Familial Cortical Tremor, Epilepsy, and Mental Retardation

A Distinct Clinical Entity?

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Objective: To describe a European family with cortical tremor, epilepsy, and mental retardation, the pedigree of which indicates an autosomal dominant inheritance of the disease.

Design: Clinical, laboratory, neurophysiological, and neuroimaging data were studied.

Setting: Institute for research on mental retardation.

Patients: Two siblings (aged 25 and 28 years) and their 49-year-old mother had postural and action tremor, seizures, and mental retardation. Only tremor was present in the maternal grandmother (aged 68 years). The electroencephalogram showed diffuse spike-and-wave complexes and/or posterior spikes, and a photoparoxysmal response in the 4 subjects. The typical electrophysiologic features of cortical reflex myoclonus, such as giant somatosensory evoked potentials, enhancement of the C-reflex, and jerk-locked premyoclonus spikes, were found in all patients.

Conclusion: This syndrome may represent a specific form of familial cortical tremor with a benign form of epilepsy and a new genetic model of cortical hyperexcitability inherited with an autosomal dominant mechanism.

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CORTICAL TREMOR (CT) is the term coined by Ikeda et al to define an action and postural tremor, often accompanied by seizures, characterized by the electrophysiologic traits usually found in cortical reflex myoclonus (CRM), such as giant somatosensory evoked potentials (SEPs), enhancement of C-reflex, and premyoclonus spike detected by means of the jerk-locked averaging method.1 Nineteen subjects with CT have been described to date.1-4 Although a family history of tremor and/or seizures was previously reported in some patients with CT,1-3 recently 3 Japanese families have been described with a similar clinical condition, inherited as an autosomal dominant trait and called familial cortical myoclonic tremor.4

We describe here a European family with CT, epilepsy, and mental retardation in which the pedigree suggests an autosomal dominant inheritance of the clinical and neurophysiological features.

The pedigree of the family is shown in Figure 1; there was no consanguinity between parents or grandparents. Subjects II-2 and II-3 were reported to be affected by finger tremor and subject III-5 to have both tremor and epilepsy.

CASE 1

A 68-year-old woman (patient III-4) had an 11-year history of nonprogressive postural and action tremor of the fingers. She never manifested seizures. No other neurologic abnormalities were found in this patient. Lysosomal enzyme activities, including β-hexosaminidase A and B, α-fucosidase, α-N-acetylglucosaminidase, β-glucuronidase, β-galactosidase, and neuraminidase, were normal. Optic fundi were normal. Electroencephalogram (EEG) polygraphic recording showed rare spikes mostly localized over the left posterior regions. Intermittent photic stimulation (IPS) at frequencies between 10 and 25 Hz triggered occipital spikes and spike-and-wave complexes. Surface electromyogram (EMG) recording of wrist muscles showed tremor characterized by rhythmic (8- to 10-Hz) rapid contractions, mostly synchronous on extensor and flexor muscles, not associated with clear EEG paroxysmal abnormalities (Figure 2).

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CASE 2
A 49-year-old woman (patient IV-5) complained of a tremor mostly involving her hands. Her prenatal and perinatal history was uneventful. Psychomotor development was reported as being normal. At 18 years of age, she had noticed difficulty in holding objects in her hands because of the presence of finger tremor. At the same time, she suffered her first seizure of the generalized tonic-clonic type during nocturnal sleep. The tremor did not worsen substantially thereafter. Seizures became rare after treatment with phenobarbital, and the last attack occurred at the age of 39 years. Results of physical examination were unremarkable, and mental status was normal. Neurologic examination showed a fine tremor mostly involving her fingers, elicited by outstretching both arms or moving the hands. Emotional stress aggravated the tremor. There were no abnormalities in the optic fundi.

