Predominant cortical dysfunction in Guadeloupean parkinsonism

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Atypical parkinsonism is extremely frequent in Guadeloupe and may have an environmental cause. One-half of the patients with this tauopathy have dopa-resistant parkinsonism, tremor, subcortical dementia and abnormal eye movements suggestive of progressive supranuclear palsy (PSP). They also have hallucinations, dysautonomia, which are not characteristic of PSP. Furthermore, the oculomotor abnormalities and the tremor, which is jerky, differ from what is observed in classical PSP patients. We therefore undertook an electrophysiological study to characterize these features in greater detail. Nine representative Guadeloupean PSP-like (Gd-PSP) patients were selected for electro-oculographic recordings of horizontal eye movements [visually guided saccades (VGS), antisaccades (AS) and smooth pursuit], clinical evaluation of vertical saccade velocity and electrophysiological analysis of abnormal limb movements [electromyographic polygraphy, EEG jerk-locked-back-averaging (JLBA) and long-loop C-reflex]. Vertical saccade velocity was reduced in five patients. The velocity of horizontal VGS was normal, although the latencies were increased and horizontal smooth pursuit (HSP) was mostly saccadic. The AS error rate was above 70% in most patients. Myoclonus was detected in 89% of the Gd-PSP patients. It was mainly small amplitude rest and action myoclonus in the upper limbs, characterized by short arrhythmic 24–76 ms bursts and was of cortical origin, as confirmed by JLBA in five patients. In conclusion, Gd-PSP patients have cortical myoclonus and cortical oculomotor impairments, but only minor signs of brainstem oculomotor dysfunction, suggesting that cortical dysfunction predominates over brainstem impairments. This electrophysiological study, added to previous clinical, neuropsychological and neuroradiological studies, has enriched the characterization of Guadeloupean atypical parkinsonism, which thus appears to be a new clinical entity.

Keywords: myoclonus; eye movements; Guadeloupean parkinsonism; tauopathy; PSP

Abbreviations: Acc = accelerometer; AS = antisaccades; CBD = cortico-basal degeneration; DBL = dementia with Lewy bodies; ECR = extensor carpi radialis; EMG = electromyographic; FAB = frontal assessment battery; FCR = flexor carpi radialis; IDIO = 1st dorsal interosseous; Gd-PSP = Guadeloupean progressive supranuclear palsy; HSP = horizontal smooth pursuit; JLBA = EEG jerk-locked-back-averaging; LLCR = long-loop C-reflex; MMSE = mini-mental status examination; MSA = multiple system atrophy; PSP = progressive supranuclear palsy; PSP-P = PSP-parkinsonism; RBD = REM sleep behaviour disorder; REM = rapid eye movement; RS = Richardson’s syndrome; SAM = small amplitude myoclonus; SWJ = square wave jerks; UPDRS = unified Parkinson’s disease rating scale; VGS = visually guided saccades

Received April 26, 2008. Revised August 8, 2008. Accepted August 11, 2008
Introduction

