Probable dysimmune epilepsia partialis continua manifesting as epileptic moving toes syndrome: electroclinical features of a challenging case

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ABSTRACT – Epilepsia partialis continua (EPC) is a rare form of focal status epilepticus. We describe a 22-year-old woman with EPC manifesting with isolated toe movements, prevalent over the left side and initially misdiagnosed as psychogenic, clinically almost indistinguishable from those observed in "painful legs and moving toes syndrome". The continuous involuntary movements with EMG correlates of twitches lasting <100 ms, the sharp waves over fronto-central regions on EEG, and the marked asymmetry in somatosensory evoked potentials with higher cortical amplitude over the right side following peripheral stimulation over the left foot confirmed the epileptic nature of the symptoms, leading to the diagnosis of EPC. The toe movements were markedly reduced following steroid therapy, whereas the infusion of immunoglobulins caused aseptic meningitis. Despite an extensive diagnostic work-up (including a search for antibodies for paraneoplastic and autoimmune encephalitis), an ultimate aetiological diagnosis was not reached, although the dramatic response to corticosteroids strongly supported an underlying dysimmune pathophysiology. Diagnosing EPC can be challenging, especially if movements are confined to a very small body region or strongly resemble movements encountered in other conditions. EEG-EMG monitoring should be performed in patients with continuous involuntary muscular jerks in order not to overlook a diagnosis of EPC. [*Published with video sequences on www.epilepticdisorders.com*].

Key words: autoimmune encephalitis, diagnosis, epilepsia partialis continua, painful legs and moving toes syndrome

Epilepsia partialis continua (EPC) is a rare form of focal status epilepticus and is defined as "spontaneous regular or irregular clonic muscular twitching affecting a limited part of the body, sometimes aggravated by action or sensory stimuli, occurring for a minimum of one hour, and recurring at intervals of no more than ten seconds" (Thomas *et al.*, 1977; Obeso *et al.*, 1985; Bien and Elger, 2008). The diagnosis requires the presence of epileptiform EEG discharges or other neurophysiological abnormalities such as giant somatosensory evoked potentials (SSEPs), demonstrating the cortical origin of the muscle jerks (Cockerell *et al.*, 1996).

In most cases, EPC is caused by vascular, immune-mediated, neoplastic or metabolic/toxic disorders (Bien and Elger, 2008). Cortical dysfunction within the primary motor area is indispensable in the pathophysiology of EPC (Thomas *et al.*, 1977; Obeso *et al.*, 1985; Cockerell *et al.*, 1996), although subcortical structures may contribute to its generation (Juul-Jensen and Denny-Brown, 1966; Guerrini, 2009). Virtually every region of the body can be affected in EPC. The part of the body affected can sometimes be small, with only some muscles selectively involved. Cases of EPC restricted to the tongue have been reported (Nayak *et al.*, 2006; Vukadinovic *et al.*, 2007; Bien and Elger, 2008; Iyer and Ramalingam Ramakrishnan, 2014) or the abdominal muscles (Ribeiro *et al.*, 2015).

This is the first report of EPC manifesting with isolated toe movements, initially misdiagnosed as psychogenic, clinically almost indistinguishable from those observed in "painful legs and moving toes syndrome".

Case study

A 22-year-old, previously healthy woman came to the emergency room due to continuous, irregular movements of her toes on the left foot, which in a different hospital had been previously diagnosed as psychogenic. Her familiar history was negative for neurological disorders including epilepsy, but positive for autoimmune disorders (her maternal grandparents were diagnosed with rheumatoid arthritis and psoriatic arthritis). Pregnancy, birth, and early development were uneventful, and she did not take any drugs.

One week before, she had noticed continuous, irregular and involuntary movements involving the toes of the left foot. On the first day, the movements appeared and she also noticed similar involuntary movements involving the toes of the contralateral (right) foot, which lasted for about two hours and then disappeared. The patient reported that these movements involving both feet were synchronous. The continuous, involuntary movements on the left side had

continued without interruption since then. She also reported very brief (a few seconds), shock-like dysaesthetic feelings over her left hemibody.

Neurological examination showed continuous, irregular, non-rhythmic and involuntary flexion movements involving the toes of the left foot, sometimes associated with brisk movements (myoclonic-like) of plantar flexion and supination (*video sequence 1*). Movements were momentarily suppressed by voluntary action. No similar movements were observed on the right side. No deficit in sensitivity was reported. Strength and reflexes were normal. The remaining neurological examination was unremarkable.

Eight days after admission, similar involuntary movements appeared in the toes of the contralateral right foot; these movements were asynchronous with movements persisting on the left side, more evident during hyperventilation (*video sequence 2*).

A combined EEG-needle EMG recording (electrodes placed in the *extensor digitorum brevis* and *flexor digiti minimi* of both feet) showed intermittent sharp waves over fronto-central regions bilaterally, slightly predominant over left regions. The sharp waves were less evident in Stage I NREM sleep, disappearing completely in Stage II NREM. The EMG showed simultaneous activation of extensors and flexors in both feet; movements recorded in the right foot were not synchronous with those recorded from the left foot. Most EMG bursts lasted less than 100 ms. The movements involving the left foot persisted during the whole EEG recording during wakefulness and Stage I NREM sleep, but completely disappeared in Stage II NREM, reappearing again after awakening (*supplementary figure 1*). Mental efforts (serial subtractions and spelling words backwards) consistently increased the movements, as clearly demonstrated by a marked increase in amplitude of EMG activity (*supplementary figure 2A, B*), whereas tactile or painful stimulation on the plantar foot had no effect. Imagining moving the left foot without actually moving it also had no effect. Hyperventilation led to a dramatic increase in amplitude of toe movements in the left foot and the appearance of similar movements contralaterally, with widespread sharp waves on the EEG (*supplementary figure 3A-C*).

