Familial Cortical Myoclonic Tremor and Epilepsy, an Enigmatic Disorder: From Phenotypes to Pathophysiology and Genetics. A Systematic Review

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Abstract

Background: Autosomal dominant familial cortical myoclonic tremor and epilepsy (FCMTE) is characterized by distal tremulous myoclonus, generalized seizures, and signs of cortical reflex myoclonus. FCMTE has been described in over 100 pedigrees worldwide, under several different names and acronyms. Pathological changes have been located in the cerebellum. This systematic review discusses the clinical spectrum, treatment, pathophysiology, and genetic findings.

Methods: We carried out a PubMed search, using a combination of the following search terms: cortical tremor, myoclonus, epilepsy, benign course, adult onset, familial, and autosomal dominant; this resulted in a total of 77 studies (761 patients; 126 pedigrees) fulfilling the inclusion and exclusion criteria.

Results: Phenotypic differences across pedigrees exist, possibly related to underlying genetic differences. A “benign” phenotype has been described in several Japanese families and pedigrees linked to 8q (FCMTE1). French patients (5p linkage; FCMTE3) exhibit more severe progression, and in Japanese/Chinese pedigrees (with unknown linkage) anticipation has been suggested. Preferred treatment is with valproate (mind teratogenicity), levetiracetam, and/or clonazepam. Several genes have been identified, which differ in potential pathogenicity.

Discussion: Based on the core features (above), the syndrome can be considered a distinct clinical entity. Clinical features may also include proximal myoclonus and mild progression with aging. Valproate or levetiracetam, with or without clonazepam, reduces symptoms. FCMTE is a heterogeneous disorder, and likely to include a variety of different conditions with mutations of different genes. Distinct phenotypic traits might reflect different genetic mutations. Genes involved in Purkinje cell outgrowth or those encoding for ion channels or neurotransmitters seem good candidate genes.

Keywords: Familial, cortical, myoclonus, tremor, epilepsy, genetics

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Introduction

Autosomal dominant familial cortical myoclonic tremor and epilepsy (FCMTE) has over the years accumulated several names and acronyms including autosomal dominant cortical myoclonus and epilepsy (ADCME), benign adult familial myoclonic epilepsy (BAFME), cortical tremor (Crt Tr), familial adult myoclonic epilepsy (FAME), familial cortical myoclonic tremor (FCMT), familial cortical tremor with epilepsy (FCTE), familial essential myoclonus and epilepsy (FEME), familial benign myoclonic epilepsy of adult onset (FMEA), and heredofamilial tremor and epilepsy (HTE) (Table 1).1 FCMTE will in the manuscript serve as the acronym for all abbreviations, as suggested in 2005,2 and as currently classified by the HUGO Gene Nomenclature Committee (HGNC).3 The syndrome was first described in the 1990s in Japan, in families with hereditary tremor (distal tremulous myoclonus) and epilepsy.4–7 Subsequently, over a hundred pedigrees have been identified in different countries, which have proven to be genetically heterogenic in linkage studies.

Symptoms of FCMTE are tremor-like cortical myoclonus, which can mimic essential tremor (ET), and epileptic seizures. Distal tremulous...
movement are usually the first symptom, usually with an onset in the second or third decade. Seizures, most often unprovoked generalized tonic–clonic seizures without aura, start later in life, frequently in the third or fourth decade. Diagnosis is based on clinical characteristics and family history, and is supported by electrophysiological investigations, after exclusion of other tremulous disorders and epileptic syndromes. Treatment is symptomatic, usually with anti-epileptic drugs such as valproate and clonazepam.

Additional symptoms have also been described, possibly extending the spectrum of the disease. These include mild cognitive decline, but also psychiatric symptoms, nystagmus, and migraine. Clinical anticipation has been described in Asian pedigrees. It is unknown which of these symptoms are part of FCMTE or are co-incident, and which symptoms might differentiate between underlying genetic mutations.

FCMTE maps to different loci including 8q23.3-q24.13 (Online Mendelian Inheritance in Man [OMIM], 22 HGNC, 23 FCMTE1) in Japanese families and a Chinese pedigree, 27 2p11.1-q12.2 (OMIM, 28 HGNC, 23 FCMTE2) in multiple Italian pedigrees, 8,9,17,29–33 a Spanish family, and a family from New Zealand/Australia with ancestors from Austria, 16 5p15.31-p15 (OMIM, 35 HGNC, 23 FCMTE3) in a French family, and two Chinese pedigrees, 39 40,41 and 3q26.32-3q28 (OMIM, 42 FCMTE4) in a Thai family. Also, an autosomal recessive form of FCMTE (OMIM, 44 FCMTE5) has been identified in an Egyptian family where a mutation has been localized in the contactin 2 (CNTN2) gene, which is associated with potassium channel stability. 45 In autosomal dominant FCMTE, several possible gene mutations have been proposed as causative on the FCMTE loci. 27,46–48 Recently, a mutation was found in a Dutch FCMTE3 pedigree in the catenin delta 2 (CTNND2) gene, supported by functional tests. 39

Neurophysiological, imaging, genetic, and pathology findings have shed some light on the pathophysiology underlying FCMTE. A cortical origin of the myoclonus in FCMTE is proven by electrophysiological investigation consistent with reduced cortical inhibition. 14 Pathology findings in a Dutch FCMTE pedigree indicate Purkinje cell changes, resembling the abnormal neuronal morphology in Claud2 mutant mice. 1,39,50 Congruent imaging findings include decreased fiber density, 51 functional connectivity alterations 52 and gray matter loss in the cerebellar motor area. 53 It has been hypothesized that, via the cerebello-thalamo-cortical loop, reduced input from the cerebellum can lead to cortical hyperexcitability. 54 However, the question arises if the cerebellum is the primary generator of cortical hyperexcitability in all FCMTE types. Alternatively, cortical functional changes could underlie the symptoms, with or without coexisting cerebellar pathology.

This review will bring together evidence concerning the clinical spectrum including treatment on the one hand, and, on the other hand, pathophysiological and genetic studies, adding the latest insights. 1 The current review aims to not only summarize studies into FCMTE, but also be of guidance to the clinician encountering a patient with suspected FCMTE. A second aim is to link insights from pathophysiological studies to genetic studies to better understand the underlying disease mechanisms and be a guide for future research and better treatment of these patients.

**Methods**

We conducted a PubMed search on November 15, 2017, for the period January 1, 2011, to November 15, 2017, using a combination of the following search terms: cortical tremor, myoclonus, epilepsy, benign course, adult onset, familial, autosomal dominant, and the different acronyms for FCMTE fully written; see Appendix A for complete search terms. The search delivered a total of 1,180 articles, and one additional from reference lists, from which 33 fulfilled the selection criteria (flow chart, Figure 1). The search conducted for our previous review in 2011 had already revealed a total of 44 publications published before 2011, 1 which are also included in the current review (Tables 2 and 3).

