Original article

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Early and long-term electroclinical features of patients with epilepsy and *PCDH19* mutation

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ABSTRACT – *Aims*. Protocadherin 19 (*PCDH19)* mutations have been identified in epilepsy in females with mental retardation as well as patients with a "Dravet-like" phenotype. We aimed to elucidate the electroclinical phenotype associated with *PCDH19* mutation, which is currently difficult to identify at onset leading to a delay in diagnosis.

Methods. We retrospectively reviewed clinical and EEG data for 13 consecutive patients with *PCDH19* mutations or deletions diagnosed at our centers from 2009 to 2011, and followed these patients into adolescence and adulthood.

Results. We identified a specific temporal sequence of electroclinical manifestations, identified as three main stages. During the first two years of life, previously healthy girls presented with clusters of afebrile focal seizures. Early seizures were recorded on video-EEG in 10/13 patients, and were focal (*n*=8) with temporo-occipital and frontal onset. Three patients with strictly stereotyped focal seizures underwent a pre-surgical work-up. Two patients started with generalized seizures, one presenting with early-onset atypical absences and the other generalized tonic-clonic seizures. During the course of the disease, from two to 10 years, seizures became fever-sensitive and continued to recur in clusters, although these were less frequent. Seizures were mainly described by eyewitnesses as generalized tonic-clonic, even though three of five seizures, recorded on EEG, showed a focal onset with fast bilateral spread. Atypical absences and fever-induced tonic-clonic seizures remained frequent in only one patient until the age of

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16 years. No specific treatment or combination appeared to be more effective over another. Various degrees of cognitive or behavioural impairment were reported for all patients, but it was in the second decade that behavioural disturbances prevailed with hetero-aggressiveness and behaviour associated with frontal lobe abnormalities leading to psychosis in two.
Conclusion. Early recognition of the above features should improve early diagnosis and long-term management of patients with epilepsy and *PCDH19* mutations.

Key words: early-onset epilepsy, intellectual disability, Dravet syndrome, EFMR, *PCDH19*, afebrile focal seizures, fever-sensitive seizures

Epilepsy associated with protocadherin 19 (*PDH19*) mutation is associated with a large electroclinical spectrum, from "self-limited" epilepsies to epileptic encephalopathies (Dibbens *et al.,* 2008; Depienne *et al.,* 2009, 2011; Specchio *et al.,* 2011a; Depienne and LeGuern, 2012; Higurashi *et al.,* 2012; Marini *et al.,* 2012; Lyons *et al.,* 2017).
PCDH19 is a non-clustered delta 2 protocadherin belonging to the cadherin family, which are calcium-dependent adhesion proteins. *PCDH19* is encoded by a gene located on Xq22.3. It is hypothesized that delta protocadherin participates in the development and functioning of the neuronal circuitry (Kim *et al.,* 2011). *PCDH19*-related epilepsy presents with an unusual X-linked mode of inheritance, affecting only heterozygous females, whereas homozygous males are asymptomatic. To explain this specific pattern of inheritance, a mechanism of "cellular interference" has been proposed (Depienne *et al.*, 2009).
Mutations in the *PCDH19* gene are rare and were first identified in epilepsy in females with mental retardation (EFMR) (Dibbens *et al.,* 2008). The EFMR phenotype includes seizure onset before two years of age, variable seizure types, fever-induced seizure in more than half of the cases, delayed cognitive development either from seizure onset or pre-existing prior to seizures, and major psychiatric -sometimes autistic- features. In the large families reported, affected females were related to unaffected transmitting males (Scheffer *et al.,* 2008). In two families, the inheritance was associated with parental mosaicism (Dibbens *et al.,* 2011).
Furthermore, some patients with *PCDH19* mutation were shown to have a phenotype mimicking Dravet syndrome (DS). Screening a population of 150 *SCN1A* mutation-negative patients diagnosed with DS led to the identification of 12 *PCDH19*-mutated patients (Depienne *et al.,* 2011). These all presented with the clinical criteria of DS, *i.e.* early seizure onset, febrile and afebrile seizures, and mental delay following initially normal development (Depienne *et al.,* 2009, 2011; Marini *et al.,* 2010). However, some distinctive features that differ between *PCDH19*-related epilepsy and DS have been identified and the phenotypic spectrum associated with *PCDH19* mutation relates more to girls with early-onset febrile or afebrile seizures, clusters of focal seizures and status epilepticus that is not long-lasting, and a less severe cognitive outcome (Depienne *et al.,* 2011; Nabbout *et al.,* 2011; Trivisano *et al.,* 2016).
We report a series of 13 girls with *PCDH19* mutation and describe the temporal sequence of clinical and EEG features from onset through to long-term follow-up. Our report aims to provide a clearer delineation of the *PCDH19* phenotype allowing early diagnosis as well as a better understanding of the long-term outcome in order to improve patient diagnosis and management.