Routine biochemistry examinations and screening for vasculitis yielded normal results. Thyroid function tests showed normal anti-thyroglobulin antibodies, anti-thyroid peroxidase and anti-TSH receptor antibodies, and normal thyroid hormones. Anti-transglutaminase and gliadin antibodies were also negative. A comprehensive autoimmune screening for antibodies directed towards intracellular (including Hu, Ri, Yo, CV2, and Ma/Ta), synaptic intracellular (amphiphysin and GAD), and neural surface antigens (including NMDAR, AMPA1, AMPA2, GABARB1

and GABARB2, and VGKC-complex and its associated proteins CASPR2 and LGI1) was unremarkable (both in serum and cerebrospinal fluid). Serology and PCR-based analyses of cerebrospinal fluid for enteroviridae, EBV, HSV1, HSV2, VZV, *Borrelia burgdorferi,* and *Toxoplasma gondii* yielded negative results.Sensory and motor nerve conduction studies were normal, and the EMG showed a normal recruitment pattern in the muscles of both upper limbs and lower limbs with no evidence of myokymia, fasciculations, neuromyotonia, or other pathological, involuntary patterns.

Transcranial magnetic stimulation showed normal central and peripheral motor conduction time, whereas SSEPs showed a marked (>50%) asymmetric cortical response, with higher cortical amplitude (7.64 μV) over the right side following left posterior tibial nerve stimulation (*supplementary figure 4*). Brain 3 Tesla MRI, including T1, T2 and fluid-attenuated inversion recovery (FLAIR) sequences, diffusion-weighted imaging with apparent diffusion coefficient mapping, and contrast-enhanced intracerebral angiography, showed no abnormality. Ultrasound examination revealed a thyroid gland with normal volume, with a small nodule and colloidal cyst in the left lobe in slightly inhomogeneous and hypoechogenic parenchyma.

Because of the presence of several clinical and neurophysiological features pointing to neuronal hyperexcitability involving the cortex, an initial treatment with levetiracetam, up to 3,000 mg/day, was started. An attenuation in movements was observed; the brisk myoclonic-like movements of plantar flexion/supination of the left foot disappeared, yet the flexion movements of the toes, predominantly on the left foot, persisted. Eslicarbazepine (up to 1,200 mg/day) was then added. A decrease in movements of both sides was observed and the patient experienced longer periods without these movements. However, she started complaining about minimal twitching under her skin, affecting all four extremities irregularly (lasting 1-2 seconds) and the lips (more on the left side), bilateral very brief tinnitus (1-2 seconds) mostly on the right ear, hyperhidrosis, and insomnia. Furthermore, she reported shock-like dysaesthesic feelings, lasting for a few seconds, which were no longer limited to the left hemibody, but involved different body regions.

The EMG recording showed fasciculations involving different muscles with normal recruitment in the muscles of both upper and lower limbs, whereas conduction velocities were normal. Treatment with high-dose steroids (methylprednisolone at 1,000 mg/day over five days) was initiated (two months after symptom onset). Following steroid administration, dysaesthesic feelings, tinnitus, and fasciculations completely disappeared, while toe movements were markedly reduced. Antiepileptic drugs were maintained unchanged. Steroids were continued at a dosage of 1 mg/kg/day for the following two weeks and then tapered off to a minimum maintenance dosage of 50 mg prednisolone, once daily. In the first weeks following steroid therapy, the patient experienced a marked reduction in toe movements, which subsequently reappeared. Intravenous immunoglobulins (0.4 g/Kg) were hence administered, but 48 hours after the first infusion, the patient experienced severe headache, fever, nuchal stiffness, photophobia, and vomiting. A lumbar puncture revealed lymphocytic pleocytosis, with normal glucose and elevated protein levels; cultures indicated negative bacterial aetiology and serology and PCR-based analyses of cerebrospinal fluid for enteroviridae, EBV, HSV1, HSV2, and VZV were negative. A diagnosis of aseptic meningitis was made, and treatment with immunoglobulins was immediately withdrawn, with regression of symptoms within the following 24 hours.

Brain MRI was repeated with normal results. A total-body CT scan combined with full-body and cerebral 18-fluorodeoxyglucose positron emission tomography (PET) was unremarkable. A comprehensive search for antibodies associated with paraneoplastic and autoimmune encephalitis, mentioned above (including antibodies to glutamate receptor type 3 [GluR3]), was repeated in blood and CSF with negative results. The repeated SSEPs showed persistence of a marked (>50%) asymmetric cortical response, with higher cortical amplitude (7.65 μV) over the right side following peripheral stimulation in the tibial nerve (*supplementary figure 4*).

In the following months, due to the persistence of involuntary toe movements, lamotrigine was added with marked symptom improvement. Eslicarbazepine and levetiracetam were therefore gradually reduced and withdrawn. Prednisolone was also reduced over the following two months, and then withdrawn. The patient is currently taking lamotrigine at 150 mg/day, and for the last five months has not experienced involuntary toe movements.

Discussion

The reported case presents several peculiarities. The continuous, involuntary toe movements were clinically indistinguishable from those characterizing "painful legs and moving toes syndrome" (Hassan *et al.*, 2012) (*video sequence 3*) and volitional toe movement (*video sequence 4*) (Ondo, 2018), although some clinical and neurophysiological features pointed to cortical hyperexcitability. The association with brief, shock-like dysaesthetic feelings over the left hemibody (where the toe movements were predominant)

and the marked increase in movement amplitude following hyperventilation and mental efforts, were highly suspicious of cortical hyperexcitability (Bien and Elger, 2008). The presence of continuous involuntary movements with EMG correlates of twitches lasting <100 ms (Obeso *et al.*, 1985; Cockerell *et al.*, 1996), the EEG demonstration of sharp waves over fronto-central regions, and the marked asymmetry in SSEPs with higher cortical amplitude over the right side following peripheral stimulation over the left foot confirmed the epileptic nature of the symptoms, leading to the diagnosis of EPC. The PET was unremarkable, probably because it was performed when the patient had already experienced a marked reduction in toe movements. However, the negative PET results could also be explained by the fact that metabolic hypo- or hyperactivity is difficult to detect with this technique, considering the small area of toe representation in the primary motor cortex.