Included were reports published in English describing pedigrees with the following diagnostic criteria as previously reported: 1) distal action and postural tremor/fine myoclonus; 2) generalized tonic–clonic seizures and/or electrophysiological features of cortical reflex myoclonus including giant somatosensory evoked potentials (SEPs) and/or enhanced long loop reflexes (LLRs/C reflex); and 3) a family history of tremor/epilepsy consistent with autosomal dominant inheritance. Excluded were pedigrees and cases with another cause for tremor and epilepsy (including autosomal recessive FCMTE 45), structural lesions on magnetic resonance imaging (MRI), and additional symptoms such as clear parkinsonism, dementia, and/or ataxia pointing to a different syndrome.

| Acronym | Description |
|---------|-------------|
| ADCME  | Autosomal dominant cortical myoclonus and epilepsy |
| BAFME  | Benign adult familial myoclonic epilepsy |
| Ctr. Tr | Cortical tremor |
| FAME   | Familial adult myoclonic epilepsy |
| FCMT   | Familial cortical myoclonic tremor |
| FCMTE  | Familial cortical myoclonic tremor with epilepsy |
| FCTE   | Familial cortical tremor with epilepsy |
| FENE   | Familial essential myoclonus and epilepsy |
| FMEA   | Familial benign myoclonus epilepsy of adult onset |
| HTE    | Heredofamilial tremor and epilepsy |

**Table 1. Familial Cortical Tremor/Myoclonus Syndromes**
Results

In total 77 publications (126 pedigrees; 761 patients) were retrieved from the combined current PubMed search and the 2011 search. For an overview of additional pedigrees since our last review, see Table 2. Since 2011, 70 additional pedigrees in 33 publications, including 48 from India, have been extensively described (providing clinical and electrophysiological data, Table 2). Descriptions of the pedigrees comply with autosomal dominant inheritance. The reports used uniform criteria for diagnosing FCMTE, and one paper explicitly stated they used the diagnostic criteria from our last review. The reports vary in detail in their description of the neurological examination, the presence or absence of cerebellar signs, of cognitive assessment, comorbid psychiatric disorders, effect of anti-epileptic drugs on tremor/epileptic seizures, drug dosage, clinical anticipation, structural imaging, and electrophysiological investigation including jerk-locked back averaging (JLA). Owing to insufficient clinical/electrophysiological data, several new families were not included in Table 2.

Figure 1. Article Selection Flowchart. Literature search for the identification of new pedigrees, genetic/linkage or imaging studies since our last review. Thirty-three articles were eligible for analysis: 17 reported on clinical and electrophysiology findings with or without linkage analysis, nine reported on neuroimaging, and seven reported on new potential pathogenic mutations. Abbreviations: DAT-SPECT, Dopamine Transporter, Single Photon Emission Tomography; DTI, Diffusion Tensor Imaging; FCMTE, Familial Cortical Myoclonus Tremor And Epilepsy; fMRI, Functional Magnetic Resonance Imaging; 1H-MRS, Proton Magnetic Resonance Spectroscopy; VBM, Voxel Based Morphometry.
| Descent Genetics | Origin, # Family | Clinical features | Electrophysiology | Imaging (cases) | Additional Symptoms, Other Findings |
|------------------|------------------|-------------------|-------------------|----------------|-----------------------------------|
|                  |                  | Myoclonus | Seizures | Seizure Type | JLA | Giant SEP | LLR | EEG |                          |
| Asian 8q, SLC30A8 Chinese, 1<sup>13</sup> | 26 (13–36) 34 (29–46) GTC | n.d. | + | + | n.a. | n.a. (1) | No CA; M lower limbs (n:2) |
| 8q, UBR5 Japanese, 1<sup>13</sup> | ? | ? | G | n.d. | n.d. | n.d. | n.a. (1) | M worse aging |
| 22q, PLA2G6 Chinese, 1<sup>13</sup> | 29 (21–38) 39 (36–46) G, GTC, Ph | n.d. | + | + | PSW, PMR | n.a. (1) | M rest; Head; Lower limbs (n:1) |
| 3p Chinese, 2<sup>40,41</sup> | >18 | >30 | G, GTC, Ph | n.d. | + | n.d. | PSW, PRA | n.d. | Non-progressive; Headache |
| 3q Thai, 1<sup>41</sup> | 19 (10–33) 25 (19–33) G, GTC | + | + | + | PSW, SW, PPR, PMR | n.d. | Early-onset seizures |
| 8q, n.d. Chinese, 9<sup>41</sup> | 31 (15–59) 36 (19–64) GTC, Ph | n.d. | + | + | G-E, Sp, Sw | n.d. | S before M (n:5); Headache; M worse aging; Higher severe M, AED use |
| n.d. Chinese, 1<sup>41</sup> | 30 (20–40) 39 (28–46) GTC | n.d. | n.d. | n.d. | E, Sp, Sw | + (7) | Rest fMRI abnormalities |
| n.d. Indian, 4<sup>41</sup> | 25 maj (14–40) GTC, CP, Ph | n.d. | + | + | PSW, F, PPR | n.a. (48) | Anxiety (83%); Unique HLA Nadar community |
| Seizures possibly first symptom 48% |
| n.d. Indian, 1<sup>41</sup> | >15 | ? | GTC | n.d. | n.d. | n.d. | PSW, Sw, PPR | n.a. (3) | Cognitive decline; M axial; M worse aging |
| European 2p Italian, 1<sup>41</sup> | 28 (19–40) 34 (5–63) GTC, M, Ph | + | + | + | G-E, PSW, Sw, PPR | n.a. (7) | Psychiatric comorbidity; M worse aging; Gait disability; Cognitive decline (n:2); Migraine; TMS reduction rest motor threshold |
| 2p, ACMSD Spain, 1<sup>41</sup> | >17 (17–23) 19 (17–22) GTC, PSG | n.d. | + | + | PSW, PPR | + (2) | Parkinsonism (n:1); Cognitive decline (n:1); M, Ph |
| 2p, ADRA2B Italian, 1<sup>41</sup> | (18–50) | ? | GTC, CP, F | + | + | + | G-paxoxysmal activity | n.a. (5) | Cognitive imparity (n:1); Age-related dementia |
| n.d. South Africa, 1<sup>41</sup> | 16 (12–20) 39 (30–45) GTC | n.d. | + | + | G-E, TLE, PSW | n.d. | ADL and MRS affected by M severity; |
## Clinical spectrum.