Methods

We retrospectively reviewed the medical records of 13 consecutive patients diagnosed with either a mutation or a deletion in the *PCDH19* gene, between 2009 and 2011, and followed in our centre from seizure onset. We documented age at onset, seizure type, seizure frequency and triggering factors, ictal and interictal EEG (both early and during evolution), long-term follow-up, and antiepileptic drugs (AEDs) administered at onset and during follow-up. Seizure semiology, as well as ictal and interictal EEG patterns, were also documented. The description of seizures was based on eyewitnesses (*reported* seizures) and EEG recordings (*recorded* seizures). These were distinguished for seizures at onset and seizures during follow-up. Seizures were classified according to ILAE classification and terminology (Fisher *et al.,* 2017). When the seizure frequency within a given period (usually over a day or a few days) exceeded the average seizure frequency over a longer period, this was considered as a cluster (Blume *et al.,* 2001).
Cognitive evaluation was assessed using the Wechsler tool (Wechsler, 2004, 2005) and psychoeducative profile (Schopler *et al.,* 2005) using both cognitive and behavioural subscales for all patients.

Intellectual disability was classified as mild (IQ/DQ 50-70), moderate (IQ/DQ 35-49), severe (IQ/DQ 20-34), and profound (IQ/DQ < 20).
Diagnosis of autism spectrum disorders (ASDs) was based on clinical evaluation by a child psychiatrist using the DSM-5 (American Psychiatric Association, 2013), according to the following ASD criteria: deficits in all three of the Social Communication criteria (deficits in socio-emotional reciprocity; non-verbal communicative behaviour; and developing, maintaining, and understanding relationships) and at least two of the four criteria listed under Restricted and Repetitive Behaviours (RRBs: stereotyped or repetitive movements or use of objects, insistence on sameness, restricted or fixed interests, and hyper or hyporeactivity to sensory inputs). A larger evaluation for cognition and ASDs was reported previously for five patients (Patients 1, 4, 5, 12, and 13) (Breuillard *et al.,* 2016).
All patients had been screened for *SCN1A* gene mutation as well as fever sensitivity at a particular stage of the disease and were negative. Screening for *PCDH19* mutation was achieved by direct sequencing and MLPA to identify deletions or duplications, as described previously (Depienne *et al.,* 2011). None of the patients in this series underwent gene panel testing for epilepsy.

Results

Clinical and neuropsychological data are reported in *table 1*.

Genetics

Eleven girls had *de novo PCDH19* mutations and two showed deletions (Patients 3 and 13). Ten mutations were located in exon 1 corresponding to the extracellular domain of the PCDH19 protein and one mutation was located in intron 4, leading to abnormal mRNA splicing. Two mutations were inherited, one from the mother (Patient 9) and one from the father (Patient 10), who were asymptomatic. One patient with a *de novo* deletion had a family history of febrile seizures (Patient 3).

Seizures: clinical features

Mean age at seizure onset was 10.6 ± 5.6 months (range: 4-23 months). The first seizures occurred in clusters in 12/13 patients and were afebrile in 9/13.
At onset, *reported* seizures were focal in six and generalized in seven patients. For the patients with *reported* focal seizures at onset (Patients 3-5, 7, 8, and 12), the predominant clinical features were tonic extension of the upper arms, deviation of the head and eyes, and pallor of the face and an expression of fear, with screaming reported in half of the patients (3/6).
Seizures tended to occur in clusters, each seizure lasting up to 50 seconds but recurring almost every hour over a total duration of five hours to seven days.
Three patients (Patients 3, 4 and 8) had stereotyped seizures with behavioural symptoms, mainly fear, screaming, and crying with lateralized motor signs on the same side, leading to a suspicion of structural focal epilepsy with presurgical work-up.
For patients with *reported* generalized seizures at onset (Patients 1, 2, 6, 9-11, and 13), six presented generalized tonic-clonic (GTC) seizures, occurring in clusters as in the focal group, and one (Patient 9) presented with daily typical and atypical absences with eyelid myoclonia and ocular revulsion.
At follow-up (mean: 12 years; median: 11 years; SD: 5.9), seizures continued to occur in clusters, but the frequency of clusters tended to decrease, from monthly at onset to yearly or less at the last follow-up visit.
Seizures were reported as generalized in nine patients (Patients 1-5, 8, and 10-12) and focal in three (Patients 6, 7, and 9). One patient (Patient 13) became seizure-free at six years of age and AEDs were stopped at 12 years of age without seizure recurrence.
In the group with *reported* focal seizures at onset, in 5/6 patients (Patients 3-5, 8, and 12), including the three who underwent presurgical work-up (Patients 3, 4, and 8), seizures were described by eyewitnesses during follow-up as GTC and no longer as focal. Only in one (Patient 7), seizures continued to be reported as focal.
Mean age for the appearance of tonic-clonic movements during seizures was 2.8 ± 0.9 years (2-4 years). One patient had additional myoclonic jerks induced by stress (Patient 8).
For patients with *reported* generalized seizures at onset (Patients 1, 2, 6, 9-11, and 13), during follow-up, 5/7 (Patients 1, 2, and 9-11) seizures were still described as GTC and Patient 9 continued to present with daily atypical absences and later developed fever-induced generalized tonic-clonic seizures. In one patient (Patient 6), seizures were reported as focal and one patient (Patient 13) was seizure-free.
Fever sensitivity, as the major and almost unique triggering factor for seizures, was apparent in all patients at a mean age of 30 months (median: 21 months; SD: 24), around 20 months after the first clusters, and persisted unchanged into adulthood.

