Unravelling the enigma of cortical tremor and other forms of cortical myoclonus

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ABSTRACT

Cortical tremor is a fine, small amplitude, rhythmic oscillation involving distal upper limbs, linked to increased sensorimotor cortex excitability, as seen in cortical myoclonus. Cortical tremor is the hallmark feature of Autosomal Dominant Familial Cortical Myoclonic Tremor and Epilepsy, a syndrome not yet officially recognized but well-delineated, characterized by clinical and genetic heterogeneity. Cortical tremor is considered a rhythmic variant of cortical myoclonus, and together with reflex/spontaneous cortical myoclonus, epilepsia partialis continua and myoclonic epilepsy, is part of the so-called "spectrum of cortical myoclonus", i.e. a wide range of clinical motor phenomena which may be caused by abnormal sensorimotor cortical discharges. The aim of this paper is to review the spectrum of these disorders, with particular emphasis on genetics and pathophysiology, and to describe the possible mechanisms that result in the range of phenotypes observed in cortical myoclonus.

INTRODUCTION

In 1990, Ikeda et al. described two patients who presented with "shivering-like tremor in fingers and/or hands in the outstretched posture and aggravated by action"[1]. These patients were clinically regarded as "essential tremor", but the lack of response to beta-blockers and other atypical features, such as history of seizures and irregular and brisk twitching at rest in one subject, made the authors question the diagnosis. They therefore performed electrophysiological tests that disclosed action tremor, at a frequency of approximately 9 Hz, linked to increased sensorimotor cortex excitability, as found in cortical myoclonus. They called it "cortical tremor", which is in fact a rhythmic variant of cortical myoclonus. Since then, many similar cases, under several different names and acronyms, have been reported in over 100 pedigrees worldwide, leading to the characterization of a cortical tremor syndrome, with well-known clinical features but still uncertain pathophysiology and genetic aetiology.

The aim of this paper is to review the spectrum of cortical tremor syndrome, with particular emphasis on genetics and pathophysiology, and to provide a detailed analysis of the mechanisms defining cortical myoclonus.

In the first part of this paper we review the clinical and genetic features of the cortical tremor syndrome; in the second part we discuss how cortical tremor fits into the "spectrum of cortical myoclonus", as described by Obeso et al. in 1985[2]. These conditions, which range from cortical myoclonus to epilepsia partialis continua (EPC) and myoclonic epilepsy, are all caused by abnormal discharges in sensorimotor cortex and appear to be part of a continuum of conditions with related pathophysiology. We end by speculating on the possible mechanisms that generate the discrete clinical elements of this spectrum.

CORTICAL TREMOR SYNDROME

Although it is not yet officially recognized by the International League Against Epilepsy and its nosological placement is still debated, cortical tremor syndrome is a well-delineated condition characterized by the association of cortical tremor, myoclonus and epileptic seizures, inherited in an autosomal dominant pattern, and with genetic heterogeneity[3-5]. The lack of an agreement on its nosology is reflected by the use, over the years, of several different names and acronyms to describe it. In this manuscript we use the term autosomal

dominant familial cortical myoclonic tremor and epilepsy (FCMTE), as suggested in 2005[6] and as currently used by the HUGO Gene Nomenclature Committee.

Clinical Features

Cortical tremor

Cortical tremor is a fine, small amplitude, rhythmic oscillation involving the distal upper limbs (hands and fingers) which occurs mainly during posture and action, but is also sometimes present at rest. In many cases, a combination of rhythmic involuntary movements (tremor) and superimposed arrhythmic erratic jerks (myoclonus) during both action and rest, have been described in a single patient [7-11].The clinical distinction of the two can be difficult, but in the literature they have been often described as separated. Nevertheless, since they are both forms of cortical myoclonus (see below), they can be considered part of the same phenomenon and therefore part of the clinical picture of cortical tremor.

The jerks, which are either regular or irregular, can also involve legs, head, trunk, proximal upper limb and facial muscles, especially eyelids[7-9, 12-15]. When present in the lower limbs, the jerky movements may lead to gait disturbance[16-18] and even ‘‘drop attacks’’[19]. Cortical tremor can be stimulus-sensitive especially to touch[6, 19], but also to photic stimulation[8, 16, 19]. Multiple factors have been reported to exacerbate it, such as stress, emotion and sleep deprivation; a response to alcohol was described in two pedigrees[18, 19].

The onset is typically in the second or third decade but ranges from the age of 3 to 70[5]. Cortical tremor severity varies considerably among and within pedigrees, from being not troublesome to causing severe impairment of hand function and gait. It generally remains stable over the years but can be slowly progressive. Long-term follow-up studies have found worsening of the symptoms related to disease duration[18, 20]. Genotypic-phenotypic correlation is detailed in the genetic paragraph.

