Distinctive abnormalities of facial reflexes in patients with progressive supranuclear palsy

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Summary
Spontaneous and voluntary eyelid motility is often abnormal in patients with progressive supranuclear palsy. In contrast, their eyelid reflex responses are relatively preserved, and only those generated by an acoustic startle have been found absent or severely reduced. We hypothesized that, because of their relevant brainstem pathology, patients with progressive supranuclear palsy might have other brainstem reflex abnormalities which, on detection, could help with their neurophysiological characterization. In this study, we examined facial reflex responses in 14 patients with progressive supranuclear palsy, 12 patients with multisystem atrophy, 10 patients with Parkinson’s disease, six patients with corticobasal ganglionic degeneration, 11 patients with various non-parkinsonian neurological illnesses and 10 normal subjects. EMG activity was simultaneously recorded from the orbicularis oculi and mentalis muscles following electrical stimulation of the median nerve at the wrist. Mentalis responses were obtained in two normal subjects and in all patients except one with Parkinson’s disease, one with progressive supranuclear palsy and one with corticobasal ganglionic degeneration; there were no differences between groups of subjects regarding latency or peak amplitude. Orbicularis oculi responses were always present in control subjects and patients who exhibited mentalis responses, with the significant exception of patients with progressive supranuclear palsy, in whom only the response of mentalis was obtained. Blink-reflex responses to supraorbital nerve electrical stimuli were present at a normal latency and amplitude in all patients. An abnormally enhanced blink-reflex excitability recovery curve to paired stimuli was found in a similar percentage of patients with progressive supranuclear palsy, multisystem atrophy and Parkinson’s disease, but in only two patients with corticobasal ganglionic degeneration. Patients with progressive supranuclear palsy have a functional involvement of circuits mediating orbicularis oculi responses to median nerve electrical stimuli, that is a distinctive feature with respect to other parkinsonian syndromes.

Keywords: progressive supranuclear palsy; parkinsonian syndromes; brainstem reflexes; palmomental reflex; blink reflex

Introduction
The lack of voluntary control of the eye and eyelid motility is a cardinal feature for the clinical diagnosis of progressive supranuclear palsy (Steele et al., 1964; Duvoisin et al., 1987; Lees, 1987; Golbe and Davis, 1993; Tolosa et al., 1994; Vidailhet et al., 1994). Abnormalities of spontaneous or voluntary eyelid motility include reduced blinking rates (Karson et al., 1984), lid retraction (Maher and Lees, 1986), blepharospasm (Jackson et al., 1983) and supranuclear palsy of eyelid opening (Lepore and Duvoisin, 1985; Esteban and Gimenez-Roldán, 1988) and eyelid closing (Golbe et al., 1989). Reflex eyelid motility has also been found abnormal with acoustic startling stimuli but not with trigeminal inputs (Vidailhet et al., 1992). We report here a clinical and electrophysiological observation, made in the course of an investigation of the palmomental reflex, that contributes to recognition of reflex eyelid motility disorders in patients with progressive supranuclear palsy. This observation is the lack of EMG activity in the orbicularis oculi muscle when a response in the mentalis muscle is induced by an electrical stimulus to the median nerve at the wrist. This abnormality is a distinctive feature of patients with progressive supranuclear palsy in comparison with other parkinsonian syndromes.

Subjects
The study was carried out in 14 patients with progressive supranuclear palsy, 12 patients with multisystem atrophy, 10 patients with idiopathic Parkinson’s disease and six patients...
Diagnoses were made according to the established clinical criteria for each disease. Patients with progressive supranuclear palsy had supranuclear downgaze palsy and fulfilled accepted standard criteria for the clinical diagnosis (Lees, 1987; Koller, 1992; Tolosa et al., 1994). Patients with multisystem atrophy had parkinsonian signs in association with cerebellar, pyramidal or dysautonomic symptoms and signs, and had a poor or absent response to L-dopa therapy (Quinn, 1989). The patients with Parkinson’s disease had responded to L-dopa therapy for >2 years and exhibited no symptoms or signs of other neurological disease (Duvoisin and Golbe, 1989; Koller, 1992). Patients with corticobasal ganglionic degeneration had signs of cortical dysfunction on top of dystonia, myoclonus or parkinsonism (Riley et al., 1990). The main clinical syndrome and other clinical features of all patients are described in Table 1. We also studied 10 healthy volunteers (four men and six women, 28–63 years old), who served as control subjects, and 11 patients with other (non-parkinsonian) neurological diseases. These patients were chosen because they all had a prominent palmo mental reflex, which we considered abnormal when it was elicited repeatedly by at least five consecutive strokes to the palm, without signs of habituation. They were three patients with amyotrophic lateral sclerosis, three patients with Alzheimer’s disease, three with a peripheral neuropathy related to alcoholism, one with hepatic encephalopathy and one with a trigeminal neuronopathy in the context of a Sjögren’s syndrome. The palmo mental reflex was also abnormal in eight patients with progressive supranuclear palsy, six patients with multisystem atrophy, six patients with Parkinson’s disease, two patients with corticobasal ganglionic degeneration and one control subject (a male, 32 years old), who otherwise had no signs suggesting neurological dysfunction. All subjects were informed on the nature of the examination, and warned about the possible elicitation of some pain (see below). All control subjects and patients gave informed consent to participate, and the study protocol was approved by the Review Board of the Department of Medicine of the University of Barcelona.