Atypical parkinsonism is abnormally frequent on the French Caribbean Island of Guadeloupe (Caparrós-Lefebvre et al., 1999). Epidemiological and experimental evidence suggest that it might have an environmental cause (Caparrós-Lefebvre et al., 1999; Lannuzel et al., 2002, 2003, 2007; Champy et al., 2004, 2005; Escobar-Khondiker et al., 2007). In one-half of the patients with this atuopathy (Caparrós-Lefebvre et al., 2002), a combination of axial levodopa-resistant parkinsonism, supranuclear gaze abnormalities and sub-cortical dementia, suggested that the disease might be a form of progressive supranuclear palsy (PSP), which was termed Guadeloupean-PSP (Gd-PSP). A prospective clinical, neuropsychological and radiological study on a much larger cohort of patients (Lannuzel et al., 2007) has shown, however, that Gd-PSP patients, as well as the other patients with atypical parkinsonism but no oculomotor abnormalities, had several characteristics that are not usually found in patients with classical PSP, including hallucinations, dysautonomia, rapid eye movement (REM), sleep behaviour disorder (RBD) and a peculiar jerky tremor, suggestive of myoclonus. Hallucinations are reported by 59% of Gd-PSP patients (Lannuzel et al., 2007). They are predominantly well-formed visual hallucinations (vivid animals, faces, people who were deceased), less often auditory and are not related to medications. Forty-one per cent developed orthostatic hypotension at 4 ± 0.8 years after disease onset, unrelated to dopaminergic treatments (Lannuzel et al., 2007). Patients with Guadeloupean atypical parkinsonism and their spouses reported insomnia, dream enactment and violence during sleep, which is suggestive of RBD (Lannuzel et al., 2007). Symptomatic RBD was confirmed by overnight video polysomnography in seven of nine Gd-PSP patients (78%) (De Cock et al., 2007). In comparison, only 13% of patients with classical PSP developed symptomatic RBD (Arnulf et al., 2005). The pattern of RBD in Gd-PSP, in which the latency and percentage of REM sleep was normal, differed from that observed in patients with classical PSP, who had delayed and shortened REM sleep. To further characterize this disease entity, we performed electro-oculographic study and electrophysiological analysis of abnormal limb movements.

Material and Methods

Patients

Nine Gd-PSP patients were selected from the group of 51 patients with Gd-PSP recruited prospectively in the Neurology Department of the University Hospital of Pointe-à-Pitre, between September 2003 and September 2005, and extensively characterized (Lannuzel et al., 2007). Between December 2005 and March 2006, the patients were admitted to the Department of Neurology of the Saint Antoine University Hospital in Paris, for electrophysiological and oculomotor examinations. Before the recordings were made, each patient underwent a clinical examination by neurologists with expertise in movement disorders (M.V., E.R.). Parkinsonian symptoms were scored (S.V.) with the Part III (motor score) of the Unified Parkinson’s Disease Rating Scale (UPDRS III). The velocity of vertical saccades was determined by clinical inspection and scored 3 (complete palsy), 2 (markedly reduced), 1 (slightly reduced), 0 (normal). Cognition was assessed with the Mini-Mental Status Examination (MMSE) and the Frontal Assessment Battery (FAB) (Dubois et al., 2000). Abnormal limb movements were recorded in the Department of Physiology of the Saint-Antoine University Hospital (E.A.). Electro-oculography was performed in the INSERM research unit 679, at the Pitie-Salpetriere University Hospital (B.G.). A group of 15 healthy subjects (mean age: 69 ± 8.0 years) with no history of neurological disorders served as controls for the oculomotor tests and clinical evaluations of eye movements. All but two of the patients were on levodopa during the study; they were recorded during the ‘on’ period. None of them received serotonine reuptake inhibitors or antipsychotic drugs. Five patients (Patients 4–7 and 9) received treatment for hypertension and three (Patients 4, 8 and 9) for diabetes. Other medications were: allopurinol (Patient 8), bromazepam (Patient 4), clonazepam (Patient 2), domperidone (Patients 1 and 4), donepezil (Patients 2 and 6), meprobamat (Patient 3), pravastatin (Patient 6), salicylic acid (Patients 6 and 9) and valproic acid (Patient 8).

Oculomotor recordings

Horizontal eye movements were recorded by electro-oculography with a standardized protocol, as previously described (Pierrot-Deseilligny et al., 1989; Meyniel et al., 2005). In brief, the patients were seated with their heads immobilized, in complete darkness, 95 cm from a panel of green and red light emitting diodes (visual angle, 0.18°; luminance, 5 cd/m²). Data were acquired with a sampling frequency of 200 Hz (bandwidth 0–100 Hz) and stored for offline analysis. The total duration of a recording session did not exceed 30 min.