Intriguingly, toe movements involving both feet were reported to be synchronous at the very beginning. Later on, the muscular jerks of the right foot disappeared and when they reappeared about two weeks later, they were asynchronous with those of the contralateral foot (*supplementary figure 5*). The initially synchronous movements may have been the result of a transcallosal transmission from right to left primary motor cortex (*supplementary figure 6A*). However, the later asynchrony argues against transcallosal transmission, as in this case one would have expected to observe almost simultaneous movements or, to be more precise, a delay of about 10 ms (Woods *et al.*, 2015). It is therefore possible that, during the course of the disease, the patient developed two independent epileptic foci, each responsible for the different clinical symptoms.

Of note, previous studies have revealed that the connections between cortico-spinal tract fibres of toes and the contralateral primary motor cortex were greater than those with cortico-spinal tract fibres of the fingers, suggesting that the leg motor network exhibits greater bilaterality than the finger motor network in the normal human brain (Luft *et al.*, 2002; Kapreli *et al.*, 2006; Yeo and Jang, 2012). This may explain the asynchronous involvement of both feet, probably not mediated by transcallosal transmission (Jang *et al.*, 2009) but by a main epileptic focus over the right primary motor cortex and a contralateral mirror focus (McCarthy *et al.*, 1997) (*supplementary figure 6B*).

As previously reported for EPC (Bien and Elger, 2008), psychic efforts may increase the amplitude and frequency of the movements. Interestingly, we found that hyperventilation had the same effect (a phenomenon not previously recognized). Indeed, hyperventilation-related clinical and EEG changes seem to be particularly relevant within the context of immune-mediated forms of epilepsy (Steriade *et al.*, 2016; Vogrig *et al.*, 2018). Furthermore, in our patient, the involuntary movements attenuated during Stage I NREM and completely disappeared in Stage II NREM. The disappearance of muscle jerks is observed in up to 20% of patients (Löhler and Peters, 1974), which is inconsistent with the term "continua" that describes the continuous nature of EPC.

The lack of continuous or rhythmic epileptic activity on the EEG does not argue against such diagnosis, as EPC may be associated with a completely normal EEG, even when the entire rolandic cortex is carefully explored (Niedermeyer, 1954). In a case series of 11 patients with EPC, no epileptiform potentials on EEG were reported in more than 50% of cases (Bien and Elger, 2008). This feature of EPC is somewhat astonishing, as one may expect an EEG showing continuous epileptiform discharges contralaterally over the involved motor cortex. However, even ictal EEG of rolandic focal motor seizures may lack precise focal epileptiform discharges. This dissociation between epileptiform discharges over the motor cortex and the motor correlates, a phenomenon known as vertical inhibition (Elger and Speckmann, 1983), has been investigated in animal models (Elger and Speckmann, 1980). Spiking in lamina V following local penicillin administration leads to contralateral twitching without concomitant spiking recorded on the cortical surface. A motor correlate of epileptic activity was observed only when epileptic discharges involved the superficial and deep cortical layers (Elger and Speckmann, 1980). Furthermore, it should be noticed that at least 10 cm2 of synchronous cortical activity is required to record an ictal rhythm on scalp EEG (Tao *et al.*, 2005), and this explains why in more than 50% of EPC cases the scalp EEG is normal.

Interestingly, the needle-EMG recording showed simultaneous activation of agonists and antagonists (*i.e.* extensors and flexors) in both feet (*supplementary figure 7*). This finding is usually observed in dystonia (Bertolasi *et al.*, 2003) and is typical for EPC (Obeso *et al.*, 1985, Cockerell *et al.*, 1996). Indeed, this does not argue against simultaneous cortical activation of nearby motor neurons located in a restricted area of the primary motor cortex controlling agonists and antagonists of the contralateral foot. The resulting movement following this cortical activation of nearby motor neurons controlling agonist and antagonist muscles probably depends on the magnitude of the cortical representation of foot muscles. In the presented case, the net result of the cortical epileptic discharge involving the motor neurons in the primary motor cortex, corresponding to the representation of the foot, resulted in toe flexion movements, as toe

flexors are possibly represented to a greater extent than extensors.

Unfortunately, in our patient, as in 19% of EPC cases (Cockerell *et al.*, 1996), despite all the diagnostic efforts, an ultimate aetiological diagnosis was not reached. The shock-like dysaesthetic feelings lasting a few seconds and initially confined to the left hemibody, but later involving different body regions, the hyperhidrosis, the brief episodes of tinnitus, the widespread fasciculations and myokymia, and the presence of insomnia strongly suggested underlying neuromotor hyperxcitability involving both cortical and spinal neurons, and probably also the autonomic system. Although an extensive and repeated search for antibodies typically associated with autoimmune encephalitis (including antibodies directed towards the VGKC-complex and its main targets, LGI1 and CASPR2) yielded negative results, the dramatic response to corticosteroid administration strongly supported an underlying dysimmune

pathophysiology. Moreover, this conclusion is supported by the recently validated Antibody Prevalence in Epilepsy (APE) scoring system (Dubey *et al.*, 2017), in which a score equal or superior to 4 is highly suggestive of an autoimmune aetiology (a score of 4 in this case was based on: new-onset seizure activity [+1], autonomic dysfunction including hyperhidrosis [+1], and seizures refractory to at least two antiseizure medications [+2]). Despite the negative antibody results, the case described here presents several similarities to the recently expanded spectrum of LGI1/CASPR2 syndromes (Gadoth *et al.*, 2017).

