Autosomal dominant cortical myoclonus and epilepsy (ADCME) with complex partial and generalized seizures
A newly recognized epilepsy syndrome with linkage to chromosome 2p11.1-q12.2

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Summary

We describe a pedigree in which eight individuals presented with a non-progressive disorder with onset between the ages of 12 and 50 years. It was characterized by predominantly distal, semi-continuous rhythmic myoclonus (all patients), generalized tonic–clonic seizures (all patients) and complex partial seizures (three patients). Most individuals had rarely suffered seizures and had a normal cognitive level, but three individuals with intractable seizures had mild mental retardation. The pattern of inheritance was autosomal dominant with high penetrance. We defined this disorder as autosomal dominant cortical myoclonus and epilepsy (ADCME). All patients had frontotemporal as well as generalized interictal EEG abnormalities. A neurophysiological study of the myoclonus suggested a cortical origin. Back-averaging of the data generated a series of waves with a frequency that mirrored the frequency of EMG bursts. Frequency analysis identified significant peaks with coherence between EMG and EEG, which were recorded over the contralateral rolandic area in five patients. The frequency of coherence was 8–25 Hz and phase spectra confirmed that EEG activity preceded EMG activity by 8–15 ms. In two individuals there was also significant coherence between the ipsilateral EEG and EMG, consistent with the transcallosal spread of myoclonic activity. The C-reflex at rest was enhanced and somatosensory and visual evoked potentials were of high amplitude. The resting motor threshold intensity to transcranial magnetic stimulation was significantly reduced (38%; SD ± 7; $P = 0.01$) and the post-motor evoked potential silent period (101 ms; SEM ± 10) was significantly shortened compared with the controls (137 ms; SEM ± 18). These clinical and neurophysiological characteristics suggest diffuse cortical hyperexcitability and high propensity for intra-hemispheric and inter-hemispheric cortical spread, as well as rhythmic myoclonic activity. Genome-wide linkage analysis identified a critical region spanning 12.4 cM between markers D2S2161 and D2S1897 in 2p11.1-q12.2, with a maximum two-point LOD score of 3.46 at θ 0.0 for marker D2S2175. Multipoint LOD score values, reaching 3.74 around D2S2175, localize the *ADCME* gene to the centromeric region of chromosome 2. The exclusion of the locus for familial adult myoclonic epilepsy on chromosome 8q23.3-q24 from linkage to our family and the new localization of the responsible gene to chromosome 2cen, together with the different phenotype, define a new epilepsy syndrome. We hypothesize that the responsible gene causes cortical hyperexcitability that is widespread but particularly involves the frontotemporal circuits.

Introduction

The study of genetic epilepsies with Mendelian inheritance has led to the identification of six genes that cause epilepsy (Steinlein *et al*., 1995; Charlier *et al*., 1998; Singh *et al*., 1998; Wallace *et al*., 1998; De Fusco *et al*., 2000; Escayg *et al*., 2000*a*, *b*). Although epilepsies with simple inheritance represent only a minority of the genetically determined epilepsies (Berkovic and Scheffer, 1997), study of the segregation of the disease trait within families and cloning of responsible genes have improved our understanding of the pathophysiology of human epilepsy and have led to the formulation of new concepts defining the spectrum of idiopathic epilepsy syndromes (Scheffer *et al*., 1995; Scheffer and Berkovic, 1997). We now know that both voltage-gated and ion-gated ion channel dysfunction are causes of idiopathic epilepsy (Steinlein *et al*., 1995; Singh *et al*., 1998; Wallace *et al*., 1998), that the epilepsy-producing dysfunction may be specifically age- and localization-related and clinically heterogeneous and that epilepsy can co-segregate with other paroxysmal neurological disorders, namely paroxysmal dyskinesias (Szepetowsky *et al*., 1997; Guerrini *et al*., 1999).

Nosology of monogenic epilepsies has, until now, shown that the main subdivision of the idiopathic epilepsies into distinct focal and generalized forms is confirmed by clustering of either form in distinct families (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), implying that epilepsy-producing genes are responsible for either focal or generalized epileptogenesis. Amongst the generalized epilepsies, a syndrome known as familial adult myoclonic epilepsy (FAME), has been described in several pedigrees from Japan (Mikami *et al*., 1999; Plaster *et al*., 1999). FAME is characterized by adult onset cortical tremor, i.e. a form of rhythmic distal cortical reflex myoclonus, generalized myoclonic jerks, rare generalized tonic–clonic seizures, generalized EEG abnormalities and normal IQ. A locus for this form of epilepsy has been mapped to chromosome 8q23.3-q24.1 through linkage analysis in Japanese families (Mikami *et al*., 1999; Plaster *et al*., 1999). Clinical and EEG characteristics suggest that FAME is a form of idiopathic generalized epilepsy akin to juvenile myoclonic epilepsy (Plaster *et al*., 1999).

Here, we describe an Italian pedigree in which, in addition to some clinical and neurophysiological characteristics similar to FAME and to frontotemporal and generalized EEG abnormalities present in all affected individuals, three of the eight living patients presented with complex partial seizures.

Genome-wide linkage analysis identified a critical region spanning 12.4 cM between markers D2S2161 and D2S1897 on chromosome 2p11.1-q12.2, with a maximum two-point LOD score of 3.46 at θ 0.0 for marker D2S2175. These findings indicate that the combination of rhythmic cortical myoclonus with generalized tonic–clonic seizures does not necessarily represent an expression confined to idiopathic generalized epilepsy. Furthermore, the exclusion of the FAME locus on chromosome 8q23.3-q24 from linkage to our family and the new localization of the responsible gene to chromosome 2cen, together with the different phenotype, define a new epilepsy syndrome.

Patients and methods
Patients

The proband (IV-4, Fig. 1) of a family from Tuscany, Italy, was referred for investigation of intractable seizures. A detailed family pedigree was constructed by collecting clinical histories on all putatively affected, as well as unaffected, individuals and spouses. There were 11 affected individuals (of whom eight are living) over five generations. We obtained genealogical information on 72 family members (including 10 spouses) and conducted a detailed evaluation of 19 individuals (Fig. 1 and Table 1). The inheritance pattern was autosomal dominant. Clinical characteristics in affected family members included: (i) adult onset of symptoms (all members); (ii) non-progressive course (all members); (iii) distal, fairly rhythmic myoclonus, enhanced during movement or posture maintenance (all members); (iv) generalized tonic–clonic seizures (all members); and (v) complex partial seizures (three patients: III-8, IV-2 and IV-4). Written informed consent was obtained from all patients included in the study. This study was fully approved by the Ethics Committee of the Institute for Medical Research, Stella Maris Foundation.

Clinical and video-electrophysiological studies

All but one of the affected individuals (III-13) were evaluated by video-EEG and simultaneous EMG monitoring while awake and asleep with bipolar and referential montages using silver–silver chloride surface cup electrodes. Long-term video-EEG monitoring was performed on two patients with refractory epilepsy. An EEG recording including sleep was also performed in five clinically unaffected individuals (III-9, III-10, III-12, IV-3 and V-1). Scalp electrode placement
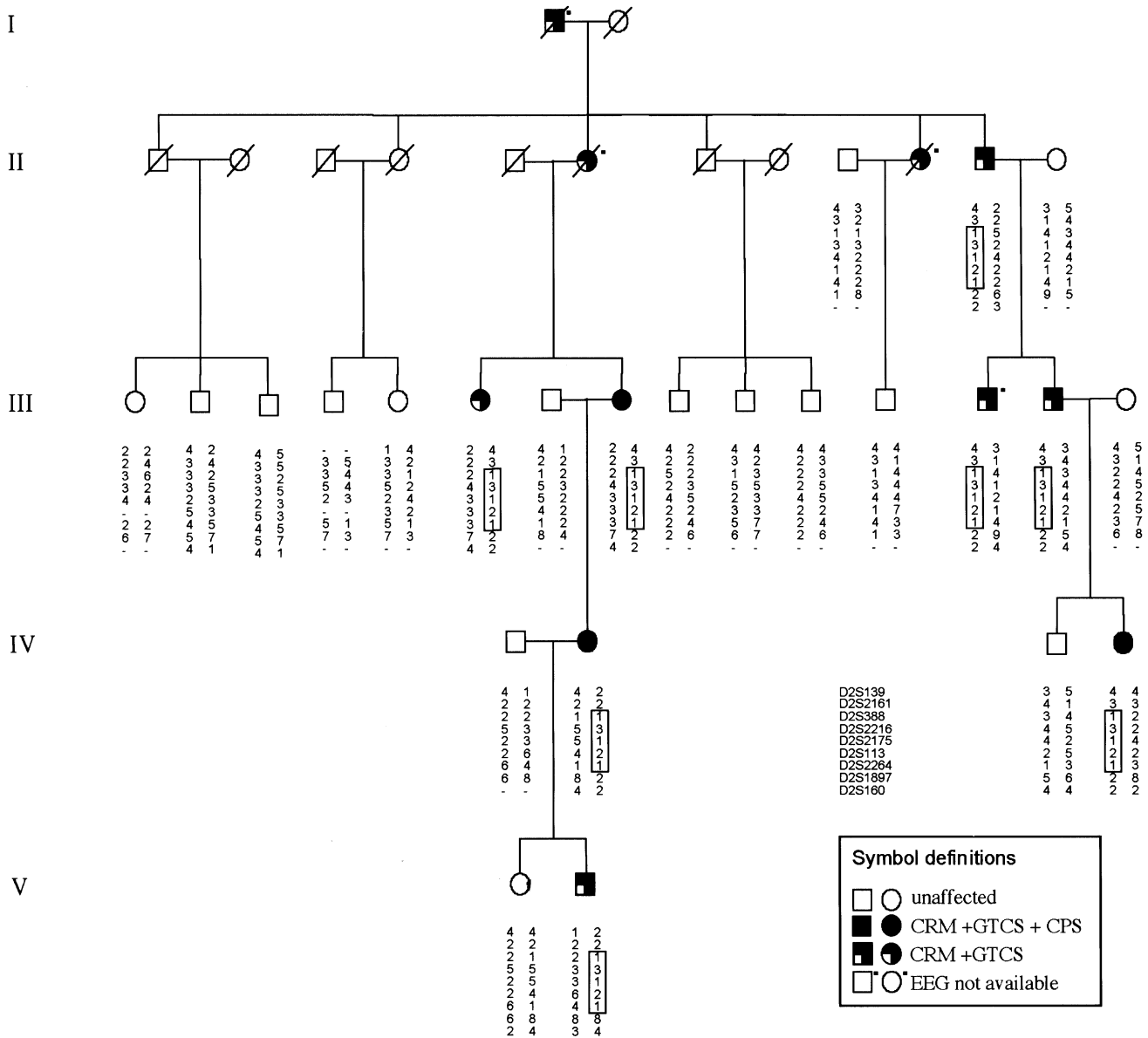
Fig. 1 Family pedigree showing haplotypes at the ADCME locus. The disease haplotype is boxed.