Results of urinalysis and routine blood analysis and both lactate and pyruvate levels in the serum were within the normal range. Plasma amino acid concentrations and lysosomal enzyme activities, including β-hexosaminidase A and B, α-fucosidase, α-N-Ac-glucosaminidase, β-glucuronidase, β-galactosidase, and α-neuraminidase, were also normal. Karyotype was 46,XX. Polygraphic recording showed the presence of EEG spikes over the posterior regions of both hemispheres and of diffuse sharp waves; tremor was recorded by surface EMG from the wrist muscles, which showed short, rhythmic (8-Hz) contractions synchronous on extensors and flexors, apparently not accompanied by any particular EEG potential. The use of IPS at frequencies between 10 and 25 Hz induced the appearance of parieto-occipital spikes and spike-and-wave complexes spreading to the frontal regions. Results of motor and sensory nerve conduction studies were normal.

Cerebral magnetic resonance imaging disclosed mild enlargement of the subarachnoid spaces and of the lateral ventricles, especially the right one.

CASE 3
A 28-year-old woman (patient V-2) was the daughter of patient IV-5. She had been born at term by cesarean section. Psychomotor development was slightly delayed; she spoke her first words at about 3 years of age. She began to manifest generalized tonic-clonic seizures at the age of 5 years, which were completely controlled by treatment (phenobarbital and clobazam) at 16 years of age. At the age of 12 years she began to have tremor involving both hands that interfered substantially with her daily activities.

Results of physical examination, urine and blood analyses, plasma lactate and pyruvate levels, thyroid function, electrocardiogram, and motor and sensory conduction studies were normal. Karyotype was 46,XX. DNA testing for dentatorubral-pallidoluysian atrophy by polymerase chain reaction was negative. The patient was affected by moderate mental retardation (mental age, 7 years). At neurologic examination, a postural and action tremor was evident involving predominantly her fingers; it was aggravated by emotional stress and remained almost unchanged from the time of onset. Fundi oculi were normal.

The EEG was characterized by a 7-Hz background activity, diffuse spike-and-wave complexes, and posterior spikes. Diffuse spike-and-wave complexes were elicited by IPS at 10 to 30 Hz. Also in this case, rapid synchronous contractions of the agonist and antagonist muscles of the forearms were evident at surface EMG recording. Magnetic resonance imaging of the brain showed a mild enlargement of the subarachnoid spaces and of the lateral ventricles, predominantly on the left side.

CASE 4
A 25-year-old man (patient V-3), the brother of patient V-2, had been born at term, and his prenatal and perinatal history was uneventful. Psychomotor milestones were normally achieved. Since the age of 5 years he had suffered from frequent generalized tonic-clonic sei-
zures, sporadic episodes of status epilepticus, and absences, until the age of 21 years. At the time of admission he was taking carbamazepine. Results of physical and neurologic examination were normal, except for the presence of finger tremor that was more evident when the arms were outstretched, which had not shown worsening since childhood. The patient was moderately mentally retarded. Urine, blood, and neurometabolic analyses, fundus oculi, needle EMG, and magnetic resonance images of the brain were normal. Slow background activity and diffuse slow waves or spike-and-wave complexes were evident on the EEG recording. Numerous synchronous and asynchronous brief contractions of the extensor and flexor wrist muscles, not correlated with the above-mentioned EEG paroxysmal abnormalities, were present in the surface EMG recording. The use of IPS at frequencies between 25 and 30 Hz induced a photoparoxysmal response similar to that observed in the other 3 patients.

**NEUROPHYSIOLOGICAL STUDIES**

The following neurophysiological studies were performed in all patients. The EEG was recorded from 19 scalp electrodes referred to linked ears, with a bandpass filter of 0.1 to 100 Hz. The EMG was recorded by means of a pair of surface electrodes placed over the extensor and flexor muscles of both forearms; frequency response of the amplifiers was 100 to 2000 Hz. The EEG and EMG signals were sampled and digitized at 512 Hz. Fifty consecutive 500-millisecond artifact-free EEG epochs, centered at the onset of the rectified EMG bursts, were obtained and averaged.