In conclusion, several diagnostic difficulties arise when facing EPC, especially if continuous movements are confined to a very small body region or strongly resemble movements encountered in other conditions. It is therefore strongly advisable to maintain a low threshold for EEG-EMG monitoring in the event of involuntary continuous muscular jerks, as a diagnosis of EPC may mask a treatable underlying pathology. □
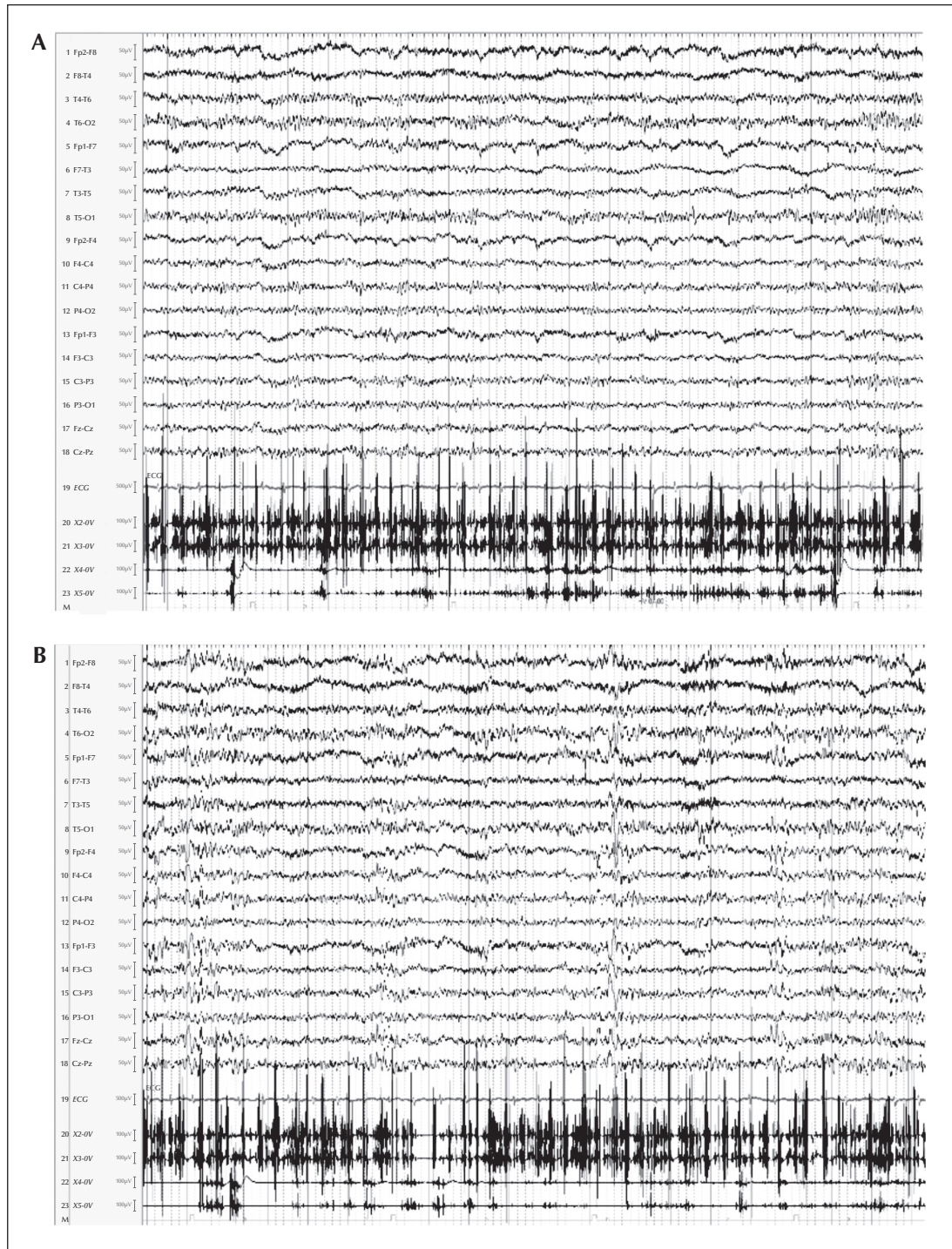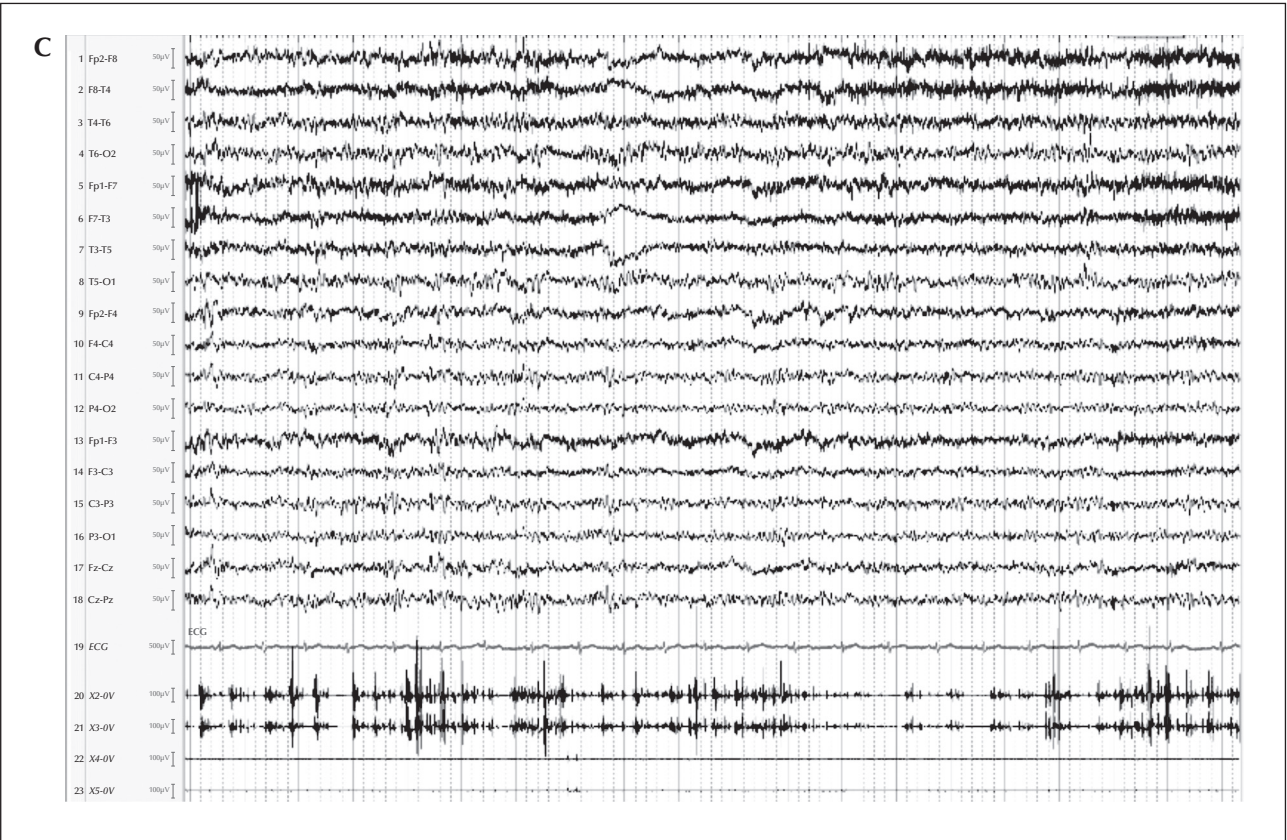
SUPPLEMENTARY FIGURES.
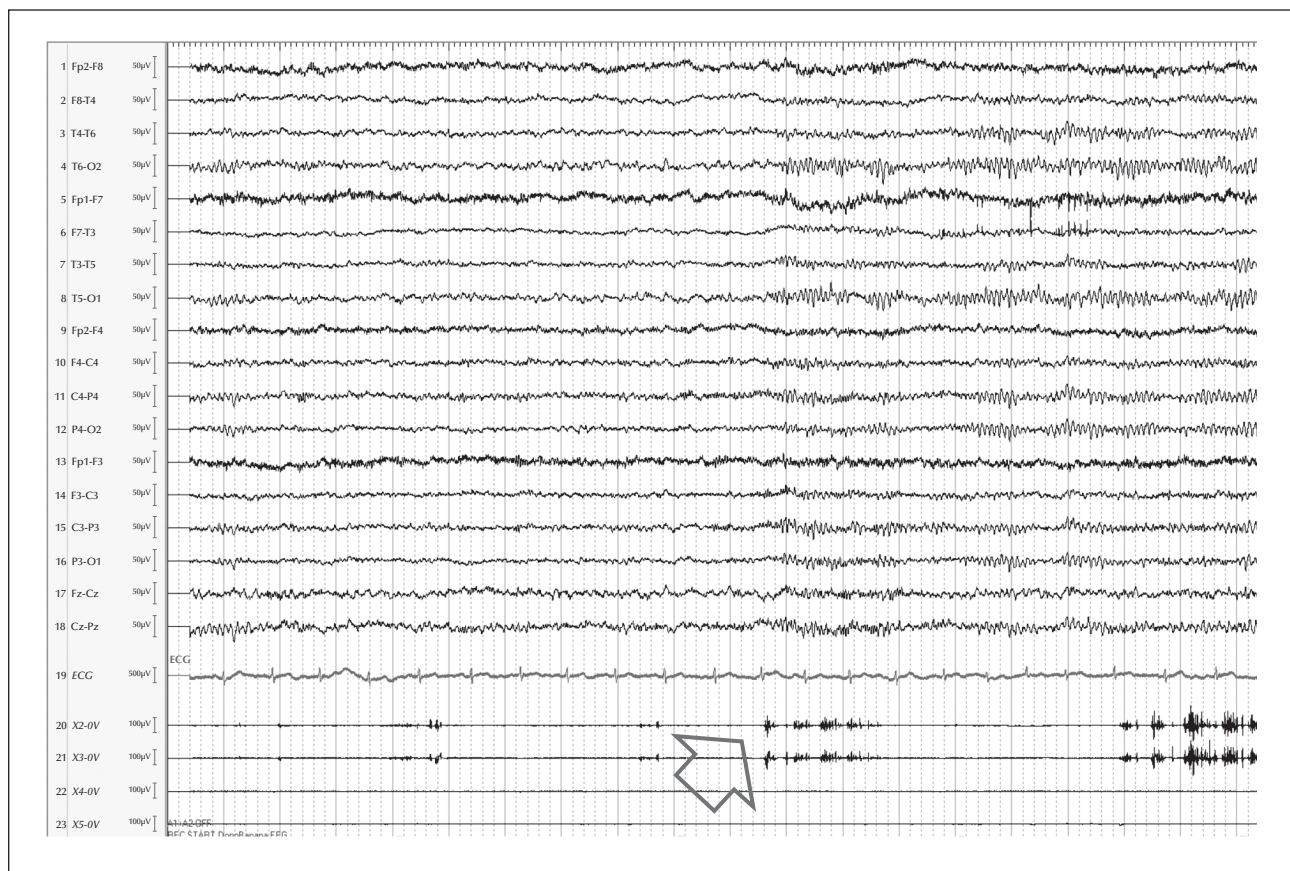
Supplementary figure 1. Baseline EEG-EMG recording. EMG channels show the extensor *digitorum brevis* of the left foot (20), flexor *digiti minimi* of the left foot (21), extensor *digitorum brevis* of the right foot (22), and flexor *digiti minimi* of the right foot (23). The movements involving the left foot disappear during Stage II NREM and reappear after awakening (red arrow). Sensitivity: 7 µV; LF: 0.53 Hz; HF: 70 Hz. Speed: 20 sec/page. EMG channels: 20.