was performed according to the international 10–20 system. Recording included overbreathing and intermittent photic stimulation. EMG activity was recorded during movement and at rest using pairs of electrodes applied 3 cm apart over the masseter, orbicularis oris, deltoid, biceps, finger flexors and extensors, abductor pollicis brevis (APB) and tibialis anterior muscles. EEG–EMG activity was recorded on a computer for later analysis. Back-averaging of EEG activity data related to the EMG bursts was performed in all but one of the patients (III-13), using either APB or wrist extensor muscles as triggering muscles. The EEG signal was filtered using a bandpass of 1–100 Hz and digitized at the sampling rate of 1024 Hz. The average of 100–120 consecutive 500 ms artefact-free EEG epochs centred at the onset of the EMG burst (burst-locked EEG averages) was computed.

At least two averages were generated for each patient to ensure reliability between trials. Consistency of the responses was verified using the coefficient of variation, in terms of the ratio between standard deviation of each sample of peak latency measurements and relative mean [coefficient of variation = (standard deviation/mean) × 100]. A threshold of 5% was set to define the measurements as statistically reproducible. Frequency analysis was also performed between EEG and rectified EMG in seven patients using previously described techniques (Brown *et al.*, 1999).

Visual and somatosensory evoked potentials and C-reflex

Visual (V) and somatosensory (S) evoked potentials (EPs) were recorded in all but one of the patients (III-13). For the

Table 1 *Clinical and neurophysiological findings in eight patients with autosomal dominant cortical myoclonus and epilepsy*

| Patients | Age at | IQ | | | Epilepsy | | | | Myoclonus | | | SEP | | | C-reflex |
Pedigree reference	follow-up (years)	FSIQ	VIQ	PIQ	Age at onset (years)	Type of seizures	Seizure frequency	Interictal EEG abnormalities	Back-AVG Age at onset (years)	Frequency	Latency of pre-myoclonus spike N20P30 (w. Ext) (ms)	Amplitude P30N35 (µV)	APB (µV)	Latency APB (ms)	Cl C-reflex (ms)
II-11	81	91	89	95	59	GTC	1 seizure only	Bilat T + diffuse	50	8–15	19 (CV = 4)	20	29	47	abs
III-6	73	NA	67	NA	12	Myocl-GTC	Monthly	LT + diffuse	12	8–15	22 (CV = 1)	11	19	42	57
III-8	67	69	69	72	15	CP-SGTC	Weekly Seizure free since age 47	LT + diffuse	15	10–15	24 (CV = 2)	22	38	42	48
III-13	53	NA	NA	NA	34	GTC	2 seizures only Seizure free since age 47	NA	30	8–12	NA	NA	NA	NA	NA
III-14	57	94	96	91	27	Myocl-GTC	3 seizures only Seizure free since age 38	Bilat F-T + diffuse	20	8–15	18 (CV = 4)	20	28	45	55
IV-2	43	74	79	71	20	CP-SGTC	Monthly to daily	Bilat F-T (>R) + diffuse	20	8–15	19 (CV = 2)	8	10	39	47
IV-4	25	49	58	43	15	CP-GTC	Daily CP rare GTC	RT + diffuse	20	8–15	21 (CV = 1)	16	24	43	52
V-2	22	86	93	78	20	GTC	2 GTC	Bilat F-T (>R) + diffuse	17	8–14	22 (CV = 3)	12	14	42	48

abs = absent; AVG = averaging; bilat = bilateral; C = cortical; Cl = contralateral; CP = complex partial; CV = coefficient of variation; EEG = electroencephalography; FSIQ = full-scale IQ; F-T = frontotemporal; GTC = generalized tonic–clonic; LT = left temporal; myocl = myoclonal; NA = not available; PIQ = performance IQ; RT = right temporal; SEP = somatosensory evoked potential; SGTC = secondary generalized tonic–clonic; VIQ = verbal IQ; W. Ext = wrist extensor muscles.

flash VEPs, we measured amplitude and latency of the greatest positive peak. Control data were obtained from 10 age-matched healthy subjects.

SEPs were recorded from centroparietal (C3′, C4′ = 2 cm behind the International 10–20 system C3 and C4) regions, at the level of the seventh cervical spine, and from Erb's point, using several referential montages. Scalp electrodes were referred to the homologous contralateral area and contralateral mastoid, the seventh cervical spine to the anterior neck (thyroid cartilage) and Erb's point to the contralateral equivalent location. The C-reflex at rest was sought simultaneously by recording EMG activity from the following muscles: masseter, orbicularis oris, finger extensors and flexors, APB and tibialis anterior. The median nerve was electrically stimulated at the wrist, with a frequency of 1 Hz and a duration of 0.2 ms. The EEG signal was filtered with a bandpass of 1–2000 Hz. Blocks of 50–250 ms consecutive artefact-free responses were averaged. Trials were replicated to ensure reproducibility of the responses. Peak latency and amplitude were measured for each recognizable component at the C3′, C4′ electrodes. The amplitude was measured from the preceding peak of the opposite polarity. The nomenclature of each wave was the same as that used in other studies of cortical myoclonus (e.g. see Ikeda *et al*., 1995). SEPs were considered giant when the amplitude was >2.5 SD above the mean normal value (Shibasaki *et al*., 1985), established in 10 normal subjects aged 10–20 years (mean ± standard deviation, 16 ± 2.3 years). In selected patients, multiple channel SEPs were collected using average reference and displayed as topographic voltage maps. Taps to fingers were also employed to produce reflex myoclonic jerks. The C-reflex to both electrical and tapping stimulation was also studied in six unaffected individuals (III-9, III-10, III-11, III-12, IV-3 and V-1) using electrical stimuli at or just above motor threshold (Shibasaki *et al*., 1978).

Transcranial magnetic stimulation

A Cadwell magnetic device (Cadwell Laboratories, Kennewick, Wash., USA) was used to elicit motor evoked potentials (MEPs) in all but one of the patients (III-13), employing a flat, single round coil (outer diameter of 9.5 cm) placed on the vertex and C7 region. Threshold stimulation intensity (TI) and central motor conduction time (CMCT) were evaluated according to international guidelines (Rossini *et al*., 1994). In brief, the EMG electrodes were positioned bilaterally over the APB muscles. For each patient, TI (defined as the stimulus intensity required to produce a MEP of at least 50 μV amplitude in at least three out of five trials) was measured (Reutens *et al*., 1993). The intensity of transcranial magnetic stimulation was increased from sub-threshold levels by increments of 5% of maximum intensity. MEPs were then acquired for five stimuli at an intensity 10% above TI. In order to measure CMCT, peripheral latency was measured utilizing cervical stimulation at an intensity of 100% with the coil centred over the C7 spinous process.