Differential diagnosis includes other causes of kinetic tremor or myoclonus and epilepsy, such as essential tremor (ET) and progressive myoclonus epilepsies (PME). Compared to ET, cortical tremor can show typical cortical myoclonic features such as irregularity of the jerks and stimulus sensitivity; however, when manifesting as a rhythmic, fine and fast tremor-like movement, the diagnosis is based on other clinical features (i.e. seizures), absent response to beta-blockers and electrophysiological findings. FCMTE can be differentiated from PME due to the more benign progression of the disease, the absence of substantial cognitive

impairment and of severe ataxia[21]. Nevertheless, cortical tremor secondary to the most common causes of PME has been described [22], and it is recommended to rule them out [6]. For differential diagnosis, spinocerebellar ataxias, juvenile myoclonus epilepsy or drug-induced tremor/myoclonus (for instance due to valproate), should also be considered. Cortical tremor can be secondary to other disorders, such as Angelman syndrome[23], ischaemic brain lesions involving sensorimotor cortex[24, 25], it may occur after removal of frontal lobe meningioma[26] and in patients with no other neurological abnormality[22]; however, in some of these cases, the descriptions resembled EPC more than cortical tremor.

The treatment of cortical tremor consists of antiepileptic drugs and benzodiazepines, the most effective being valproate and clonazepam, in combination or not[5]. Proposed diagnostic criteria are summarised in Table 1.

Epilepsy

Epilepsy is commonly associated with cortical tremor, although it is not always present and is not a necessary feature for the diagnosis of FCTME. It has been estimated that 50% of patients affected by FCMTE have epilepsy[17], but it varies among the families described. The age of the first seizure is variable, but generally occurs in the third or fourth decade, usually following the onset of cortical tremor. The most common type of seizures are generalized tonic-clonic seizures (GTCS), but focal seizures with impaired awareness[7, 27-29] and myoclonic seizures have been also described[9, 16]. Mesial temporal focal seizures manifesting with deja vu and fear were observed only rarely[19]. GTCS are often not preceded by any warning signs, but in some cases they can be heralded by progressively increasing myoclonic jerks[3, 19, 29]. Seizures can be provoked by sleep deprivation, stress, excitement and often by photic stimulation[8, 15, 19, 27, 30-32]. The frequency of seizures is usually low, but more severe cases (more than 10 seizures per year) and drug-resistant epilepsy have been reported[7, 33].

Additional clinical features

Cortical tremor and epilepsy can be present as isolated features of FCMTE or combined with other neurological symptoms and signs. Cognitive impairment is often described in FCMTE families; it can manifest as mild-to-moderate mental retardation[7, 8], executive dysfunction or memory impairment for recent events[32]. Logopenic syndrome, reduced verbal fluency and visuospatial impairment have been also reported[27, 34, 35]. While ataxia does not appear to be a clear feature of FCMTE[15, 16, 19, 30, 32, 36], other cerebellar signs, such as gait instability, downbeat nystagmus and dysarthria have been described[6, 16, 17, 27, 33]. Other clinical findings

include migraine[16, 19, 27, 37], night blindness[6, 38], motionless state[39] and parkinsonism[40, 41]. Psychiatric comorbidity, such as mood and anxiety disorders, have been noted in some families[16, 20, 29], and schizophrenia in a Chinese pedigree[42].

Electrophysiology

Cortical tremor

The distinction between tremor and myoclonus is based on the rhythm of the jerks. In tremor, motor unit entrainment is synchronised at a specific frequency (i.e. it is rhythmic) and strong enough to produce a clear peak in the electromyographic (EMG) power spectrum. EMG recording of myoclonus, in contrast, shows arrhythmic muscle activity of variable duration, depending on the source of myoclonus; therefore, a clear peak at the power spectrum is usually not seen. In cortical tremor, both rhythmic and arrhythmic jerks can be recorded; the former are usually at a frequency of 8-12 Hz while a larger range of frequencies (10-20 Hz) has been reported for the latter[3, 5, 7]. EMG discharges mostly involve distal muscles of the upper limbs, are synchronous between agonist and antagonist muscles and are of about 50 ms duration[1, 3, 6-8, 19, 41].

Unlike other forms of tremor, cortical tremor has the same distinguishing electrophysiological features as cortical myoclonus[43]. The definitive criteria consist of electroencephalographic discharges time-locked to individual myoclonic jerks (detected with jerk-locked back averaging - JLBA), giant cortical somatosensory evoked potentials (SEP) and enhanced long-latency reflexes (C-reflex) (Figure 1 and 2). These findings suggest that the movements are generated by an abnormal sensorimotor discharge and that cortical tremor is a rhythmic form of cortical myoclonus. However, these electrophysiological abnormalities have not been detected in all FCTME affected individuals[3, 6, 8, 9, 19, 22]. The lack of these abnormalities has been attributed to the use of the antiepileptic drugs[3, 22], but a limitation of the techniques used cannot be excluded[43]. For instance, JLBA is not reliable in high frequency cortical myoclonus. In this event, electroencephalography (EEG)-EMG coherence analysis can be helpful in confirming the cortical origin of the jerks[44]. One study showed strong EEG-EMG coherence in the 8- to 30-Hz range in cortical tremor, but not in ET and healthy controls[45].

Epilepsy

EEG background activity is usually normal or slightly slow, in the lower alpha band, in FCTME patients. EEG abnormalities include paroxysm of generalized polyspikes, spikes and waves, and/or focal epileptiform discharges (usually temporal or fronto-temporal), but it can also be normal[3, 6]. A photoparoxysmal response is frequently found and a photomyogenic response (i.e. muscular, mainly anterior, response synchronous with photic stimulation) may also be present[3, 6-8, 16, 19, 31, 32].