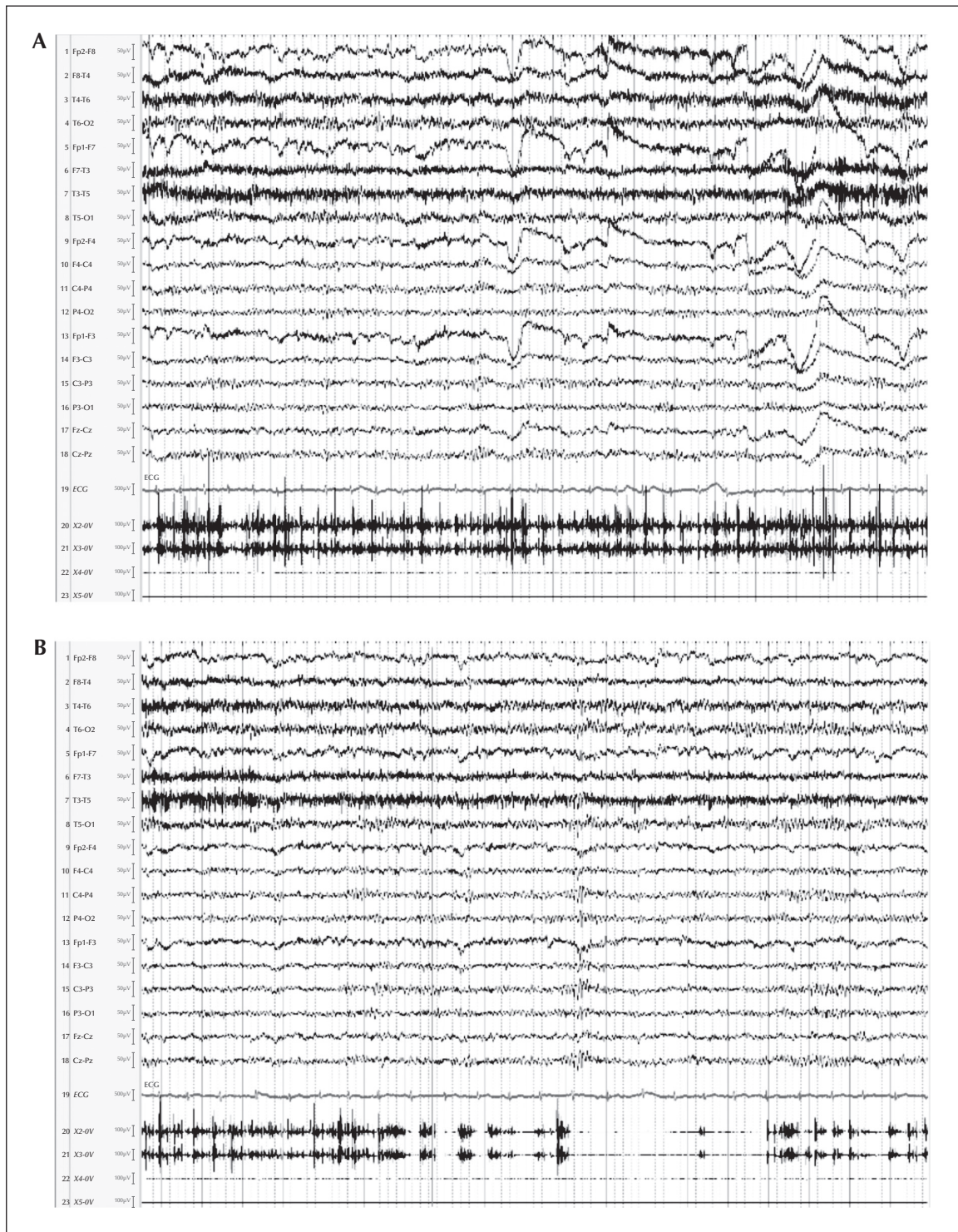
Supplementary figure 2. Baseline EEG-EMG recordings. (A) EMG channels show the extensor *digitorum brevis* of the left foot (20), flexor *digiti minimi* of the left foot (21), extensor *digitorum brevis* of the right foot (22), and flexor *digiti minimi* of the right foot (23). A marked increase in amplitude of left foot movements is evident during mental efforts (serial subtractions and spelling words backwards). Sensitivity: 7 μV; LF: 0.53 Hz; HF: 70 Hz. Speed: 20 sec/page. (B) EMG channels show extensor *digitorum brevis* of the left foot (20), flexor *digiti minimi* of the left foot (21), extensor *digitorum brevis* of the right foot (22), and flexor *digiti minimi* of the right foot (23). Reduction in amplitude of left foot movements is observed one minute after the end of mental efforts. Sensitivity: 7 μV; LF: 0.53 Hz; HF: 70 Hz. Speed: 20 sec/page.