CMCT was calculated by subtracting the peripheral latency from total latency. We also evaluated the post-MEPs silent period following transcranial magnetic stimulation (Cantello *et al*., 1992) during rhythmic EMG bursting patterns of hand myoclonus accompanying voluntary movement. For this purpose, patients were instructed to exert a steady voluntary isometric contraction of target muscle at two-thirds of the maximum and the level of force was monitored with the EMG level. Stimulation intensity was set at 10% above TI.

Control data were obtained from 10 age-matched healthy subjects. Statistical comparisons were performed using Student's *t*-test for unpaired data. Intracortical inhibition and facilitation could not be tested using the paired pulse technique (Kujirai *et al*., 1993).

Neuropsychological testing

Seven patients (II-11, III-6, III-8, III-14, IV-2, IV-4 and V-2) were submitted to a battery of cognitive and memory tests which were performed in two sessions. In the first, general intellectual abilities were assessed with the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955). One patient (III-6) could only be tested with the verbal subtests of the WAIS since she was visually impaired. For five patients, (III-8, III-14, IV-2, IV-4 and V-2) the pre-morbid level of verbal intellectual functioning was estimated with the Brief Intelligence Test (TIB; Sartori *et al*., 1995), the Italian version of the National Adult Reading Test (NART) (Nelson and O'Connell, 1978). TIB scores are highly correlated with WAIS verbal IQ, performance IQ and full-scale IQ in normal Italian adults. Patients II-11 and III-8 were not evaluated with the TIB because of non-compliance and presence of syllabic reading, respectively. In the second session, short-term and long-term verbal and non-verbal memory were evaluated as well as graphomotor abilities. The order of test presentation was the same for all patients, i.e. word-list learning (Mauri *et al*., 1997), Corsi's Block Tapping Span Test (Orsini *et al*., 1987), Supraspan learning of Corsi's block sequence (Splinnler and Tognogni, 1987), the Developmental Test of Visuo-Motor Integration—Revised (Beery, 1997), paired associate learning (Novelli *et al*., 1986) and Rey's Complex Figure (Rey, 1968). The patient's performance was compared with Italian normative data matched for chronological age, gender and years of education. No adult Italian norms were available for the Developmental Test of Visuo-Motor Integration—Revised, thus, only raw scores were considered. Five patients were submitted to the entire memory battery and graphomotor test, and two patients had limited assessment (Patient III-6 was unable to perform non-verbal memory and drawing tasks because of her poor vision, and Patient II-11 was not tested with the Rey's Complex Figure because of severe difficulties in the copying phase).

Neuroimaging

Six patients (II-11, III-6, III-14, IV-2, IV-4 and V-2) underwent brain MRI, using 1.5 T instrumentation. Single voxel 1H

spectroscopy was performed to study the rolandic cortex using the short TE (echo time) stimulated echo acquisition mode technique [TR (repetition time) = 2010 ms, TE = 30 ms, TM (mixing time) = 13.7 ms, 256 scans accumulated for signal averaging, VOI (volume of interest) dimension = 3.4 cc]. Raw data were analysed off-line and compared with normal values obtained from the same VOI location in 20 age-matched healthy subjects.

Genetic linkage studies

A genome-wide linkage mapping was performed by using highly polymorphic fluorescence-labelled markers, spanning all the chromosomes at an average reciprocal distance of ~10 cM. These preliminary data were analysed by the MLINK programme of the LINKAGE software package (Lathrop *et al.*, 1984; ftp://linkage.rockefeller.edu). Selected chromosomal regions were further investigated using additional markers which mapped telomeric and centromeric markers to the candidate loci. For linkage calculations, autosomal dominant cortical myoclonus and epilepsy (ADCME) was modelled as an autosomal dominant trait with 0.90 penetrance, mutation rate was assumed to be 10^{-4}. Recombination frequencies for males and females were assumed to be equal. Markers' alleles were considered equally frequent in the preliminary screening, whereas published allelic frequencies were used for candidate loci calculations. Multi-point linkage analysis was performed using the LINKMAP program (Lathrop *et al.*, 1984; at http://www.hgmp.mrc.ac.uk) moving the disease locus on subsets of four fixed markers.

Results

Clinical and neurophysiological data are summarized in Table 1.
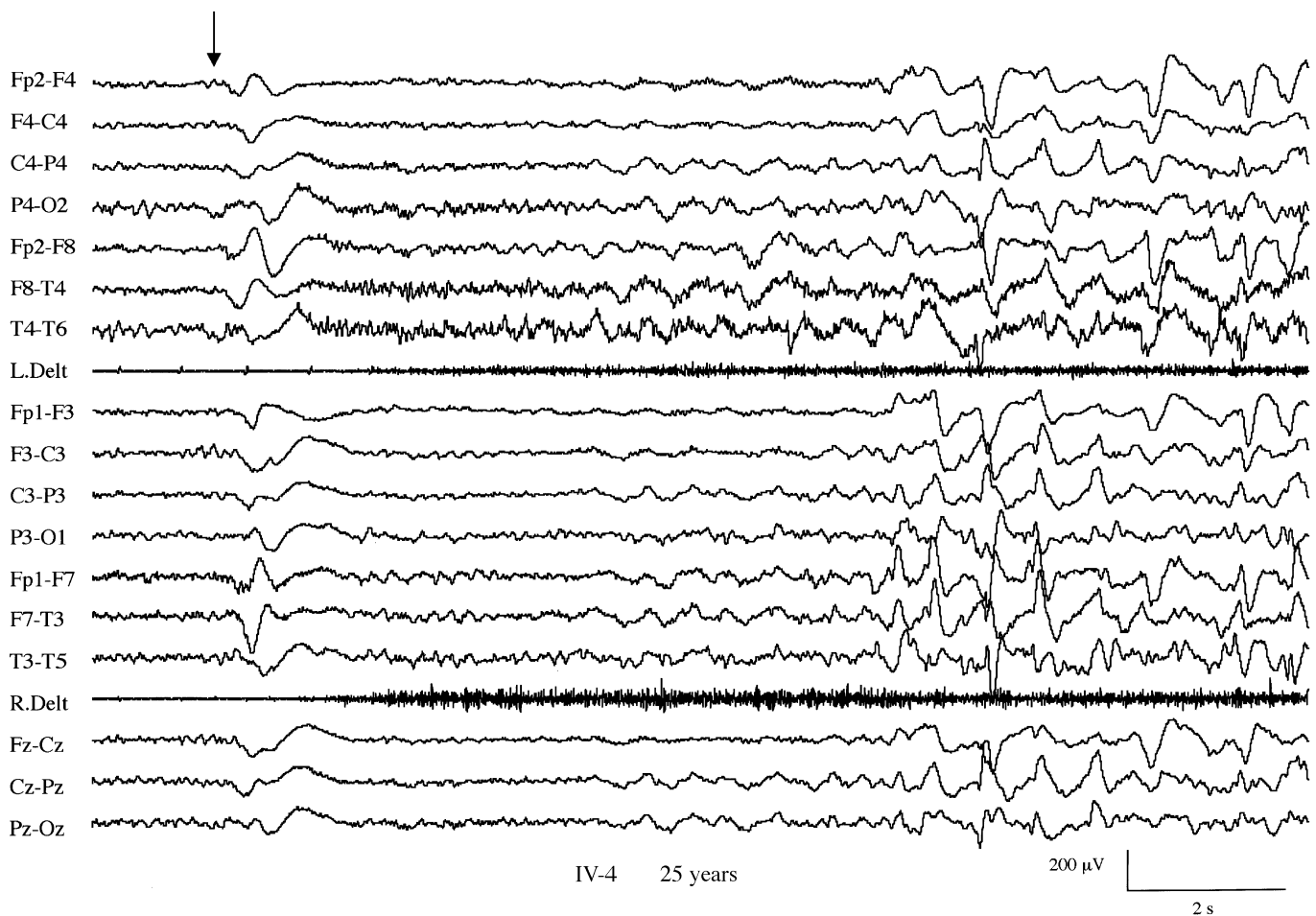
Fig. 2 Patient IV-4. Ictal EEG recording during a complex partial seizure. The patient, who was sitting on the bed, became suddenly unresponsive with a motionless stare (arrow), grimaced and nodded slowly. After being motionless for ~20 s, she gradually regained responsiveness, without any post-ictal language or motor deficit. EEG ictal onset is characterized by bilateral flattening of background activity, more pronounced on the right, followed 1 s later by rhythmic fast ictal activity with maximum over the right midtemporal and occipital electrodes. Ten seconds after seizure onset progressive slowing of EEG with superimposed slow spike and wave discharges is seen on all leads. L. = left; R. = right; Delt. = deltoid.

Clinical data

The parents of Patients I-1 and I-2 originated in Italy. There was no known consanguinity in the family. All patients had suffered from apparently generalized tonic–clonic seizures (GTCSs) both while awake and asleep. These seizures appeared without warning (Table 1), although in two patients (III-6 and III-14) some GTCSs were heralded by a cluster of generalized myoclonic jerks. The total number of GTCSs was variable but generally low (Table 1). Age at onset varied between 12 and 59 years (mean 25 years).