FCMTE usually starts with tremor-like, cortical myoclonus of the distal limbs, with onset in the second or third decade (range 3–70 years). Epileptic seizures usually start in the third or fourth decade (range 5–76 years), for which patients often seek medical attention. However, epileptic seizures can also be the first symptom.\(^{1,7,21,43,56}\)

The tremulous movements are in fact small, high-frequency myoclonic jerks, induced by posture or action. They can be mild, but can also be more incapacitating.\(^{17,27,47,57,58}\) When present in the lower limbs, these may lead to gait disorders\(^ {17,36–38,58,61}\) and even "drop attacks".\(^ {16,18}\) These tremor-like movements during action can easily be mistaken for ET. Electrophysiological measures can distinguish FCMTE from ET, showing short irregular electromyography (EMG) bursts during action and a cortical drive. Stimulus-sensitive myoclonus, frequently present in FCMTE, may be triggered or worsened by alcohol, emotional stress, sleep deprivation, tactile stimuli, and photic/phonie stimulation.\(^ {16,17,21,37,47,56,57,62,63}\) Twitching movements can involve facial/axial muscles.\(^ {16,21,57,58}\) Alcohol responsiveness has been reported in two pedigrees.\(^ {16,58}\) Myoclonus may remain stable, but long-term follow-up is not always present.\(^ {10,16,21,36,57,58,63}\)

Epileptic seizures are usually generalized tonic-clonic seizures, but can also be complex partial seizures.\(^ {8,17,37,46,56}\) Recently, the latter were renamed as focal seizures with impaired awareness (International League Against Epilepsy [ILAE] 2017 classification).\(^ {64}\) Moreover, they can be drug resistant.\(^ {16} \) Focal seizures with mesiotemporal symptoms or motor symptoms (dēja vu and fear) have been reported in four patients.\(^ {13,16}\) Generalized seizures mostly start without a warning sign but sometimes are preceded by severe myoclonus.\(^ {16,56}\) Also, myoclonic seizures have been described.\(^ {11,17,18}\) Seizures are reported to be induced by sleep deprivation, photic stimulation, stress, excitement,\(^ {16,37,47,62}\) or snow.\(^ {21}\) Frequency is usually low. Over five seizures per year is uncommon,\(^ {13,16,21,37,47,57,58}\) but more severe cases (20+ seizures per year) have been described.\(^ {10,18,57}\)

Additional clinical findings, possibly extending the clinical spectrum, are listed below.

- Cerebellar findings include in French pedigrees mild ataxia and gait instability.\(^ {17,37,56,62}\) (downbeat) nystagmus increasing with hyperventilation in a Dutch pedigree,\(^ {14}\) and dysarthria in South African/French pedigrees.\(^ {10,38}\) Ataxia is not a feature of FCMTE\(^ {16,17,27,47,57,58,60,65}\) but subtle cerebellar signs have not explicitly been ruled out.
- Mild cognitive decline, not including dementia, has been noted in some papers.\(^ {8–12,52,57}\)
- Psychiatric comorbidity has been noted in seven Italian families (FCMTE2),\(^ {13,17}\) anxiety in Indian patients,\(^ {65}\) schizophrenia in a Chinese pedigree,\(^ {66}\) and psychiatric comorbidity in a Turkish family.\(^ {18}\)

The results section covers both the previously identified and novel pedigrees.

### The FCMTE phenotype: core characteristics and less common findings

Clinical spectrum. FCMTE usually starts with tremor-like, cortical myoclonus of the distal limbs, with onset in the second or third decade (range 3-70 years). Epileptic seizures usually start in the third or fourth decade (range 5-76 years), for which patients often seek medical attention. However, epileptic seizures can also be the first symptom.\(^ {1,7,21,43,56}\)

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- Mild cognitive decline, not including dementia, has been noted in some papers.\(^ {8–12,52,57}\)
- Psychiatric comorbidity has been noted in seven Italian families (FCMTE2)\(^ {13,17}\) anxiety in Indian patients,\(^ {65}\) schizophrenia in a Chinese pedigree,\(^ {66}\) and psychiatric comorbidity in a Turkish family.\(^ {18}\) State anxiety (measured by a scoring list), depression, and
Table 3. Described Pedigrees (up until 2011) with Core Disease Characteristics

| Descent | Genetics | Origin, # Family | Clinical features | Electrophysiology | Structural | Additional Symptoms, Other Findings | Summary |
|---------|----------|------------------|-------------------|-------------------|------------|------------------------------------|---------|
|         |          |                  | Tremor, Myoclonus | Seizures | Seizure Type | JLA giant SEP | LLR | EEG | Imaging (cases) | PA (cases) |                          |
| Age at Onset (mean) |
| Asian | 8q | Japanese, 57,25 | 18–45 | ? | GTC | + | + | + | G-PSW, PPR, atr (3) | n.a. | n.d. | – | Classical phenotype |
| maj >30 |                  | PSW, PMR (>14) |          |          |          |          |          |          |          |          |          |          |          |          |
| n.d. | Japanese, 357-7 | 16–70 | 17–54 | GTC, Ph | + | + | + | PSW, PPR, SW, Sp | atr (3) n.a. | n.a. (4) | Rare: night blindness | No other neurological signs |
| maj >25 | maj >30 | inf (11) |          |          |          |          |          |          |          |          |          |          |          |          |
| Excl 2p, 8q | Chinese, 16 | 5–? | ? | GTC, M | n.d. | n.d. | n.d. | M, SW, PSW | n.d. | n.d. | Schizophrenia in family | Classical phenotype with earlier age of onset in the youngest generations |
| (34) | | | | | | | | | | | | |          |
| Presymptomatic changes detected |
| European | 2p | Italian, 29 | 11–50 | 12–50 | G, GTC, Ph | + | + | + | Sp, SW, PPR | atr (3) n.d. | Visuospatial impairment; Symptoms appear earlier |
| maj >20 | maj >25 | CP, M | Also in presymptomatic | PMR, GPA, PSW, SW | n.a. (27) | Eyelid twitching; Voice | Complex partial seizures |
| 3/79 | | | | | | | | | | | | | Migraine |
| Absent in 1 pedigree |
| n.d. | Italian, 12 | 12–57 | 5–18 | GTC, Abs | + | + | + | Sp, SW, PPR | atr (2) n.d. | – | |
| n.d. | Turkish, 13 | 29–7 | 30 | GTC | n.d. | n.d. | n.d. | G-8p, SW, PPR | n.a. (1) | n.d. | Migraine |
| 3p | French, 16–38 | 10–47 (30.8) | 24–41 | GTC, Ph | + | + | + | Sp, PPR, PS | n.d. | n.d. | Migraine |