Horizontal visually guided saccades (VGS)

The subjects were instructed to look at a central green fixation point (3500–4200 ms), then to trigger a saccade as quickly as possible towards a red target (1000 ms) that appeared, randomly, 25° to the right or the left. There was a 200-ms gap between central target offset and lateral target onset. The mean prosaccade latency was calculated by averaging 36 prosaccade latencies in each direction. Saccade accuracy was determined by saccade gain (amplitude of the first saccade over target eccentricity). Saccade amplitude was scored 3 (complete paralysis), 2 (hypometric with a gain <50%), 1 (hypometric with a gain between 50% and 90%) and 0 (gain >90%). Square wave jerks (SWJ) were scored 0 (absent), 1 (rare), 2 (frequent), 3 (numerous).

Antisaccades (AS)

The subjects were instructed to look at a red central fixation point (3500–4200 ms), then to trigger as soon as possible a saccade in the opposite direction to a red 25° right or left target. The subjects were questioned to confirm that they had correctly understood the instruction. The AS error rate (percentage of saccades directed towards the lateral target) was calculated from 18 trials in each direction.

Horizontal smooth pursuit (HSP)

The subjects were instructed to follow the sinusoidal movement of a target with a peak velocity of 15°/s. Performance was scored 3 (complete paralysis), 2 (severely saccadic), 1 (slightly saccadic), 0 (normal).
Physiology of Guadeloupean parkinsonism

In order to characterize tremor and myoclonus, a detailed neurophysiological examination including surface multichannel electromyographic (EMG) and accelerometric (Acc) recordings, long-loop C-reflex (LLCR) studies and EEG jerk-locked-back-averaging (JLBA) was performed with a Viking IV device (Nicolet Biomedical, Madison, WI, USA).

Movement was recorded with a linear piezo-resistive unidirectional Acc (MEI, Montreuil, France) and band-pass filtered at 0.5–100 Hz. EMG signals obtained from pairs of 9-mm diameter silver/silver chloride electrodes (Medtronic, Minneapolis, MN, USA) placed 2 cm apart on muscle bellies and were band-pass filtered at 20 Hz–10 kHz. Sample rate was set at 2000 Hz. This sampling rate was low, compared with the 10 kHz low band-pass filter. Nevertheless, as dominant frequencies for surface EMG are below 1000 Hz, there is likely not to be any signal in the high frequencies to be aliased (Nilsson et al., 1993). The electrode impedances were set below 10 KΩms. The patients sat upright in a chair with their wrist supported by a cylindrical pillow. The Acc was firmly attached to the first phalanx of the index finger. EMG signals were obtained from first dorsal interosseous, flexor (FCR) and extensor carpi radialis (ECR) muscles of the more affected arm. When clinically involved, biceps brachii or tibialis anterior muscles were also recorded. Tremor and myoclonic jerks were recorded during rest, posture and action. To detect parkinsonian tremor, the effect of mental calculation or verbal enumeration was tested at rest. Stimulus sensitive myoclonus was elicited with a slight distal touch, a pinprick and passive mobilization of the wrist. Postural and action tremor and myoclonus were analysed during tonic contraction and slow elementary non-goal-directed movements and during goal-directed movements. The frequency of tremor was assessed by visual inspection on a 2 s EMG sample. The duration of 10 consecutive positive bursts composing the episode of tremor and myoclonus was measured at rest and during tonic contraction. Negative myoclonus was defined as an EMG silence interrupting a tonic EMG activity, excluding the inhibition that can follow a positive myoclonus.

EEG back-averaging was triggered on-line by the EMG-rectified signal obtained from a limb muscle making numerous well-identified jerks with a good signal/noise ratio. The triggering mode was an amplitude EMG threshold. Acquisitions were performed during slight voluntary extensions of the wrist or fingers. EEG signals were recorded with subcutaneous single-use needles placed over the C3, C4 and CZ regions according to the 10–20 EEG international system with a linked A1–A2 reference. The EEG filtering band pass was set at 2 Hz–1.5 kHz. Sample rate was set at 6000 Hz. The EEG electrode impedances were set below 5 KΩms. Two series of a minimum of 100 jerks each were subsequently averaged. In order to detect short-latency premyoclonic potentials in central cortical areas, the period of analysis went from −100 to +100 ms relative to the onset of myoclonus. JLBA was considered technically unreliable if myoclonus was too infrequent or intermingled with tremor.