Three patients (III-8, IV-2 and IV-4) had also suffered from intractable complex partial seizures, which were often followed by secondary generalization. Ictal symptomatology of partial seizures was constant for each patient and varied slightly amongst patients. Patient IV-4 became suddenly unresponsive with a motionless stare, grimaced and nodded slowly, gradually recovering responsiveness after 20–30 s, without any language or motor deficit. She did not report any subjective symptoms. Several such seizures were recorded on video-EEG telemetry showing right temporal ictal activity (Fig. 2). Secondary generalization was very rare. Patient III-8 experienced an initial rising epigastric sensation, accompanied by sweating of the hands and followed by unresponsiveness with a motionless stare. Secondary generalization frequently ensued after ~15 s. Patient IV-2 reported an ill-defined unpleasant sensation accompanied by sweating of the hands, became unresponsive and slowly fell, without incurring any injury. In this patient too, secondary generalization also occurred frequently ~30 s after seizure onset.

All eight patients presented with rapid, fairly rhythmic myoclonic jerks of the hands of fluctuating amplitude, causing a tremor-like movement of variable severity. The patients with the most severe distal myoclonus were those who had suffered from intractable seizures (III-8, IV-2 and IV-4). Their hand jerking was obvious at rest, was exacerbated by posture maintenance and was accompanied by isolated arrhythmic multifocal jerks of the proximal arms, and eyelid twitching on some occasions. In the less severely affected individuals, only arm stretching or wrist extension uncovered the rhythmic jerking. Jerks disappeared during sleep. Age at onset of myoclonus ranged from 12 to 50 years (mean = 23 years) and, in most patients, slightly preceded or coincided with that at onset of the first seizure. The maximum severity of myoclonus was reached within the first year from its onset. Age at onset of both epilepsy and myoclonus did not show any systematic change across generations (see Table 1), in particular, there was no evidence for anticipation.

Patients II-11 and III-13 had only suffered one or two isolated GTCSs and were not treated with antiepileptic drugs. Patient III-14 had initially suffered three GTCSs followed by 20 years remission while treated with phenobarbital and phenytoin initially, and with valproate monotherapy subsequently. He refused to suspend his treatment. Patient V-2 had two initial GTCSs and was subsequently treated with valproate. In the following two years he suffered an additional similar episode after sleep deprivation. Patient III-8 had been seizure free over the last 20 years on phenobarbital and phenytoin, after having experienced several years of seizure intractability. She refused treatment simplification. Patient III-6 suffered from GTCSs, which had proven resistant to phenobarbital monotherapy and were only slightly improved after the addition of carbamazepine. The two remaining patients suffered intractable complex partial and generalized seizures in spite of polypharmacy (valproate + primidone + clonazepam in Patient IV-2 and primidone + levetiracetam + clonazepam in Patient IV-4). Both patients had previously undergone multiple antiepileptic drug trials.

In three patients (VI-2, VI-4 and V-2), myoclonus was considered to be severe or socially disabling enough to require treatment with clonazepam *per se*, with mild improvement. All three patients who had been treated with carbamazepine because of their seizures had experienced severe worsening of myoclonus (III-6, IV-2 and IV-4). While the drug was discontinued in two of them, the third patient (III-6) wanted to continue with carbamazepine treatment, which had improved her GTCSs.

Patients II-11 and III-14 reported that occasional intake of mild to moderate amounts of alcohol did not affect myoclonus.

Electrophysiological studies

EEGs showed normal background activity and interictal generalized epileptiform discharges in all seven patients studied and in two unaffected relatives (IV-3 and V-1). Six patients had focal temporal or frontotemporal spikes or spike and wave discharges as well as more diffuse abnormalities (Table 1 and Fig. 3). None of the patients showed more than one focus. The remaining patient (II-11), aged 81, had bilateral temporal predominant EEG abnormalities only. Transition from wakefulness to sleep produced an increase in interictal discharges. Intermittent photic stimulation at low rates (1–10 Hz) elicited a photoparoxysmal driving in which each flash triggered an occipital spike. There was neither clinical response to intermittent photic stimulation, nor a history of visually induced seizures.

EMG showed synchronous bursting of agonist and antagonist muscles with a mean frequency of 12 Hz (SEM $\pm$ 0.4; range 8–15 Hz) and a mean burst duration of 40 ms (SD $\pm$ 4). Each burst alternated with a period of EMG silence or near silence. On visual inspection of EEG-EMG traces, individual myoclonic potentials were not time-locked to any EEG transient (Fig. 4). Back-averaging generated a series of waves, with a frequency that mirrored the frequency of EMG bursts. The biggest of these consisted of a reproducible positive–negative biphasic transient in the hemisphere contralateral to the jerking hand (Fig. 5). The positive component of this transient had a mean duration of 37 ms (SD $\pm$ 6) and its peak occurred 21 ms (SD $\pm$ 2) before the onset of the EMG bursts when these were recorded
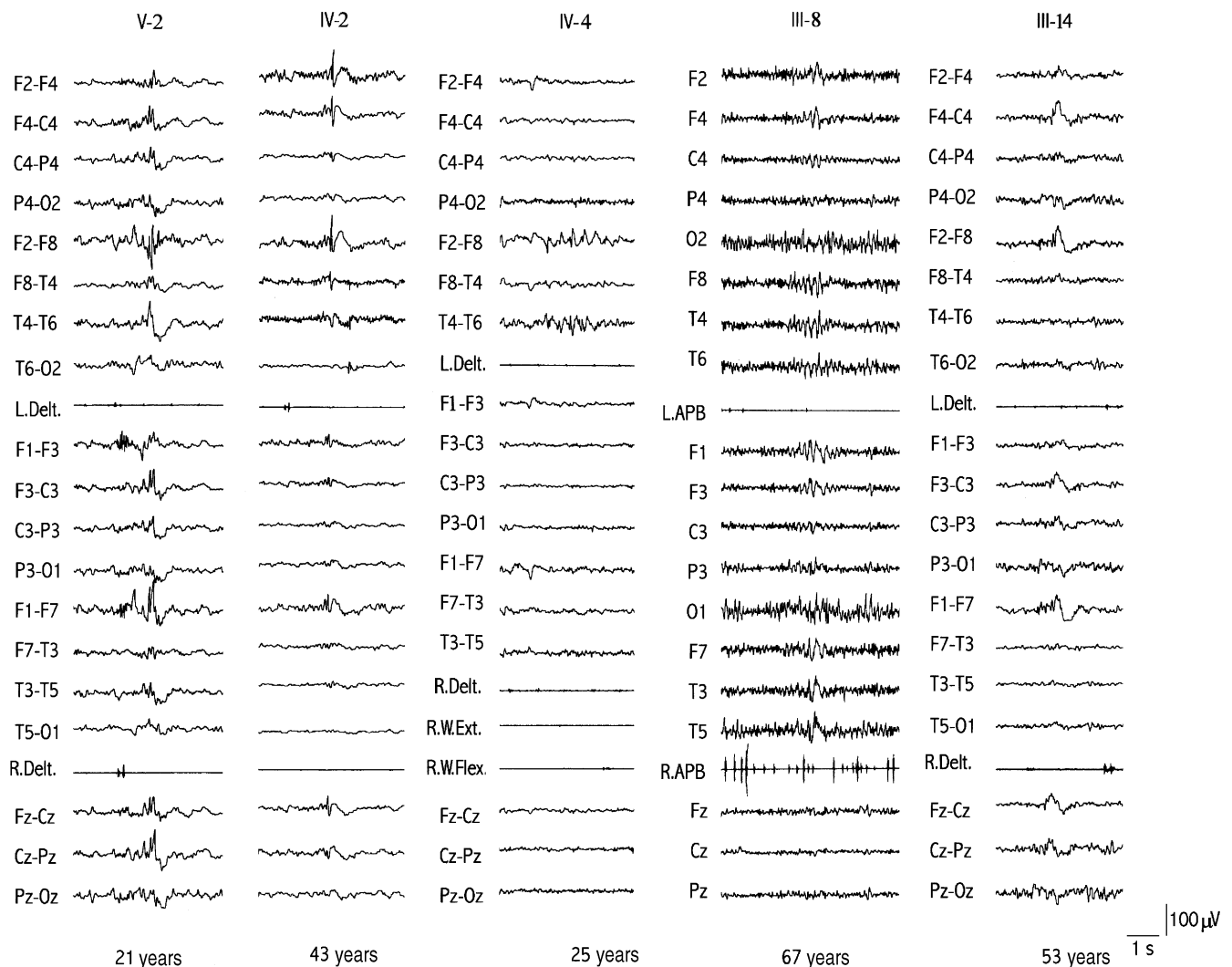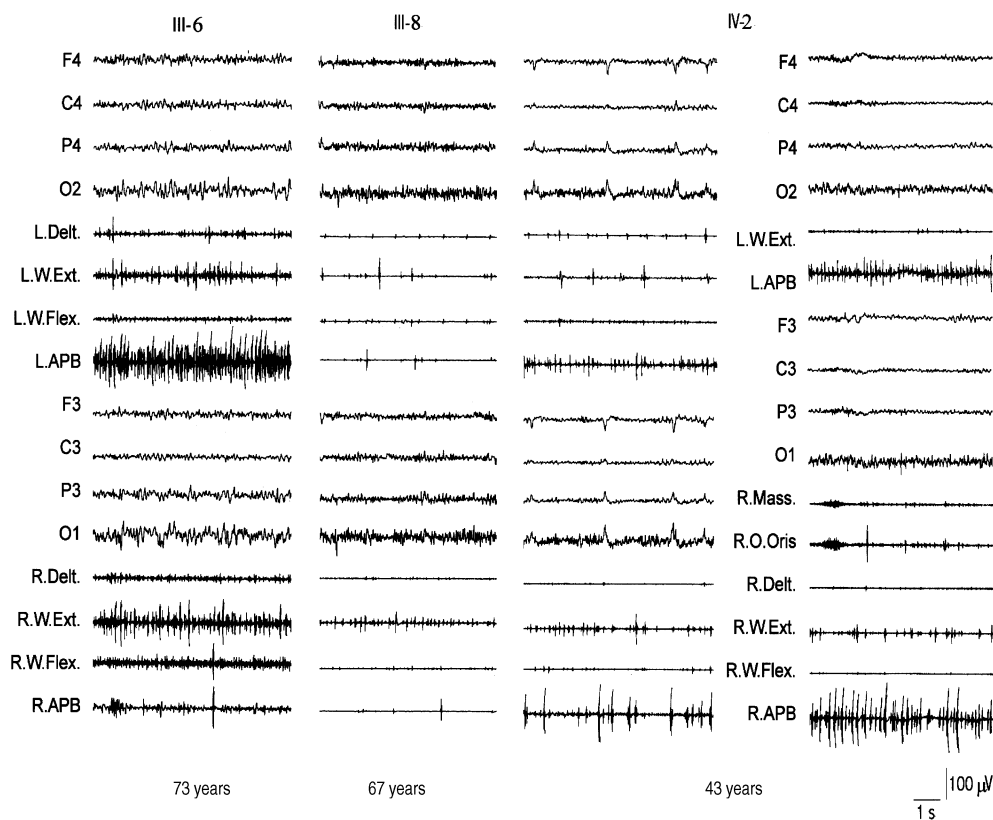
Fig. 3 Interictal EEG-EMG recordings during relaxed wakefulness in Patients V-2 (male), IV-2 (female), IV-4 (female), III-8 (female) and III-14 (male). Interictal discharges show equipotentiality over the right frontotemporal in Patients V-2 and IV-4, although are more diffuse in V-2. Similar right frontal spike and waves are seen in Patients IV-2 and III-14. Diffuse sharp waves with left frontotemporal predominance were recorded in Patient III-8, who also presented rhythmic myoclonic potentials in the right APB. In patient III-8 all scalp electrodes were recorded against a common average reference channel. L. = left; R. = right; Delt. = deltoid.