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### Table 3. Continued

| Descent Genetics | Origin, # Family | Clinical features | Electrophysiology | Structural | Additional Symptoms, Other Findings | Summary |
|------------------|------------------|-------------------|-------------------|------------|-----------------------------------|---------|
|                  |                  | Tremor, Myoclonus | Seizures          | Seizure Type | JLA giant SEP LLR EEG Imaging PA (cases) |         |
| 5p, CTNND2       | Dutch, 12,13,14,15,16,17 | 12–45 (23.5) | 13–44 (43) | GTC, M, Ph | – + + | SW, PPR atr (2) *+(3) | TMS cortical hyperexcitability; Cerebellar dysfunction |
| Excl 2p, 8q     | Spanish, 181     | 30–60 (41) | 30–67 (44.6) | GTC | + + + | G-PSW n.a. (5) | Childhood onset, Pyramidal signs |
| Italian, 162     | 3–12             | 23–34             | GTC, CM          | + + + | SW, PMR, Sp | n.d n.d | Prominent photic induced |
|                  |                  |                   |                   |             | Ph myoclonus and epilepsy; Changing symptoms with age; Mild axial ataxia; Behavioral disorder |
| South African, 210 | 13–31 (20.9) | ?                  | GTC              | + + + | Abnormal background, atr (8) +*(1) | Frequent seizures; Cognitive impairment; Signs of pyramidal and cerebellar dysfunction; |
|                  |                  |                   |                   |             | PSW, Sp | n.a. (2) |                     |

Abbreviations: Abs, Absence; atr, Atrophy; CM, Cortical Myoclonus; CP, Complex Partial; CTNND2, Catenin Delta 2; EEG, Electroencephalography; excl, Excluded; G, Generalized; GPA, Generalized Paroxysmal Activity; giant SEP, Giant Somatosensory Evoked Potential; GTC, Generalized Tonic–Clonic; inf, Infarct; JLA, Jerk Locked Back Averaging; LLR, Long Latency Reflex; maj, Majority; M, Myoclonic; n.a., No Abnormalities; n.d., Not Done; PA, Pathology; Ph, Photosensitivity; PMR, Photomyoclonic Response; PPR, Photoparoxysmal Response; PSW, Polyspike-Wave Complexes; PS, Partial Seizures; Sp, Spikes; SW, Spike-Wave Complexes; TMS, Transcranial Magnetic Stimulation; +, Abnormal; -, Normal; #, Number Of Described Families; ?, Not Known.

1The table was originally published in our previous review. 1 We have added the table to the manuscript with minimal changes.
personality disturbances (hypochondriasis and schizophrenia) were more prevalent in Italian FCMTE pedigrees than juvenile myoclonic epilepsy and healthy controls.13

- Clinical anticipation has been recognized in Japanese patients with unknown linkage: tremor started at a younger age and seizures newly appeared in the next generation.19,20 Possibly, maternal transmission is associated with this phenomenon.20 In Chinese patients paternal transmission was noted in the earlier onset of tremor but not of seizures.21

- Other findings include migraine,15–18 ophthalmic migraine,37 headaches,40 logopenic syndrome,67 visual intolerance,61 frontal dysfunction,61 night blindness,63 motionless state,69 absence seizures,16 parkinsonism,60 reduced verbal fluency,70 sensitivity to glucose deprivation or vibration as an aggravating factor,37,38 and visuospatial impairment.9,52

Electrophysiological findings. Additional investigations in patients suspected of FCMTE to aid the diagnosis include electroencephalography (EEG), EMG, SEP, LLR, JLA, and corticomuscular (EEG-EMG) coherence analysis.

EEG findings may include generalized (poly) spikes and waves, photoparoxysmal response, and photomycogenic responses (Tables 2 and 3). EMG shows arrhythmic/semi-rhythmic high-frequency (≥10 per second) burst-like discharges of about 50 ms, which can be synchronous between agonist and antagonist muscles, typical for cortical myoclonus.71

Often features of cortical reflex myoclonus are present, including giant SEP, enhanced LLR, and/or cortical spikes preceding myoclonus with JLA.71 EEG-EMG coherence analysis indicated strong cortico-muscular coherences around 20 Hz with a cortical drive.72 With aging giant SEP and JLA cortical spike amplitude can be enhanced in FCMTE patients.16,73 Not all patients have giant SEPs or LLR, possibly due to anti-epileptic drug (AED) use,33 although giant SEP amplitude can also increase with AED use.22

Imaging. Structural imaging with MRI is normal in most cases. Although slight cerebellar atrophy (e.g., vermii)30 has been described,9–11,68 In one patient corticospinal degeneration was present.40 In three patients basal ganglia/periventricular white matter changes were observed.10

Treatment. The treatment of FCMTE consists of the prevention of epileptic seizures and/or reduction of troublesome tremor/myoclonus mainly with AEDs and benzodiazepines. Valproate is the drug most often reported to be effective with or without clonazepam.15,16,17,27,43,47,48,56,58,60,65,74 Because of teratogenicity, this should not be prescribed to women of childbearing age. Newer AEDs with a good effect are levetiracetam13,17,37,38,43,46,48,58,74 and lamotrigine.37,58 Other drugs prescribed to prevent seizures in FCMTE are phenobarbital, phenytoin, carbamazepine, clonazepam, oxcarbazepine, and primidone.1,16,40,43,47,48,58,60,74

One report observed a reduction in tremulous movements from a β-blocker.19 One to three AEDs usually prevents seizures or reduces them to once a year. Gabapentin has been reported to precipitate myoclonic status.76

Pathophysiology

Cortical hyperexcitability can be considered the hallmark of FCMTE. However, cerebellar changes have been described in neuroimaging and pathology studies.

Cortical hyperexcitability. Electrophysiological findings in FCMTE point to cortical hyperactivity and a cortical origin of the tremulous myoclonic movements. Functional fMRI-EMG also indicated cortical activity linked to the tremulous movements.77 Transcranial magnetic stimulation (TMS) in European pedigrees revealed a reduction in short interval cortical inhibition compared with healthy controls, reflecting hyperexcitability of the cortex.5,14 In Japanese FCMTE patients the giant SEP was enhanced, lacking the long-term depression effect seen in healthy controls after quadrupulse TMS over the primary motor cortex.78 However, post-mortem pathology studies in three Dutch cases revealed limited involvement of the sensorimotor cortex.1,14,50

Cerebellar involvement. Evidence for cerebellar involvement differs between FCMTE types (Table 4, imaging overview). For FCMTE1 and 4 there are no imaging or pathology studies available. In FCMTE2 a proton magnetic resonance spectroscopy (MRS) study indicated cerebellar dysfunction.79

