Review article

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Autosomal dominant cortical tremor, myoclonus and epilepsy

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ABSTRACT – The term 'cortical tremor' was first introduced by Ikeda and colleagues to indicate a postural and action-induced shivering movement of the hands which mimics essential tremor, but presents with the electrophysiological findings of cortical reflex myoclonus. The association between autosomal dominant cortical tremor, myoclonus and epilepsy (ADCME) was first recognized in Japanese families and is now increasingly reported worldwide, although it is described using different acronyms (BAFME, FAME, FEME, FCTE and others). The disease usually takes a benign course, although drug-resistant focal seizures or slight intellectual disability occur in some cases. Moreover, a worsening of cortical tremor and myoclonus is common in advanced age. Although not yet recognized by the International League Against Epilepsy (ILAE), this is a well-delineated epilepsy syndrome with remarkable features that clearly distinguishes it from other myoclonus epilepsies. Moreover, genetic studies of these families show heterogeneity and different susceptible chromosomal loci have been identified.

Key words: cortical tremor, myoclonus, epilepsy, genetics, autosomal dominant, progressive myoclonus epilepsies

In 1990, Ikeda *et al*. described an action and postural tremor originating from the cerebral cortex, which was thus defined as a cortical tremor. Due to its electrophysiological features, this involuntary movement was considered to be a variant of cortical reflex myoclonus (Ikeda *et al*., 1990). Uyama and colleagues reported 54 patients in 7 families, estimating a prevalence of approximately 1:35,000 based on their observation in Kumamoto Prefecture (Uyama *et al*., 2005).

Cortical tremor was recognized to occur in families often in association with generalized tonic-clonic seizures, and this observation led to the definition of a peculiar autosomal dominant (AD) trait named '*benign adult familial myoclonic epilepsy*' (BAFME). BAFME was first described in Japanese families and the genetic locus mapped to chromosome 8q24. However, several European families fulfilling the diagnostic criteria for BAFME have been described and in these families, linkage to chromosome 8q24 has been excluded (reviewed in Striano & Zara [2010]). These findings suggest a worldwide distribution and genetic heterogeneity for this condition.

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Guerrini *et al*. (2001) described a family who also presented drug-resistant focal seizures and mild intellectual disability in three affected individuals and considered this phenotype as a peculiar syndrome named '*AD cortical myoclonus and epilepsy*' (ADCME). The mapping of a gene on chromosome 2p11.1-q12.2 reinforced the hypothesis that ADCME was an independent (genetically distinct from BAFME) clinical entity. A founder effect may possibly explain the high frequency of families originating from the same topographic areas of Japan and southern Italy (Uyama *et al*., 2005; Madia *et al*., 2008). An in-frame insertion/deletion in the α_2-adrenergic receptor subtype B gene (*ADRA2B*), encoding the α2-adrenergic receptor subtype B, has been reported in two apparently unrelated ADCME pedigrees of Italian origin (De Fusco *et al*., 2014). This mutation alters several conserved residues of the third intracellular (3i) loop and alters the binding with the scaffolding protein called spinophilin upon neurotransmitter activation, thus increasing epinephrine-stimulated calcium signalling.

Additional loci have also been mapped to 5p15.31-p15 and 3q26.32-q28 in single families of French (Depienne *et al*., 2010) and Thai (Yeetong *et al*., 2013) origin. Stogmann *et al*. (2013) recently described a consanguineous Egyptian family presenting focal epilepsy, neuropsychiatric features, borderline cognitive level, and myoclonus, resembling BAFME, but inherited in an autosomal recessive manner. A homozygous deletion (c.503_503delG) leading to a frameshift in the coding region of *CNTN2* and segregating in the 5 affected family members was identified. The *CNTN2* gene (mapped at 1q32.1) encodes for contactin 2, a glycosylphosphatidylinositol-anchored neuronal membrane protein, which is necessary to maintain voltage-gated potassium channels at the juxtaparanodal region. Finally, a unique south Indian community, including 241 patients with ADCME belonging to 48 families has been described. The 48 families are domiciled in 2 southern districts of Tamilnadu, India, which belongs to the Nadar community, and their origin is confined to these southern districts, with reported unique genetic characteristics. This is the largest single report of ADCME worldwide (Mahadevan *et al*., 2016).