EEG features

We reviewed a mean of 10 EEGs (range: 2-28) for each patient.
Interictal EEG recordings were documented at onset during follow-up for all patients. *Recorded* seizures

Table 1. Clinical data at onset and during follow-up.

	PCDH 19 mutation	Onset						Follow-up						
		Age (m)	Reported seizures	Recorded seizures	Clusters	Fever sensitivity	All used AEDs	Age (y)	Reported seizures	Recorded seizures	Fever sensitivity (age of onset, m)	IQ (intellectual delay)	ASD	AEDs at last visit
1	c.2675+1G>C intron 4	4	G	F	Yes	No	VPA,CLZ, VGB	9	G	Not recorded	Yes (54)	62 (mild)	No*	LEV, CLB
2	c.1023C>G/ p.Asp341Glu exon 1	8	G	F	Yes	Yes	PB,CLB, CLZ,VPA, STP	15	G	Not recorded	Yes (8)	68 (mild)	Yes	TPM,CLB, STP
3	c.1956_ 1959delCTCT/ p.Ser653ProfsX6 exon 1	5	F	F	Yes	No	PB,VPA, VGB,CLB	24	G	Not recorded	Yes (36)	60 (mild)	Yes	STP,CZP, CBZ
4	c.695A>G/ p.Asn232Ser exon 1	12	F	F	Yes	Yes	VPA,CLZ, LTG,CBZ, LEV	4	G	Not recorded	Yes (12)	50 (mild)	Yes*	LTG,LEV
5	c.242T>G/ p.Leu81Arg exon 1	11	F	F	Yes	No	PB,VPA, PHT,STP	14	G	F to bilat TC	Yes (96)	40 (mode-rate)	Yes*	VPA,CLB, STP
6	c.730dupG/ p.Ala244GlyfsX76 exon 1	9	G	Not recorded	Yes	No	PB,PHT, VGB,STP, CBZ,TPM	9	F	Not recorded	Yes (48)	43 (mode-rate)	Yes	LVT, CBZ
7	c.1019A>G/ p.Asn340Ser exon 1	6	F	F	Yes	Yes	VPA,CLZ, STP,CLB	6	F	Not recorded	Yes (9)	45 (mode-rate)	Yes	STP,VPA, CLB
8	c.1091dupC/ p.Tyr366LeufX10 exon 1	14	F	F	Yes	No	PB,VPA, CBZ	20	G	G	Yes (21)	70 (mild)	No	STP,CBZ

Table 1. Clinical data at onset and during follow-up (*Continued*).

	PCDH 19 mutation	Onset						Follow-up						
		Age (m)	Reported seizures	Recorded seizures	Clusters	Fever sensitivity	All used AEDs	Age (y)	Reported seizures	Recorded seizures	Fever sensitivity (age of onset, m)	IQ (intellectual delay)	ASD	AEDs at last visit
9	c.1700C>T/ p.Pro567Leu exon 1°	23	G	G	No	No	VPA,ETX, LTG	17	G	G	Yes (20)	70 (mild)	Yes	VPA,LTG, LEV,CLB
10	c.1628T>C/ p.Leu543Pro exon 1°°	6	G	Not recorded	Yes	No	VPA,VGB, CBZ,CLB	11	G	F	Yes (33)	64 (mild)	No	STP, CLB, TPM
11	c.569T>G/ p.Leu190Arg exon 1	20	G	Not recorded	Yes	No	VPA	5	G	Not recorded	Yes (26)	63 (mild)	Yes	LEV
12	c.2656C>T/ p,Arg886X exon 4	10	F	F	Yes	No	VPA, CLB	10	G	F to bilat TC	Yes (20)	70 (mild)	No*	VPA,CLB, LTG
13	c.506del/ p.Thr169SerfsX43 PCDH19 exon 1	10	G	G	Yes	Yes	VPA, CZP	15	Seizure free	Not recorded	Yes (18)	85	Yes*	No treatment

M: months; y: years; F: focal; G: generalized; bilat TC: bilateral tonic-clonic; PB: phenobarbital; PHT: phenytoin; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ETS: ethosuximide; LEV: levetiracetam; LTG: lamotrigine; STP: stiripentol; TPM: topiramate; VGB vigabatrin: VPA; valproate.
°Inherited from the mother. °°Inherited from the father. *Extended cognitive and ASD assessment was performed in these patients and reported by Breuillard *et al.* (2016).

