Cortical Reflex Myoclonus in Rett Syndrome

Renzo Guerrini, MD,* Paolo Bonanni, MD,* Lucio Parmeggiani, MD,* Margherita Santucci, MD,+ Antonia Parmeggiani, MD,‡ and Ferdinando Sartucci, MD$.

Rett syndrome (RS) is one of the most frequent causes of mental retardation in females. As there are no known biochemical, genetic, or morphological markers, diagnosis is based on clinical phenotype including severe dementia, autism, truncal ataxia/apraxia, loss of purposeful hand movements, breathing abnormalities, stereotypies, seizures, and extrapyramidal signs. Myoclonus, although reported in some series, has never been characterized. We studied 10 RS patients, age 3 to 20 years, and observed myoclonus in 9. Severity of myoclonus did not correlate with that of the other symptoms or with age. Multifocal, arrhythmic, and asynchronous jerks mainly involved distal limbs. Electromyographic bursts lasted 48 ± 12 msec. Burst-locked electroencephalographic averaging generated a contralateral centroparietal premyoclonus transient preceding the burst by 34 ± 7.2 msec. Motor evoked potentials showed normal latencies, indicating integrity of the corticospinal pathway. Somatosensory evoked potentials were enlarged. The C-reflex was hyperexcitable and markedly prolonged (62 ± 4.3 msec), mainly due to increase in cortical relay time (28.4 ± 4.5 msec). We conclude that RS patients show a distinctive pattern of cortical reflex myoclonus with prolonged intracortical delay of the long-loop reflex.


Rett syndrome (RS) is a neurological disorder affecting females with clinical and neuropathological findings indicating early developmental arrest.15 An X-linked dominant inheritance, lethal in males, has been hypothesized, although an X-autosomal mechanism and non-Mendelian inheritance are also possible.6 With a prevalence of 1 per 10,000 to 15,000 girls, RS could be the second most frequent specific cause of mental retardation in females, next to Down syndrome.3 Diagnosis of RS is based only on the clinical phenotype,3 because, to date, there are no known biochemical, genetic, or morphological markers.

The clinical presentation and course of classic RS show a characteristic pattern indicating extensive and progressive involvement of the nervous system, with definable staging.7,8 After normal development to the age of 7 to 18 months, stagnation occurs, followed by a "destructive" stage, leading to severe dementia within 1.5 years from onset. This, in turn, is followed by a stable course for several decades. Deterioration of higher brain functions is accompanied by autism, truncal ataxia/apraxia, loss of purposeful hand movements, hyperventilation, stereotypic behavior, seizures, and acquired microcephaly. Extrapyramidal signs are present in most patients; although a hyperkinetic movement disorder is observed in younger girls, older patients tend to be bradykinetic.9,10

Myoclonus has been estimated to occur in about 50% of patients older than 4 years.10 However, in spite of its high frequency, neurophysiological analysis of myoclonus in RS has so far never been addressed.

We used repeated long-term video-electroencephalographic (video-EEG) and simultaneous electromyographic (EMG) recordings to study 10 girls with stage 2 to 4 RS, detecting myoclonus in 9 of them. Jerk-locked back-averaging of EEG activity, somatosensory evoked potentials (SEPs), and long-loop evoked responses (C-reflex) demonstrated a cortical reflex origin of myoclonus. Although myoclonus in itself did not represent a dominant clinical feature in this patient population, it appeared relatively early and showed peculiar characteristics that could be useful to provide support for diagnosis.

Patients and Methods

Patients

Ten girls with classic RS, referred consecutively to two centers (ICNP-Pisa and DCNP-Bologna), were included in the study. Criteria used for clinical diagnosis and staging were those proposed by the Rett Syndrome Diagnostic Criteria Work Group.9 Age at the time of study ranged between 3 and 20 years (mean: 9 years; median: 8 years). Progression of the disease had been followed clinically and with serial EEGs for 2 to 17 years (mean: 7 years). To ensure comparability of
neurophysiological parameters between patients andagematched controls, we calculated mean values by dividing both patients and controls into two subgroups, i.e., age 9 years and younger and age 10 years and older.