Supplementary figure 3. Baseline EEG-EMG recordings. (A) EMG channels show the extensor *digitorum brevis* of the left foot (20), flexor *digiti minimi* of the left foot (21), extensor *digitorum brevis* of the right foot (22), and flexor *digiti minimi* of the right foot (23). An extremely marked increase in amplitude of left foot movements during hyperventilation, with appearance of asynchronous movement in the contralateral foot, is evident. Sensitivity: 7 μV; LF: 0.53 Hz; HF: 70 Hz. Speed: 20 sec/page. (B) EMG channels show the extensor *digitorum brevis* of the left foot (20), flexor *digiti minimi* of the left foot (21), extensor *digitorum brevis* of the right foot (22), and flexor *digiti minimi* of the right foot (23). Appearance of widespread sharp waves on the EEG during hyperventilation is evident.
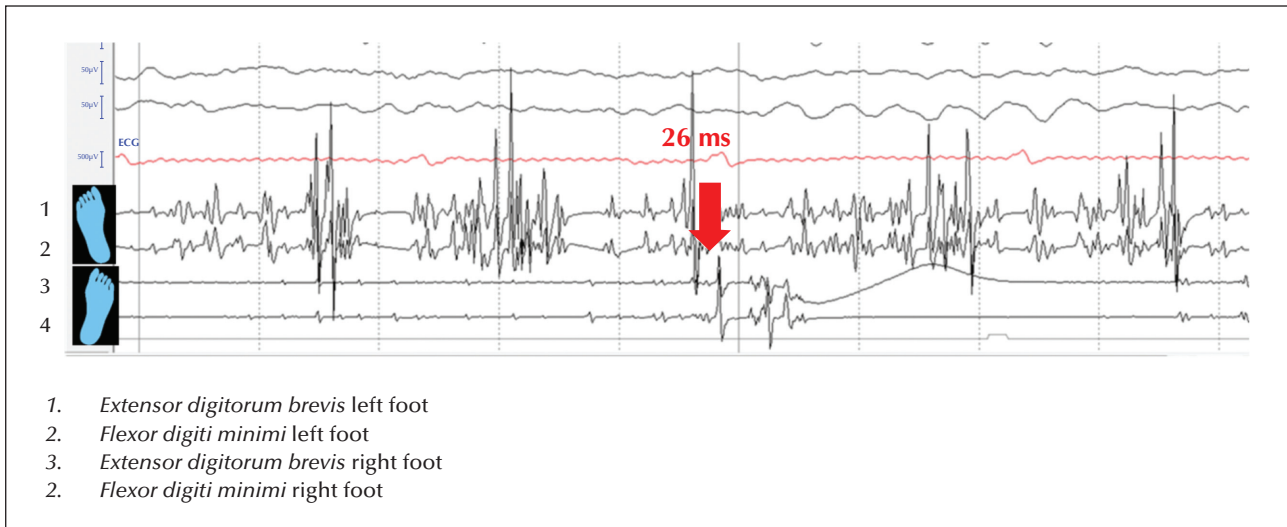
Supplementary figure 3. (*Continued*) (C) EMG channels show the extensor *digitorum brevis* of the left foot (20), flexor *digiti minimi* of the left foot (21), extensor *digitorum brevis* of the right foot (22), and flexor *digiti minimi* of the right foot (23). Reduction in amplitude of left foot movements and disappearance of involuntary movements of the right foot, about 10 minutes after the end of hyperventilation, is evident. Sensitivity: 7 μV; LF: 0.53 Hz; HF: 70 Hz. Speed: 20 sec/page.
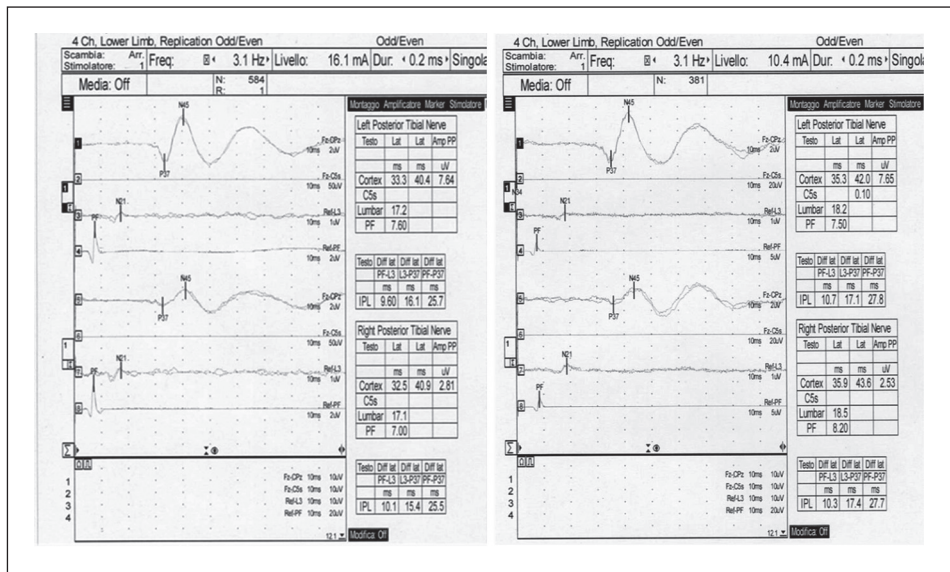