In the Dutch FCMTE3 pedigree, with a C7/8ND2 gene mutation39 several findings point to cerebellar changes. These include, in certain family members, a downbeat nystagmus upon hyperventilation4 and in three deceased cases there was Purkinje cell loss in the cerebellar cortex and abnormal morphology of Purkinje cells during pathological examination.1,14,50

In family members of these deceased Dutch patients a mutation was found in the C7/8ND2 gene that led to abnormal neuronal sprouting in mice neurons, resembling the aforementioned cerebellar pathology.39 Moreover, imaging findings in the same pedigree showed decreased cerebellar fiber density51 and gray matter loss in the cerebellar motor area.53 In a Chinese pedigree in which 8q and 2p linkage was excluded, MRS indicated cerebellar dysfunction45 and an fMRI study indicated alterations between the cerebellum and supratentorial structures after network analysis.82 A South African pathology case, from a pedigree in which 8q and 2p linkage was excluded, revealed focal Purkinje cell loss, neuronal atrophy in the dentate nucleus, and neuronal loss with gliosis in the olives and pallidum.50

Other findings. A functional MRI/voxel-based morphometry (VBM) study indicated gray matter loss in cortical and subcortical structures with connectivity alterations.70 In a resting state fMRI study, compared to ET and healthy controls, the right fusiform gyrus and the posterior cingulate cortex showed decreased amplitude of low-frequency fluctuation (ALFF), and the frontal lobe showed increased ALFF that correlated with disease duration.55 In two FCMTE patients with gait difficulties but no benefit from L-dopa in one, MRI showed frontal atrophy and single positron emission computed tomography (SPECT) showed dopamine depletion.63 In a FCMTE patient with a language disorder and short-term memory problems, MRI showed frontal...
| Reference        | Origin, Linkage | Imaging Modality | Design | Cerebellum | Other Findings in FCMTE |
|------------------|-----------------|------------------|--------|------------|--------------------------|
| Buijink et al.   | Dutch, 5p       | MRI (VBM)        | 8 FCMTE, 45 ET, 39 HS | Total volume; Crus I, lobules IX, X | n.d. |
|                  |                 |                  |        |            | Total/local cerebellar volume |
| Buijink et al.   | Dutch, 5p       | MRI (DTI)        | 7 FCMTE, 8 ET, 5 HS | Cerebellum | n.d. |
|                  |                 |                  |        |            | Fractional anisotropy; MDV |
| Magnin et al.    | French, 5p      | DAT-SPECT, MRI   | Case report (n:1) | Atrophy: cerebellum | Atrophy: cortical structures |
| Magnin et al.    | Case report (n:2) |                  |        |            | DAT: striatum; cortical perfusion |
| Striano et al.   | Italian, 2p     | 1H-MRS           | 11 FCMTE, 11 HS, Neurochemical ratios | Cho/Cr ratio | n.a. |
| Long et al.      | Chinese, excl. 2p, 8q | RS (MRI) (BOLD)  | 11 FCMTE, 15 HS | DN: R crus I with L frontal + R lobule IX | n.d. |
|                  |                 |                  |        |            | Functional connectivity |
|                  |                 |                  |        |            | AN: L lobule VII with temporal, |
|                  |                 |                  |        |            | R putamen and L crus I |
|                  |                 |                  |        |            | CN: L lobule VIIb and R frontal |
| Long et al.      | Chinese, excl. 2p, 8q | 1H-MRS           | 12 FCMTE, 12 HS, Neurochemical ratios | NAA/Cho ratio | n.a. |
| Zeng et al.      | Chinese, excl. 2p, 8q | RS (MRI + VBM)   | 11 FCMTE, 15 HS | n.d. | Gray matter: R hippocampus; R temporal |
|                  |                 |                  |        |            | Gray matter; Functional connectivity |
|                  |                 |                  |        |            | L orbitofrontal; L prefrontal |
|                  |                 |                  |        |            | FC: R hippocampus with R parietal |
|                  |                 |                  |        |            | cingulate; L precuneus, L precentral gyrus |
| Wang et al.      | Chinese, n.d.   | RS (MRI)         | 7 FCMTE, 7 ET, 10 HS | n.d. | R fusiform gyrus; cingulate |
|                  |                 |                  |        |            | BOLD; ALFF |
|                  |                 |                  |        |            | Frontal lobe |

Abbreviations: ALFF, Amplitude Of Low Frequency Fluctuation; AN, Attention Network; BOLD, Blood-Oxygen-Level Dependent; Cho, Choline; CN, Control Network; Cr, Creatinine; DAT, Dopamine Transporter; DAT-SPECT, Dopamine Transporter, Single Photon Emission Computed Tomography; DN, Default Network; DTI, Diffusion Tensor Imaging; ET, Essential Tremor; excl, Exclusion; FCMTE, Familial Cortical Myoclonus Ternor And Epilepsy; FC, Functional Connectivity; HS, Healthy Subjects; 1H-MRS, Proton Magnetic Resonance Spectroscopy; L, Lef; MDV, Mean Diffusivity Volume; MRI, Magnetic Resonance Imaging; n, Number; n.a., No Abnormalities; NAA, n-Acetylaspartate; n.d., Not Done; R, Right; RS IMRI, Resting State Functional Magnetic Resonance Imaging; VBM, Voxel Based Morphometry; ↑ Increase; ↓ Decrease.
atrophy and SPECT indicated loss of dopamine transporters in the left striatum.

**Genetic linkage, proposed mutations**

In several FCMTE pedigrees, causative mutations have been proposed (Table 5). In a Dutch pedigree a mutation in CTNN2, supported by functional tests, has recently been discovered. However, functional tests have not been performed for every mutation. Linkage studies indicated several loci: 8q23.3-8q24.13 (FCMTE1), 2p11.1-q12.2 (FCMTE2), 3q26.32-3q28 (FCMTE4). Furthermore, there are several families (Chinese, Spanish, Italian, South African) in which 2p and/or 8q linkage was excluded. Below we summarize the findings in FCMTE1–4 and FCMTE-like disorders.

Linkage to the FCMTE1 locus on chromosome 8q23.3-8q24.13 was found in several Japanese families and one Chinese family. In the Chinese pedigree a single nucleotide variant (SNV) was identified in the SLC30A8 (solute carrier family 30 [zinc transporter]) gene after whole-exome sequencing (WES). However, there is no expression of this gene in the brain, making it irrelevant. Besides, sequence and copy number variant analysis of the genes located on the 8q23.3-8q24.13 locus did not reveal any mutation.