Clinical and Video-Electrophysiological Studies

All patients were evaluated using long-term video-EEG and simultaneous EMG monitoring with bipolar and referential montages, using silver/silver chloride surface cup electrodes. All neurophysiological recordings were performed in the same center (ICNP-Pisa). Scalp electrode placement was performed according to the International 10–20 system. EMG activity was recorded by using pairs of electrodes applied 3 cm apart over the masseter, orbicularis oris, deltoid, biceps, finger flexors and extensors, abductor pollicis brevis (APB), and quadriceps femori muscles. EEG/EMG activity was recorded by computer for later analysis. Back-averaging of EEG activity related to the EMG bursts was performed in the 9 patients with clinically significant myoclonus (Patients 1–8 and 10). The EEG signal was filtered, using a bandpass of 1 to 100 Hz, and digitized at the sampling rate of 1,024 Hz. The average of 100 to 120 consecutive 500-msec artifact-free EEG epochs centered 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. Averages of 100 to 120 consecutive 500-msec artifact-free EEG epochs related to EMG silent periods (SPS) (silence-locked EEG averages) were generated from the same EEG data. Consistency of the responses was verified by using the coefficient of variability (CV), in terms of the ratio between standard deviation of each sample of peak latency measurements and relative mean [CV = (SD/mean) × 100]. A threshold of 5% was set to define the measurements as statistically reproducible. Back-averaged EEG was displayed as topographic voltage maps to identify electrical field distribution via a computerized EEG system.

To define myoclonus severity, a score of 0 to 4 was assigned. The score was determined by the number of spontaneous jerks per minute occurring in the EMG of wrist flexors and extensors bilaterally at rest (quantification of jerks was unreliable during movement). The jerks were quantified during 15 minutes of awake and drowsy recordings. The patient showing the highest number of jerks per minute was assigned a score of 4 (100%), and the other patients were subsequently assigned scores of 3 (<75%), 2 (<50%), 1 (<25%), and 0 (<5%).

Somatosensory Evoked Potentials and C-Reflex

SEP were recorded in all patients from centroparietal (C3’ and C4’) = 2 cm behind the International 10–20 system C3 and C44 regions, at the level of the seventh cervical vertebra (C7), and from Erb’s point (EP), using several referential montages. Scalp electrodes were referenced to the homologous contralateral area and contralateral mastoid. C” to the anterior neck (thyroid cartilage), and EP 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 quadriceps femori. The median nerve was stimulated electrically at the wrist, using an intensity strong enough to produce a visible twitch of the thenar muscle, with a frequency of 1 Hz and a duration of 0.2 msec. The EEG signal was filtered with a bandpass of 1 to 2,000 Hz. Blocks of 50 to 250 consecutive artifact-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’ and C4’ electrodes. The amplitude was measured from the preceding peak of the opposite polarity. The nomenclature of each wave was established based on the work of Ikeda and colleagues. SEPs were considered to be giant when the amplitude was greater than 2.5 SD above the mean normal value. Established in 10 normal subjects, of whom 5 were age 3 to 9 years (6.4 ± 1.3 years; mean ± SD) and 5 were age 10 to 20 years (16 ± 2.3 years). C-reflex with muscular facilitation was sought simultaneously in the same control population. Statistical comparisons were performed by using Student’s t test for unpaired data. In selected patients, multiple-channel SEPs were collected by using the average reference and displayed as topographic voltage maps. Taps to fingers were also used, to produce myoclonic jerks.

Transcranial Magnetic Stimulation

A Novametrix Magstim 200 magnetic device was used to elicit motor evoked potentials (MEPs) in 6 patients (Table), using a flat, single round coil (inner diameter, 9.5 cm) placed on the scalp. The EMG surface-recording electrodes were placed in the APB. The effects of peripheral nerve, cervical, and transcranial magnetic stimulation (TMS) on voluntary motor contraction were also analyzed. Single TMSs were delivered to the contralateral side of the scalp. Stimulus intensity was 100% of the stimulator’s output (1.5 T). Cervical stimulation was delivered with the coil centered over the C7. Trials were replicated at least four times to ensure reproducibility of responses. Control data for TMS, including total motor conduction time (TMCT), peripheral direct and indirect (F wave) motor conduction times, direct and indirect (F wave) central motor conduction times (CMCT), amplitude of responses, and post-MEP SP were obtained from 10 healthy subjects, age 4 to 10 years (7 ± 2 years), and from 10 healthy subjects, age 15 to 30 years (25.6 ± 2.3 years). Statistical comparisons were performed by using Student’s t test for unpaired data.