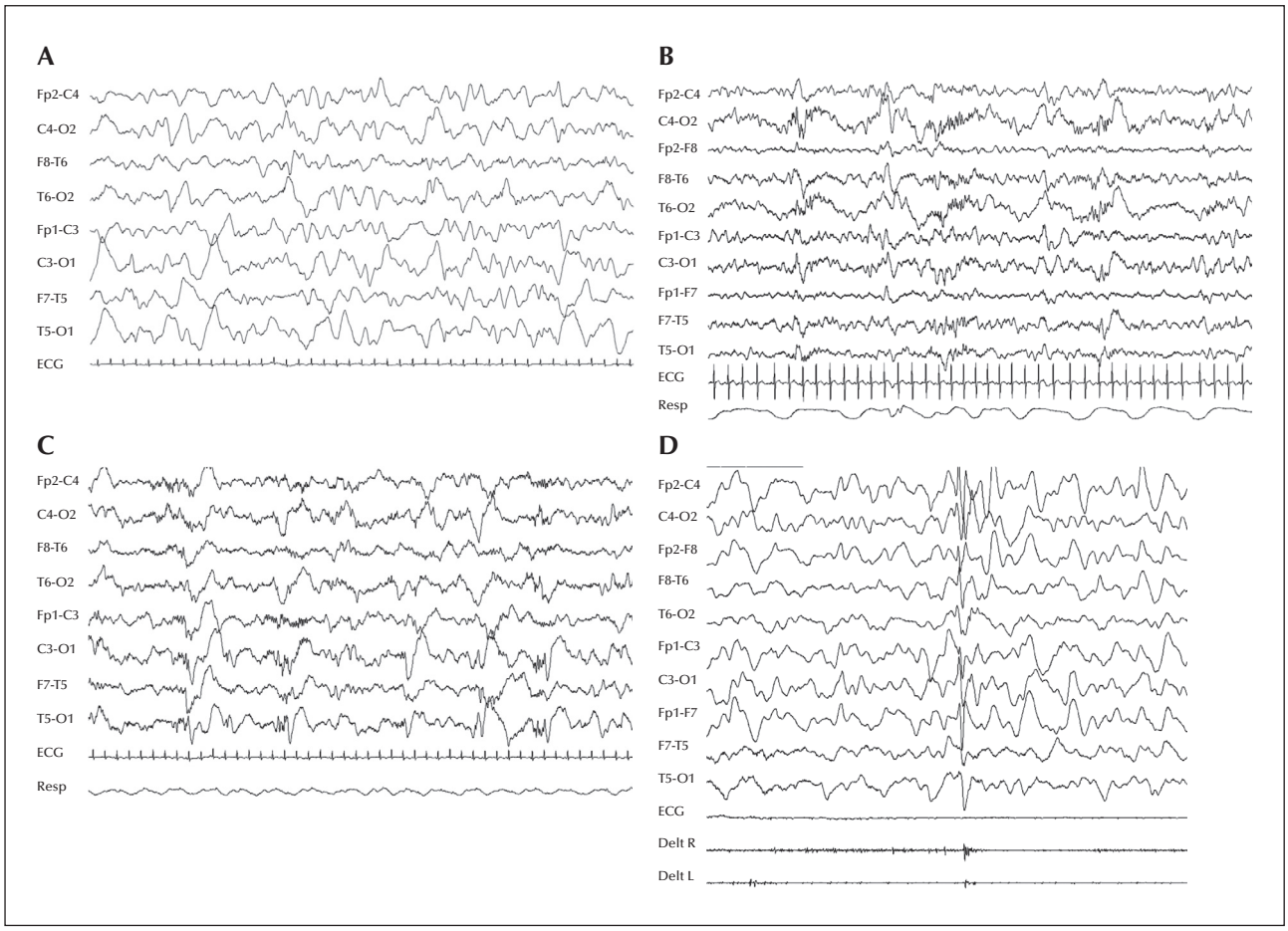

Figure 1. Interictal EEG in the first two years. (A) Slowing of background activity with focal spikes and slow waves during a cluster of seizures in Patient 7. (B, C) Temporo-occipital slow waves with superimposed rapid rhythms in Patient 1 and 7 during sleep. (D) An interictal generalized burst of spike-waves in Patient 1 during sleep.

(video-EEG) were documented for 10 patients at onset and proved to be focal in eight (Patients 1-5, 7, 8, and 12) and generalized in two (Patients 9 and 13). During follow-up, *recorded* seizures were documented for five patients and were focal in three (Patients 5, 10, and 12) and generalized in two (Patients 8 and 9).

Interictal EEG

In the group with *recorded* focal seizures at onset, interictal EEG showed slow background activity and focal spikes and slow waves during a cluster of seizures in all eight patients (*figure 1A*). Additionally, two of them (Patients 4 and 7), including one with pre-surgical work-up (Patient 4), had unusual temporal-occipital slow waves superimposed with rapid rhythms, emphasizing a suspicion of structural abnormality (*figure 1B, C*).

In both patients with recorded generalized seizures at onset (Patients 9 and 13), interictal EEG disclosed generalized bursts of spike-waves (*figure 1D*).