Linkage to the FCMTE2 locus on chromosome 2p11.1-q12.2 was found in Italian, 8,9,17,29–33 Spanish, 29,34 and Australian/New Zealand pedigrees (with European ancestors). A founder haplotype was identified in Italian FCMTE2 pedigrees from the same geographical area. A mutation in two Italian family members within the FCMTE2 locus was found on the α2-adrenergic receptor subtype B (ADRA2B) gene with next-generation sequencing (NGS). Identity by descent mapping (IBD), which is able to detect genetic loci among pedigree unrelated individuals, refined the FCMTE2 locus to 2p11.1-q11.1 without excluding the ADRA2B mutation. In a Spanish pedigree, WES indicated an SNV in the FCMTE2 locus to 2p11.1-q11.1 without excluding the ADRA2B gene. In cortical mouse neurons led to abnormal neuronal sprouting which resembled abnormal Purkinje cell morphology in deceased FCMTE patients. However, in the French family a mutation in SEMA5A (semaphorin-5A) and CTNN2 genes was excluded using direct sequencing. Carr et al. have named their gene SLC30A8 which encodes for an enzyme that is part of the kynurenine pathway of tryptophan and linked to neurodegenerative diseases and epilepsy.

FCMTE3, with linkage to 5p15.31-p15, has been identified in two Chinese families, 10,14 a Dutch pedigree, 9 and a French family. In the Dutch family after WES, a mutation was found in the CTNN2 gene. Knockdown of Ctnnd2 in cortical mouse neurons led to abnormal neuronal sprouting which resembled abnormal Purkinje cell morphology in deceased FCMTE patients. However, in the French family a mutation in SEMA5A (semaphorin-5A) and CTNN2 genes was excluded using direct sequencing. Carr et al. have named their gene SLC30A8 which encodes for an enzyme that is part of the kynurenine pathway of tryptophan and linked to neurodegenerative diseases and epilepsy.

FCMTE4, with linkage to 3q26.32-3q28, has recently been discovered in a Thai family. No causative gene has yet been identified. Two candidate genes have been proposed for FCMTE4: HTTRD3 (5-hydroxytryptamine receptor 3D) and KCNMB3 (calcium-activated potassium channel subunit beta 3).

### Table 5. Mutations Found in Different Pedigrees

| Reference        | FCMTE | Origin | Linkage | Gene, Chromosome | Mutation | Causative? |
|------------------|-------|--------|---------|------------------|----------|------------|
| Cen et al. 27    | FCMTE1| Chinese|         | SLC30A8, 8q24.11 | N:2, N:1 | Missense, p.Y69F, c.206A |
| Felix Marti-Masso et al. 48 | FCMTE2| Spanish|         | ACMSD, 2q21.3 | N:3, N:1 | SNV, p.Trp26Stop, c.77G |
| De Fusco et al. 46 | FCMTE2| Italian|         | ADRA2B, 2q11.2 | N:2, N:2 | Indel, c.675_686delTGGTGGGG |
| Rootselaar et al. 39 | FCMTE3| Dutch  |         | CTNND2, 5p15    | N:3, N:1 | Missense, p.Glu1044Lys |
| Gao et al. 47     | FCMTE4| Chinese|         | SLC30A8, 22q13.1| N:3, N:1 | Missense, p.Ala159Thr, c.475C |
| Kato et al. 59    | FCMTE#| Japanese|        | UBR5, 8q22.3   | N:5, N:1 | Missense, p.Arg1907His, c.5720G |
| Russel et al. 49  | FCM#  | Canada  |         | NOL3, 16q22.1  | N:1, N:1 | Missense, p.Pro1537Leu, c.4611G->A |

Abbreviations: ACMSD, Aminocarboxymuconate Semialdehyde Decarboxylase; ADRA2B, 2-Adrenergic Receptor Subtype B; ARJP, Autosomal Recessive Inherited Juvenile Parkinsonism; AS, Angelman Syndrome; CTNND2, Catenin Delta 2; EODP, Early Onset Dystonia Parkinsonism; FCMTE, Familial Cortical Myoclonic Tremor And Epilepsy; FCM, Familial Cortical Myoclonus; giant SEP, Giant Somatosensory Evoked Potential; KS, Krabbe Syndrome; N, Number; NOL3, Nucleolar Protein 3; PD, Parkinson Disease; PLA2G6, Phospholipase A2 Group 6; PME, Progressive Myoclonus Epilepsy; SLC30A8, Solute Carrier Family 30 (zinc transporter), Member 8; SNV, Single Nucleotide Variant; UBR5, Ubiquitin Protein Ligase E3 Component n-recognin 5; ULD, Unverricht–Lundborg Disease; -, Negative; #, Unknown linkage.
Genetic findings in FCMTE-like disorders. In a family from Canada with familial cortical myoclonus without seizures (a potential new disorder), linkage analysis and WES identified a missense mutation on 16q22.1 in the nucleolar protein 3 (NOL3) gene. Pathogenicity is doubtful because NOL3 knockout mice did not exhibit myoclonic symptoms and had normal SEPs. Moreover there is an autosomal recessive form of FCMTE, caused by a single base pair deletion in CNTN2, crucial for the stability of potassium channels.

Diagnostic criteria and clinical spectrum

The pedigrees presented in this review share the core features of FCMTE, including autosomal dominant inheritance, distal myoclonic tremor with signs of cortical reflex myoclonus, and/or generalized tonic–clonic seizures. Myoclonus is typically the first symptom, while seizures, usually occurring later in the disease course, are a common reason for patients to seek medical care. However, seizures might in a number of cases be the first symptom.

EEG findings in FCMTE include generalized spikes/waves and photoparoxysmal or photomyogenic responses. Other possible clinical features include mild progression of symptoms with aging, and/or generalized tonic–clonic seizures. Myoclonus is typically the first symptom, while seizures, usually occurring later in the disease course, are a common reason for patients to seek medical care. However, seizures might in a number of cases be the first symptom.

Focal EEG abnormalities and a slower posterior dominant rhythm might be features of FCMTE. Also, EEG may show generalized spikes and waves preceding later onset of epilepsy. FCMTE is differentiated from other tremor-like disorders (including ET) with electrophysiological recordings. FCMTE can be differentiated from the progressive myoclonus epilepsy syndromes and juvenile myoclonic epilepsy (JME) in the absence of severe cognitive decline and absence of severe ataxia. Unlike FCMTE, JME presents with myoclonus in the morning and shows no features of cortical reflex myoclonus.

Criteria for the diagnosis of FCMTE are the following:
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: giant SEP and LLR point to cortical hyperexcitability; polymyography showing discharges of <30 ms suggest cortical myoclonus; and EEG-EMG coherence analysis or JLA can support a cortical origin of the tremulous movements.
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.

Are phenotypical differences related to specific mutations?