Neuroimaging

Eight patients underwent brain magnetic resonance imaging, using 0.5- or 1.5-T instrumentation. The remaining 2 patients underwent brain computed tomographic scans.

Effects of Piracetam on Myoclonus

All patients were treated with various antiepileptic drugs because of epileptic seizures or severe epileptiform EEG abnormalities. To assess the effects of piracetam on myoclonus, 400 mg/kg of the drug was administered intravenously over 30 minutes in 3 patients (Patients 4, 5, and 10). Intravenous testing was chosen in order to assess drug efficacy acutely, thereby allowing an immediate decision on the suitability of long-term oral treatment without an additional video-EEG recording. The number of myoclonic jerks recorded synchronously in the EMG of wrist extensors and flexors from both

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Table. Neurophysiological Data on 10 Patients with Rett Syndrome

<table>
<thead>
<tr>
<th>Patient no./age (yr)</th>
<th>Myoclonus Severity</th>
<th>Disease Stage</th>
<th>Back-Averaged EEG</th>
<th>SEPs (measured at C4' and C3')</th>
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<tr>
<td></td>
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<td>Latency (Wrist Flex) (msec)</td>
<td>N20 Latency (msec)</td>
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<td>CV (msec)</td>
<td>Duration (msec)</td>
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<td>3.4</td>
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<tr>
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<tr>
<td>Mean (≥10 yr)</td>
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NE = not elicitable; ND = not done.

'SEP latency = (N20 latency + TMCT).

This patient was excluded from mean calculation because of lack of myoclonus.

*p < 0.005; *0.005 < p < 0.05 (t test).

EEG = electroencephalogram; SEPs = somatosensory evoked potentials; MEPs = motor evoked potentials; CV = coefficient of variability; TMCT = total motor conduction time; CMCT = central motor conduction time; SP = silent period; Flex = flexors; APB = abductor pollicis brevis; ND = not done; NE = not elicitable; NC = not calculated.

Results

The Table summarizes the stage of the disease, the severity of myoclonus, and the neurophysiological findings in the 10 patients.

Clinical and Video-Electrophysiological Analysis of Myoclonus

Nine patients exhibited multifocal myoclonus, varying greatly in severity. By assigning a score of 100% to the patient with the highest number of jerks per minute at rest (Patient 4), we found that the only patient with no clinically observable myoclonus (Patient 9) had a score of 3%.

Myoclonus occurred at rest in isolated and arrhythmic multifocal jerks and was enhanced by voluntary movement. At rest, jerks were predominantly distal but also involved one entire limb or facial muscles. Synchronous EMG bursting of agonist and antagonist muscles had a mean duration of 48 ± 12 msec. Bilateral or generalized myoclonus was never recorded. Myoclonus at rest was exacerbated during drowsiness and attenuated to the point of disappearance, during deep sleep. In all patients, EEG showed slow background activity (3–6 Hz) with the subcontinuous 4- to 6-Hz rhythmic sinusoidal pattern typical of RS. Superimposed multifocal epileptiform abnormalities were present, clearly predominating over the frontocentral areas.