During follow-up, interictal EEG distal to clusters showed normal background activity in 11 patients (*figure 2A, B*). Interictal bursts of generalized spike waves were recorded in two (Patients 9 and 12), only during hyperventilation in Patient 9. In one patient who underwent the presurgical work-up (Patient 8), frontal slow waves were present.

None of the patients presented with photo- or pattern-sensitive seizures except for two patients (Patients 9 and 12). These patients presented with clinical photosensitivity and increased EEG discharges on photic stimulation.

Ictal EEG

Seizures were recorded at onset (within the first two years of life) in 10 patients.

In 8/10 (Patients 1-5, 7-8, and 12), *recorded* seizures were focal; six patients had *reported* focal seizures and the other two patients (Patients 1 and 2) had seizures that

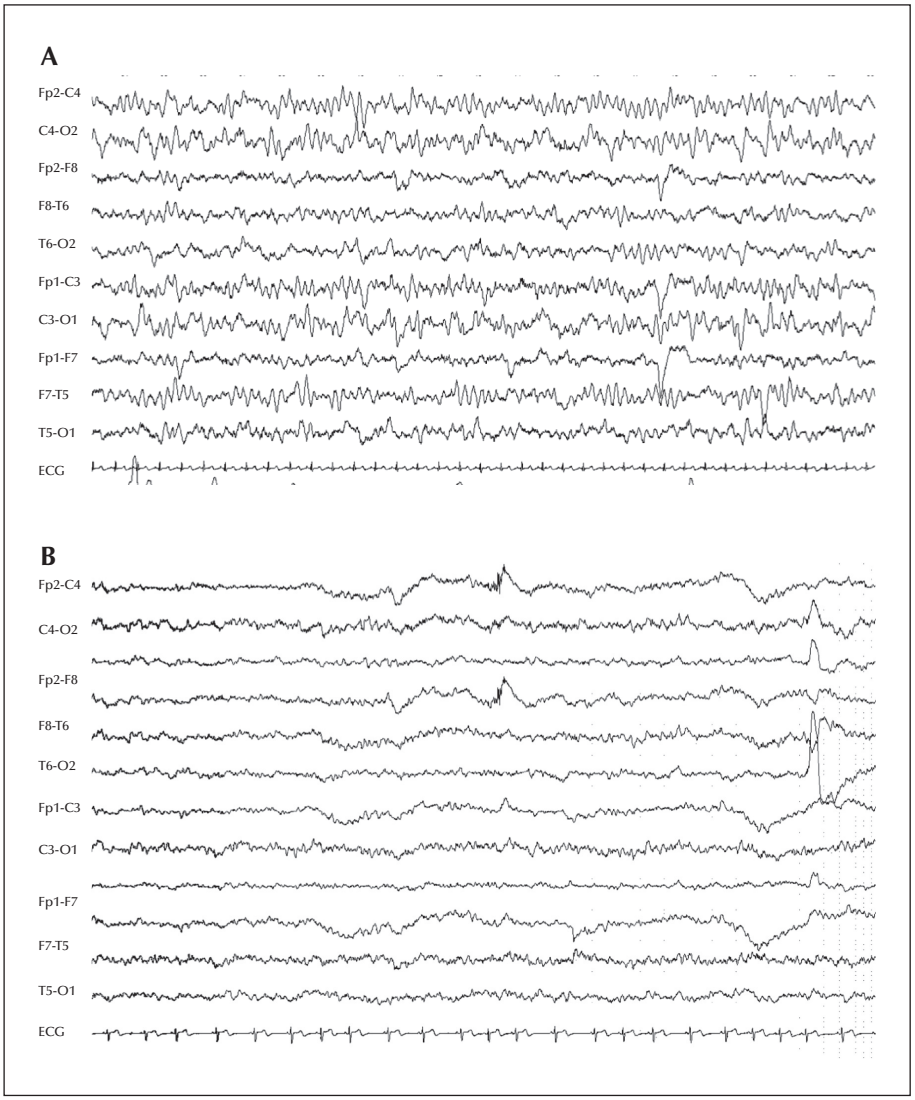

Figure 2. Interictal EEG during follow-up. (A, B) Normal background activity in two patients, distal to seizure clusters, at three years (A) and five years (B).

were wrongly reported as generalized and proved to be focal upon recording.

In the three patients who underwent presurgical work-up, frontal focal seizures were recorded. In one of these (Patient 8), infraclinical rhythmic discharges of frontal slow wave activity were recorded. In the remaining five patients, seizures proved to be temporal and/or occipital (*figure 3A*). In three of these, the discharge began with rapid, alpha band rhythms that quickly diffused to the contralateral hemisphere, followed by rhythmic high-amplitude slow waves.

In only 2/10 patients (Patients 9-13), recorded seizures proved to be generalized, consistent with the description of reported seizures. In one of these patients (Patient 9), atypical absences were recorded (*figure 3B*).

During follow-up, seizures were less frequent and could be recorded in only five patients (*figure 3C*).

