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LETTER TO THE EDITOR

Cortical tremor: a tantalizing conundrum between cortex and cerebellum

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We read with interest the recent 'Update' (Latorre *et al.*, 2020) providing a detailed analysis of the mechanisms defining cortical tremor, the leading symptom in familial cortical myoclonic tremor and epilepsy (FCMTE) or familial adult myoclonic epilepsy (FAME).

Tremor and myoclonus are common hyperkinetic movement disorders and their correct classification on clinical and electrophysiological features enables the search for aetiological diagnosis and guides tailored treatment (Zutt *et al.*, 2019).

We agree that cortical tremor should be included within the 'spectrum of cortical myoclonus', originating from an abnormal sensorimotor cortical excitability and resulting in rhythmic cortical myoclonus. This view is supported by the electrophysiological findings in these patients, namely (i) an electromyographic pattern consistent with irregular, arrhythmic (or semi-rhythmic) and high-frequency (~10/s) myoclonic jerks occurring in busts lasting ~50 ms, synchronous between agonist and antagonist muscles (versus the regular agonist/antagonist alternate pattern observed in tremor); (ii) jerk-locked averaging analysis demonstrating a positive-negative, biphasic, pre-myoclonic spike (or less frequently a complex pattern of wavelets) related to myoclonus on the contralateral sensorimotor regions; (iii) enhanced somatosensory-evoked potentials (P25-N33 amplitude $>$ 8.5 μV); (iv) increased long-loop reflex I (C-reflex) response evoked by stimulation of the peripheral nerve; and (v) strong cortical and intermuscular coherence in an 8–30-Hz range (Striano *et al.*, 2005; Uyama *et al.*, 2005).

We also agree that cortical hyperexcitability can result from a decreased cortical inhibition by the cerebellum via the cerebellar-thalamocortical projections, in line with rare post-mortem studies showing cerebellar pathology (Uyama *et al.*, 2005), and MRI spectroscopy data showing elevated choline/creatine ratio in the cerebellum cortex of patients (Striano *et al.*, 2009) as well as brain magnetic resonance diffusion tensor imaging evidence for decreased mean fractional anisotropy (i.e. microstructural damage of the cerebellar white matter) in FCTME compared with essential tremor patients (Buijink *et al.*, 2013).

Regarding the treatment, cortical tremor is not responsive to alcohol or levodopa but improves with antiseizure medications, especially if combining both anti-epileptic and anti-myoclonic activity, e.g. valproate, levetiracetam, and benzodiazepines (Striano *et al.*, 2005; Uyama *et al.*, 2005; Coppola *et al.*, 2011) whereas some drugs, such as gabapentin, may precipitate a severe myoclonic status (Striano *et al.*, 2007).

Cerebellum receives information from the motor cortex and that cerebellar output influences different neuronal populations in the motor cortex (Striano *et al.*, 2013). However, it remains to be elucidated whether the excessive excitability is due to the enhanced intrinsic rhythmic activity of cortical generators or the abnormal reciprocal interactions with subcortical structures. Alternatively, decreased cortical inhibition may be caused by dysfunction of the cerebellar-thalamocortical loop secondary to primary cerebellar pathology,

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especially at the level of the cerebellar cortex. Moreover, clinical observations suggest a correlation between clinical severity and patients' ages, indicating that the clinically evident progression of the disease reflects—at least in part—the effect of physiological ageing (Coppola *et al.*, 2011).

The recent discovery that this condition is caused by intronic pentameric expansions with a high somatic instability in distinct genes (*SAMD12*, *STARD7*, *MARCH6*), highly expressed in the cerebellum, suggests the formation of repeat-containing RNA structures that aggregate in the nucleus of cells (RNA foci), trapping numerous proteins that are unable to function properly (Lagorio *et al.*, 2019). This finding shed new light on the pathophysiology of the disease and offers hope of preventive or curative options, such as RNA-targeting treatments. Further studies are needed to explore the cerebellar-cortical connectivity and the sensory-motor cortical hyperexcitability in this disease.

Data availability

The dataset supporting the conclusions of this article are included within the article.

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References

Buijink AW, Caan MW, Tijssen MA, Hoogduin JM, Maurits NM, van Rootselaar AF. Decreased cerebellar fiber density in cortical myoclonic tremor but not in essential tremor. Cerebellum 2013; 12: 199–204.

Coppola A, Santulli L, Del Gaudio L, Minetti C, Striano S Zara F, et al. Natural history and long-term evolution in families with autosomal dominant cortical tremor, myoclonus, and epilepsy. Epilepsia 2011; 52: 1245–50.

Lagorio I, Zara F, Striano S, Striano P. Familial adult myoclonic epilepsy: a new expansion repeats disorder. Seizure 2019; 67: 73–7.

Latorre A, Rocchi L, Magrinelli F, Mulroy E, Berardelli A, Rothwell JC, et al. Unravelling the enigma of cortical tremor and other forms of cortical myoclonus. Brain 2020; awaa129. doi: 10.1093/brain/awaa129.

Striano P, Coppola A, Madia F, Pezzella, M, Ciampa, CZara F, et al. Life-threatening status epilepticus following gabapentin administration in a patient with benign adult familial myoclonic epilepsy. Epilepsia 2007; 48: 1995–8.

Striano P, Caranci F, Di Benedetto R, Tortora F, Zara F, Striano S. MR spectroscopy indicates prominent cerebellar dysfunction in benign adult familial myoclonic epilepsy. Epilepsia 2009; 50: 1491–7.

Striano P, Louis ED, Manto M. Autosomal dominant cortical tremor, myoclonus, and epilepsy: is the origin in the cerebellum? Editorial. Cerebellum 2013; 12: 145–6.

Striano P, Madia F, Minetti C, Striano S, Zara F. Electroclinical and genetic findings in a family with cortical tremor, myoclonus, and epilepsy. Epilepsia 2005; 46: 1993–5.

Uyama E, Fu YH, Ptacek LJ. Familial adult myoclonic epilepsy (FAME). Adv Neurol 2005; 95: 281–8.

Zutt R, Elting JW, Tijssen M. Tremor and myoclonus. Handb Clin Neurol 2019; 161: 149–65.