The pathophysiological and biochemical bases of this condition also remain largely speculative. Both clinical and electrophysiological features of the syndrome suggest a cortical hyperexcitability, which may be the result of decreased cortical inhibition by the cerebellum via its cerebello-thalamo-cortical projections (Striano *et al*., 2005). Sporadic post-mortem histological studies have shown evidence of cerebellar pathology (Uyama *et al*., 2005).

Clinical features

Age at onset is highly variable (ranging from 11 to 50 years) but the disease usually starts with a slight hand 'tremor' within the second decade of life and progresses to rare tonic-clonic seizures and myoclonus by the third or fourth decade of life. Prevalence is unknown, but this condition is likely to be under-recognized. The dominant clinical picture is characterized by cortical tremor, myoclonus and epilepsy.

Cortical tremor is an action and postural fine shivering movement consisting of continuous, arrhythmic, mainly distal, fine twitches in the hands. There is no significant progression over time, but a worsening of the disturbance may be observed over the age of 70. The cortical tremor is enhanced by emotion or fatigue and may be easily misdiagnosed as essential tremor, but may be distinguished from the latter clinically (*figure 1A*). To definitively distinguish between cortical tremor and benign essential tremor requires a neurophysiological demonstration of cortical origin (Striano *et al*., 2005).

In addition to cortical tremor, most patients present distal segmental, arrhythmic, erratic myoclonic jerks in the upper limbs which are exacerbated by posture and action. The involvement of more proximal, as well as facial, muscles, particularly the eyelids, is also possible. The onset of myoclonus is difficult to clearly establish but usually starts at around the same age as that for cortical tremor (Striano & Zara, 2010).

Most patients experience generalized tonic-clonic seizures starting later than the tremor. The age at first seizure ranges widely between 12 and 67 years, with a peak around the age of 30. Seizures are generally rare (up to 5-10 episodes over the person's lifetime) and are not preceded by any warning. However, in some cases, they may be heralded by progressively increasing myoclonic jerks. Precipitating factors, such as sleep deprivation, emotional stress, and photic stimulation are often reported (Striano *et al*., 2005; Uyama *et al*., 2005). In rare cases, patients may also present with drug-resistant complex partial seizures and focal EEG abnormalities (Guerrini *et al*., 2001).

Patients usually present normal cognitive levels. However, mild-to-moderate intellectual disability may be present in some cases, particularly at a more advanced age (*figure 2*) (Striano *et al*., 2005; Coppola *et al*., 2011). Night blindness, with a reduced b-wave response on electroretinography, has been reported in three patients from Japan and migraine attacks have been reported as a predominant feature in a Turkish family (reviewed by Striano *et al*. [2005] and Uyama *et al*. [2005]).

Instrumental diagnostic procedures

Detailed electrophysiological investigations are essential to confirm the cortical origin of myoclonus. However, some of these electrophysiological features may be masked by antiepileptic treatments. The EEG background activity is usually normal or slightly slow in the slower alpha band. Generalized paroxysmal abnormalities and photoparoxysmal responses are frequently found in patients without therapy (Striano *et al*., 2005; Uyama *et al*., 2005). Furthermore, a photomyogenic response (*i.e*. a muscular, mainly anterior

