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CHAPTER 7

A Dutch family with ‘familial cortical tremor with epilepsy’: clinical characteristics and exclusion of linkage to chromosome 8q23.3-q24.1

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Abstract

Purpose: To describe the clinical characteristics of a large Dutch family with cortical tremor with epilepsy (FCTE) and to test for genetic linkage of FCTE to chromosome 8q23.3-q24.1. *Background:* FCTE is an idiopathic generalized epilepsy of adult onset with autosomal dominant inheritance. It is characterized by kinesigenic tremor and myoclonus of the limbs, generalized seizures, and electrophysiological findings consistent with cortical reflex myoclonus. Genetic analysis has been performed in five Japanese families. In all families, linkage was shown to chromosome 8q23.3-q24.1. *Methods:* Clinical and electrophysiological data of a four-generation family, suspected of autosomal dominantly inherited FCTE, were collected and linkage analysis was performed. *Results:* Clinical and electrophysiological findings were consistent with a diagnosis of FCTE. Of 41 relatives examined, 13 subjects were considered to be definitely affected, 3 were probably affected and 10 were unaffected. In 15 relatives, the diagnosis could not be established. Linkage to chromosome 8q23.3-q24.1 was excluded. *Conclusions:* In this family with autosomal dominant FCTE, specific clinical and electrophysiological features were identified. Exclusion of linkage to chromosome 8q23.3-q24.1 indicates that genetic heterogeneity exists for FCTE.

Keywords

Familial cortical tremor, myoclonus, epilepsy, linkage analysis.

Introduction

‘Cortical tremor’ was first described in 1990 by Ikeda et al. in two patients with a fine action tremor resembling essential tremor that was unresponsive to β -blockers¹. Both patients suffered from occasional epileptic seizures. Electrophysiological studies revealed features of cortical reflex myoclonus, such as giant somatosensory evoked potentials (g-SEPs), enhanced long loop reflexes (C-reflexes), and premovement cortical spikes¹. It was concluded that the tremor originated from the cerebral cortex and should be designated as a variant of cortical reflex myoclonus^{1,2}. Subsequently, cortical tremor has been described in both sporadic and familial cases with autosomal dominant inheritance³⁻⁷. Five Japanese and one European family have been described so far with this syndrome, named ‘familial cortical tremor with epilepsy’ (FCTE), ‘familial adult myoclonic epilepsy’ (FAME) or ‘benign adult familial myoclonic epilepsy’ (BAFME)⁵⁻⁷. In these pedigrees, the disorder was characterized by a non-progressive ‘essential-tremor-like’ tremor, infrequent seizures and in some cases myoclonus. Results of electrophysiological studies were consistent with cortical reflex myoclonus, and electroencephalograms (EEG) showed spikes, spike-wave complexes, and polyspike-wave complexes^{1,2,5-7}. In the European family, mental retardation was an additional finding⁴. Genetic analysis in five Japanese families showed linkage to chromosome 8q23.3-q24.1^{6,7}.

Recently, we have identified a Dutch family with cortical tremor and epilepsy. As far as we know, this is the largest pedigree described until now. The objectives of the present study were (1) to describe the clinical and electrophysiological characteristics of this family; and (2) to examine whether linkage to chromosome 8q23.3-q24.1 could be established. Knowledge of the genetic basis of the syndrome might give insight into the pathogenesis of FCTE and could be a first step towards a specific treatment.

Methods

Patients

After having obtained written informed consent from 26 relatives and spouses (figure 1, pedigree), medical and family histories were taken and venous blood samples for genetic testing were drawn (by FvR and MT). In all participating relatives and spouses, special attention was given to tremor and epilepsy. If relatives had ever visited a neurologist before, existing clinical data were obtained (II:3, 7, 11, 13; III:3, 5, 10, 19 and 20). If possible, adult relatives with a tremor participated in electrophysiological studies (III:1, 5, 10; IV:1 and 2). Other diseases with tremor and epilepsy (progressive myoclonus epilepsies, MERRF, and spinocerebellar ataxias) were excluded or made unlikely with magnetic resonance imaging of the brain in III:3 and 10, normal lactate and pyruvate levels and exclusion of spinocerebellar ataxia (SCA) types 1, 2, 3, 6 and 7 in patient III:10, and no ragged-red-fibres in a muscle biopsy in patient III:3.