LLCR studies were conducted at rest and during slight tonic contractions of the recorded muscle in order to facilitate the response. Recordings were made from a pair of surface electrodes placed over the abductor pollicis brevis muscle and two series of 10 electrical stimulations were delivered to the median nerve at the wrist. The F-wave latency was recorded simultaneously.

Statistical analysis

Statistical comparisons were performed using the STATVIEW 4.51.1 package for PC. Results are presented as the percentage or mean ± SD. Between group comparisons were made with the Chi-square or the Fisher exact test, as appropriate for non-parametric variables and with the t-test for parametric variables. A P-value <0.05 was considered significant. Saccade latency and AS error rates in patients were compared with those of the control group. Saccade latency in a patient was considered abnormal if outside an interval defined as the mean of the control group ± 2 SD. The error rate in the AS task in each patient was considered abnormal if outside the normal range defined in the control group.

Results

Clinical characteristics of the Gd-PSP patients

The clinical characteristics of the patients are summarized in Table 1. The patients, three women and six men, were considered to be representative of the group of 51 patients with Gd-PSP (Lannuzel et al., 2007) as a whole, in terms of age (70.1 ± 9.8 years old versus 73.9 ± 1.2 for the total group, P = 0.08) and the severity of their parkinsonism, evaluated with Part III (motor score) of the UPDRS III (42.2 ± 13.4 versus 38.7 ± 2.4 for the total group, P = 0.05). Disease duration was of 6.4 ± 1.2 years (3–13 years). All patients had bradykinesia and rigidity. Rigidity predominated in axial muscles in three patients. Tremor was observed in seven patients (78%). It was observed at rest in five, associated in four of them to postural and/or intentional tremor. The response to levodopa was absent in four patients or moderate (25–40%) in three. Myoclonus was observed at clinical examination in seven patients. Three of them had limb or neck dystonia. Clinical examination of eye movements was especially oriented to vertical saccades since this cannot be precisely studied by electrooculography. Five patients (55%) had reduced velocity of vertical eye movements but none had complete vertical ophthalmoplegia. Horizontal saccades and pursuit were abnormal in eight patients (89%). Horizontal abnormalities were characterized by electrooculography (see below). All patients had cognitive impairment. Five of the nine patients experienced hallucinations. They were well-formed visual hallucinations (vivid animals, faces, people who were deceased), associated in two patients (Patients 2 and 7) with auditory hallucinations. Seven patients had RBD, which were confirmed in six of them by overnight videopolysomnography (De Cock et al., 2007). Autonomic dysfunction was found in four patients. It consisted of orthostatic falls in blood pressure, defined as a decrease in systolic pressure of at least 30 mmHg or a decrease in diastolic pressure of 15 mmHg, associated in one case with urinary incontinence.
Recording of eye movements

VGS

In the control group, the latencies of rightward and leftward VGS did not differ significantly and were therefore pooled (Table 2). The mean VGS latencies of the patients [236 ms (SD 59.6) rightwards, 280 ms (SD 129.7) leftwards] were significantly higher than in the controls [182 ms (SD 20.3)]. However, saccade latencies were normal in four patients (Patients 4–6 and 7), markedly increased in three patients (Patients 2, 3 and 8) and near the upper limit of the controls (mean + 2 SDs) in two patients.