Visual evoked potentials

In one study, visual evoked potentials (VEP) were reported to have a higher amplitude than in controls[7]. In the same patients there was no history of visually-induced seizures and intermittent photic stimulation at low rate (1-10Hz) elicited a photoparoxysmal response in which each flash triggered spike confined to the occipital region, but no clinical response. There are no studies investigating VEP in FCMTE patients with myoclonus sensitive to photic stimulation; however according to Artieda and Obeso, VEP were normal in a groups patients with photic cortical reflex myoclonus[46].

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) has been used in some studies to investigate cortical excitability in patients affected by FCMTE[7, 8, 47]. Resting motor threshold has been found reduced in two studies[7, 8] and normal in one[47], while active motor threshold, recruitment curve and intracortical facilitation were normal[8, 47]. Reduced inhibition within the primary motor cortex (M1), reflected by reduced cortical silent period[7, 8] and short-interval intracortical inhibition[7-9, 47], has been reported, whereas sensorimotor integration, measured by short and long-latency afferent inhibition, was found to be normal in patients who did not have giant SEPs[8]. Overall, this data suggests that there is reduced intracortical inhibition mediated by GABAergic interneurons, but normal sensorimotor integration, at least in patients with cortical tremor who lack hyperxcitability of the primary somatosensory cortex (S1). Reduced intracortical inhibition is in line with findings in myoclonic epilepsy and cortical myoclonus[48] and supports the hypothesis that cortical myoclonus is due to hyperexcitability of the sensorimotor cortex.

The central conduction time is normal in FCMTE[7], and rules out damage to central motor pathways.

Genetics

FCMTE is characterized by a wide genetic heterogeneity, having hitherto been linked to four different loci and several possibly causative genes worldwide.

In 1999, the first FCMTE locus (FCMTE1) was mapped to chromosome 8q23.3-q24.11 in a three-generation Japanese pedigree[49]. All 17 affected individuals showed tremulous finger movements and/or myoclonus of the extremities starting at a mean age of 30 (range 18-45 years) and most of them experienced infrequent GTCS throughout their life[49]. Consistent SEP, VEP, and generalized EEG abnormalities were recorded in all investigated patients, and both myoclonus and epilepsy responded to valproate and clonazepam[49]. Linkage to the same genetic locus was confirmed in four small Japanese and a large Chinese families whose affected members presented with a similar phenotype[50, 51]. To date, at least 60 Japanese and 23 Chinese kindreds with FMCTE related to 8q24 chromosome region (OMIM# 601068) have been reported[52-55]. A rare missense mutation c.206A>T (p.Tyr69Phe) in the SLC30A8 gene (8q24.11) was identified in the original Chinese FCMTE1 pedigree through whole-exome sequencing (WES), but the causative role of this gene in FMCTE1 was not supported by in silico study[51]. WES also detected that a c.20G>C (p.Trp7Ser) variant in the *DCAF13* gene (8q23.3) and a c.983T>C (p.Ile328Thr) variant in the *NOV* gene (8q24.12) cosegregated with the FMCTE in another large Chinese kindred[55]. Interestingly, clinical anticipation of cortical tremor and/or GTCS, which is more frequently associated with maternal than paternal transmission, was observed in some Japanese FMCTE families, thus suggesting a repeat expansion disorder[56-58]. In keeping with this observation, the expansion of TTTCA and TTTTA pentanucleotide repeats in intron 4 of the SAMD12 gene (in 8q24) was recognized as the pathogenic variant of FCMTE1 in 85 patients from 49 Japanese kindreds and 105 patients from 18 Chinese pedigrees in 2018[52, 53]. This finding has recently been confirmed in other Chinese families[54, 59]. The length of expanded repeats showed intergenerational instability and negative correlation with age at onset of both cortical tremor and epilepsy[52, 59]. A novel expanded intronic TTTGA insertion, at the same site as the previously reported TTTCA insertion in SAMD12, was recently identified in a FCTME Chinese pedigree with no TTTCA insertion {Cen, 2019 #665}. SAMD12 encodes sterile alpha-motif domain-containing 12, a predicted intracellular protein of unknown function highly expressed in the brain (the highest expressed region in the brain are frontal cortex followed by cerebellum)[60]. Mild albeit diffuse loss of Purkinje cells in the cerebellar cortex, as well as amorphous deposits around their cytoplasm, were observed in one patient with homozygous mutations in SAMD12[52]. Slightly reduced levels of SAMD12 protein product and the presence of RNA foci with UUUCA

repeats in neuronal nuclei were detected in autopsied brains with expanded repeats in SAMD12. The same expanded-repeat motifs have also been recognized in other FCMTE-related genes, thus indicating that neurotoxicity due to RNA molecules containing expansions of UUUCA and UUUUA rather than altered physiological function of specific genes might play a crucial role in the pathophysiology of FCMTE[52].

