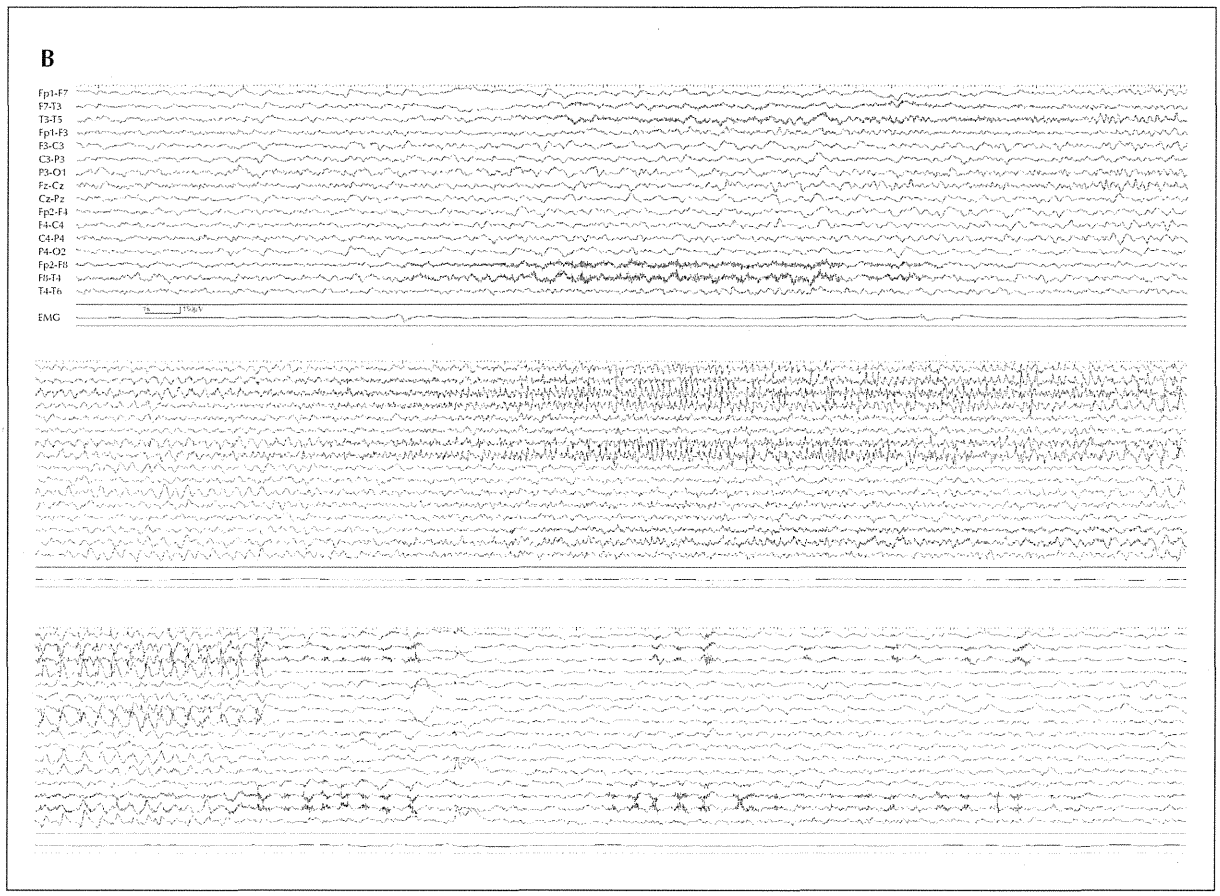

Figure 1. *(Continued).* (B) Ictal EEG of Patient 1 during the same series of clusters. The ictal rhythmic sequence was predominantly on the left side.