Table 1  Clinical characteristics of the nine Gd-PSP patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
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<tr>
<td>Age (years)</td>
<td>64</td>
<td>76</td>
<td>75</td>
<td>62</td>
<td>75</td>
<td>84</td>
<td>53</td>
<td>78</td>
<td>64</td>
</tr>
<tr>
<td>Disease evolution (years)</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

Parkinsonism

- Akathisia and rigidity syndrome
- Tremor
- UPDRS global (off/on)
- L-dopa equivalent (mg/day)
- L-dopa clinical benefit (%)
- Falls and postural instability
- Falls delay

Eye movements

- Vertical saccade velocity
- Horizontal smooth pursuit
- Other symptoms
  - Myoclonus
  - Dystonia
  - Alien hand
  - Sensory loss
  - Dysautonomia
- Cognition
  - Frontal lobe syndrome
  - MMSE score (/30)
  - FAB score (/18)
  - Hallucinations
  - Clinical REM sleep disorders

Table 2  Characteristics of eye movements in 9 Gd-PSP patients and 12 controls

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Control</th>
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<td>VGS latency, mean±SD (ms)</td>
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<tr>
<td>Right</td>
<td>263±161*</td>
<td>265±114**</td>
<td>310±108**</td>
<td>137±24</td>
<td>221±69</td>
<td>213±96</td>
<td>189±71</td>
<td>324±89**</td>
<td>205±42</td>
<td>203±30</td>
</tr>
<tr>
<td>Left</td>
<td>228±68*</td>
<td>583±128**</td>
<td>330±151**</td>
<td>160±37</td>
<td>215±55</td>
<td>215±92</td>
<td>189±99</td>
<td>352±102**</td>
<td>244±70</td>
<td>198±20</td>
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<tr>
<td>VGS gain</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>SWJ</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<td>Antisaccade error rate, % (range)</td>
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<tr>
<td>Right</td>
<td>19</td>
<td>100</td>
<td>94</td>
<td>75</td>
<td>92</td>
<td>83</td>
<td>55</td>
<td>94</td>
<td>33</td>
<td>11 (0–25)</td>
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<tr>
<td>Left</td>
<td>48</td>
<td>100</td>
<td>100</td>
<td>65</td>
<td>91</td>
<td>100</td>
<td>50</td>
<td>89</td>
<td>16,5</td>
<td>10 (0–21)</td>
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<tr>
<td>HSP</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
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</table>

VGS gain: 0 = gain >90%, 1 = 90–50%, 2 = gain <50%, 3 = complete palsy; SWJ: 0 = absence, 1 = rare, 2 = frequent, 3 = numerous; HSP: 0 = normal, 1 = slightly saccadic smooth pursuit, 2 = severely saccadic smooth pursuit, 3 = complete paralysis. *near the upper limit of the controls, **markedly increased.
(Patients 1 and 9) (Table 2). Saccade gain was decreased (saccade hypometria) in seven patients (Fig. 1A).

**SWJ**

SWJ were observed, although infrequently, in only two patients (Patients 4 and 5) (Table 2).

**AS**

The range of the AS error rate in the control group was 0–25 rightwards and 0–21 leftwards. The AS error rate was markedly increased in all nine patients (Fig. 1B). This was not due to poor understanding of the task, since the patients generated corrective saccades after errors. Only one patient made 100% errors bilaterally.

**HSP**

HSP was severely saccadic in five patients (Patients 1–5) (Fig. 1C), moderately saccadic in three patients (Patients 6–8) and normal in one patient (Patient 9).

**Clinical and neurophysiological characteristics of tremor and myoclonus**

**Myoclonus**

Myoclonus was observed in all patients except one. It was a small amplitude myoclonus (SAM) in seven and a more extensive myoclonus of higher amplitude in one (Table 3). The SAM was located predominantly at the distal part of upper limbs and had an arrhythmic pattern. It occurred mostly during rest and posture (wrist or finger extension or abduction) and was not enhanced by goal-directed movements. It was frequently asymmetrical or unilateral. Finger jerks were often multidirectional. Occasionally, not all fingers were involved. SAM did not impair motor function. An extensive stimulus-responsive multifocal myoclonus, involving the face and the proximal and distal parts of the limbs, was seen in Patient 4.

The neurophysiological characteristics of myoclonus were similar in all patients. The polygraphic recordings showed positive myoclonus composed of short bursts [45 ± 7 ms (mean ± SD)] with a range of 24–76 ms. Synchronous bursts were frequently recorded from agonistic and antagonistic muscles. Negative myoclonus, strictly speaking, was absent. Representative recordings of SAM and more extensive cortical action myoclonus are shown in Fig. 2A and B, respectively.