In 2001, the second locus linked to FCMTE (FCMTE2) was mapped to chromosome 2p11.1-q12.2 in a five-generation Italian pedigree including 8 affected individuals with age of onset between 12 and 59 years[7]. Patients with FCMTE2 (OMIM# 607876) showed a slightly different phenotype, encompassing cortical tremor/myoclonus, GTCS, frontotemporal EEG abnormalities and, in some cases, intractable complex focal seizure with temporal or frontotemporal focus and mild to moderate intellectual disability[7]. Linkage to the same chromosome region was then recognized in other Italian families[3, 8, 10, 16, 61-63], a large Spanish kindred[64], and a six-generation pedigree of Austrian descent from New Zealand/Australia[19], all showing either a FCMTE1-like phenotype or the more severe clinical picture compared to the first Italian FCMTE2 pedigree described by Guerrini et al.[7]. A founder effect was proposed in Italian FCMTE2 families from the same geographical area[16, 62] and then confirmed in a larger cohort of pedigrees of European ancestry[63]. Among several candidate genes screened in FCMTE2 locus, De Fusco and colleagues identified one likely pathogenic in-frame insertion/deletion variant in the ADRA2B gene (2q11.2) in two Italian kindreds with a common ancestor, but this finding was not confirmed in other FCMTE2 families[28].

In 2010, FCMTE was linked to chromosome 5p15.31-p15 (FCMTE3) in a large French pedigree with 16 members affected by the age of 27 on average (range 10-41 years)[65]. In addition to classical FMCTE features, FCMTE3 phenotype (OMIM# 613608) encompassed generalized and focal seizures, with simple visual hallucinations, transient loss of consciousness without automatisms, and worsening of the symptoms due to hypoglycemia, fatigue, and vibration[65]. Linkage to the same genetic locus was subsequently found in two Chinese kindreds and a four-generation Dutch family previously reported not to show linkage to FCMTE1 and FCMTE2 loci[66-68]. By contrast, in the two South African families reported as having familial adult myoclonic epilepsy type 3 in 2007, a linkage to the FCMTE1 and FCMTE2 loci was excluded, but no investigations on chromosome 5p were performed[33]. WES identified a missense mutation c.3130G>A (p.Glu1044Lys) in the catenin delta 2 (CTNND2) gene in the Dutch FCMTE3 pedigree, with functional tests on CTNND2 knockdown mouse supporting the causative role of this gene in FCMTE3.

In 2013, the fourth locus related to FCMTE (FCMTE4) was mapped to chromosome 3q26.32-3q28 in a Thai family by genome-wide linkage study[69]. All 13 family members affected showed a benign FCMTE phenotype (OMIM# 615127) characterized by cortical myoclonus and infrequent GTCS, with age of onset ranging from 10 and 33 years and good response to valproate, clonazepam, or levetiracetam in most cases. Although no causative gene has been identified so far, the HTR3D and KCNMB3 genes encoding ion channel proteins have been proposed as candidate genes[69].

The FCMTE5 locus has been assigned to an autosomal recessive condition (OMIM# 615400) described in a consanguineous Egyptian kindred with 5 affected members showing cortical tremor, complex focal seizures and/or GTCS from adolescence[70]. In this pedigree, the single base pair deletion c.503delG (p.Trp168CysfsX163) was detected in the CNTN2 gene (1q32.1), which is crucial for the stability of potassium channels[70]. However, the classification of this disorder as a form of FCMTE is controversial[71].

By using WES, a number of possibly FCMTE-related genes have hitherto been reported but none had sufficient evidence of a causative role in FCMTE. A rare missense variant c.5720G>A (p.Arg1907His) in the UBR5 gene (8q22.3), which maps close to the FCMTE1 locus, was found in a Japanese FCMTE pedigree in 2012[72]. In 2013, a rare missense mutation c.77G>A (p.Trp26Stop) in the ACMSD gene (2q21.3), which lies near the FCMTE2 locus, was detected in a large Spanish family[40]. In a Chinese kindred, a novel c.475C>T (p.Ala159Thr) missense mutation in the PLA2G6 gene (22q13.1) was recently found[30]. Interestingly, some of the negative Japanese families tested for expansions in SAMD12 by Ishiura and coworkers showed identical expansions of TTTCA and TTTTA repeats in TNRC6A (FCMTE6, OMIM# 618074) and RAPGEF2 genes (FCMTE7, OMIM# 618075), and this finding was replicated for RAPGEF2 in one Chinese pedigree[52 59].

Table 2 summarizes genetic and molecular characterization of FCMTEs and their geographical distribution.

SPECTRUM OF CORTICAL MYOCLONUS

The term myoclonus describes brief and jerky involuntary movements, arising in the central nervous system[2] that are produced either by abrupt muscle contraction (positive) or sudden cessation of ongoing muscular activity (negative)[74]. Cortical myoclonus refers to jerks caused

by abnormal electrical discharges arising in the cerebral cortex. It manifests with a wide range of clinical features, which, as proposed by Obeso and coworkers[2], form a continuum from (1) cortical reflex myoclonus, in which jerks are not present at rest, but which can be provoked by sensory input; (2) spontaneous cortical myoclonus and cortical tremor, where jerks can arise spontaneously but which are often confined to a small group of muscles; (3) EPC and myoclonic epilepsy in which there is more widespread abnormal cortical activity.