On visual inspection of the polygraphic traces, myoclonus was only occasionally time-locked with spike EEG activity. However, in all 9 patients with myoclonus, jerk-locked back-averaging of EEG activity generated a reproducible premyoclonic negative–positive–negative or positive–negative spike in the centroparietal region of the hemisphere contralateral to the jerking sides after the end of the infusion was then calculated from the first 15 minutes of wakeful rest within 1 hour from drug administration. Results were then compared with the number of jerks occurring in similar circumstances and over identical time samples in the EMG preceding the infusion. Statistical comparisons were performed by using Student’s t test for unpaired data. In addition, the effect of piracetam administration on the motor pattern was monitored clinically, comparing videotape recordings made during an hour of observation before the infusion and during the 2 subsequent hours. Further similar assessment of myoclonus was performed 3 months later, after the 3 patients had been taking piracetam orally (300 mg/kg/day).
<table>
<thead>
<tr>
<th>SEP (measured at C4' and C3')</th>
<th>Myoclonic Latency (C-Reflex)</th>
<th>SEP-Myoclonus</th>
<th>MEPs</th>
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<tr>
<td>N20–N35 Amplitude (μV)</td>
<td>Median Taps (Wrist Flex) (msec)</td>
<td>P30- Myoclonus (Wrist Flex) (msec)</td>
<td>TMCT (msec)</td>
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<tr>
<td>N20–P30 Amplitude (μV)</td>
<td>P30–N35 Interval (msec)</td>
<td>Cortical Relay Time (msec)</td>
<td>(APB)</td>
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<tr>
<td>26.4</td>
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<td>15.9</td>
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</table>

Muscle (Fig 1). Premyoclonic positivity had a mean duration of 101 ± 29 msec; peak latency was 34 ± 7.2 msec when EMG bursts were recorded from the belly of the wrist extensors. The Table shows the level of reproducibility of latency values for each patient.

EEG mapping of premyoclonic spikes showed maximal positive distribution over the P3 or P4 electrode and a concomitant maximal negative distribution over frontal leads (Fig 2A and B). Silence-locked EEG averages did not generate a potential related to the EMG silence in any of the 9 patients.

Age at onset of myoclonus was between 2 and 7 years (mean, 5 years; median, 5 years 6 months) but could have been earlier because mild myoclonus may have been unrecognized. There was no correlation of severity of myoclonus with that of the other symptoms or with age.

**Somatosensory Evoked Potentials and C-Reflex**

Responses recorded at EP (N9), C7 (N13), and the N9–N13 interpeak time were within normal values in all patients. Central conduction time (CCT = latency difference between the cervical N13 and the scalp N20) was significantly increased (>3 SD) in 7 patients (Patients 1, 2, 4, 6, 7, 9, and 10) and borderline in the remaining 3 (Patients 3, 5, and 8). The N20–P30–N35 complex appeared broad in morphology (Fig 3; see Fig 2C). In particular, in some patients, the N35 wave was ill defined in the parietal area, being better represented in more anterior leads. N20–P30 and N20–N35 intervals were significantly delayed in all patients (+6.7 SD and +3.5 SD, respectively). Mean baseline peak amplitude of the N20 component was in the normal range. In the 9 patients with myoclonus...
Fig 2. Patient 4. (A) Back-averaged electroencephalographic (EEG) activity (n = 100; average reference; rectified electromyogram) in relation to spontaneous myoclonic jerks of the left wrist extensor (LWE) muscle. A negative–positive–negative complex with higher amplitude over the P4 electrode precedes the jerk by 22 msec (latency from the positive peak to the jerk onset). Only activity from the P4 lead is shown, to show morphological similarities of the spontaneous premyoclonic complex and the somatosensory evoked potential (SEP) shown in C. (B) Topographic map analysis of the initial positive wave of the premyoclonic complex shown in A (at arrow). (C) Cortical SEP to electrical stimulation of the left median nerve at the wrist, mastoid reference, average of 50 shocks. An enlarged N20–P30–N35 complex is followed, 28 msec after the positive P30 peak, by a C-reflex in the left abductor pollicis brevis (LAPB). The shock–C-reflex latency is 58 msec. (D) Topographic map analysis of the initial positive peak of SEP as shown in C (at arrow). The electrical field distribution of the premyoclonic complex and of the SEP are overlapping.