The SEPs were recorded from 19 scalp electrodes (international 10-20 system), and linked ears were used as a reference. An analysis time of 150 or 205 milliseconds was used, and 128 single responses were averaged twice for each median nerve separately. Signals were bandpass filtered at 1 to 300 Hz and sampled to obtain 512 data points for each

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**Figure 3.** Polygraphic recording during wakefulness in patient 4 showing diffuse slow waves and numerous synchronous and asynchronous contractions prevalent on the extensor muscles of the forearms (Ext) not correlated with the electroencephalographic paroxysmal abnormalities. Flex indicates flexor muscles of the forearm; R, right; and L, left.

**Figure 4.** Jerk-locked averaging of electroencephalogram in patient 2 showing a positive deflection preceding the electromyographic burst of 27 milliseconds. The topographical mapping of this wave is also shown. Ext indicates extensor muscles of the forearm; R, right; and L, left.
RESULTS

Jerk-locked averaging of the EEG, triggered by the tremor activity of the forearm muscles, showed the presence, in all subjects, of a cortical positive wave over the fronto-central midline regions that occurred approximately 25 to 30 milliseconds before the jerk; this wave was followed by a negative peak at approximately 20 milliseconds after the jerk onset over the contralateral central parietal areas (Figure 4).

The SEPs elicited by median nerve stimulation showed a “giant” (30- to 50-µV) P25-N40 complex, with the negative peak mostly localized over the parietal regions contralateral to the stimulation. Figure 5 shows SEPs recorded in patients 1 to 4.

In all patients, an enhanced long-latency EMG response (C-reflex) was also recorded from the abductor pollicis brevis muscle with an onset latency of approximately 40 milliseconds after stimulation. The father of patients 3 and 4 did not present such an enhanced long-loop response (Figure 6).

COMMENT

The clinical and neurophysiological features of our patients are indistinguishable from those of CT, originally reported by Ikeda et al: (1) postural and action 6- to 8-Hz tremor, mimicking an essential tremor; (2) presence of seizures and EEG paroxysmal abnormalities; and (3) giant SEPs, enhanced C-reflex, and premyoclonus spike shown by the jerk-locked method. These electrophysiologic traits are usually also detected in CRM, one of the most common forms of reflex myoclonus, characterized by the presence of a discrete sensitive area on a limb, the stimulation of which results in a myoclonic jerk. There are many causes of CRM, such as sialidosis, adult-onset lipofuscinosis, Lafora body disease, Ramsay-Hunt syndrome, cerebral anoxia, and head injury. On the other hand, CT has been reported in idiopathic cases, but also in association with progressive myoclonic epilepsy, cerebral anoxia, and opsoclonus-myoclonus syndrome. According to the results obtained by scalp topography and magnetoencephalography in patients with CRM, myoclonus seems to be generated in the sensory cortex, which may activate the motor neurons by spinal interneurons or, alternatively, may drive motor output through its connections with the precentral cortex. Furthermore, CT seems to depend on a central generator rather than on a peripheral feedback loop, as demonstrated by the fact that transcranial magnetic stimulation but not peripheral nerve stimulation is able to influence tremor rhythm. These clinical and neurophysiological similarities have induced some authors to propose CT as being a common variant of CRM.

In our patients, jerk-locked EEG averaging disclosed the presence of a cortical premyoclonus transient with a positive peak over the fronto-central midline, similar to that described by Wilkins et al in a group of 11 patients affected by a condition called minipolymyoclonus of central origin. However, several clinical and neurophysiological differences can be seen between these patients and our subjects: (1) the patients with minipolymyoclonus were affected by Lennox-Gastaut syndrome, Alzheimer disease, familial progressive myoclonic epilepsy, and degenerative disease of unknown nature; (2) their myoclonic jerks were often bilateral and synchronous; and (3) the premyoclonus potential was negative in polarity and often with an earlier prejerk onset.