In 3/5 patients (Patients 5, 10, and 12), *recorded* seizures were focal, despite the reported description by parents as generalized. In 2/5 (Patients 8 and 9), recorded seizures proved to be generalized, consistent with the description of reported seizures for only one (Patient 8).

Treatments

Clusters responded to benzodiazepines with, in the case of delayed administration, a need for PICU admission. Five patients (Patients 1, 2, 5, 6, and 13) had two PICU admissions during their follow-up because of clusters of seizures between age two and

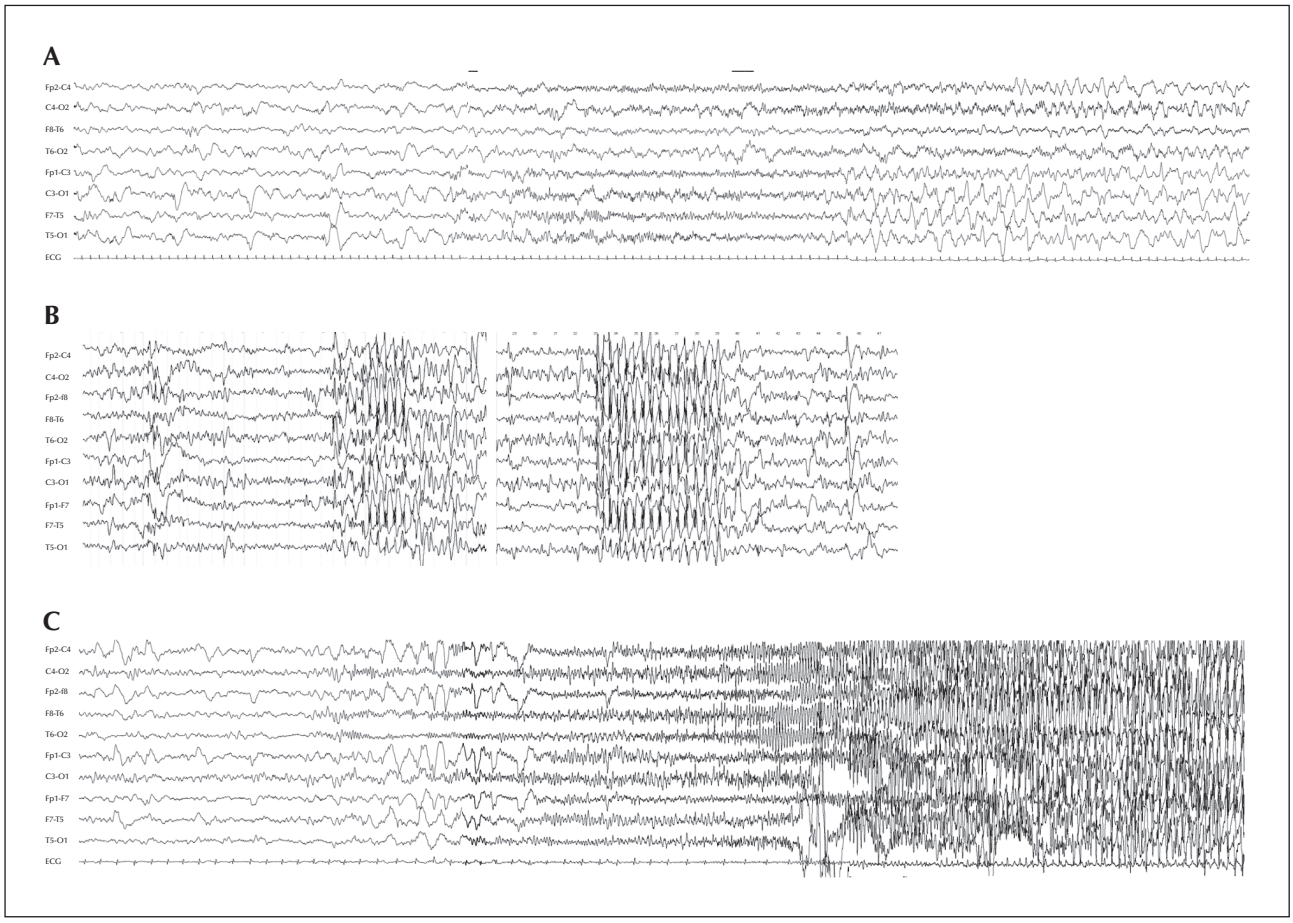

Figure 3. Ictal EEG. (A) Ictal EEG of a nine-month-old girl (Patient 7) presenting with a focal seizure. Bilateral temporal occipital slow waves are followed by alpha band rapid rhythms, predominating on left temporal occipital areas and rapidly diffusing to the contralateral hemisphere, followed by rhythmic slow waves predominating on the left side. (B) Ictal EEG of atypical absences of Patient 9 with bilateral high-amplitude spike-waves discharges, predominating on the frontal regions. (C) Ictal EEG of an 11-year-old girl presenting with a focal seizure (Patient 5). Right temporal-occipital alpha band with rapid rhythms diffuses into the left hemisphere with rapid generalization, followed by diffuse and synchronous high-amplitude spike-waves at the end of the seizure.