JLBA was carried out in eight patients but was reliable in only six. A short-latency pre-myoclonic positivity (Fig. 3A) was detected over the sensorimotor cortex contralateral to the myoclonus in 83% of recordings, demonstrating the cortical origin of the jerks. The mean pre-myoclonic latency was −27.2 ± 3 ms (range: −22.4 to −30 ms). The mean amplitude of the pre-myoclonic potential was 5.6 ± 2.9 μV (range: 3–10 μV).

An LLCR was found in two patients, but only under facilitation (Fig. 3B), demonstrating the weak stimulus responsiveness of the long loop transcortical circuit. The mean latency of the F-waves was 28.7 ± 2.8 ms (range, 23.6–31.6 ms).

**Tremor**

At the time of neurophysiological examination, rest tremor (frequency range: 3–6 Hz) was present in only three patients, with a postural component in two and sometimes intermingled with myoclonus. Although the appearance of the tremor was complex, polygraphic analysis clearly distinguished tremor from myoclonus because of its rhythmic pattern and the longer duration of the bursts (Table 3). The rest tremor agonist–antagonist pattern recorded in the forearm was alternating in all cases, as typically seen in
parkinsonian rest tremor. The postural tremor agonist–antagonist pattern was alternating in Patient 5 and synchronous in Patient 8. The frequency of postural tremor exceeded the rest tremor frequency by at least 2 Hz (Patient 5) and 1.6 Hz (Patient 8) and postural tremor appeared almost immediately. These data suggested that this postural tremor may not be a re-emergent resting tremor.

Discussion
In this electrophysiological study of nine representative patients with Gd-PSP, we found that eight had myoclonus, mainly of cortical origin, and a pattern of oculomotor disturbances that suggested minimal impairment of brainstem oculomotor structures but marked cortical abnormalities.

The oculomotor abnormalities in Gd-PSP patients differ from those in classical PSP
Oculomotor abnormalities are a major characteristic of PSP (Vidailhet et al., 1994). They result from dysfunction in both the brainstem and the cerebral cortex. Lesions in the brainstem and cerebellum cause reduced saccade velocity, especially in the vertical direction (mesencephalic reticular formation) (Bhidayasiri et al., 2000; 2001), marked saccade hypometria (Waitzman et al., 2000), severely saccadic smooth pursuit (Malessa et al., 1994) and abundant SWJ (Rascol et al., 1991). In contrast, abnormal saccade latencies results from impaired cortical oculomotor structures (review in Pierrot-Deseilligny et al., 2002). In particular, lesions in the prefrontal cortex (Blin et al., 1990) result in a severe inability to suppress reflexive saccades, illustrated by a high error rate in the AS task (Vidailhet et al., 1994; Pierrot-Deseilligny et al., 1989). Although oculomotor cortical and brainstem–cerebellar symptoms may appear at different stages of PSP, patients with disease durations of at least 2 years usually have all of these disorders (Rivaud-Pechoux et al., 2000).

In Gd-PSP patients, however, brainstem–cerebellar dysfunctions (vertical and horizontal saccade slowing, SWJ) were minimal, whereas cortical dysfunctions (increased saccade latencies and high AS error rates) were important.

Table 3
Clinical and neurophysiological characteristics of tremor and myoclonus in Gd-PSP patients

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<th>Patient</th>
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<tr>
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<tr>
<td>Frequency (Hz)</td>
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<td>3.5</td>
<td>3.0</td>
<td>3.9</td>
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<tr>
<td>Postural and action tremor</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Frequency (Hz)</td>
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<tr>
<td>Bursts length (Hz)</td>
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Clinical and polygraphic characteristics

Small amplitude myoclonus

More profuse myoclonus

Location

Symmetry

Stimulus responsiveness

Abundance

Rest myoclonus

Postural myoclonus

Action myoclonus

Bursts duration (ms): mean ± SD

Range

Long loop C-reflex

Jerk-locked back-averaging

Cortical pre-myoclonic positivity

Latency (ms)