Electrophysiology

Electrophysiological measurements included surface electromyography (EMG) with tremor registration and long-latency reflex recording (C-reflex), somatosensory evoked potentials (SEP), electroencephalography (EEG), and jerk-locked averaging of cortical potentials. Electrophysiological findings were considered positive if a giant SEP (our laboratory standard: P27-N35 > 4 μ V) in combination with a C-reflex were found. If not, they were considered inconclusive.

Diagnostic criteria

(based on disease characteristics as described by Elia, Okuma, Mikami, and Plaster)⁴⁻⁷

Definitely affected: (1) a history of tremor and myoclonus, and myoclonic or epileptic seizures, and on neurological examination characteristic signs: kinesigenic tremor resembling essential tremor and distal action myoclonus of

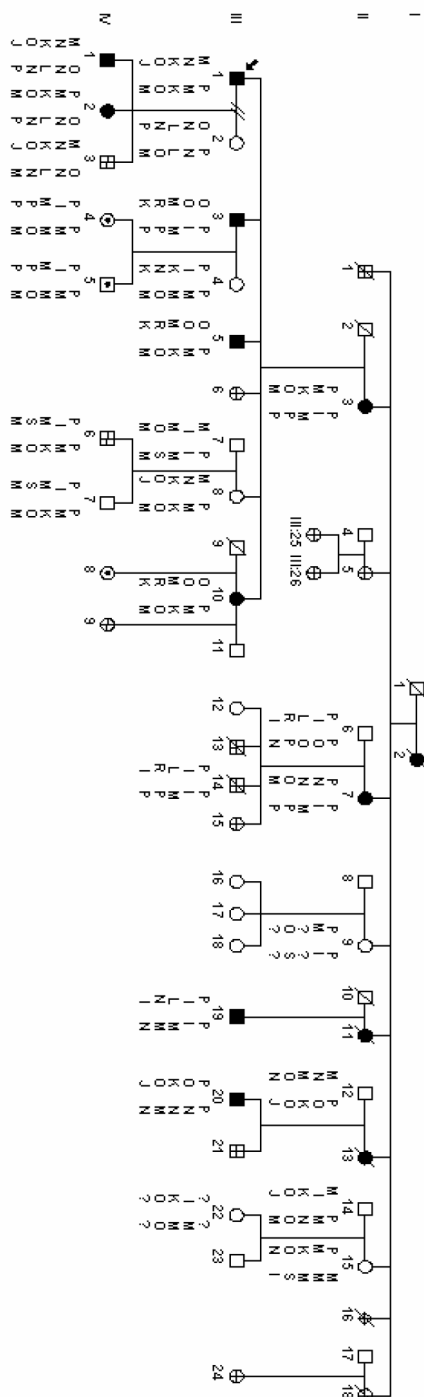


Figure 1

Pedigree of our Dutch family with familial cortical tremor with epilepsy (FCTE). Black symbols are definitely affected persons, and persons with a black dot are probably affected. Diagnosis could not be established in persons with a plus. Regarding the linkage analysis: diagnosis is considered to be unknown in all but the definitely affected persons. The proband is indicated by an arrow.

all limbs; or (2) a history of tremor without myoclonic or epileptic seizures but on examination a characteristic tremor and myoclonus plus positive electrophysiological findings (giant SEP and C-reflex).

Probably affected: a history of tremor, with or without use of anti-epileptic drugs. On examination a characteristic tremor and myoclonus but inconclusive or absent electrophysiological data.

Possibly affected: a history of tremor, no anti-epileptic drug treatment and on examination no characteristic tremor. Inconclusive or no electrophysiological data.

Unaffected: 50 years of age or older, without anti-epileptic drugs. No characteristic signs on examination.

No diagnosis: inconclusive or incomplete data.