Differences in symptomatology have been reported, possibly linked to different mutations. Japanese and Chinese pedigrees, linked to 8q (FCMTE1; also known as BAFM) suffer from a more “benign” form of FCMTE, with age of onset in the third decade, infrequent seizures, and no cognitive decline. Usually, FCMTE1 patients present with rhythmic distal myoclonus of the upper extremities, but more extensive involvement of the lower extremities and facial muscles has also been reported.

Pedigrees with linkage to 2p (FCMTE2) exhibit a more severe form of myoclonus (proximal involvement) that progresses with aging and leads to gait disability. Specific for Italian 2p pedigrees, psychiatric comorbidity is frequently present. Atypical symptoms in pedigrees with a possibly pathogenic mutation were present in Spanish pedigrees (n:1 parkinsonism and mild ataxia) and in 2p ADRA2B patients (focal seizures and age-related dementia).

Linkage to 5p (FCMTE3) in two Chinese pedigrees is related to a benign course with age of onset in the fourth decade, and, during short-term follow-up, no disease progression. However, in French FCMTE3 pedigrees, progression of symptoms, gait disability, frontal syndrome, cognitive changes, and logopenic syndrome were described. Also, in a Dutch FCMTE3 pedigree subjective cognitive decline was present.

In a Thai pedigree, with linkage to 3q (FCMTE4), myoclonus presented earlier, in the second decade, and seizures started in the third decade. No cognitive decline was present.

In patients with unknown linkage the following findings were reported: clinical anticipation was present in Asian pedigrees (measured with rating scales). Mild cognitive decline was present in Asian patients. European patients (or with European ancestors) suffered from mild cognitive decline, focal seizures, mild ataxia and/or gait instability.
and migraine.\textsuperscript{15–18} Atypical features were also described in a Turkish family, including absence seizures, early onset of seizures (14–17 years), negative LLR (while using AEDs), and frequent myoclonic seizures (once a month).\textsuperscript{18}

There are a number of possible explanations for the reported phenotypical differences between pedigrees/FCMTE types. Firstly, different mutations, extensively described in a limited number of pedigrees, could lead to clinical diversity.\textsuperscript{39,46–48,59} For instance, more severe disease course,\textsuperscript{17,36} cognitive decline,\textsuperscript{67} and/or the pathological/neuroimaging changes in the cerebellum\textsuperscript{1,51,53} might be related to specific FCMTE mutations. Secondly, other possible explanations might be differences in genetic trait other than FCMTE; heterogenic prescription regimes, including AED use per country, or environmental factors. A third explanation is reporting bias. Documentation, investigations, and follow-up differ substantially between pedigrees.

**Pathophysiology**

The primary symptoms of FCMTE, cortical myoclonus, and epilepsy seem to have their origin in the sensorimotor cortex. Electrophysiological findings indicate cortical hyperexcitability with generalized spikes and waves on EEG, giant SEP, LLR, and reduced cortical inhibition. Use of AEDs might result in loss of Purkinje cells with dendritic sprouts, neuronal loss in the dentate nucleus and microglia activation with limited changes in the sensorimotor cortex. Use of AEDs might result in loss of Purkinje cells. Notwithstanding, cerebellar pathology findings in FCMTE patients differ from changes seen in patients with chronic idiopathic epilepsy who used phenytoin\textsuperscript{85} and rats chronically exposed to valproic acid.\textsuperscript{40} Also, Dutch patients who did not use AEDs had a downbeat nystagmus upon hyperventilation, indicating cerebellar dysfunction.\textsuperscript{14}

Moreover, a mutation in\textit{CTNND2} was found in the same Dutch pedigree, related to FCMTE3, as the gene\textit{CTNND2} is located on the same linkage area.\textsuperscript{39} A mutant version of this gene was responsible for abnormal neuronal sprouting in mouse neurons, resembling cerebellar pathology findings in the same Dutch pedigree.\textsuperscript{39} In a French FCMTE3 pedigree a mutation in\textit{CTNND2} was excluded using direct sequencing.\textsuperscript{37} It could be there are several mutations located on the same linkage area or the mutation was undetectable due to the technique used.

Pathological cerebellar involvement is in line with cerebellar signs in European FCMTE pedigrees; these include downbeat nystagmus,\textsuperscript{14} mild ataxia (although possibly difficult to judge in the presence of tremulous myoclonus),\textsuperscript{37,56} dysarthria,\textsuperscript{10,38} and imaging findings revealing cerebellar involvement.\textsuperscript{51,58,79}

Further evidence for cerebellar involvement in FCMTE arises from imaging studies in FCMTE, indicating functional connectivity changes between the cerebellum and cortical/subcortical structures.\textsuperscript{52} Supratentorial gray matter loss outside the motor circuit might be secondary.\textsuperscript{70} Also, cerebellar atrophy and ataxia have frequently been noted in patients with epilepsy.\textsuperscript{87} Repetitive TMS over the cerebellar cortex was able to reduce seizure frequency in drug-resistant epilepsy.\textsuperscript{87,88} The cerebellum might be involved in psychiatric disorders.\textsuperscript{69} In several FCMTE pedigrees anxiety and depressive comorbidity was reported.\textsuperscript{15,56}

With aging, Purkinje cells become atrophic in healthy adults and the amount of white matter is reduced in the cerebellum.\textsuperscript{90} The degeneration of Purkinje cells might be enhanced in FCMTE patients leading to defective compensatory input to cortical structures. Clinically, this could explain the later onset of seizures and the worsening of symptoms with aging.\textsuperscript{16} Moreover, cortical hyperexcitability seems to increase with aging in Japanese patients, reflected by higher giant SEP amplitude.\textsuperscript{73}

Pathology, imaging, genetic, and clinical findings indicate cerebellar changes. This offers a possible explanation for the decreased cortical inhibition. Deficient stimulation of the dentate nucleus by Purkinje cells in the cerebellum may lead to increased cortical facilitation via the cerebello-thalamo-cortical loop, a hypothesis already raised for cortical myoclonus and epilepsy.\textsuperscript{54,87,91} Purkinje cell changes might however not be the (sole) explanation for the symptoms observed in FCMTE.

The cerebellar changes might be specific for certain FCMTE types, with the strongest evidence for FCMTE3. Future research is needed to indicate whether cerebellar involvement, including pathological cerebellar changes, is a general finding in FCMTE. In some FCMTE types it might be co-existent, secondary due to primary cortical pathology, or even absent.