from the belly of the wrist extensors. This waveform could be identified in all patients and the averages were analysed. Nevertheless, as both myoclonus-related EMG and EEG activities were rhythmic, it was difficult to establish with absolute certainty from back-averages which of the various waves time-locked to the EMG discharge bore the most fixed temporal relationship to the EMG trigger. Conventionally it is assumed that the biggest in a train of waves is the most highly correlated with the EMG, but this is only true if all waves are of similar amplitude before averaging. We therefore complemented our back-averages with frequency analysis, and found significant peaks in coherence between EMGs and EEGs recorded over the contralateral rolandic area in five (II-11, III-6, III-8, III-14 and IV-2) out of the seven patients studied. The frequency of coherence was 8–25 Hz. More

importantly, phase spectra confirmed that EEG activity preceded EMG activity (Fig. 6), although, as in other studies, the EMG lag (8–15 ms) tended to be shorter than that derived from back-averaging (see above) and brief for even the fastest corticomuscular pathways (discussed in Brown, 2000). Nevertheless, the frequency analysis results indicate that the apparent coupling of EEG with EMG was unlikely to arise through EMG or other contamination of the scalp EEG. Coherence was greatest over the rolandic area contralateral to the myoclonus, while EMG contamination would have been expected to be symmetrical and to cover a broader band of frequencies. Cortex precedes muscle, excluding volume conduction as an explanation of coupling, while artefact related to eye movement would have been expected to involve lower frequencies, to have been more symmetrical and not

Fig. 4 Interictal EEG–EMG recordings during wakefulness in Patients III-6, III-8, and IV-2 (all female). These samples have been chosen to show the rhythmic bursting pattern produced by cortical myoclonus on the EMG channels, regardless of EEG activity. All scalp electrodes were recorded against a common average reference. L. = left; R. = right; Delt. = deltoid; W. Ext = wrist extensors; W. Flex. = wrist flexors; Mass. = masseter; O. Oris = orbicularis oris.

to exhibit any systematic phase coupling with myoclonic bursts. In two individuals (III-6 and IV-2), there was also significant coherence between the ipsilateral EEG and EMG, consistent with the transcallosal spread of myoclonic activity during spontaneous and action-induced myoclonus. The latter was further supported by the finding of coherence between EMG bursts in the right and left forearms.

### Visual and somatosensory evoked potentials and C-reflex

Flash VEP responses showed a significant increase in amplitude of the greatest positive peak compared with controls. For SEP responses recorded at Erb's point (N9), the seventh cervical spine (N13), N9–13 and N13–20 (expression of the central conduction time) interpeak times were within normal values. Mean baseline peak amplitude of the N20 component was within the normal range. In all patients, a significant increase was observed in interpeak amplitudes of the N20–P30 (16 μV; SD ± 5) and P30–N35 (23 μV; SD ± 10) complexes (+3 SD and +3 SD, respectively).

All patients presented hyper-excitable C-reflexes to electrical and mechanical stimulation at rest (Fig. 7). Their

ipsilateral response had a latency of 43 ms (SD ± 3) and was followed by a contralateral response after ~8 ms. This inter-side latency is similar to that previously reported in cortical myoclonus, and is compatible with transcallosal spread (Brown *et al.*, 1991). Spread of myoclonic activity was also evident within the stimulated limb (Fig. 8). Mapping of multi-channel SEPs (P30 wave) showed the same field distribution as that of the premyoclonic spike. None of the six clinically unaffected individuals in whom C-reflex was studied had an abnormal response.

Transcranial magnetic stimulation

MEPs showed total motor conduction time and CMCTs were within normal limits in all patients. The resting motor threshold intensity was significantly reduced (38%; SD = ±7; $P = 0.01$), despite the fact that five out of seven patients were tested while on antiepileptic drug treatment. When tested active, with an intensity of resting threshold of 120%, transcranial magnetic stimulation induced a post-MEP silent period lasting 101 ms (SEM = ±10). These values were markedly shortened compared with those obtained in controls (137 ms; SEM = ±18). The EMG activity following
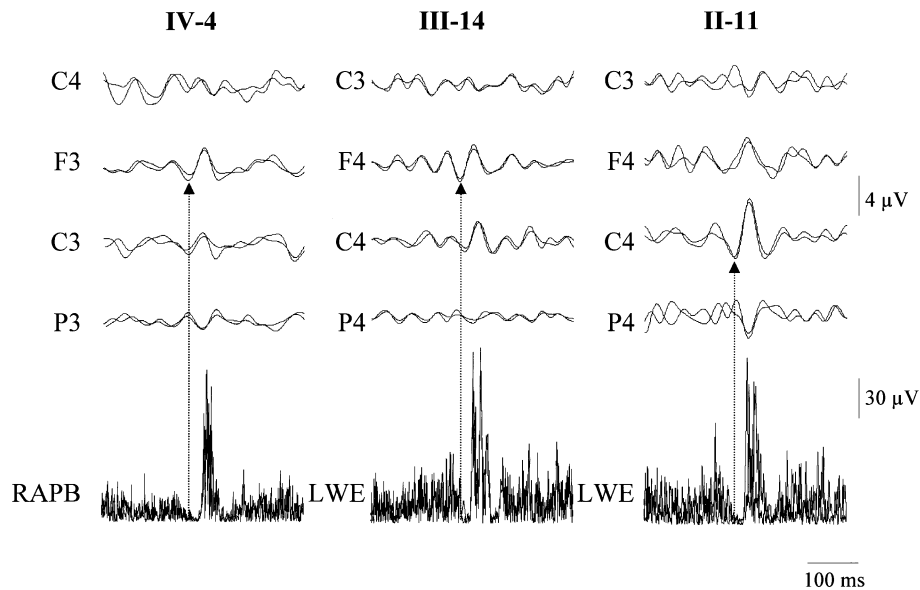
Fig. 5 Patients IV-4 (proband, left), III-14 (father, middle) and II-11 (grandfather, right). Back-averaged EEG activity ($n = 100$; rectified EMG) in relation to spontaneous focal jerks involving right APB or wrist extensor muscles. A positive–negative potential, recognizable over the contralateral frontocentral electrodes, preceded the jerk by ~15–20 ms. Upward pointing arrowed lines indicate the positive peaks from which latencies were measured. All scalp electrodes were recorded against a common average reference. RAPB = right abductor pollicis brevis; LWE = left wrist extensor.

the silent period immediately resumed the rhythmic bursting pattern of the pre-stimulus period.