Supplementary figure 4. Left: SSEPs showing a marked (>50%) asymmetric cortical response, with higher cortical amplitude (7.64 μV) over the right side following stimulation of the left posterior tibial nerve. Right: after two years, SSEPs reveal the persistence of a marked (>50%) asymmetric cortical response, with higher cortical amplitude (7.65 μV) over the right side following peripheral stimulation in the left foot.

1. *Extensor digitorum brevis* left foot
2. *Flexor digiti minimi* left foot
3. *Extensor digitorum brevis* right foot
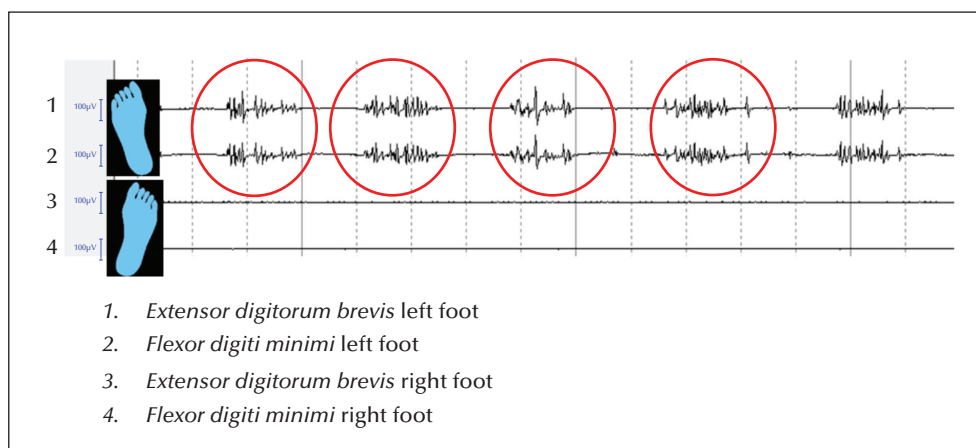2. *Flexor digiti minimi* right foot