with rare frontal dominant spike waves. Most seizures occurred during sleep and two clusters with six convulsive seizures were recorded by video-EEG. In the first seizure (*video sequence 2*), the patient was awakened by massive jerks as if startled and started to sit up. Then, she slowly raised both arms tonically while vocalizing. Her eyes deviated first to the right, then to the left, and progressively to the right again. Her pelvis also moved to the right and left. Her right hand was open wide, and her left hand closed. Her limbs and fingers were fluttering or jerking less synchronously, similar to Patient 1. At the end of the seizure, more synchronized jerks were repeatedly observed with a slow rolling movement of the arms. In the postictal phase, the patient mumbled. The seizures usually lasted one minute and tended to occur every 0.5 to 1 hour in a cluster for 12 to 36 hours, usually with high fever. The ictal EEG (*figure 2A*) started with left posterior temporal sharp transients subclinically. The recruiting rhythms appeared predominantly in the left fronto-temporal region, and then spread bilaterally. In the postictal period, a motion artefact due to postictal automatism was observed on the bilateral temporal leads. The bilateral deltoid EMG did not show marked discharges, but the EEG resembled the sGTC pattern. Another seizure was recorded one year later during sleep. Massive axial jerks occurred first, and then she seemed upset and tried to sit up while vocalizing. Her eyes deviated to the right, and then her face and body turned to the left. All the limbs were extended in a mild tonic manner. The fluttering movements of the hands and fingers were less marked than in the first recorded seizure. After the seizure, she soon fell asleep without postictal automatism. The ictal EEG (*figure 2B*) began with fast waves emerging predominantly over the right hemisphere.

Patient 3

Patient 3 was 3 years old at the time of the study. She had no remarkable perinatal problems or specific medical