Neuropsychological testing

Three patients (III-6, III-8 and IV-4) had mild to moderate mental retardation and one (IV-2) had borderline intellectual functioning according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders; American Psychiatric Association, 1994). In the remaining three patients tested, intelligence was in the low average range. Full scale IQ ranged from 49 to 94 in the six patients submitted to the entire scale. The verbal IQ score was higher than performance IQ score in four patients, but in all six, the worst performance was always found in the Performance Scale in Visuo-Constructive Subtests (Digit symbol and/or Object assembly). Estimated pre-morbid verbal intelligence ranged from 79 to 104. Estimated verbal IQ was higher than WAIS verbal IQ in the three patients with complex partial seizures (III-8, IV-2 and IV-4). Pre-morbid verbal intelligence was in line with verbal IQ in the other patients. Verbal memory was preserved and was in the average to above-average range in all patients except in the two patients with persistently intractable complex partial seizures (IV-2 and IV-4). These two patients displayed below average or impaired verbal memory performance. Non-verbal memory was generally less preserved than verbal memory and was in the below-average range in patients with generalized seizures only, and impaired or in the borderline range in the three patients who also suffered complex partial seizures. All five patients who

were submitted to the Rey Complex Figure Test displayed marked difficulties in drawing the figure from memory. Myoclonus affected copying performance in four out of six patients. No patient displayed major spatial errors in copying performance in the Developmental Test of Visuo-Motor Integration—Revised.

Neuroimaging

Brain MRIs were normal. Spectra acquired on rolandic cortex exhibited no signal abnormalities when compared with our normal values.
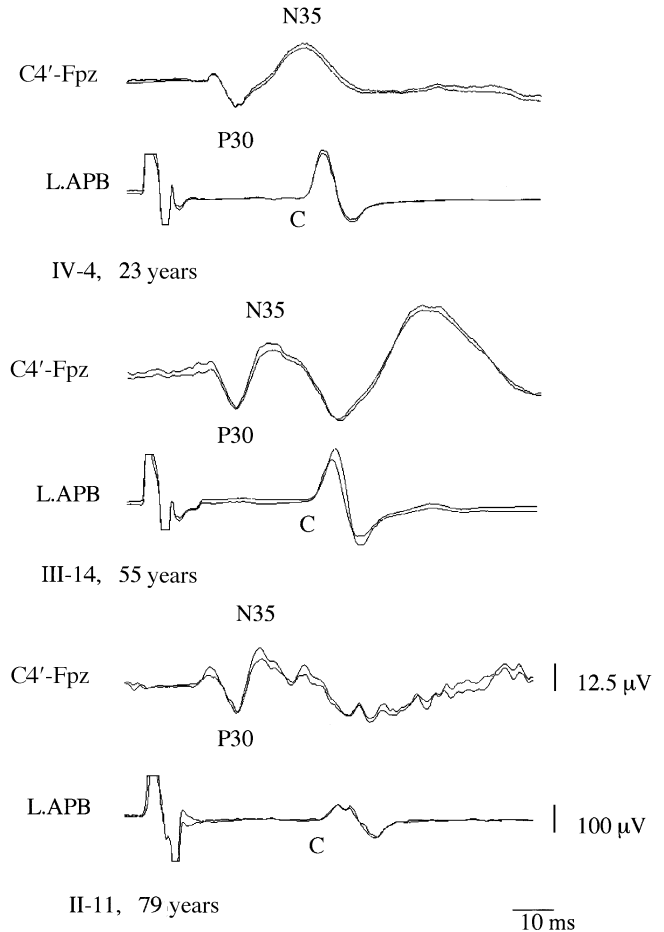
Genetic linkage studies

Known loci previously reported to be associated with myoclonic epilepsy (*EPM1*, *EPM2*, *EJM1*, *EJM2*, *FAME*, *EIM* and *CACNB4*, the human orthologue of the mouse epilepsy lethargic gene) were excluded. We tested the probability of detecting significant linkage by simulation analysis of 400 replicate pedigrees by using SLINK (linkage simulation program, enclosed in the LINKAGE package) considering the phenotype with a frequency of 1×10^{-5}. The maximum pairwise LOD (logarithm of the odds) score obtained from 400 simulated pedigrees was 3.4 at θ 0.0. In the genome-wide screening, only affected pedigree members were included. Selected loci suggestive of linkage (in 2cen and 3p26–25) were further characterized by locally increasing the marker density and by including all the available pedigree members. Chromosome 2 locus was significantly confirmed
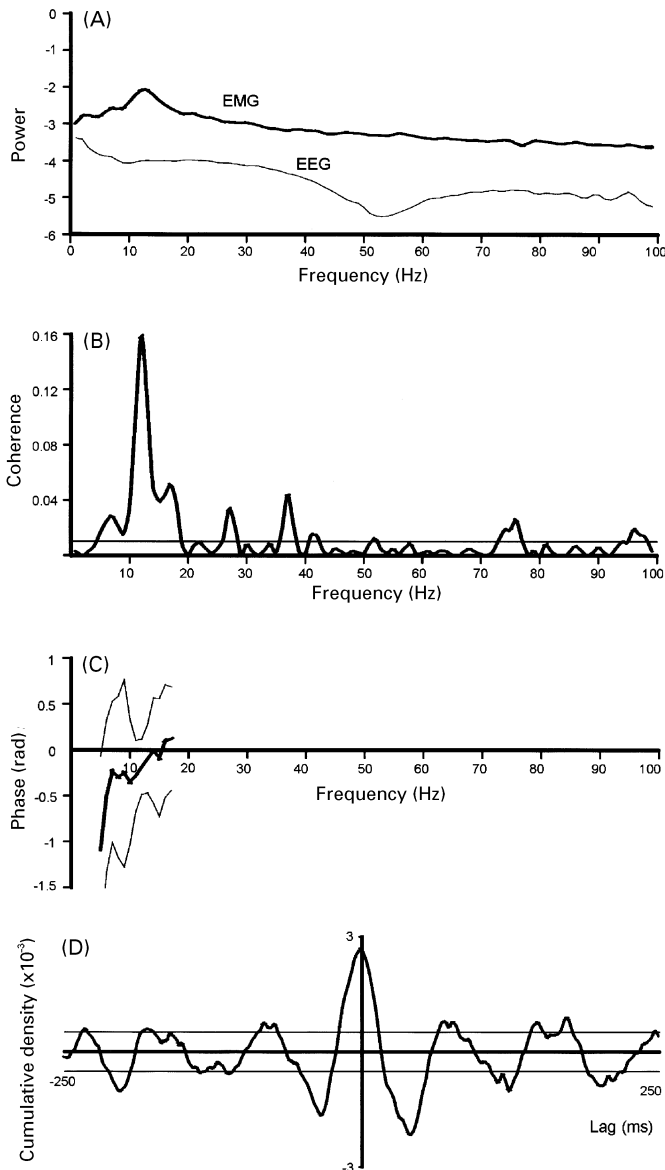
Fig. 6 Frequency analysis in Patient IV-2. (**A**) Autospectra of F4–C4 EEG and rectified EMG from left wrist extensor muscle. (**B**) Coherence between wrist extensor EMG and F4–C4 EEG. (**C**) Phase spectrum. Note linear phase relationship over the frequencies at which there is strong coherence. EEG precedes EMG by 8.5 s. (**D**) Cumulant density estimate. Thin lines in **B–D** indicate upper and lower 95%-confidence limits. Data derived from a continuous recording of 112 s.


Fig. 7 Patients IV-4 (proband, top), III-14 (father, middle) and II-11 (grandfather, bottom). Cortical SEPs to electrical stimulation of the left median nerve at the wrist. An enlarged N20-P30-N35 complex on the right centroparietal region is followed by C-reflex in the left APB. The shock-C-reflex latency is ~45 ms. L. = left; C = cortical reflex.

(Table 2) to be in linkage with ADCME linkage, reaching a LOD score value of 3.46 for D2S2175at θ 0.0. A common haplotype (1_3_1_2_1; Fig. 1) shared by all the affected individuals was identified with markers D2S388, D2S2216, D2S2175, D2S113 and D2S2264. A wide multi-point linkage analysis was performed with markers D2S139, D2S161, D2S388, D2S2216, D2S2175, D2S113, D2S2264, D2S1897 and D2S293. The graph (Fig. 9) shows a multi-point LOD score value of 3.74 around D2S2175, thus placing the localization of the *ADCME* gene in the centromeric region of chromosome 2.