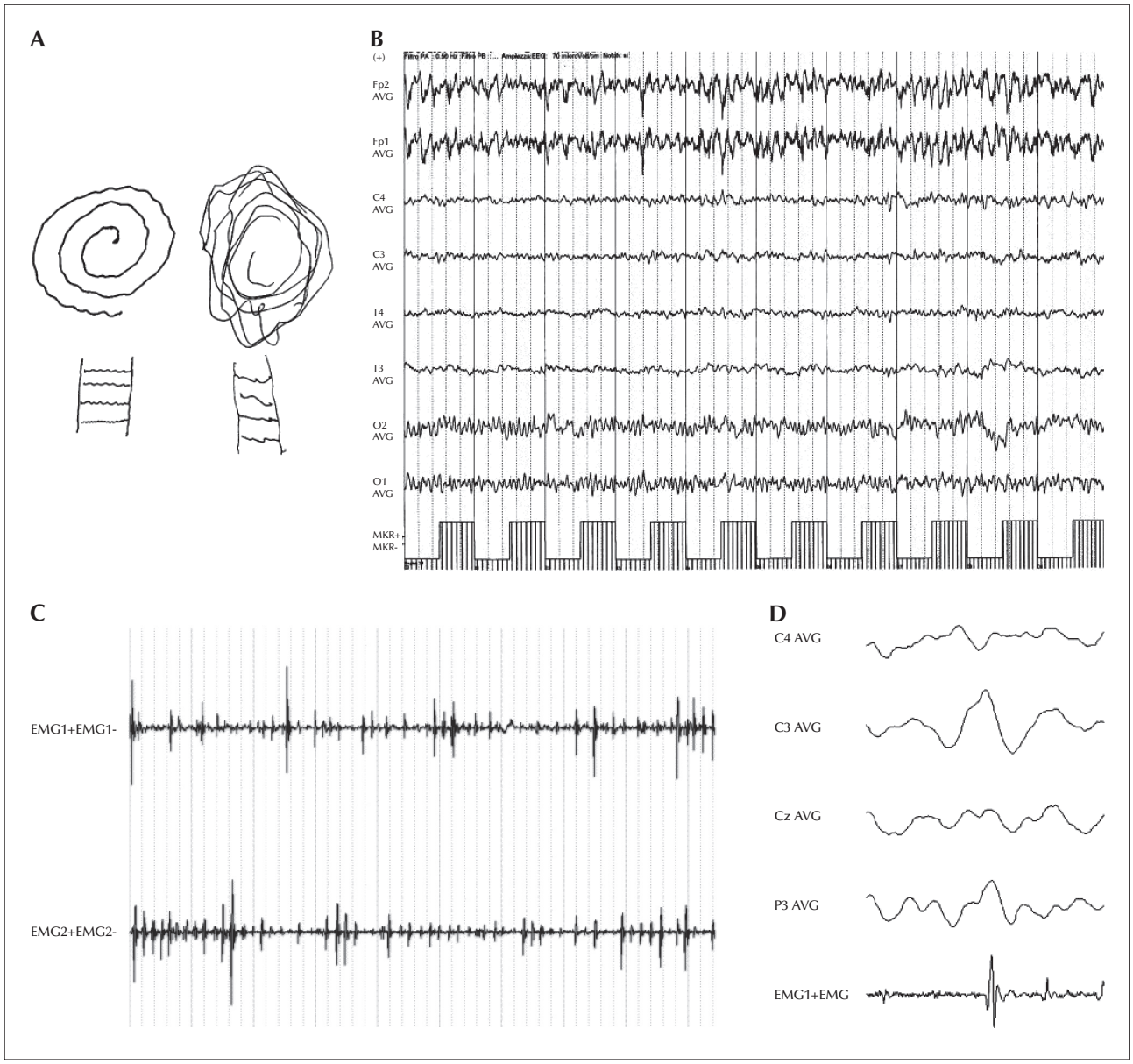

Figure 1. Electroclinical and MRI features of familial cortical tremor, myoclonus and epilepsy. (A) free-hand drawing (Archimedes' spiral and ladder) showing the differences between essential (left) and cortical (right) tremors. The cortical tremor is fairly irregular, and sudden, brisk jerks cause disruption to the drawing. (B) EEG of a patient during photic stimulation with eyes closed, showing the photomyoclonic response consisting of increasing, mainly anteriorly, myogenic potentials related to each flash stimuli. (C) EMG recording of bursts between agonist and antagonist muscles (EMG1: right wrist extensor; EMG2: right wrist flexor) with extended arms; irregular, high-frequency, short EMG bursts without the regular alternating pattern typically found in tremors. (D) Jerk-locked averaging analysis shows a positive-negative potential, recognizable over the left centroparietal electrodes, preceding myoclonus by about 30 ms (right wrist extensor muscle; number of triggers = 100).