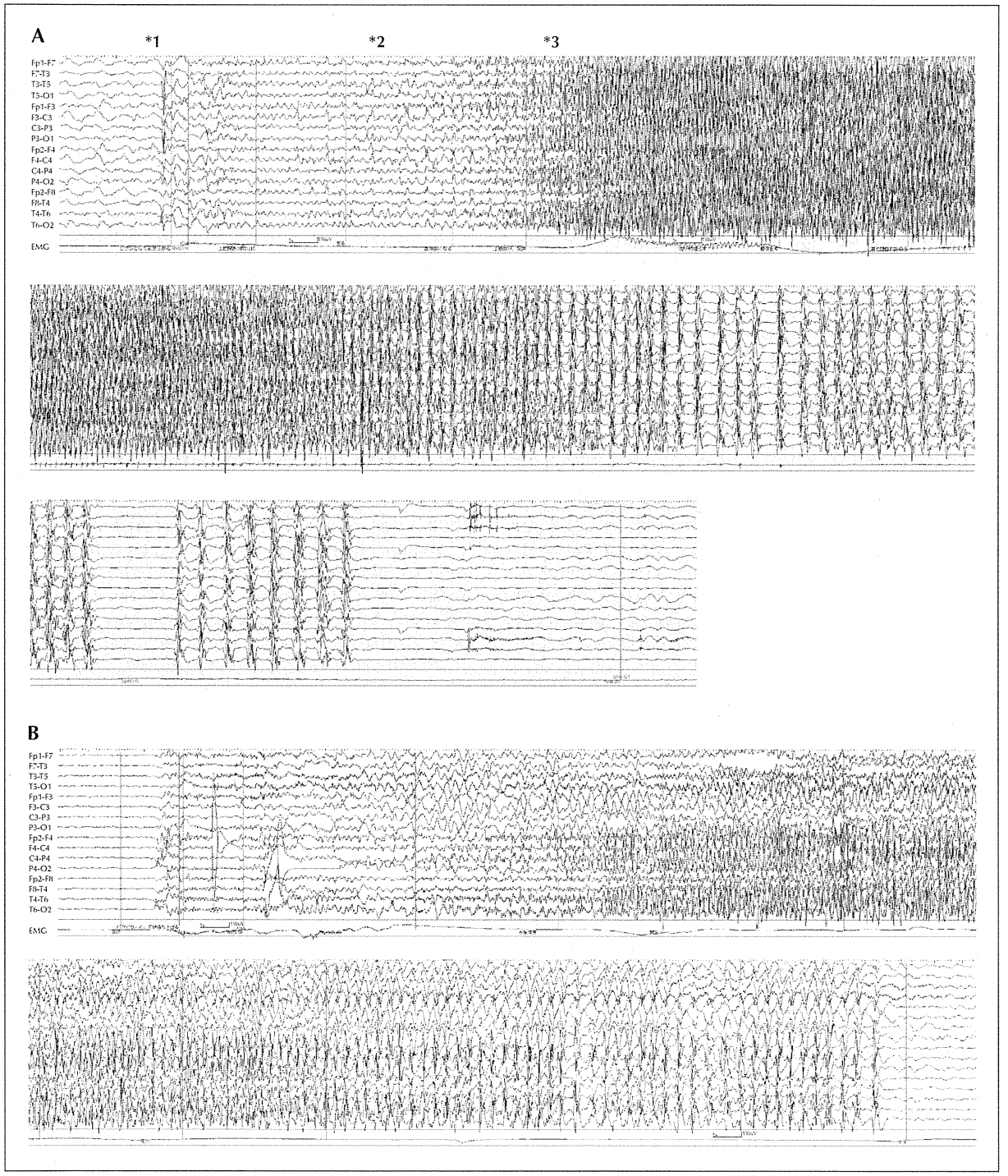

Figure 2. Ictal EEG of Patient 2. (A) EEG changes began with sharp transients at T5-O1 subclinically (*1). After irregular slow waves (probably representing motion artefacts), recruiting rhythms appeared predominantly at the left fronto-temporal region (*2) and then spread diffusely (*3); thereafter, these rhythms gradually changed to generalised spike and wave bursts. Motion artefacts due to postictal oral automatism were present on bilateral temporal traces. (B) Another seizure recorded one year later. Recruiting fast waves emerged predominantly over the right hemisphere and gradually changed to spike and wave bursts on the right side and slow wave bursts on the left side.

history. She had normal development before the onset of the seizures but gradually showed mild intellectual disability and delayed motor development. Her IQ was 49 at the age of 2 years, and she was found to have autism.

The patient had a *PCDH19* hemizygous whole-gene deletion, and her aunt on the mother's side had a single febrile seizure. She experienced her first cluster of seizures induced by high fever at nine months of age. From the age of 1 year, she began to have seizures approximately four or five times a day over a two-day period, with each seizure lasting for less than one minute. These clusters recurred four or five times per year with high fever. She was given levetiracetam (LEV), but the seizures repeated. LEV, VPA, oxcarbazepine, and clorazepate were all ineffective. CZP was temporarily effective, but discontinued because of hypersalivation and irritability.

The interictal EEG showed irregular slow waves and independent sharp waves at the left or right frontal region. All 14 convulsive seizures were recorded during sleep, starting with multiple jerks. It appeared as though she was trying to get up but failing to do so, apparently owing to tonic contraction. Her right and left legs were extended sequentially. Both arms were extended tonically, and her eyes deviated to the left. Thereafter, all her limbs and fingers started to jerk rhythmically and synchronously in a mild form, similar to Patients 1 and 2. In the postictal phase, oral automatism was observed. Each seizure lasted almost 70 seconds. Ictal EEG began with bilateral diffuse irregular sharp waves and slow waves, followed by semi-rhythmic bursts of slow waves, which were replaced by recruiting rhythmic waves of alpha range. Left rhythmic waves preceded right-sided waves. These rhythmic waves decreased in frequency at the end. In the late phase, the spikes on the left and right sides did not completely synchronize with each other. A slight lag was observed among spikes from different areas. In the postictal period, the delta waves mixed with artefacts of oral automatism over bilateral temporal regions, continuing with predominance in the left side. Although the ictal EEG looked like the sGTC pattern, surface EMG was missing for both deltoid muscles except in the initial tonic phase.

Discussion

Mutations in *PCDH19* have been reported to be associated with various neurological manifestations, which expand the phenotypic variability. We report three patients with convulsive seizure clusters that consisted of a few to dozens of seizures associated with fever. Although hot water immersion-induced seizures have been reported (Higurashi *et al.*, 2011), our patients did not show any such episodes. Moreover, the seizure frequency was not high in our patients, usually occurring every one to three months. The phenotype of PCDH19RE includes features of generalised epilepsy, focal epilepsy, and Dravet syndrome (Scheffer *et al.*, 2008; Depienne *et al.*, 2009, 2011; Marini *et al.*, 2010). PCDH19RE has been reported to include generalised tonic-clonic, focal, tonic, absence, or myoclonic seizures (Higurashi *et al.*, 2011; Specchio *et al.*, 2011; Higurashi *et al.*, 2013). PCDH19RE has also been shown to exhibit a distinctive electroclinical pattern of focal seizures with affective symptoms on ictal video-EEG, however, there are few reported detailed studies of convulsive seizures (Marini *et al.*, 2012). In this report, we investigated convulsive seizures, considered as secondary generalised seizures, that are also seen in PCDH19RE, in addition to focal seizures.