Supplementary figure 5. EMG recording showing asynchronous toe movements in the right and left foot. Note the time delay greater than 10 ms, arguing against transcallosal transmission and suggestive of activation of a secondary independent contralateral mirror focus.
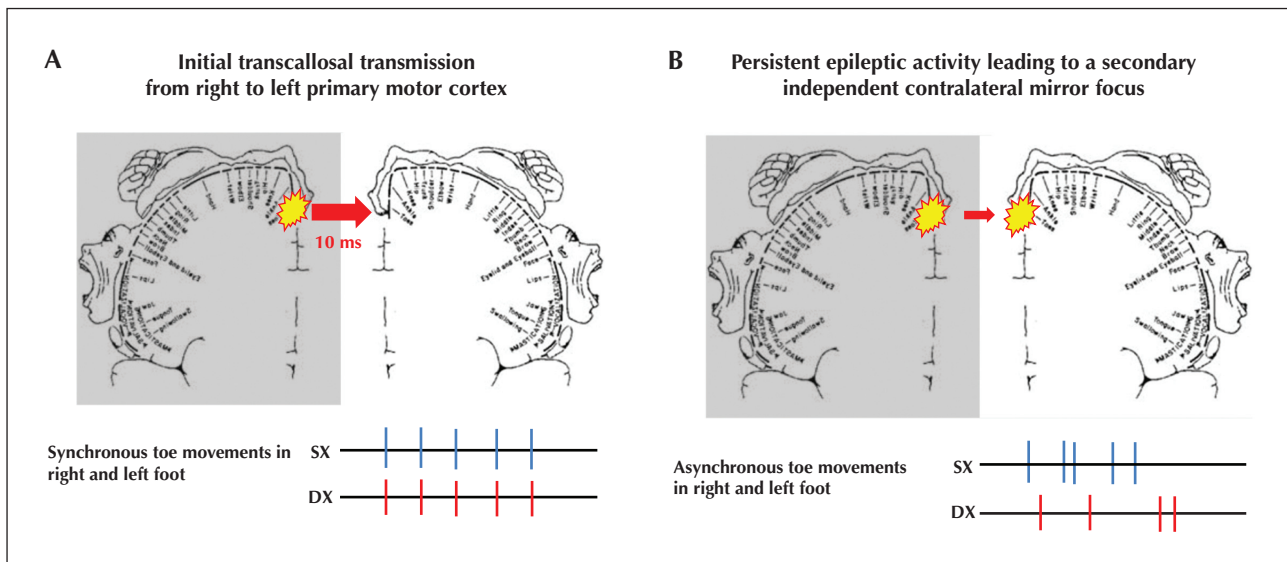
Supplementary figure 6. (A) Proposed interpretation of the synchronous toe movements in the right and left foot at the very beginning of symptom onset. The initially synchronous movements may have been the result of transcallosal transmission from the right to left primary motor cortex. (B) Proposed interpretation of the asynchronous toe movements in the right and left foot observed during the course of the disease. Transcallosal transmission is unlikely to account for such an asynchrony, as in this case one would have expected to observe a delay of about 10 ms in toe movements between the two feet. Thus, the asynchronous involvement of both feet was probably not mediated by transcallosal transmission, but by a main epileptic focus over the right primary motor cortex and a secondary independent contralateral mirror focus.

1. *Extensor digitorum brevis* left foot
2. *Flexor digiti minimi* left foot
3. *Extensor digitorum brevis* right foot
4. *Flexor digiti minimi* right foot

Supplementary figure 7. EMG recording showing simultaneous activation of extensors and flexors in the right foot.

Legend for video sequences

Video sequence 1

Continuous, irregular, non-rhythmic and involuntary flexion movements involving the toes of the left foot, sometimes associated with brisk movements (myoclonic-like) of plantar flexion and supination.

Video sequence 2

During hyperventilation, involuntary movements appear involving the toes of the right foot; these movements are asynchronous with movements on the left side.

Video sequence 3

Spontaneous movements of the toes of a patient with painful legs and moving toes syndrome (available at Neurosigns.org: http://neurosigns.org/wiki/Painful_legs_and_moving_toes - content reproduced under Creative Commons Attribution-ShareAlike; accessed 16th April 2018).

Video sequence 4

Volitional movement of toes in a 35-year-old healthy woman. These movements are characterized by digit flexion and extension during relaxed wakefulness and arise from normal muscular volitional activity.

Key words for video research on www.epilepticdisorders.com

Phenomenology: not applicable
Localization: central motor
Syndrome: focal non-idiopathic (localization not specified)
Aetiology: encephalitis

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TEST YOURSELF

(1) Epilepsia partialis continua (EPC):
A. is a rare form of focal status epilepticus
B. is defined by clonic muscular twitching affecting a limited part of the body, occurring for a minimum of one hour, and recurring at intervals of no more than ten seconds
C. none of the above

(2) The diagnosis of Epilepsia Partialis Continua:
A. relies on clinical features alone
B. requires demonstration of a cortical origin of the muscle jerks
C. is always straightforward
D. does not require an EEG recording

(3) Simultaneous activation of agonists and antagonists:
A. is never encountered in dystonia
B. does not require a simultaneous EEG-EMG recording
C. is typically encountered in EPC
D. never points to a cortical origin of the muscle jerks

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".