Amplitude (μV)

Definite cortical myoclonus

Probable cortical myoclonus

Possible sub cortical myoclonus

aAt the time of neurophysiological examination; bstimulus responsiveness to touch, pinprick or passive displacement; abundance = absent; +/− = rare; + = moderate; ++ = middle; +++ high; f = LLCR obtained with facilitation; ur = unreliable; ctechnical JLBA pitfall due to myoclonus rarity; dtechnical JLBA pitfall due to the mixed myoclonus and tremor in both rest and posture.

r = right; l = left; LL = lower limb; UL = upper limb; d = distal; p = proximal.
This suggests that cortical oculomotor areas, especially the prefrontal cortex, are impaired in our Gd-PSP patients, whereas brainstem–cerebellar structures are relatively spared. If these had been classical PSP patients with the same disease durations (average, 6.4 years; range, 3–13 years) and a similar frontal impairment (AS error rate), they would also have had a clear reduction in saccade velocity with marked saccadic smooth pursuit. Therefore, cortical oculomotor dysfunction predominates in Gd-PSP, whereas brainstem–cerebellar dysfunction is prominent in classical PSP. This is in accordance with the severity of cognitive impairments found in this group, and with neuropathological findings described in Gd-PSP (Caparros-Lefebvre et al., 2002).

Furthermore, neuroimaging studies also found signs of moderate brainstem atrophy with, in contrast, clear frontal cortical atrophy (Lannuzel et al., 2007). The pattern of oculomotor abnormalities observed in Gd-PSP patients is therefore not typical of PSP.

**Cortical myoclonus is a major characteristic of Gd-PSP**

Myoclonus was present in all but one of the nine Gd-PSP patients (89%) that participated in our study. In most cases, it was a small amplitude distal rest and action myoclonus that responded little to stimuli. Only one of the patients had a more extensive multifocal myoclonus. The myoclonic bursts were brief, which is strongly suggestive of a cortical generator. This was confirmed by the JLBA technique that demonstrated the cortical origin of both the small amplitude and multifocal myoclonus in five patients.

The average latency from the initial peak of the cortical transient to myoclonus EMG discharge (mean: $-27.2 \pm 3$ ms; range: $-22.4$ to $-30$ ms) was similar to the premyoclonic delay recorded in cortical myoclonus in the...
context of other parkinsonian syndromes such as idiopathic Parkinson’s disease (mean: −26 ms; range: −15 to −40 ms) (Caviness et al., 2002) or dementia with Lewy body (mean: −27 ms; range: −23 to −30 ms) (Caviness et al., 2003), but slightly longer than in cortical reflex myoclonus of multisystem atrophy of parkinsonian type (about 20 ms) (Okuma et al., 2005). However, the absence of a cortical transient preceding myoclonus in Patient 3, despite adequate recording conditions, suggests that SAM may also be of subcortical origin.

Cortical myoclonus in Gd-PSP may result from intrinsic cortical pathology or from disinhibition of the motor cortex secondary to basal ganglia dysfunction. The somatosensory cortex seems poorly implied, given that SAM respond little or not to somesthetic stimuli. Neuropathological data from three Gd-PSP patients, showing tau accumulations in the motor cortex, as well as in sub-cortical structures (Caparros-Lefebvre et al., 2002), support the putative role of intracortical pathology in myoclonus genesis. Cortical hyperexcitability in Gd-PSP patients might result from pyramidal cortico-spinal neurons pathology or from a loss or alteration of inhibitory interneurons within primary motor cortex. Transcranial magnetic stimulation studies of cortical excitability and more detailed neuropathological studies are needed to address this issue. Abnormal glutamate- and calcium-dependent regulation of pyramidal cell excitability by glial cells, which can contain abnormal tau deposits in Gd-PSP patients (Caparros-Lefebvre et al., 2002), might also facilitate abnormal discharges of pyramidal cortico-spinal neurons, which are the final pathway conveying myoclonus (Angulo et al., 2004; Kang et al., 2005). Finally, myoclonus in the Gd-PSP patients might also have been facilitated by dopaminergic stimulation. In idiopathic Parkinson’s disease, multifocal action or spontaneous myoclonus is occasionally observed in states of intermediate dopaminergic stimulation (Shafiq and Lang, 2002). However, two of the Gd-PSP patients were not receiving levodopa and the six who had none (Patients 2, 3 and 8) or little (Patients 1, 4 and 5) improvement with the treatment, suggesting that dopaminergic stimulation has little effect on myoclonus.