10 years. The patients were administered IV benzodiazepines and only one received 24-hour mechanical ventilation.

The appearance of fever sensitivity led to the introduction of stiripentol (STP) in six patients (Patients 2, 3, 5, 7, 8, and 10). Two of these patients received STP in combination with CLB and VPA, two in combination with CLB, and two in combination with VPA. The introduction of STP decreased seizure frequency by more than 50%. Vigabatrin had a negative impact on behaviour in two patients with seizure worsening and was stopped. We were unable to report clinically relevant efficacy of any other treatment on cluster occurrence. Patients did not show seizure worsening on other drugs, especially lamotrigine or carbamazepine. Lamotrigine was effective in the patient with atypical absences (Patient 9). None of our patients received steroids as chronic treatment or to stop clusters.

Other features

Psychomotor development was normal in 11 patients prior to seizure onset, but slightly delayed in two (Patients 4 and 6). Later on, various degrees of cognitive or behavioural impairment were reported for all patients.

During the first decade, all patients but three (Patients 3, 4, and 6) acquired language including the ability to build sentences. All three presented with autistic features and were later diagnosed with an ASD. We found no evident correlation between seizure frequency and cognitive impairment, as seizures occurred in less than monthly clusters in these three patients with worst cognitive outcome, as in the other patients. No patient presented with motor impairment or ataxia. All patients attended a special school with a psychomotor and/or speech therapy programme.

Cognitive outcome showed moderate to mild delay in all but one patient who was free of seizures with no therapy at the last evaluation (Patient 13). Nine patients had ASD (*table 1*).

Over 10 years, eight patients developed behavioural/psychiatric features, including aggressiveness, agitation, and behaviour associated with frontal lobe abnormalities, as evaluated by a child psychiatrist. These disorders tended to become more evident with age.

Brain MRI was normal in all patients, including MRI performed in adulthood in two patients. 18FDG-PET (positron emission tomography) was performed in three patients due to a suspicion of structural epilepsy early during the course of the disease. This showed bilateral temporal hypometabolism in two patients (Patients 3 and 4) but no evidence of focal asymmetry of metabolism (Patient 8). Based on EEG, only one patient (Patient 4) presented with an unusual activity of temporal-occipital slow waves superimposed with rapid rhythms, and all three ictal EEGs showed frontal focal seizures.

Discussion

We report a series of 13 patients with *PCDH19* mutation, focusing on both early electroclinical features and the long-term course into adolescence and adulthood. We identify a specific temporal sequence of electroclinical manifestations, identified as three main stages (*figure 4*). In order to provide a reliable description and emphasize any discrepancies, seizures were considered that were reported by eyewitnesses (*reported*) and recorded on EEG (*recorded*).

During the first stage (0-2 years), the age at onset and recurrence of seizures in clusters, in previously healthy girls, should lead to a suspicion of *PCDH19*-related epilepsy. In our population, even though *reported* seizures were both generalized and focal, *recorded* seizures proved to be mostly focal, with temporal-occipital onset and rapid contralateral diffusion in most of them, as reported in other series (Marini *et al.*, 2010; Specchio *et al.*, 2011a). Emotional symptoms and screaming were frequent but not constant (Marini *et al.*, 2012). Stereotyped focal electroclinical seizures in some patients could evoke the differential diagnosis of a structural focal epilepsy and lead to presurgical investigations. Interictal EEG in *PCDH19*-mutated patients, distal to clusters, is mostly normal and might remain normal during follow-up. Unusual focal temporal-occipital anomalies can be identified in a few patients and raise the possibility of a structural lesion. Interestingly, in the literature, a recent study (Kurian *et al.*, 2018) has reported, for the first time, an association between focal cortical malformations (focal cortical dysplasia and nodular heterotopia) and early-infantile epilepsy and *PCDH19* mutation in five female children. Two of these patients underwent surgery with an improvement in seizure control.

At this stage, EEG can help orienting the diagnosis, since bilateral, and not strictly focal, interictal abnormalities are usually present from the earliest stage in *PCDH19*-mutated patients.

Such an association of focal and bilateral features, along with the occurrence of seizures in clusters, could provide an early characteristic of the *PCDH19* mutation phenotype. Since this phenotype does not appear to exclude the presence of a structural lesion, its association with a recurrence of stereotyped focal seizures should raise a suspicion and prompt a search for focal cortical malformation.

In the second stage, from two to 10 years, fever sensitivity and focal to bilateral tonic-clonic seizures are the main features. Fever sensitivity is a common feature of both DS and *PCDH19*-related epilepsy (Dravet, 2011; Specchio *et al.*, 2011b; Lyons *et al.*, 2017). Interestingly and unlikely, from what has been reported in other studies (Lyons *et al.*, 2017), in our series, seizures at onset were mostly afebrile and became systemically fever-sensitive only during the course of the disease.