In the family we studied, 4 subjects showed the clinical and neurophysiological features of CT, and tremor was reported in another 3 members, 1 of whom also mani-
fested seizures. Thus, the abnormal phenotype seemed to be expressed in 5 consecutive generations; for this reason, an autosomal dominant inheritance of the disease can be suggested. In the previous reports of CT, patient 1 of Ikeda et al had 1 sister and 1 brother with finger tremor and seizures. Toro et al described another patient with CT who had “a positive family history of essential tremor.” The patients of Oguni et al had a poorly defined family history of “tremor of the hands, generalized epilepsy or both.” Terada et al reported on 6 patients from 3 Japanese families with familial cortical myoclonic tremor, an autosomal dominant entity characterized by the same neurophysiological features of sporadic CT. All of these patients started in adulthood to show a progressively worsening postural and action tremor, involving both upper and lower extremities. Three of these patients also showed rare and poorly defined episodes of loss of consciousness; 4 of them had epileptiform abnormalities and photoparoxysmal response to IPS. None of them was affected by cerebellar ataxia, mental retardation, or dementia. Although some neurophysiological findings of the patients of Terada et al were rather different from those of progressive myoclonic epilepsies, lymphocyte lysosomal enzymatic activities were within normal limits only in 1 patient, and biopsy and DNA testing for dentatorubral-pallidoluysian atrophy were not performed.

Tremor occurred during adulthood in our patients 1 and 2, similarly to the subjects with CT previously described, but it appeared much earlier in patients 3 and 4. Furthermore, it seems remarkable that the siblings V-2 and V-3 had a more severe clinical picture; in fact, they were also affected by mental retardation and their seizures started during childhood. This might result from a more severe expression of the neurologic phenotype through successive generations of this pedigree.

As in 3 of the above-mentioned Japanese patients, epilepsy had a benign evolution in all affected individuals in the family we studied, although diffuse EEG paroxysmal abnormalities were evident. Familial cortical hyperexcitability in our patients and in 4 of the patients described by Terada et al was correlated not only with somatosensory but also with visual stimulation. In fact, our subjects showed a photoparoxysmal response that has already been considered a genetically transmitted trait in the literature. None of our patients showed mental deterioration or cerebellar ataxia, results of DNA analysis for dentatorubral-pallidoluysian atrophy were normal in patient 3, and lysosomal enzymatic activities were normal in all patients. Thus, this familial condition with CT and epilepsy seems to be clinically different from a form of progressive myoclonic epilepsy and particularly from dentatorubral-pallidoluysian atrophy, an autosomal dominant neurodegenerative disease characterized by progressive myoclonus, epilepsy, cerebellar ataxia, choreoathetosis, and dementia.

The disease occurred at a younger age and was more severe in our youngest patients (patients 3 and 4) than in their older affected relatives; this fact seems to suggest that a mechanism of worsening through generations might be occurring in this family. One possible model of this phenomenon is that of the instability in length of the trinucleotide repeat of the eventual transmitted abnormal gene, which might intervene in determining the neurologic phenotype, as in other genetic conditions, such as fragile X syndrome, myotonic dystrophy, spinal bulbar muscular atrophy, and dentatorubral-pallidoluysian atrophy.

Numerous experimental and clinical studies have demonstrated that a reduction of γ-aminobutyric acid–ergic inhibition can produce cortical myoclonus, and clonazepam and valproic acid are effective in the treatment of CT. In addition, oral L-5-hydroxytryptophan in therapeutic doses alters the SEP excitability cycle and attenuates the long-latency reflex EMG. These data seem to suggest that at least the serotonergic and γ-aminobutyric acid–ergic systems might participate in the pathophysiological mechanism of CT, and linkage studies of the DNA polymorphisms of γ-aminobutyric acid and serotonin receptor should be performed on families with this disorder.

In conclusion, we think that the syndrome described in this report may represent a specific form of familial CT and a new genetic model of cortical hyperexcitability inherited through autosomal dominant transmission. Further observations of familial CT will allow genetic studies for the identification of the underlying molecular abnormality.

References for publication March 2, 1998.

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