Genotyping

Venous blood samples were taken from 10 definitely affected relatives and 16 other relatives and spouses. Genomic DNA was extracted from peripheral lymphocytes using standard methods⁸. Microsatellite markers D8S1784, D8S1779, D8S1694, D8S514, and D8S1720, all from the chromosome 8q23.3-q24.1 region, were tested by polymerase chain reaction (PCR). Oligonucleotide sequences are available through the Human Genome Database (GDB). PCRs for all markers were performed using standard conditions (www.gdb.org). PCR products for each template were pooled and an aliquot was loaded onto a 6% standard denaturing polyacrylamide gel and run in an Applied Biosystems (ABI) 377 automated DNA sequencer. Allele sizes were determined on the basis of an internal standard size marker, using GeneScan 3.1 and Genotyper 2.5 ABI software. Genotypes were determined by two individuals, and checked for Mendelian segregation using a standard program.

Linkage analysis

Single- and multipoint LOD score analysis were performed using the Linkage program, version 5.1, with an affected-only model. In the linkage analysis, only definitely affected relatives were regarded as affected. Diagnosis in all other relatives - probably affected, possibly affected and unaffected - was considered unknown⁹. The syndrome was considered to be autosomal dominantly inherited with 80% penetrance, no phenocopies, a gene frequency of 0.001, and equal allele frequencies for each individual marker. Multipoint analysis was performed with the following genetic positions of the microsatellite markers (in cM), according to the database of Généthon: D8S1784: 116.8; D8S1779: 122.6; D8S1694: 124.2; D8S514: 128.9; D8S1720: 139.7.

Results*Clinical and electrophysiological findings*

Of the 41 relatives examined, 13 relatives were considered definitely affected, 3 were probably affected, and 10 relatives were unaffected (figure 1). In 15 relatives, diagnosis could not be established owing to the lack of data. The pedigree showed an autosomal dominant inheritance pattern (figure 1).

The 55-year-old proband (III:1) suffered from tremor, finger twitching and trembling of his legs from the age of 45 years. The involuntary movements were provoked by action and emotional stress, and were most intense after awaking. Propranolol was not effective but primidon reduced the tremor. At the age of 52 years, he had his first generalized seizure. On neurological examination, a kinesigenic tremor was observed with superimposed myoclonus of the fingers and toes, which made the tremor irregular. There were no signs of ataxia, nystagmus, or dysarthria. In a clinical setting, the primidon was slowly reduced. The tremor and myoclonus increased markedly and the patient suffered from a tonic-clonic seizure at night. EEG showed left parietal spike-wave complexes. Interestingly, intravenous clonazepam both

ceased the tremulous movements and normalized the EEG. Electrophysiological measurements were performed after initiated treatment with sodium valproate (2000 mg daily dose) and clobazam (10 mg daily dose). Tremor-registration showed an irregular 12-16 Hz tremor. C-reflex was not detected. Giant SEPs were measured on both arms (right P27-N30 = 6.5 μ V; left = 6.3 μ V). Jerk-locked averaging was not possible owing to the infrequency of myoclonic jerks and the interference of the tremor.

In general, tremulous movements started between the ages of 12 and 45 years (patients I:2; II:3, 7, 11, 13; III:1, 3, 5, 10, 19, 20; IV:1, 2, 4, 5, and 8, table 1). Patients could not differentiate between tremor and fine myoclonic movements. Generalized tonic-clonic seizures and myoclonic seizures started between the ages of 20 and 63 years, 1 to 33 years after the tremor. Severity of tremor, myoclonus, and seizures varied between individuals. The symptoms tended to be slightly to moderately progressive, leading to mild (III:1) to severe (II:7) handicap. Several affected relatives with seizures had complaints of memory deterioration (II:3, 7; III:3, 10).

On examination (patients II:3, 7; III:1, 3, 5, 10, 19, 20; IV:1, 2, 4, 5, and 8, table 1), a characteristic kinesigenic tremor, resembling essential tremor, and myoclonus was seen in fingers, arms, feet, and even in legs. The tremulous movements were provoked by exercise and emotional stress. Severity varied between patients and during the day, usually being worse in the morning. In addition, signs of slight cognitive impairment, such as short-term memory and attention deficits, were noticed in four patients with epilepsy (II:3, 7; III:3, 10) and reported in the medical notes of two of the deceased patients (II:11, 13). All these patients were on anti-epileptic medication: II:3, sodium valproate 1200 mg and phenytoin 800 mg dd; II:7, carbamazepine 1000 mg, phenytoin 1200 mg, phenobarbital 100 mg, clonazepam 2 mg; III:3, clonazepam 1 mg, sodium valproate 900 mg; III:10, sodium valproate 1300 mg, clonazepam 1 mg; II:11 unknown; II:13, phenobarbital 150 mg, sodium valproate 1250 mg,