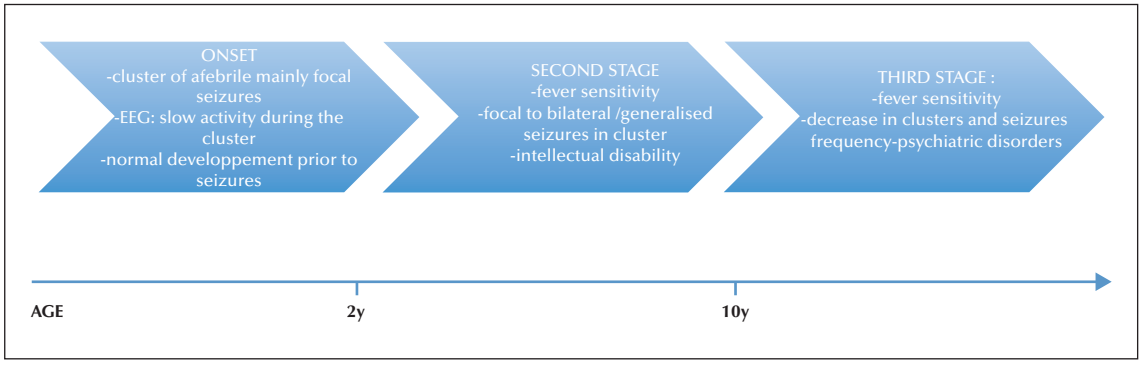

Figure 4. Evolution of the disease depicted as three main stages.

This temporal sequence is quite different from that of DS in which fever sensitivity is a frequent feature from the early stage of the disease. To our knowledge, this temporal evolution of temperature sensitivity has never been reported. This could also be due to the fact that studies usually focus more on the age at seizure onset but not the age at appearance of fever sensitivity. A prospective study would help to better clarifying this point.

The lack of status epilepticus and prolonged seizures also distinguish patients with *PCDH19* mutation from those with DS (Depienne *et al.,* 2011; Nabbout *et al.,* 2011). Furthermore, although myoclonic seizures are considered to be typical of DS and absent in *PCDH19*-related epilepsy (Trivisano *et al.,* 2016), we could record myoclonic jerks in one patient in our series, thus emphasizing the possible overlap between the two syndromes (Depienne *et al.,* 2009).

During this second phase, seizure frequency tended to decrease from monthly to yearly or less, and the reported clinical semiology was mainly GTC or tonic. Unfortunately, only a few *recorded* seizures were documented because of the trend towards a decrease in seizure frequency during follow-up. A subgroup of DS patients can present with a similar switch to brief tonic and tonic-clonic seizures, with focal onset and rapid bilateral spread, however, in this population, seizures typically occur in sleep (Losito *et al.,* 2017). We did not observe this nocturnal trend in our series of patients with *PCDH19* mutation and this was not reported in the literature. A recent study on 38 *PCDH19* mutation-positive patients (Smith *et al.,* 2018) has highlighted the occurrence of sleep deregulation, mainly in terms of difficulty in staying asleep, but the link between this observation and seizures was not explored.

In the third stage of the disease, in the second decade of life, behavioural disturbances become the main issue with slight to moderate cognitive delay. Intellectual disability and behavioural disturbances are common features of DS and *PCDH19*-related epilepsy, but cognitive deterioration seems to be milder and evolve more slowly in *PCDH19*-related epilepsy (Cappelletti *et al.,* 2015). On the other hand, behavioural issues seem to be fairly important, as we have observed in our population and in line with what is reported by Breuillard *et al*. (2016), who found a high rate of ASDs in a population of eight *PCDH19*-mutated patients presenting with epilepsy. This psychiatric phenotype is not frequent in DS. In line with this, Smith *et al*. (2018) have underlined the prevalence of neuropsychiatric and behavioural disorders in their series of patients with *PCDH19* mutation, mainly represented by autistic features, but also associated with obsessive compulsive symptoms.

Despite various degrees of intellectual disability, motor development was normal in our patients, in contrast to DS patients in whom motor skills, especially coordination and gait disorders, are reported to be strongly impaired (Chieffo *et al.,* 2011; Takayama *et al*., 2014).

Altogether, these features at onset and during follow-up may lead to identification of an electroclinical phenotype associated with *PCDH19* mutation at specific stages during the course of the disease which is distinct from those of DS and EFMR.

There are, however, significant limitations to this study. Our cohort was recruited in a single centre from patients with fever sensitivity, tested for *PCDH19* mutation. However, this point is interesting as it emphasizes the differences with *SCN1A* mutation-positive DS patients even though both sets of patients recruited share a major common feature. Also, the number of patients in this study is relatively small because of the rarity of this syndrome.

These characteristics may help to provide an earlier diagnosis for patients with *PCDH19* mutations, a diagnosis at later stages for girls presenting with this specific temporal electroclinical pattern, and ultimately may curtail the diagnostic odyssey families endure and provide better long-term management. □

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What are the main typical clinical features of patients with *PCDH19* mutation?

(2) What is the main differential diagnosis?

(3) What neurodevelopmental complications and comorbidities can occur in patients with a *PCDH19*-related epilepsy phenotype?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".