**Possible candidate genes**

Possible candidate causative genes include a trinucleotide repeat expansion or channelopathy.\textsuperscript{89} Purkinje cell changes in deceased Dutch FCMTE patients show striking similarities with those found in spinocerebellar ataxia (SCA) type 6, characterized by ataxia and downbeat nystagmus.\textsuperscript{1,36} Patients from the same Dutch FCMTE pedigree also have a downbeat nystagmus.\textsuperscript{34} SCA type 6 is caused by a CAG repeat in a calcium channel CACNA1A heavily expressed in the cerebellum.\textsuperscript{92} Other observations that might also point to a trinucleotide repeat expansion or channelopathy underlying FCMTE include in Asian FCMTE pedigrees, progressively earlier onset of the disease with increasing severity in successive generations\textsuperscript{19,21}, presence of migraine\textsuperscript{15–18} analogous to hemiplegic migraine with mutations in calcium channels\textsuperscript{45}, and the recognition that certain epilepsy syndromes are channelopathies.\textsuperscript{45,94}

Recently, an autosomal recessive form of FCMTE has been recognized with a single base pair deletion in\textit{CVTB2}, crucial for the stability of potassium channels.\textsuperscript{45} A channelopathy could involve cerebellar cells and/or induce functional cortical changes.\textsuperscript{50,92}

Several genes have been identified as potentially causative in FCMTE. A gain of function mutation in the\textit{ADRA2B} gene has been found in Italian FCMTE2 pedigrees that could potentially alter the neuronal firing pattern and even reduce gamma-aminobutyric acid
(GABA) neurotransmission. A reduction in cortical GABA neurotransmission has been associated with cortical myoclonus in rats, progressive myoclonus epilepsy and Unverricht-Lundborg disease characterized by cortical myoclonus and ataxia along with seizures. Treatment with AEDs increasing GABA neurotransmitter levels can relieve the symptoms of FCMTE.

Another neurotransmitter implied in the pathophysiology of FCMTE2 is serotonin. A mutation in the ACMSD gene, encoding for an enzyme that is part of the kynurenine pathway, might lead to the accumulation of waste products. In mice, seizures could be induced when injecting these kynurenines in the brain ventricles. In Dutch FCMTE3 patients, a mutation in CTNND2, supported by functional tests in mice, seems to be responsible for abnormal neuronal sprouting. Hypothetically, the pathology findings in the cerebellum and the disease itself are caused by the CTNND2 mutation.

Other proposed mutations/linkage studies have not yet elucidated the pathophysiology of FCMTE and have provided conflicting results, including proposed mutations outside the known linkage areas (UBR5, PLA2G6) and a pedigree from Canada (YOL3 mutation) without seizures, possibly reflecting another illness. The lack of progress might be due to the inability of next-generation sequencing techniques to detect exon rearrangements, trinucleotide repeat expansion, and copy number variants. Even a deletion in an intron might lead to defective splicing of a gene as in Unverricht–Lundborg disease. New algorithms and WGS might lead to a breakthrough.

Future genetic studies should focus on mutations in proteins expressed in the cerebellum, involved in neuronal outgrowth, calcium, sodium, or potassium signaling, GABA neurotransmission, and genes which interact with the SCAs or other diseases with cortical myoclonic symptoms.

Limitations

Reporting bias may have influenced our results. The number of patients and follow-up differ between pedigrees. Across studies, rating scales for motor symptoms and cognitive functioning differ or have not been reported. Therefore, symptoms might have been underreported, for instance cerebellar dysfunction and cognitive deterioration in certain pedigrees. Additional investigations (MRI, electrophysiology, pathology) have not always been performed, in some cases leading to diagnostic uncertainty, but more often raising questions with respect to generalizability of findings across pedigrees. For instance, both the imaging and the pathology findings involving cerebellar changes have largely been confined to a South African patient (linkage exclusion 2p, 8q), a Dutch pedigree (FCMTE3), and Chinese patients (linkage exclusion 2p, 8q) making the generalizability of the findings problematic. Several mutations (ACMSD, ADR42B, UBR5, PLA2G6) have been proposed but pathogenicity has still to be proven.

Conclusion

FCMTE, also known under different names and acronyms, is a clinical entity not (yet) listed by the ILAE. It is characterized by cortical tremor/fine myoclonus and generalized tonic–clonic seizures with autosomal dominant inheritance. Proximal myoclonus and mild progression with aging are part of the spectrum. Electrophysiology recordings show features of cortical reflex myoclonus. Valproate (not recommended in women of childbearing age) or levetiracetam, with or without clonazepam reduce symptoms. Gabapentin should be prescribed cautiously.

FCMTE is a heterogeneous disorder, and is likely to include a variety of different conditions with mutations of different genes. Additional symptoms have frequently been reported and can be co-incidental or based on genetic differences. Pathophysiological mechanisms remain to be elucidated, but pathology, genetic, and imaging studies have given clues that indicate cerebellar involvement. The cerebellar changes might lead to reduced cortical inhibition. Alternatively, underlying genetic changes induce both cerebellar and cortical changes. Genetic heterogeneity is present in linkage studies. Several causative genes have been suggested. However, functional tests have not always been performed.

Pathophysiology and genetic studies indicate that future genetic studies should focus on mutations involving Purkinje cell outgrowth, chanelopathies, or genes responsible for neurotransmitter synthesis.

Appendix A

PubMed search

Conducted on 15-11-2017, articles were sought from 01-01-2011 to 15-11-2017.

((((cortical tremor myoclonus) OR cortical tremor epilepsy) OR (((“Tremor”[Mesh] AND “Myoclonus”[Mesh]) AND “Epilepsy”[Mesh])) OR (cortical tremor [tiab] AND epilepsy [tiab] AND myoclonus [tiab]))) OR (((“Epilepsy, Myoclonic, Benign Adult Familial, Type 1”[Supplementary Concept]) OR (“Tremor”[Mesh] AND “Epilepsy”[Mesh]) OR (“Tremor”[Mesh] AND “Myoclonus”[Mesh]) OR (“Epilepsy”[Mesh] AND “Myoclonus”[Mesh]) OR (cortical tremor myoclonus) OR cortical tremor epilepsy) OR (((cortical tremor myoclonus) OR cortical tremor epilepsy) OR (((“Tremor”[Mesh] AND “Myoclonus”[Mesh]) AND “Epilepsy”[Mesh])) OR (cortical tremor [tiab] AND epilepsy [tiab] AND myoclonus [tiab]))) OR (((“Epilepsy, Myoclonic, Benign Adult Familial, Type 1”[Supplementary Concept]) OR (“Tremor”[Mesh] AND “Epilepsy”[Mesh]) OR (“Tremor”[Mesh] AND “Myoclonus”[Mesh]) OR (“Epilepsy”[Mesh] AND “Myoclonus”[Mesh]) OR (cortical tremor myoclonus) OR cortical tremor epilepsy) OR (((“Tremor”[Mesh] AND “Myoclonus”[Mesh]) AND “Epilepsy”[Mesh])) OR (cortical tremor myoclonus) OR cortical tremor epilepsy)).

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