clobazam 50 mg. Detailed neuropsychological testing has not been performed. There were no other neurological signs or symptoms in the three probably and ten definitely and living affected members, especially no signs of cerebellar dysfunction. MRI of the brain of two patients (III:3, 10) showed slight cerebellar atrophy but no atrophy of brainstem or basal ganglia. Many anti-epileptic drug regimens had been tried, with clonazepam and sodium valproate being the most successful in diminishing the tremulous movements and the frequency of myoclonic and tonic-clonic seizures.

Table 1

Clinical and electrophysiological features of definitely and probably affected relatives.

Patient	FCTE	Age	Sex	T	M	MS	TCS	EEG	SEP, right/left (μ V)		C-reflex
									P14-N20	P27-N30	
I:2	D	†73	F	30	+	?	63	n.d.	n.d.	n.d.	n.d.
II:3	D	76	F	40	+	44?	44	n.d.	n.d.	n.d.	n.d.
II:7	D	72	F	+	+	37?	37	n.d.	n.d.	n.d.	n.d.
II:11	D	†67	F	+	+	?	+	n.d.	n.d.	n.d.	n.d.
II:13	D	†51	F	+	?	?	43	n.d.	n.d.	n.d.	n.d.
III:1	D	55	M	45	+	-	52	spike-wave, [irregular]	[0.4/0.1]	[6.5/6.3]	[-]
III:3	D	54	M	25	+	36	44	n.d.	n.d.	n.d.	n.d.
III:5	D	52	M	30	+	30	43	[spike-wave]	[1.2/0.8]	[3.8/3.9]	[+]
III:10	D	42	F	38	+	-	42	irregular	1.1/0.6	13.9/7.2	+
III:19	D	40	M	19	+	20	20	n.d.	n.d.	n.d.	n.d.
III:20	D	43	M	12	+	13?	31	n.d.	n.d.	n.d.	n.d.
IV:1	D	29	M	22	+	-	-	normal	0.6/0.6	5.4/4.7	+
IV:2	D	25	F	20	+/-	-	-	normal	0.5/0.6	9.4/12.5	+
IV:4	P	28	F	+	+	-	-	n.d.	n.d.	n.d.	n.d.
IV:5	P	24	M	20	+	-	-	n.d.	n.d.	n.d.	n.d.
IV:8	P	16	F	12	+	-	-	n.d.	n.d.	n.d.	n.d.

FCTE = familial cortical tremor with epilepsy, D = definite, P = probable, T = tremor, M = myoclonus, MS = myoclonic seizure, TCS = tonic-clonic seizure, EEG = electroencephalogram, SEP = sensory evoked potential, Pxx-Nxx = amplitude difference between Pxx-peak and Nxx-peak, C-reflex = cortical reflex, † = age of death, F = female, M = male, 30 = 30 years of age at onset, + = present, - = not observed, ? = unknown, ± = subtle, n.d. = not done, sw = spike-wave complexes, irr = irregular, n = normal, [...] = on anti-epileptic drugs, P27-N30>4.0 μ V: giant potential.

Tremor-recording showed an irregular 10-16 Hz tremor (III:1, 5, 10; IV:1, 2). C-reflexes and SEPs were studied in five persons (III:1, 5, 10; IV:1, 2, table 1). In two definitely affected members on medication, a C-reflex (III:1), or a giant potential (III:5) could not be detected. EEG examination showed individual differences between patients. Parietal spike-wave complexes but no photosensitivity was found in patient III:1; frontotemporal spike-wave complexes and epileptic changes during photo stimulation in patient III:5; and no abnormalities in patients IV:1 and 2. Back averaging showed no premovement cortical spikes.