All these clinical syndromes share a common electrophysiological entity, i.e. a sudden and brief activation of the corticospinal tract neurones (CSTN). Jerks that are caused by a loss of muscle activity may result from a sudden interruption of activity in CSTNs, although spinal inhibitory mechanisms may also contribute[75]. Although CSTN are a common element in all forms of cortical myoclonus, it is not known whether they are ever the source of the abnormal activity, perhaps because of some disorder of membrane ion channels, or whether they are passive elements that respond to abnormal input generated elsewhere. It is also important to recognise that, since the bursts of activity are so brief, there must also be a powerful inhibitory mechanism that terminates the excitation.

We propose that the spectrum of cortical myoclonus, from localised reflex jerks to widespread activation of the whole sensorimotor cortex and beyond, is due to the evolution from a spatially limited focus of heightened excitability to recruitment of more complex mechanisms that are capable of sustaining repetitive activity and which can eventually overcome the inhibitory mechanisms that restrict excitatory bursts and engage wide areas of cortex.

In the case of cortical reflex myoclonus, a normal volley of afferent input is transformed at some point in a sensorimotor loop into an abnormal burst of excitation. Evidence from somatosensory- and visually-triggered jerks suggests that this could occur either within the primary somatosensory or visual cortex (V1) or in the connections between them and motor cortex. For example, in photic reflex myoclonus, usually present in photosensitive epilepsies, there are abnormalities in contrast gain[76] and clustering of gamma-band oscillations[77]. Similarly, in the somatosensory cortex, the presence of a giant SEP usually confirms the hyperxcitability of S1 [43, 78]. Changes in the excitability of sensory-motor connections has also been described [79]. Visually-evoked muscle jerks are associated with transients in contralateral central regions time-locked with flash stimuli[80], in the absence of any evidence of hyperexcitability in V1 [81]. Although the mechanisms behind this abnormal connectivity are

unknown, abnormal LTP-like plasticity in motor cortical areas induced by visual stimulation is possible [82, 83]. Similar evidence in somatosensory reflex myoclonus is lacking; however, the presence of enhanced LLR, commonly associated to giant SEP, can be considered as a marker of abnormal interaction between S1 and M1 [43, 78].

The pathophysiology of spontaneous myoclonus, cortical tremor and EPC is clearly different since jerks in these conditions arise spontaneously, implying the existence of intrinsic mechanisms that initiate bursts of either excitatory activity (producing positive jerks) or inhibitory activity (producing negative jerks). One possibility is that the resting membrane potential of some population(s) of excitatory or inhibitory neurones lies closer to threshold than normal, and that the latter is reached intermittently due to random fluctuations in input. Alternatively, it might be due to abnormal electrical properties of neural membranes due to changes in ion channel properties or in post-synaptic receptors as in several epilepsy phenotypes [84, 85]. It is also tempting to consider that functional alterations of glia might be an important factor. For instance, it has been demonstrated that increasing extracellular potassium is sufficient to induce robust epileptiform activity in hippocampal slices from animals or humans [86, 87]. Therefore, it is possible that a failure to adequately buffer electrolytes and excitatory neurotransmitters by glia might lead to neuronal hyperexcitability and generation of spontaneous jerks [88].

However, these mechanisms would be expected to produce jerks that occur relatively randomly. To account for the more regular jerking in cortical tremor and often in EPC, requires an additional mechanism. There might be two possibilities here. The first is that there could be oscillations in local circuits linking CSTN and interneurones. In this regard, it is worth noticing that feedback inhibition might be more suited to sculpt network activity and generate clusters of activation that appear as patterns in local field potential [89]. Another possibility is that rhythmicity does not come from local interactions but is, in fact, the result of oscillations in more widespread connections. These might be unstable cortical loops, particularly in the case of EPC, where there can be extensive cortical damage [90], or subcortical structures such as occurs to parkinsonian tremor and essential tremor [91]. It is known that at least two regions within the central motor pathways, i.e. the inferior olive and the relay nuclei of the thalamus, demonstrate oscillatory behaviour under certain conditions, due to a combination of intrinsic properties of ion channels in individual neurones and because of the way the latter neurones are interconnected within central nervous system circuits [92]. Therefore, it is possible that rhythmicity of jerks in cortical tremor and EPC is

caused by an interaction between local factors within M1 and synchronization by external sources.

As noted above, in most cases the cortical discharges remain localised. However there are examples in which both reflex and spontaneous jerks appear to spread both within the motor cortex of one hemisphere as well as between the two hemispheres, generating multifocal or generalised jerking. Indeed, in myoclonic epilepsy abnormal discharges sometimes give raise to generalised seizures. It is reasonable to assume that, during the recruitment of new territories to a starting cortical discharge, the driving force is provided by glutamatergic output [93] which is usually terminated both temporally and spatially by a powerful inhibition [94]. Our interpretation is that in the case of generalised jerks and myoclonic epilepsies, the spatial progression of ictal activity coincides with a collapse of inhibition [95-97]. The mechanisms of this inhibitory collapse might include perturbations in chloride homeostasis [98, 99] and interneuronal depolarization block due to excessively strong excitatory input [100]. However, the conditions that precipitate this effect, and its precise role in spreading ictal activity, remain unclear.

Cerebellum

A special mention should be made about the cerebellum, which can be involved in all forms of cortical myoclonus. For instance, in several conditions associated with cortical myoclonus, cerebellar ataxia is a prominent feature [101] and pathological findings in cases of cortical myoclonus often involve the cerebellum [102, 103]. We speculate that the cerebellum could contribute to cortical myoclonus in a variety of ways.