Discussion

Affected members of this family presented with a homogeneous syndromic core including an association of non-progressive cortical reflex myoclonus, expressed with semi-continuous rhythmic distal jerking (cortical tremor), GTCSs (preceded in two patients by generalized myoclonic jerks) and generalized EEG abnormalities. The age at onset of cortical tremor and of GTCSs overlapped in a given individual but varied between individuals, ranging from 12 to 50 years. This clinical picture shares some features with FAME (Mikami *et al*., 1999; Plaster *et al*., 1999), identified as a form of autosomal dominant generalized epilepsy. However, all our patients had in addition focal frontotemporal EEG abnormalities, and three individuals also presented with
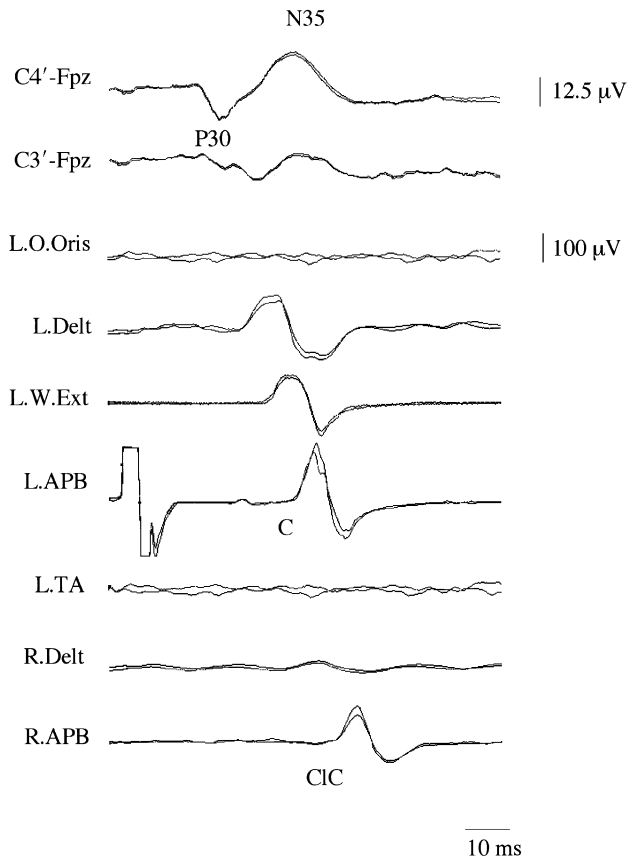
Fig. 8 Patient IV-4. Cortical SEP to electrical stimulation of the left median nerve at the wrist. An enlarged N20-P30-N35 complex is followed by C-reflex in the left deltoid, wrist extensors and APB. The ipsilateral muscular response precedes a contralateral response by ~8 ms. This delay is consistent with inter-hemispheric transcallosal spread. L. = left; O. Oris = orbicularis oris; Delt = deltoid; W. Ext = wrist extensors; C = cortical reflex; TA = tibialis anterior; R = right; ClC = contralateral cortical reflex.

complex partial seizures starting around the same age as the other manifestations, which were either intractable or, alternatively, went into remission after several years. In addition, myoclonic seizures were not a prominent feature in the family described here. We therefore decided to use the acronym ADCME, as clinical features are not consistent with a form of myoclonic epilepsy.

The distal jerking observed in all patients of this family had the characteristics of cortical tremor (Ikeda *et al.*, 1990; Toro *et al.*, 1993). A stereotyped pattern of rhythmic involuntary hand movements was evident during isometric muscle contraction, with rhythmic EMG bursts at 8–15 Hz synchronously involving agonist and antagonist muscles of the forearms. Involvement of more proximal as well as facial muscles, especially the eyelids, was noticed in some patients. Back-averaging and frequency analysis indicated that EEG activity was coherent with EMG at the frequency of the myoclonus and that EEG preceded EMG bursts. The C-reflex at rest was enhanced, SEPs were of high amplitude, motor threshold was reduced and the post-MEP silent period was shortened. Clinical and neurophysiological characteristics suggested a high propensity for intra-hemispheric and inter-hemispheric cortical spread as well as rhythmicity of myoclonic activity. In addition, intermittent photic stimulation at low rates evoked single occipital spikes in response to each flash, and flash VEPs were of very high amplitude. All these findings suggest widespread cortical hyperexcitability with deficits in inhibitory cortical mechanisms (Brown *et al.*, 1991, 1996; Uozumi *et al.*, 1992; Guerrini *et al.*, 1996; Cicinelli *et al.*, 2000). Rhythmic motor cortex excitation can originate from rhythmic generators within cortical layers IV and V (Connors and Amitai, 1997) or, alternatively, cortical neurones could be driven by a subcortical generator (Toro *et al.*, 1993).

Cortical tremor may be observed in different clinical settings, as a consequence of multiple aetiological factors enhancing motor cortex excitability. In addition to FAME (Ikeda *et al.*, 1990; Yasuda *et al.*, 1991; Terada *et al.*, 1997; Mikami *et al.*, 1999; Plaster *et al.*, 2000), it may also be observed in other genetic disorders including a form of

Table 2 *Two-point LOD score values for 2p11.1-q12.2 markers*

	0.00	0.01	0.05	0.10	0.20	0.30	0.40
D2S139	−3.18	−0.40	0.23	0.44	0.53	0.45	0.26
D2S2161	−3.41	−0.43	0.14	0.30	0.35	0.29	0.16
D2S388	2.68	2.63	2.45	2.20	1.65	1.04	0.42
D2S2216	3.04	2.98	2.73	2.40	1.70	0.99	0.39
D2S2175	3.46	3.39	3.13	2.79	2.07	1.29	0.52
D2S113	1.69	1.65	1.50	1.30	0.90	0.53	0.23
D2S2264	2.01	1.97	1.79	1.57	1.08	0.56	0.14
D2S1897	−2.29	0.62	1.10	1.13	0.88	0.52	0.21
D2S293	1.57	1.52	1.36	1.16	0.75	0.37	0.09
D2S340	0.34	0.33	0.31	0.27	0.20	0.12	0.06
D2S160	−2.73	0.25	0.79	0.88	0.75	0.48	0.21
D2S347	−3.34	−0.54	0.05	0.21	0.23	0.15	0.05
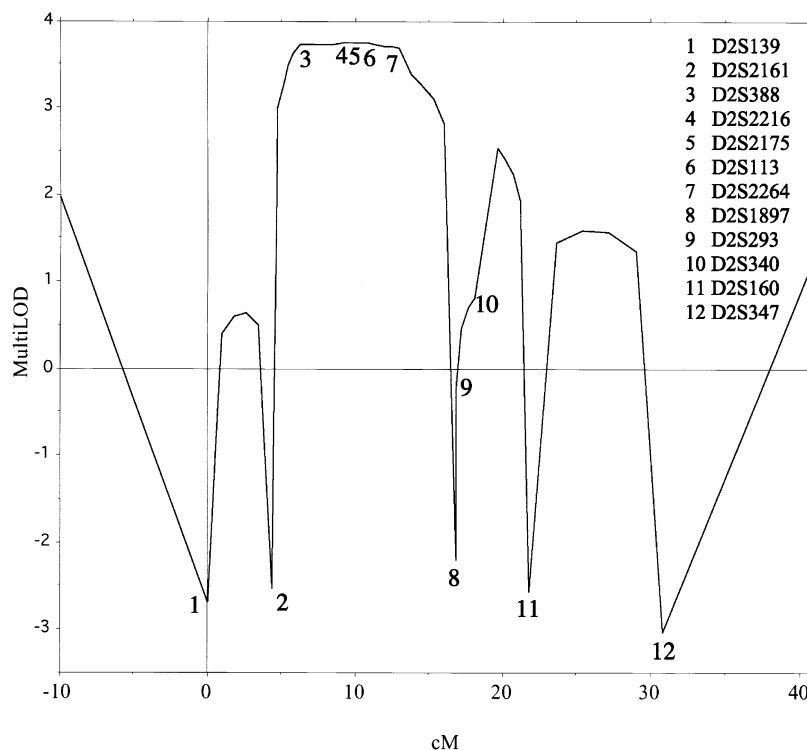
Fig. 9 Multi-point graph of the *ADCME* locus defining the critical region between D2S2161 and D2S1897.

familial mental retardation and generalized epilepsy (Elia *et al.*, 1998), Angelman syndrome (Guerrini *et al.*, 1996) and progressive myoclonus epilepsies (Toro *et al.*, 1993), in which it may be accompanied by generalized as well as focal seizures. Sporadically, patients with a clinical picture identical to FAME have also been described (Ikeda *et al.*, 1990). In addition, cortical tremor has been observed in association with focal motor seizures after ischaemic brain lesions involving the sensorimotor cortex (Schulze-Bonhage *et al.*, 1998; Wang *et al.*, 1999), or, as an isolated symptom, after surgical removal of a frontal lobe meningioma (Botzel and Werhahn, 1999) and in patients with no other neurological abnormality (Toro *et al.*, 1993). A condition that can probably be included within the spectrum of cortical tremor is mini polymyoclonus (Wilkins *et al.*, 1985). This phenomenon is characterized by quasi-rhythmic tiny finger movements due to synchronous jerks in both hands, preceded by a cortical potential. Although the original description indicated that mini polymyoclonus was related to primary generalized epileptic myoclonus (Wilkins *et al.*, 1985), current classification concepts indicate that some of the patients described had generalized symptomatic, non-genetic epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). All these observations indicate that cortical tremor is a common neurological manifestation and is often associated with epilepsy of either symptomatic or genetic aetiology.