Diagnostic classification was difficult in two family members. Patient IV:4 had suffered from infrequent complex partial seizures at the age of nine years, sometimes evolving into generalized seizures. Carbamazepine was effective and was discontinued after a seizure-free period of four years. There was no history of tremor or myoclonus. However, neurological examination at the age of 28 years showed a characteristic tremor and myoclonus. The epilepsy seemed not to be related to FCTE, but based on the clinical symptoms she was considered 'probably affected'. The other relative, a 26-year-old male (IV:6) suffered from a tremor. Neurological examination showed a fine postural tremor of both hands without myoclonus. The EEG showed focal changes but no distinct epileptiform discharges. C-reflex and giant SEPs could not be registered. His 50-year-old mother (III:8) was clinically unaffected but she may represent a non-penetrant carrier of the gene. He was therefore classified as possibly affected.

Linkage analysis

Single-point LOD scores between the selected markers on chromosome 8q23.3-q24.1 and FCTE are shown in table 2. All LOD scores were negative, suggesting absence of linkage. The multipoint LOD scores for the markers on chromosome 8q23.3-q24.1 showed exclusion of almost the entire region between markers D8S1784 and D8S1720 (LOD score < -2.0, figure 2). Only a

region of approximately 5 cM between marker D8S514 and D8S1720 did not fulfill the formal criterion for exclusion (maximum LOD score -1.91). This region was, however, outside the FCTE locus, as described in the other FCTE families^{6,7}.

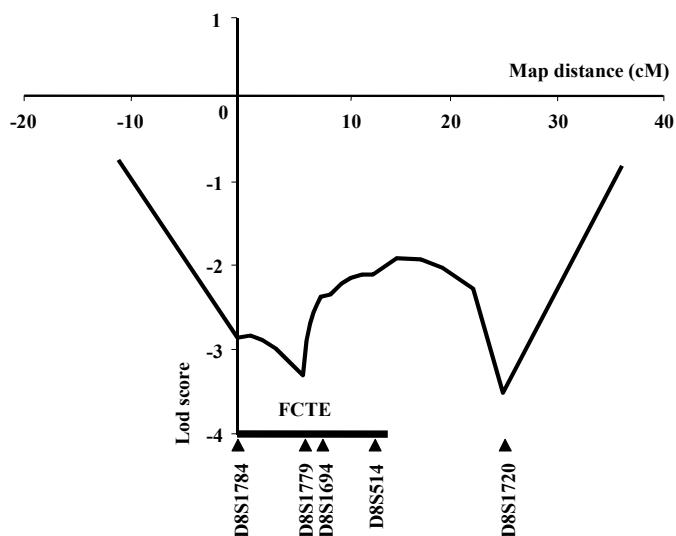
Table 2

Single-point LOD scores between FCTE and markers on chromosome 8q.

Marker	Recombination fraction (θ)					
	0.00	0.01	0.05	0.10	0.15	0.190
D8S1784	-1.715	-0.948	-0.372	-0.157	-0.061	-0.021
D8S1779	-3.326	-2.518	-1.589	-0.980	-0.611	-0.412
D8S1694	-1.463	-1.196	-0.740	-0.484	-0.329	-0.241
D8S514	-1.524	-1.486	-1.261	-0.879	-0.573	-0.394
D8S1720	-3.573	-2.428	-1.348	-0.837	-0.548	-0.391

Figure 2

Results of multipoint linkage analysis to exclude the known FCTE locus in our family with microsatellite markers from chromosome 8q23.3-q24.1, illustrating the region of exclusion.



Discussion

Our clinical findings are in line with previous studies and suggest that this epileptic syndrome can be distinguished from the other epileptic syndromes^{1,4-7}. It is characterized by (1) autosomal dominant inheritance, (2) intention-like tremor and distal myoclonus, (3) myoclonic and generalized seizures, (4) late onset, (5) moderate progressive course, (6) no pyramidal or cerebellar signs, or features of a neurodegenerative disorder, (7) electrophysiological features of cortical hyperexcitability, (8) good response to anti-epileptic drugs, especially clonazepam and valproate. The clinical criteria based on the previous reports on FCTE could be confirmed in the Dutch patients.