(Patients 1–8 and 10), a significant increase was observed in interpeak amplitudes of the N20–P30 and P30–N35 complexes (+7 SD and +3 SD, respectively). The C-reflex was hyperexcitable at rest in all of them (see Fig 2C). The response was recorded in the ipsilateral muscles after electrical stimulation in 7 patients (Patients 1–7) and after mechanical stimulation in 6 (Patients 1, 3, 5, 7, 8, and 10). In no patient was a bilateral response observed. The latency of onset of reflex myoclonus after electrical stimulation was 62 ± 4.3 msec in wrist extensors and flexors and 65 ± 5 msec in the APB. The reflex response to mechanical stimulation had a latency of 71.2 ± 8.7 msec in wrist extensors and flexors. The SEP (P30 wave)–myoclonus latency and that of the premyoclonic spike were similar (about 32.9 msec). Mapping of the multichannel SEP (P30 wave) showed the same field distribution as that of the premyoclonic spike (see Fig 2C and D).

**Transcranial Magnetic Stimulation**

MEPs showed TMCT within normal limits in all patients. CMCTs, either direct or indirect, were reduced significantly compared with controls, especially in younger patients. In addition, all patients showed a shortening of mean MEP duration after scalp stimula-
Fig 3. Patient 4. Cortical somatosensory evoked potential to electrical stimulation of the right median nerve at the wrist, average reference, average of 500 shocks. Note the relative small size of the P25 wave (C3) and the enlarged P30 (P3), N30 (F3), and N35 (C3) waves.

The post-MEP SP was significantly shortened compared with controls (see Table).

**Neuroimaging**

Neuroimaging was considered normal in 8 patients. Cavum vergae was observed in 1 patient and a small arachnoid cyst in another.

**Treatment of Myoclonus with Piracetam**

The 3 patients treated with intravenous piracetam during video-EEG–polygraphic monitoring showed a significant reduction in myoclonus (p < 0.01), with the drug being well tolerated. Clinical and neurophysiological tests performed 3 months after the beginning of oral treatment confirmed persistence of the antomyoclonic effect. However, reduction of myoclonus did not translate into substantial clinical benefit, as patients’ motor pattern remained purposeless and ataxic, although less jerky. The drug was therefore withdrawn.

**Discussion**

Patients with RS have an abnormal, jerky, purposeless, and dystonic motor pattern and are often engaged compulsively in performance of stereotypies. However, the patients’ severe mental impairment and lack of cooperation preclude unequivocal recognition of the individual components of this abnormal movement. Few clinical studies have reported myoclonus in RS, giving highly variable estimates of its frequency. By using long-term video-EEG and polygraphic monitoring, we recorded periods of quiet behavior during which multifocal myoclonus was captured in most patients, although with variable severity.

Demonstration of a cortical reflex origin of myoclonus was based on the following three findings: (1) cortical activity preceding myoclonic jerks as demonstrated by jerk-locked back-averaging, (2) enlarged cortical SEPs, and (3) an enhanced C-reflex, at rest, to either electrical or mechanical stimulation. Burst-locked EEG averaging revealed a reproducible potential preceding the EMG burst by an interval appropriate to corticomotoneuronal conduction. SEP amplitudes were consistent with the definition of “giant” SEPs, although their values were not as high as in progressive myoclonus epilepsies (PMEs) and their morphology was broader. The C-reflex had unusually long latencies (mean, 62 msec), which were noticeably longer than in PMEs (35–50 msec) and showed some similarity to the cortical reflex myoclonus seen in Alzheimer’s disease. The latency of the premyoclonus spike was likewise increased (mean, 34 msec), being twice as high as observed in PMEs (~18 msec). CMCT was short (mean, 5.44 ± 0.54 msec), as previously reported by other investigators, who considered this finding to indicate integrity and hyperexcitability of corticospinal pathways. The MEP duration was shortened, possibly indicating that only fast conducting descending motor pathways were activated by magnetic stimulation. Also, the post-MEP SP was shortened, confirming cortical hyperexcitability.