Recent experiments have shown that the gain of long latency stretch reflexes (LLSR) is adjusted to changes in task demands when movements adapt to different external conditions{Omrani, 2014 #658}{Pruszynski, 2012 #659}. Given the prominent role of the cerebellum in motor adaptation, it seems likely that cerebellar inputs play an important part in this gain control. If so, this could explain why abnormalities of cerebellar function are so often associated with heightened LLSRs and reflex myoclonus{Diener, 1984 #639}{Shibasaki, 2011 #536;Rodriguez, 1994 #660}. We propose that abnormal activity in the cerebello-thalamo-cortical projection could lead to a change in gain of sensorimotor connections and reflex myoclonus [101]. The mechanism could for example, involve the known cerebello-cortical projections to local inhibitory systems that has been indirectly demonstrated in humans (cerebello-motor cortex inhibition, CBI) [104]. Such a possibility

would be consistent with the finding that patients with atrophy of the cerebellar cortex have enhanced LLSR [105] that are reduced by applying anodal transcranial direct current stimulation in order to increase CBI [106]. Moreover, in a case recently published from our group, electrophysiological tests supported the hypothesis that a decreased cerebellar drive from one hypoplastic cerebellar hemisphere caused abnormalities in the mechanisms which regulate transmission within M1 and that these, combined with abnormal somatosensory transmission, resulted in cortical myoclonus{Rocchi, 2019 #661}.

The cerebellum is also known to be involved in the production of many types of tremor, together with the motor cortex. For instance, imaging and MEG studies have shown that a cerebello-motor cortical loop is involved in the origin of ET{Muthuraman, 2018 #662}{Schnitzler, 2009 #664}; physiological tremor can be modulated by phase-locked alternating current over the cerebellum{Mehta, 2014 #15}; and parkinsonian tremor may also involve a cerebello-cortical loop controlled by the basal ganglia{Dirkx, 2016 #663}. The existence of such loops could well be a factor in sustaining repetitive activity in cortical tremor and EPC. We propose that activity in these pre-existing loops reactivates focal discharges in the motor cortex resulting in regular muscle jerking [91, 92]. Indeed there is evidence for cerebellar abnormalities in several families with FCTME. In FCMTE2 and in a Chinese pedigree, in which linkage to gene loci 8q24 or 2p11.1-q12.2 was excluded, magnetic resonance spectroscopy indicated cerebellar dysfunction [107, 108]. More relevant information has come from pathological studies: in the Dutch FCMTE3 pedigree, with a CTNND2 gene mutation, in three deceased cases there was severe loss of Purkinje cells with dendritic sprouts, neuronal loss in the dentate nucleus and microglia activation, with limited changes in the sensorimotor cortex [47, 109, 110]. In some members of this family, a mutation has been found in the CTNND2 gene that led to abnormal sprouting in mice neurones, similar to the cerebellar pathology described in affected patients [68]. Analogous pathological abnormalities have been found in one of the two cases of the South African family described[33].

It is less clear how cerebellum is involved in EPC. EPC differs from cortical tremor in being localised and having a lower frequency around 1 Hz. Many authors consider it to be a focal motor status epilepticus[90]. Nevertheless, there are clear examples of cerebellar involvement such as a case of EPC following cerebellar haemorrhage and no evidence of cortical abnormalities [111]. The epileptogenic potential of the cerebellum remains elusive, although there is evidence supporting that seizure may also arise directly from it (“cerebellar

seizures")[112]. Interestingly, the second most common seizure semiology in lesional cerebellar epilepsy is myoclonic seizures[112].

CONCLUSION

FCTME is a rare but well-defined syndrome associated with cortical tremor, epilepsy and possible additional clinical features, as detailed above. Diagnosis is based on suggestive clinical presentation, a positive family history and supportive electrophysiology studies. The pattern of inheritance is autosomal dominant and, although the causative gene has yet been identified, it has been associated with four different loci and a number of possibly related genes have been proposed.

The core feature of FCTME is cortical tremor, which is distinguished from other forms of cortical myoclonus by its rhythmicity that in turn can make it difficult to distinguish from other common forms of action tremor. We suggest that this similarity is not a random coincidence. Instead we propose that a pre-existing cerebello-thalamo-cortical loop known to contribute to many other forms of tremor provides feedback following a cortical discharge and reactivates the focus resulting in sustained tremor.

In one study, cortical tremor EMG bursts showed a frequency of about 8-9 Hz and a large coherence between muscles in the two arms [7], suggesting the presence of a pathway that synchronizes descending activity from motor cortices of both hemispheres. We have proposed above that in some cases the cerebellum could be an integral node, as the olive-cerebellar network is presumed to drive frequency oscillations of the neocortex [113, 114]; alternatively, there is a possibility that a common drive to descending activity could be located in the brainstem, as in orthostatic tremor [115].