As it has been described before, FCTE can be differentiated from other inherited cerebellar and epileptic syndromes⁴⁻⁷. Patients with autosomal dominant cerebellar ataxias can present with a tremor but the lack of cerebellar signs, absence of known SCA-mutations and only slight cerebellar atrophy on MRI-scans make such a diagnosis unlikely. Seizures in juvenile myoclonic epilepsy have an earlier onset and occur predominantly shortly after awakening^{10,11}. Finally, the progressive myoclonus epilepsies with neurological deterioration consisting of cerebellar impairment and higher neurological dysfunction should be considered^{10,11}. The clinical course and the autosomal dominant inheritance pattern of the family presented make this diagnosis unlikely. The familial transmission pattern is not consistent with mitochondrial encephalomyopathy with ragged-red-fibres (MERRF). This was further excluded by histochemical examination of a muscle biopsy, as typical ragged-red-fibres were not observed.

Linkage to chromosome 8q23.3-q24.1 described in Japanese pedigrees with FCTE was excluded in the Dutch pedigree^{6,7}. The slightly different phenotype to previous descriptions of FCTE might explain this^{1,4-7}. The clinical picture of the Dutch patients closely resembles the features described in other known FCTE pedigrees. However, some clinical differences between pedigrees are

noticed and have been previously reported⁴. In contrast to our family, where patients always presented with tremor, patients reported by Okuma et al. (three families, seven affected members), presented either with tremor or epilepsy⁵. In addition, cognitive deterioration seems to be a symptom of Dutch patients in a more progressed stage. The negative effect of anti-epileptic drugs cannot be ruled out and further neuropsychological investigations are necessary. Interestingly, mental retardation was considered a disease feature in another European family (one family, seven affected members)⁴. This was only described in the third generation in combination with a more severe clinical picture suggesting anticipation⁴.

The observed typical tremulous myoclonus on EMG, the presence of C-reflexes and giant SEPs, and the immediate suppression of both tremulous movements and left parietal spike-wave complexes by clonazepam are in line with the diagnosis FCTE^{1,4-7}. The amplitudes of the SEP were less than 4 μ V in one definitely affected patient, due to the use of anticonvulsants^{1,5}. In contrast to other studies, EEG back-averaging was not a diagnostic tool in our family^{1,3-6}. In four Japanese families, back-averaging was not discussed⁷. The lack of a cortical correlate in the Dutch family is most likely due to the infrequency of myoclonic jerks and interference of the tremor. The tremor on which the myoclonic jerks are superimposed appears to have no cortical correlate, which makes the cortical origin of the tremor doubtful. Further detailed electrophysiological studies are needed to clear up the origin of the tremor. If the tremor does not originate in the cortex the name ‘familial cortical tremor and epilepsy’ should be reconsidered and changed in ‘familial myoclonus and epilepsy’.

The electrophysiological studies in FCTE are consistent with a lack of cortical inhibition. The main inhibitory neurotransmitter in the central nervous system, including the cerebellum, is γ -aminobutyric acid (GABA). Cortical myoclonus is associated with cerebellar changes, and changes in cerebellar inhibitory

function could be due to a changed GABA receptor function¹². Supportive for this hypothesis is that anti-epileptic drugs that affect the GABA receptor function were most effective and normalized the electrophysiological findings at the same time in FCTE. Genes encoding GABA receptor subunits are, therefore, good candidate genes for FCTE. The GABA receptor is a chloride channel receptor.

In idiopathic epilepsy syndromes and other paroxysmal neurological disorders, several mutations in genes encoding ion channels have been described: mutations in genes encoding subunits of the neuronal nicotinic acetylcholine receptor in patients suffering from autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) mutations in potassium channel genes in benign familial neonatal convulsions (BFNC) and mutations in sodium channel genes in generalized epilepsy with febrile seizures plus (GEFS⁺)¹³⁻²⁰. A channelopathy is most likely the cause of the epileptic syndrome FCTE. In conclusion, we describe a large Dutch pedigree with the typical clinical and electrophysiological features of FCTE. The lack of linkage to chromosome 8q23.3-q24.1 proves genetic heterogeneity of FCTE. This family gives a unique opportunity to further elucidate the molecular pathways leading to this syndrome.

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