Our detailed analysis of ictal video-EEG recordings revealed a unique sequential manifestation that consists of six phases: "jerk", "reactive", "mild tonic", "fluttering", "mild clonic", and "postictal". Jerks can be seen in the axial body and/or limbs with (Patient 1 and Patient 2) or without (Patient 3) coughing or gurgling sounds. The "jerks" occurred singly or repeated irregularly without spikes or waves on EEG. The second phase is the "reactive" phase, which is like a "panic" or fearful state. The patients sometimes look so startled by the initial sudden jerks during sleep that they try to turn over or sit up. Patient 2 jumped up and tried to fling her arms around a nearby person. This "reactive" or hyperactive phase may represent affective symptoms reported by Marini *et al.* (2012). Seizure symptoms look like complex gestural automatisms. The third phase is "mild tonic", which is similar to the tonic phase of the tonic-clonic seizure, but less intense compared with the typical tonic phase because of reduced involvement of the deltoid muscles. It is more or less asymmetric. EEG shows recruiting fast waves originating from unclear or different foci. The "mild tonic" phase is gradually replaced by the fourth phase, "fluttering", which includes movements which are reminiscent of a baby lying on its back. In this phase, each extremity trembles and jerks in an asymmetric, less rhythmic, and less synchronous manner, with tremulous fingers and hands. In the later phase, the movement of the limbs gradually becomes more synchronous and nearly clonic. The proximal muscle contraction is not as intense as that in typical clonic seizures. In the last phase, "postictal state", patients become motionless with or without oral automatism. This phase may be associated with postictal bilateral diffuse and continuous slow waves on EEG, especially between seizures in the same clusters. This postictal phase may be misdiagnosed as an atypical absence seizure or prolonged complex partial seizures.

The 19 of the 26 convulsive seizures (4/6: Patient 1; 6/6: Patient 2; 9/14: Patient 3) exhibited all phases. However, convulsive seizures do not necessarily exhibit all of these six phases. Some phases can be shorter or lacking, whereas others can be longer or more pronounced; this may explain the diversity of seizure manifestations reported in the literature. However, these phases do usually occur in sequential order. The most characteristic phases in the convulsive seizures are the "reactive", "mild tonic", "fluttering", and "mild clonic", predominantly appearing in the distal extremities.

In our study, the convulsive seizures were considered as focal-onset seizures with secondary generalisation. Furthermore, these seizures can originate from either side even in the same patients. We speculate that hyperexcitability of the brain is so widespread and unstable that the seizures easily propagate in PCDH19RE, like the falsely generalised seizures and unstable seizures seen in Dravet syndrome. However, the tonic and clonic phases are less intense and more dominant in the periphery compared with Dravet syndrome. It is noteworthy that most seizures in this study occurred during sleep.

In conclusion, we conducted ictal video-EEG recordings of 26 convulsive seizures in three PCDH19RE patients. Based on our analysis of these recordings, we have found that these seizures consistently progress through six sequential phases. We have also found that the EEG recordings indicate the presence of widespread hyperexcitability throughout the brain in these patients. These characteristic features of the convulsive seizures may help in the diagnosis of PCDH19RE, but a large number of patients may be needed to confirm our findings.

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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. The authors have no conflicts of interests to disclose.

Legends for video sequences

Video sequence 1

The seizure of Patient 1: the seizure began with several jerks of the body after which her body and limbs became mildly tonic. The fingers on both hands and the lower extremities repeatedly moved in a less synchronous, less rhythmic, and less intense manner. Thereafter, this movement gradually became more synchronized, nearly clonic, but less intense, synchronous, and asymmetric. In the postictal state, the patient gasped with oral automatism.

Key words for video research on www.epilepticdisorders.com

Syndrome: epileptic encephalopathy not otherwise classified
Aetiology: genetic disorder
Phenomenology: focal seizure not otherwise specified
Localization: unknown

Video sequence 2

The seizure of Patient 2: the patient was sleeping. The patient was awakened by massive jerks. Her eyes deviated first to the right, then to the left, and progressively to the right again. Her limbs and fingers were fluttering or jerking less synchronously. At the end of the seizure, more synchronized jerks were repeatedly observed with a slow rolling movement of the arms. In the postictal phase, the patient mumbled.

Key words for video research on www.epilepticdisorders.com

Syndrome: epileptic encephalopathy not otherwise classified
Aetiology: genetic disorder
Phenomenology: fear; focal seizure not otherwise specified
Localization: unknown

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TEST YOURSELF

(1) What pattern do seizures in patients with *PCDH19*-related epilepsy tend to follow?

(2) What induces seizures in patients with *PCDH19*-related epilepsy?

(3) If a patient has seizures with six sequential phases that are sometimes induced in clusters by fever, what examination would be most appropriate?

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".