One clear notion emerges from our discussion, i.e. the role of the cerebellum in the pathophysiology of all the variants of the cortical myoclonus spectrum. Indirect evidence supports the hypothesis that the hyperexcitability of the sensorimotor cortex seen in cortical myoclonus might be due to loss of cerebellar inhibitory control via cerebello-thalamo-cortical connections. Moreover, it might be possible that the reduced functional connectivity between the cerebellum and sensorimotor areas increases the gain of sensorimotor cortical reflexes, resulting in reflex cortical myoclonus. Additionally, under in certain circumstances, the cerebellum can synchronise cortical activity, increasing cortical myoclonus rhythmicity and

inducing cortical tremor or EPC. The cerebellum might also be implicated in the origin of epileptic seizures, especially myoclonic ones. Figure 3 gives a simple summary of the main conclusions.

In conclusion, the cerebellum could represent the continuum in the cortical myoclonus spectrum, but what determines the nature of the EMG discharges, and consequently of the clinical picture, still needs to be determined.

Table 1. Proposed diagnostic criteria by van den Ende et al. 2018

1) Distal action and postural tremor/fine myoclonus, accompanied by generalized tonic-clonic seizures in at least one family member. Also, mild progression of symptoms with aging and proximal muscle myoclonus can be present.
2) Electrophysiological measures support the diagnosis of cortical myoclonus (see below)
3) Autosomal dominant inheritance of epilepsy and ‘‘tremor’’/myoclonus within the family.
4) No other cause for tremor, epilepsy. No other symptoms must be present like ataxia, Parkinsonism, dementia, dystonia, spasticity.

Table 2. Genetic and molecular characterization of FCMTE and populations studied

Form	OMIM®#	Inheritance	Chromosome	Gene	Gene product	Population reported
FCMTE1	601068	AD	8q24.11-q24.12	*SAMD12*	Sterile alpha-motif domain-containing 12	Dozens of Japanese and Chinese pedigrees
FCMTE2	607876	AD	2q11.2-q12.2	[*ADRA2B*] *	Alpha 2-adrenergic receptor subtype b	Twelve Italian, one Spanish, two French, and one New Zealander/Australian (Austrian ancestry) pedigrees
FCMTE3	613608	AD	5p15.31-p15.1	*CTNND2*	Catenin delta 2	One French, one Dutch, and two Chinese pedigrees
FCMTE4	615127	AD	3q26.32-q28	?	?	One Thai pedigree
FCMTE5	615400	AR	1q32.1	*CNTN2*	Contactin 2	One Egyptian pedigree (consanguineity)
FCMTE6	618074	AD	16p12.1	*TNRC6A*	Trinucleotide repeat containing 6A	One Japanese pedigree
FCMTE7	618075	AD	4q32.1	*RAPGEF2*	Rap guanine nucleotide exchange factor 2	One Japanese and one Chinese pedigrees

AD = autosomal dominant; AR = autosomal recessive; FCMTE = familial cortical myoclonus/tremor and epilepsy; OMIM®# = Online Mendelian Inheritance in Man

* One likely pathogenic mutation in the *ADRA2B* gene was found to co-segregate in only two Italian pedigrees with a common ancestor. Further evidence is needed to confirm whether *ADRA2B* is the causative gene in FCMTE2 locus, and the search for a second causative gene in this locus is still formally possible.

Figure 1. SEP showing a larger N20-P25 and P25-N33 components (single patient recording)