All patients had rare GTCSs without any warning. Patients

with focal seizures also had generalized seizures preceded by a focal onset, although the propensity to generalization was variable. Complex partial seizures were similar in the three patients, being mainly characterized by a motionless stare with unresponsiveness for ~20–30 s, without any automatism, preceded in one by an epigastric aura and another by a non-specific warning. These seizure patterns cannot be attributed with certainty to any specific lobar origin. A frontotemporal origin is most likely and is, in part, supported by the presence of frontal and anterior temporal interictal EEG spikes in all three patients, and by the recording of partial seizures accompanied by ictal EEG activity in the right temporal lobe in one patient. Definition of the site of onset of focal seizures can be very difficult based on clinical and surface EEG findings alone when neuroimaging is normal. Attribution to a definite lobar origin may be misleading in the absence of a highly characteristic clustering of symptoms, and the epileptogenic area may not respect the anatomical limits of the cerebral lobes. A large study including 19 families with dominant partial epilepsies showed that there may be no clear boundary between the different genetic syndromes of focal epilepsy and that reliable lobar classification of the epilepsy can be difficult (Picard *et al.*, 2000). In addition, seizure spread from clinically silent areas may be rapid, producing unresponsiveness before subjective symptoms can be reported or memorized (Munari *et al.*, 1980). Certainly, electrophysiology indicated very rapid transcallosal spread between the two sensorimotor hemispheres during

myoclonic jerks in some patients. Since frontotemporal interictal EEG abnormalities were present in all affected family members, it is also possible that pronounced cortical hyperexcitability and propensity to spread may facilitate rapid seizure generalization, which obscures the focal nature of epilepsy in most patients.

As patients in this family had variable clinical severity and different drug treatments, it is very difficult to establish which antiepileptic drugs were more effective. The severity of the disorder seemed to be scarcely influenced by drugs, as demonstrated by the benign seizure outcome in the two patients who were never treated and by the drug resistance in others. In general, drugs combining antiepileptic and antimyoclonic properties such as valproate, phenobarbital and benzodiazepines produced the most benefit, while carbamazepine had paradoxical effects, causing seizure improvement and worsening of myoclonus.

Patients with well-controlled seizures displayed low average intelligence, had normal verbal memory and difficulties in some non-verbal memory tasks. Estimated pre-morbid verbal intelligence was generally in line with WAIS verbal IQ. Less preserved non-verbal memory in these patients, as well as the lower performance abilities on the WAIS, both requiring visuomotor integration, may be tied to continuous myoclonus. Patients with complex partial seizures had borderline intelligence to moderate mental retardation and global memory deficits, the latter occurring when seizures were intractable. Pre-morbid estimation of verbal intelligence indicated cognitive deterioration over time in the two patients with persistently intractable complex partial seizures, possibly as a consequence of the detrimental effect of uncontrolled seizures on cognition. This result should, however, be interpreted with caution since there is evidence that the NART overestimates intelligence at the lower end of the IQ range (Ryan and Paolo, 1992). On the whole, neuropsychological evidence indicates that low IQ may not be primarily genetically determined, but may result as a consequence of long-lasting severe epilepsy. Furthermore, the data suggest that the memory impairment observed in patients with complex partial seizures may not be tied directly to selective temporal lobe dysfunction, as performance was not impaired across all long-term memory tasks, and in some tasks, memory performance was not compromised more than general intelligence.

Two distinct phenotypes coexisted in the family reported here: a core clinical syndrome with generalized seizures and rhythmic myoclonus sharing common features with FAME, and a more severe phenotype also including complex partial seizures. This combination of symptoms in a unigenic model of epilepsy can be interpreted in different ways. One possibility is that this family has a FAME *plus* syndrome analogous to generalized epilepsy with febrile seizures (GEFS) *plus* syndrome, in which all affected individuals present febrile seizures early in life and later in life most of them develop different types of generalized seizures or, rarely, focal seizures (Singh *et al.*, 1998; Baulac *et al.*, 1999).

In this hypothesis, the same gene would be expressed with generalized as well as focal epileptogenesis, and focal seizures would just represent a non-specific expression of diffuse cortical hyperexcitability that is manifested in some patients. However, with diffuse cortical hyperexcitability we would expect multiple cortical areas to be able to generate different seizure types, while, in our patients, focal seizures were stereotyped and not polymorphous. A more likely alternative is that the responsible gene causes cortical hyperexcitability that is widespread, but particularly involves frontotemporal circuits as evidenced by the focal seizure activity in some patients, and the frontotemporal EEG abnormalities and myoclonic tremor due to involvement of the motor cortex in all patients. The implication is that the genetic defect can result in a relatively focal disturbance of cortical rhythmicity and excitability, and that generalized seizures originate from spread of regional epileptogenesis. In the case of the cortical tremor, this may involve disinhibition of the motor cortex physiological tendency to oscillatory discharge in the mu frequency range. The mu rhythm is present when a healthy subject is at rest and is attenuated (desynchronized) on tactile stimulation or voluntary muscle contraction (Tiihonen *et al.*, 1989). Nevertheless, a component of cortical activity persists in the same frequency band during isometric contraction and is coherent with EMG (Conway *et al.*, 1995; Salenius *et al.*, 1997). It is this component that we hypothesize was exaggerated in our patients with cortical tremor, as abnormal corticomuscular rhythmicity occurred in the same frequency band and under similar circumstances of isometric contraction, such as holding the arms outstretched. Interestingly, those physiological motor circuits leading to rhythmicities in the gamma band (Brown *et al.*, 1998) seem essentially spared by this condition, unlike many other myoclonic syndromes (Brown *et al.*, 1999).

Co-occurrence of focal and apparently generalized seizures has been reported in the same family on several occasions (Singh *et al.*, 1998; Baulac *et al.*, 1999; Picard *et al.*, 2000). Patients with generalized seizures have sometimes been excluded from studies aimed at characterizing focal epilepsy phenotypes for the purpose of genotype analysis (Picard *et al.*, 2000). However, studies on genetic epilepsies indicate that the same gene may be expressed to a different degree and with different regional predominance in different individuals. For example, patients with GEFS *plus* may have carrier relatives with temporal lobe epilepsy (Singh *et al.*, 1998). Some individuals with GEFS *plus* may also present with both primary generalized and focal electroclinical features (Baulac *et al.*, 1999). In partial epilepsy with variable foci different brain areas are involved in the same family (Scheffer *et al.*, 1998).

Considering the putative function of the genes mapping within the 12 cM critical region of this form of epilepsy, we identified the following candidates: downstream regulatory element antagonist modulator (DREAM) (Carrion *et al.*, 1999); calsenilin-KchIP3, a calcium binding protein that regulates voltage-gated potassium currents, and hence

neuronal excitability, in response to changes in intracellular calcium (An *et al.*, 2000) (DREAM and calsenilin are highly homologous and are predominantly expressed in brain); NPAS2 (neuronal PAS domain protein 2) (Zhou, *et al.*, 1997), a neuronal transcription factor; and GPCR45 (G protein-coupled receptor 45) (Marchese *et al.*, 1999), an integral membrane protein expressed in basal forebrain, caudate and frontal cortex. In addition, several partial transcripts encoding for potential candidate genes map to the *ADCME* locus. However, the large chromosomal area identified by the *ADCME* locus renders a positional cloning strategy quite unfeasible, while new *ADCME* pedigrees will contribute new recombination events to narrow the candidate region.

In our opinion, the manifestations of epilepsy and distal cortical myoclonus clustering in this family could be much more frequent than so far recognized. Since we started this study, we have identified several sporadic patients with similar clinical features. These patients may easily be misdiagnosed as having juvenile myoclonic epilepsy (Panayiotopoulos *et al.*, 1994), with generalized tonic–clonic seizures and proximal jerks being typical of both conditions. Complex partial seizures without automatisms seen in some of our patients are easily confused with absence seizures, and cortical tremor is interpreted as simple tremor, a relatively frequent side-effect of valproate treatment (Karas *et al.*, 1982).

Acknowledgements

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