mutation.
(Weaving et al., 2004; Scala et al., 2005). In some patients, as in ours, the seizures start in the first few months of life and the EEG pattern does not indicate this encephalopathy. We note several important points. The term ‘infantile spasms’ is synonymous with West syndrome and denotes a specific age of onset with an unique EEG pattern. The onset of infantile spasms usually occurs in the middle of the first year of life, but rarely before 3 months or after 1 year of age, which is considered the upper limit for the occurrence of the syndrome (Commission on Classification and Terminology of the International League Against Epilepsy Proposal for revised clinical and electroencephalographic classification of epileptic seizures, 1981). Later, although multifocal spikes with high amplitude delta activity could be consistent with hypsarrhythmia, there are some differences in our cases, clearly excluding the chance of an hypsarrhythmic picture. As known, hypsarrhythmia is a term to describe an EEG pattern, and the EEG pattern does not indicate this encephalopathy. Without clinical myoclonic activity or flexor spasms (Holt).

The new encephalopathy we observed is quite different as: (1) the higher (2.5–3.5 versus 0.5–3 Hz) frequency of the waves and their lower voltage (150–200 versus 300 μV); (2) the low frequency of the multifocal spikes; (3) the presence of diffuse high voltage sharp waves of 6–7 Hz during the wakefulness, not present in hypsarrhythmia; (4) the lack of the generalized high amplitude irregular slow waves followed by a generalized electrodecremental pattern (sometimes accompanied by spasms during wakefulness and drowsiness) typical of the hypsarrhythmia pattern; (5) the registered seizures phenotype (complex partial, tonic and myoclonic) different from the epileptic spasms.

We did not consider Lennox–Gastaut syndrome, a later-appearance epileptic encephalopathy, because of the absence of the typical diffuse slow spike and waves in the EEG, the lack of atypical absences (Farrel, 2001) and the presence of myoclonic seizures.

In conclusion, our study showed that patients with the CDKL5 mutation have an epileptic encephalopathy with early onset that evolves into myoclonic encephalopathy in childhood and a unique EEG pattern. Recognizing this encephalopathy could be useful in prompting clinicians to proceed further with their diagnostic work in patients not fitting the criteria of classical Rett syndrome.

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