The time interval between the P30 component and the C-reflex is usually the same as the latency between the premyoclonus spike and the jerk and as the TMCT after TMS. According to the TMCT we observed, a mean delay of 28.4 ± 4.5 msec was necessary from the time when the afferent input reached the postcentral cortex up to the origin of the descending corticomotoneuronal volley. This intracortical delay is three to four times greater than that observed in PMEs. The following sequence could therefore occur in RS patients: mildly delayed conduction of the afferent input up to the sensory cortex via the dorsal columns medial lemniscal and thalamocortical systems (N20 component), slow processing of the afferent input (delayed N20–P30 interval; mean, 11.4 msec), delayed transmission via corticocortical pathways to the precentral cortical neurons corresponding to the stimulated body segment (delayed P30–EMG response; mean, 32.9 msec), and rapid descending volley to the spinal motoneurons. Therefore, the premyoclonus EEG potential (as also the corresponding P30 wave) would appear to represent a discharge in postcentral neurons that would, in turn, slowly drive the motor output through their connections with precentral neurons.

Another possibility is that the premyoclonus EEG potential directly activates projections from the parietal cortex to spinal interneurons, which, in turn, recruit motoneurons. Regardless of the corticofugal neuronal contingent (precentral or postcentral) whose reflex activation originates the descendential volley, intracortical conduction time is likely to be markedly delayed due...
to the synaptic abnormalities that have been reported in the RS brains.29

Cortical hyperexcitability in RS was also suggested by other investigators, using both SEPs and visual evoked potentials.30,31 Our own and previous findings are apparently at variance with the considerable delay of the long-loop reflex and also with the absence of any intrahemispheric and interhemispheric spread of myoclonic cortical activity. Abnormal vertical cortical hyperexcitability and reduced horizontal corticocortical transmission could be hypothesized, resulting in enhanced activity of sensorimotor columns processing input–output volleys from and to the corresponding somatic areas, and in reduced spread of cortical activity. The pathological changes observed in RS could support this model. Selective, nonprogressive involvement of projection neurons in the motor, association, and limbic cortex was reported by Armstrong and colleagues,4 who found pyramidal neurons to show a significant shortening of the basal dendrites in cortical layers III and V in the motor and frontal cortex, of the apical dendrites in layer V of the motor cortex, and in the basal dendrites of layer IV of the subiculum. This reduction in dendritic branching is probably responsible for reduction in the total number of synapses and is considered to reflect abnormalities in circuitry and not in neuronal cells themselves.6

Abnormalities have also been found in the cerebellum, where the molecular and the granule cell layers are thinned and hemispheric Purkinje cells are small, pale, and reduced in number,32,33 showing a truncated dendritic pattern.34 Such structural abnormalities could be responsible for cortical reflex myoclonus, due to loss of cerebellar inhibitory influence on cortical mechanisms.35,36 Although several energy metabolism or neurotransmitter abnormalities have been reported in RS, they have been controversial37 and their relevance to myoclonus is uncertain.

In the 3 patients treated with piracetam, this drug confirmed its powerful antmyoclonic properties,26,38 producing a considerable reduction in the frequency and severity of jerks, both on intravenous administration and long-term use. However, piracetam treatment did not translate into a substantial clinical benefit, in that myoclonus was not producing, in itself, significant disability.

Although the behavioral phenotype of classic RS is quite characteristic, some difficulty in differential diagnosis with other disorders may be found, especially in the early stages of the disease.8 A condition that may prove difficult to differentiate clinically from RS is Angelman’s syndrome,9 in which cortical myoclonus is a constant feature.26 However, in Angelman’s syndrome, the C-reflex is not hyperexcitable. SEPs are not enlarged, and myoclonus shows a characteristic rhythmic 9- to 13-Hz pattern, producing a continuous trembling of hands.

In conclusion, RS patients show a distinctive pattern of multifocal cortical reflex myoclonus, with prolonged intracortical delay of the long-loop reflex and a low propensity for spread of myoclonic activity. These clinical and neurophysiological findings are in agreement with previous neuropathological studies indicating synaptic abnormalities and selective, nonprogressive dendritic alterations of projection neurons of the motor and association cortex.5,29 In our patients, myoclonus had a highly variable severity, showing no clear correlation with the stage of the disease and never representing a prominent clinical feature.

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