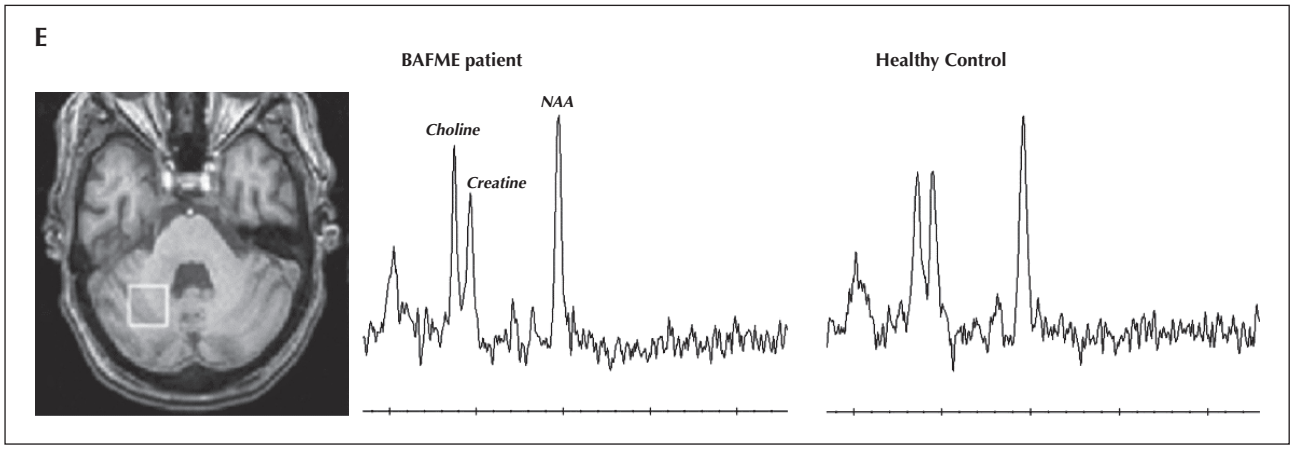

Figure 1. (E) 1H-MR Spectroscopy using a PRESS sequence (TR 1,500 ms; TE 144 ms) showing abnormal spectral peak areas at 3.22 ppm, corresponding to choline (location of the 8 cm^3 voxel: right cerebellar hemisphere). Reproduced from Striano and Zara (2010), with permission.

response, synchronous with photic stimulation) may be present (*figure 1B*). Focal paroxysmal activity can occur in some patients, in addition to generalized EEG abnormalities (Guerrini *et al*., 2001; Striano & Zara, 2010).

Polymyographic recording helps to differentiate between tremor and myoclonus. The electromyographic (EMG) pattern is consistent with irregular, arrhythmic or semi-rhythmic, high-frequency (around 10/s) myoclonic jerks. EMG bursts last about 50 ms and are usually synchronous between agonist and antagonist muscles, but do not regularly alternate between agonist/antagonist muscles, as in essential tremor (*figure 1C*). Jerk-locked averaging analysis commonly discloses a positive-negative, biphasic, premyoclonic spike or a more complex pattern of wavelets related to myoclonus on the contralateral sensorimotor regions (*figure 1D*). The evaluation of somatosensory evoked potentials and long-loop reflex I may show an enlargement of cortical components (P25-N33 amplitude larger than 8.5-15 μV) and enhanced long-latency (40 ms) C-reflex response evoked by stimulation of the peripheral nerve. A reduction in the resting motor threshold intensity and post-motor evoked potential silent period has been reported in a few patients evaluated by transcranial magnetic stimulation, indicating that central motor inhibitory mechanisms are impaired in these cases (Guerrini *et al*., 2001). MRI examination is usually normal although minor, nonspecific abnormalities (such as mild enlargement of the subarachnoid spaces of the lateral ventricles) are sometimes reported. An MRI spectroscopy study revealed an elevated choline/creatine ratio in the cerebellum cortex of patients compared with controls (*figure 1E*) (Striano *et al*., 2009).

Differential diagnosis

Cortical tremor may be easily misinterpreted as essential tremor and seizures may be overlooked or considered to be coincidental, or interpreted as a side effect of valproate treatment (Striano *et al*., 2005). The clinical observation and demonstration of cortical reflex myoclonus by means of electrophysiological investigation enables confirmation of the diagnosis.

ADCME must be differentiated from epilepsy syndromes with prominent myoclonus features. In particular, patients may easily be misdiagnosed with juvenile myoclonic epilepsy (JME) because of the occurrence of myoclonic jerks and generalized tonic-clonic seizures. However, JME clinically differs with regards to the absence of cortical tremor and predominant proximal myoclonic seizures which typically occur upon awakening. The absence of ataxia and dementia, adult onset, and the usually benign outcome of epilepsy differentiate ADCME from progressive myoclonus epilepsies (Striano & Zara, 2010; Minassian et *al*., 2016).

Treatment and evolution

Cortical tremor is not responsive to alcohol or l-dopa/carbidopa but improves with antiepileptic drugs (Ikeda *et al*., 1990; Striano *et al*., 2005; Uyama *et al*., 2005). Valproate, levetiracetam and benzodiazepines produce the greatest benefit against cortical tremors and myoclonus, combining both antiepileptic and antimyoclonic activity. In some cases, epilepsy may be difficult to treat.