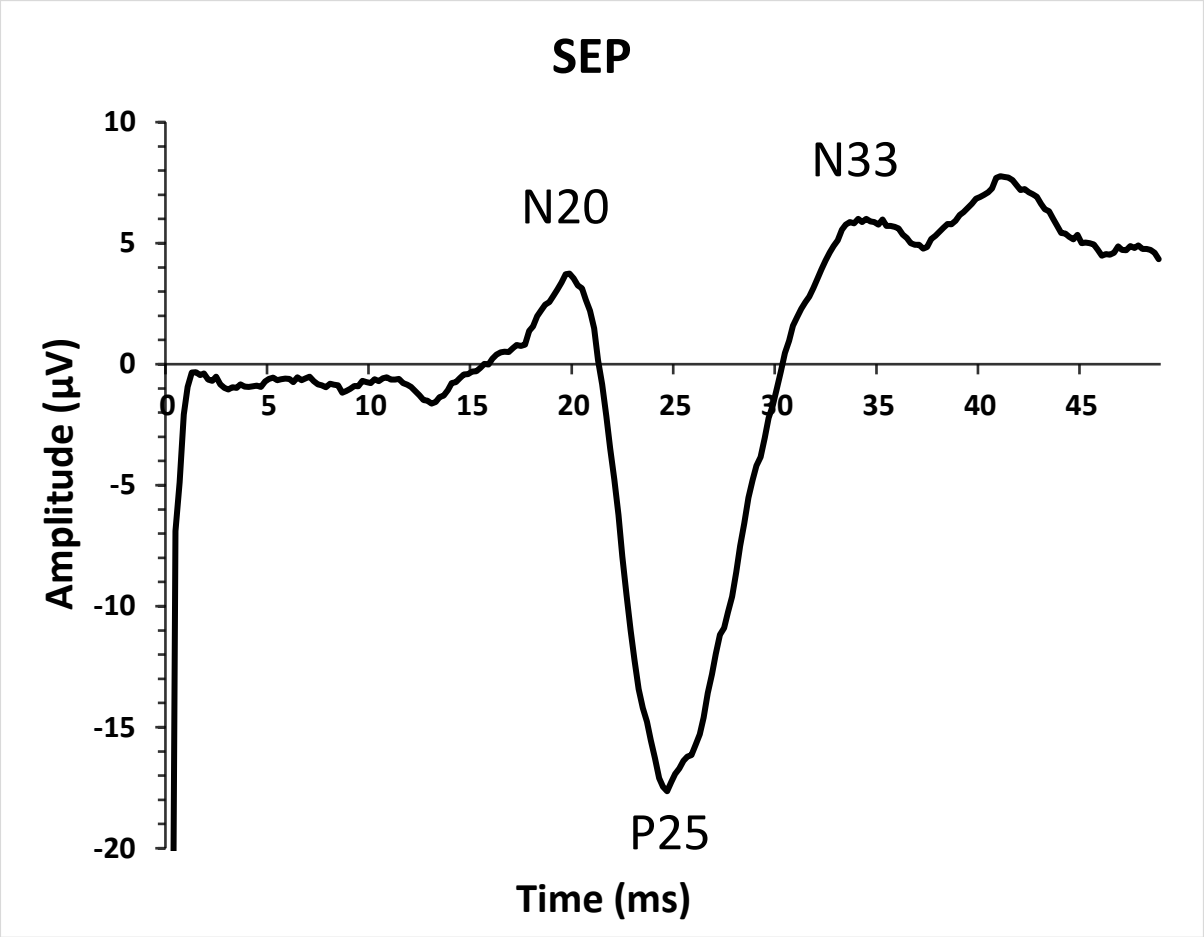
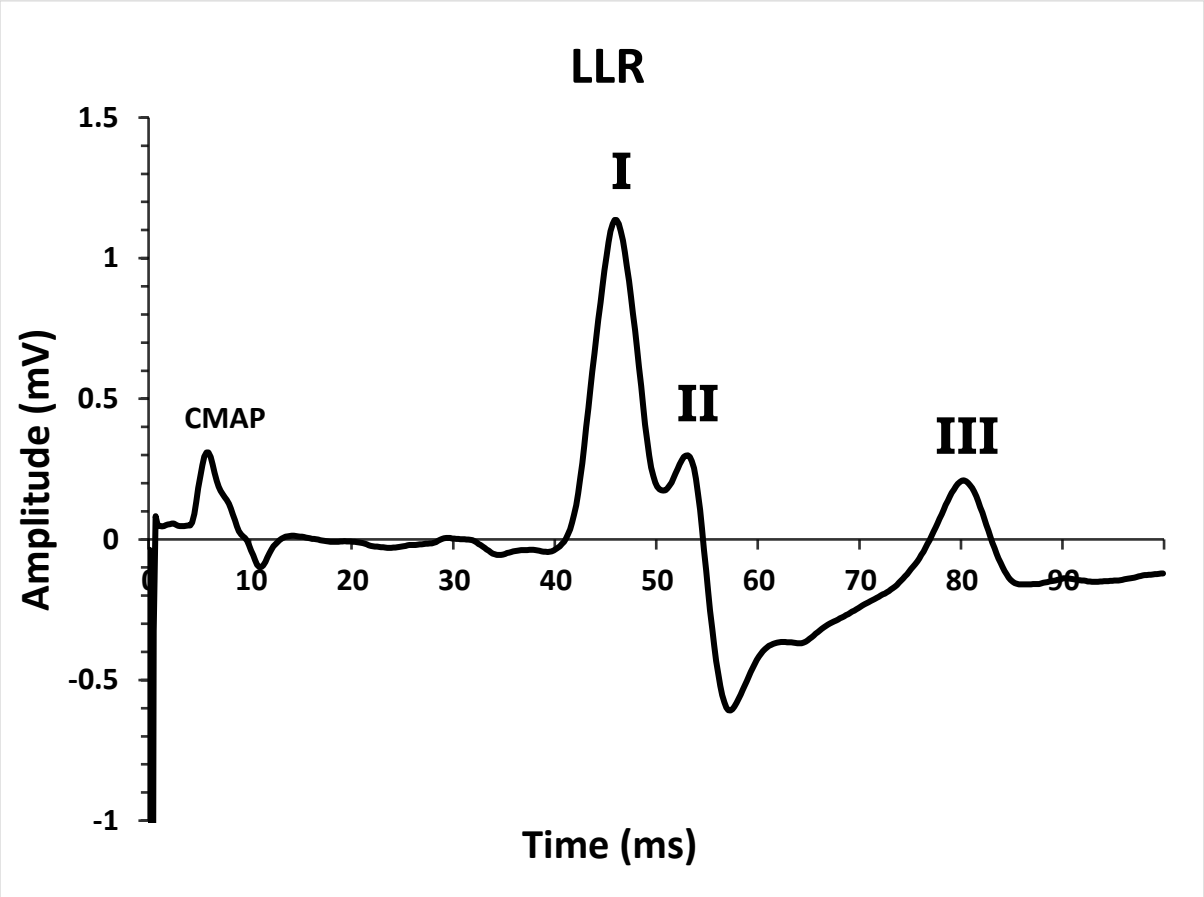


Figure 2. LLR traces showing a large EMG activity compatible with a C-reflex with onset around 40 ms, and LLR II and LLR III with onset around 50 ms and 75 ms respectively



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