**Gd-PSP and related disorders**

The frequency of myoclonus in Gd-PSP patients is one of the major features that distinguish this clinical entity from the other forms of PSP that have recently been described, PSP-parkinsonism (PSP-P) and Richardson’s syndrome (RS) (Williams et al., 2005; 2008). Gd-PSP and PSP-P are both characterized by frequent tremor. Cognitive dysfunction, however, is much more frequent in Gd-PSP (91%) (Lannuzel et al., 2007) than in PSP-P (52%) (Williams et al., 2005). The distribution of tau pathology, which is low level and mainly restricted to the brainstem in PSP-P (Williams et al., 2005; 2008), but severe and widespread in Gd-PSP (Caparros-Lefebvre et al., 2002), may be related to this difference. Interestingly, myoclonus was not reported in either PSP-P, RS or in large previously described cohorts of PSP patients (Litvan et al., 1996). An exceptional case of palatal myoclonus was described in a PSP patient with olivary hypertrophy (Suyama et al., 1997). A putative case of PSP with cortical myoclonus was also described, but associated with epilepsy (Kurihara et al., 1974). The presence of cortical myoclonus, therefore, is an important feature that distinguishes Gd-PSP as a clinical entity from other forms of PSP.

The frequency of myoclonus in Gd-PSP (89%) is closer to the frequencies reported in synucleinopathies such as multiple system atrophy (MSA) [35–48% (Caviness et al., 2002; Okuma et al., 2005)]. However, myoclonus in parkinsonian type MSA is a cortical small amplitude postural myoclonus, without jerks at rest and with prominent reflex features (Salazar et al., 2002; Okuma et al., 2005), which is much different than the poorly stimulus-responsive, rest and action myoclonus recorded in Gd-PSP. Qualitatively, the clinical and electrophysiological features of myoclonus in patients with dementia with Lewy bodies (DLB), also a synucleinopathy, seem quite similar to the myoclonus in patients with Gd-PSP, but they are much less frequent (18%) (Louis et al., 1997).

The characteristics of myoclonus in Gd-PSP are different from those recorded in patients with cortico-basal degeneration (CBD), a tauopathy. Myoclonus in CBD is focal, rest and action, proximal and distal and highly stimulus-sensitive. Polymyography shows repetitive hyper-synchronous bursts of brief duration (<50 ms), with positive LLCR, but no cortical pre-myoclonic transients are seen on JLBA (Thompson et al., 1994; Monza et al., 2003).

Thus, the electro-clinical characteristics of myoclonus in Gd-PSP (i) resemble more closely those observed in idiopathic Parkinson’s disease or DLB, (ii) differ from the cortical reflex SAM seen in MSA, although there is some overlap and (iii) is radically different from myoclonus seen in CBD. Cortical SAM may occur therefore in tauopathies such as Gd-PSP, but also in synucleopathies such as idiopathic Parkinson’s disease or DLB and is not associated with a specific type of neuropathology in atypical parkinsonism. More generally, it is interesting that at least three clinical signs, myoclonus, hallucinations and RBD, considered to be relatively specific for synucleinopathies, are frequently observed in Gd-PSP, a tauopathy, indicating that the phenotype is related to the location of the lesions in the brain, rather than to the protein that forms the neuropathologic hallmark of the disease.

**Acknowledgements**

We thank the patients and their families for their participation in this study. We gratefully acknowledge Merle Ruberg for her language expertise and critical review of the manuscript.
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