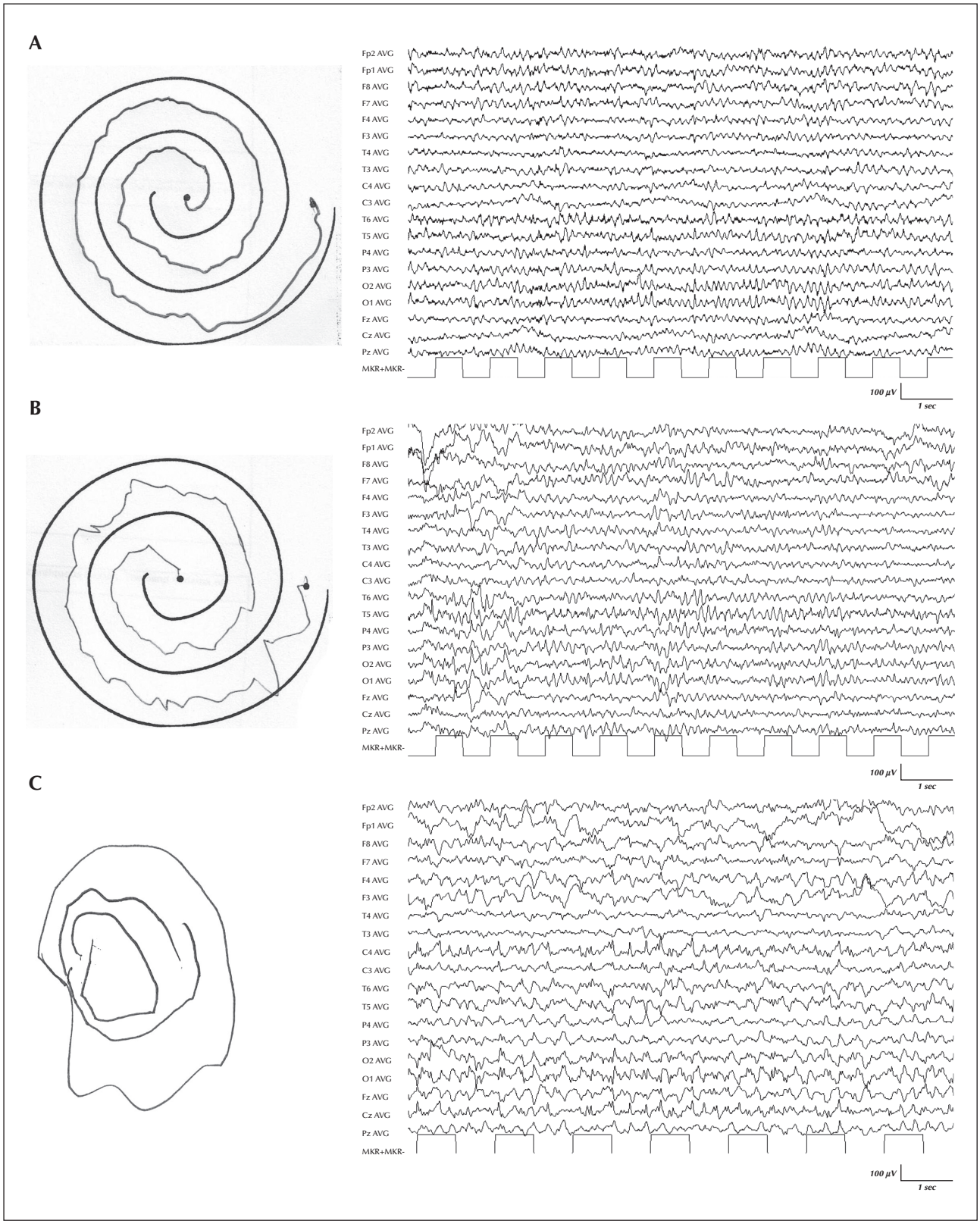

Figure 2. Free-hand drawing, Archimede's spiral hands (left) and basal EEG of patient C/3 obtained at the age of 59 (A), 70 (B), and 80 years (C), showing worsening of myoclonus and progressive slowing of EEG background activity.
Reproduced from Coppola *et al*. (2011), with permission.

As for other idiopathic generalized epilepsies, some antiepileptic drugs may precipitate myoclonic status. In these cases, a correct diagnosis and prompt discontinuation of the drug may reverse a potentially severe, life-threatening condition (Striano *et al*., 2007). In advanced age, worsening of the myoclonus is possible, as well as difficulty in walking and mild ataxia (Striano & Zara, 2010; Coppola *et al*., 2011). □

Disclosures.
None of the authors have any conflict of interest to disclose.

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