Methods
Recording and stimulation
The subjects were lying on an examination bed in a room at ambient temperature. EMG activity was recorded from the right orbicularis oculi and mentalis muscles with pairs of surface electrodes, using a MYSTRO5Plus electromyograph (Vickers Medical, Surrey, UK). The active recording electrodes were placed on the lower eyelid for the orbicularis oculi and on the lateral aspect of the chin for the mentalis. Electrical stimuli were delivered with surface electrodes to the median nerve at the wrist. The preliminary stimulus intensity was the one that induced a supramaximal compound muscle action potential in the thenar muscle. If such a stimulus did not induce any response in the facial muscles
being monitored, the intensity was progressively increased, after the subject’s consent, until a response was obtained. The search for the appropriate working stimulus intensity was terminated when facial responses were obtained or when the subject refused a further increase in stimulus intensity. We then applied a series of at least three single stimuli at the working stimulus intensity, with a resting interval of >30 s between consecutive trials. In some subjects with prominent facial responses, we averaged five consecutive epochs of rectified EMG activity, to show consistency of the responses.

**Identification of facial responses and analysis of the data**

A facial response was considered positive when a burst of EMG activity, with an amplitude >50 µV and a duration >10 ms, appeared consistently at a latency compatible with a reflex response (i.e. earlier than a voluntary reaction). A response was considered absent when no positive facial response was observed, even after delivering three shocks at the working stimulus intensity. In all subjects, we measured the percentage probability of a response as 100 × (the number of responses obtained/the number of stimuli). Onset latency and peak amplitude were measured in the responses obtained. We also measured response habituation by comparing the peak amplitude and onset latency of the response elicited by the third stimulus with those elicited by the first stimulus. Abnormally reduced habituation was arbitrarily considered when the amplitude of the response to the third stimulus was larger than 50% of that to the first stimulus.

In patients with progressive supranuclear palsy, Parkinson’s disease, multisystem atrophy and corticobasal ganglionic degeneration, we also examined the blink-reflex responses to single electrical stimuli and the blink-reflex excitability recovery curve to paired stimuli applied with inter-stimulus intervals of 100–800 ms in steps of 100 ms. Electrical stimuli were applied to the supraorbital nerve, at the supraorbital notch, at an intensity giving rise to a stable R2 response with single stimuli, usually three to five times the sensory threshold. In the responses elicited by single stimuli, we measured the onset latency and peak-to-peak amplitude of R1, R2 and R2c, as well as the duration of R2 and R2c. The area of R2 and R2c responses was obtained by multiplying the peak-to-peak amplitude by the duration of the response. In the responses obtained with paired stimuli, we calculated the percentage of excitability recovery as 100 × (the area of the R2 response to the test stimulus/the area of the R2 response to the conditioning stimulus).

**Statistical comparisons**

Responses were first analysed separately for each individual. Parametric data were pooled together for subjects belonging to one group, to obtain the mean and standard deviation. These were compared between groups of subjects, using one-factor analysis of variance (ANOVA). Probability of the responses were compared with the χ² test.

Statistical comparison of the latency, amplitude and area of the blink-reflex responses to single stimuli, as well as comparison of the percentage recovery of the response to the test stimulus with paired stimulation at inter-stimulus intervals of 100 and 200 ms, was done by using the t test with a level of significance set at P = 0.05.

**Results**

**Responses to stimulation of the median nerve at the wrist**

In normal volunteers, reflex responses to the first electrical stimulus were present in four (40%) and absent in the remaining six (60%). In two normal volunteers, the response was limited to the orbicularis oculi, while in the other two there were responses in orbicularis oculi and mentalis. Mean onset latency of the responses recorded in orbicularis oculi was 57.3 ± 7.8 ms, and those of the responses recorded in mentalis were 68 and 75 ms. Latency differences between the responses of mentalis and orbicularis oculi in the two subjects who had responses in both muscles was 8.9 ms and 13.5 ms. The peak amplitude was 237 ± 88 µV for the responses of the orbicularis oculi, and 276 µV and 130 µV for mentalis, in the two subjects who had responses of mentalis. Subsequent stimuli elicited responses of reduced amplitude and longer latency in both muscles in comparison with those elicited by the first stimulus. Responses of orbicularis oculi were absent in and beyond the second trial in one subject, and the third trial in two subjects, but persisted up to the fifth trial in the remaining subject. Responses of mentalis were absent in and beyond the third trial in one subject, but persisted up to the fifth trial in the other subject.

The probability of eliciting facial responses was higher in patients than in normal volunteers (χ² test: P < 0.05 for all groups of patients). Responses were absent in both muscles in only three patients (3.7%; one with Parkinson’s disease, one with progressive supranuclear palsy and one with corticobasal ganglionic degeneration). Responses were limited to the orbicularis oculi in one patient with Parkinson’s disease and in one patient with multisystem atrophy. Responses were limited to the mentalis in all patients with progressive supranuclear palsy, with the exception of the one patient who did not have any facial reflex responses. In two progressive supranuclear palsy patients, electrical stimuli of the largest intensity available in our stimulator gave rise to the same results (i.e. responses present in mentalis and absent in orbicularis oculi). All other patients had responses in both muscles. Statistical comparison of the probability of a response in orbicularis oculi in patients with a response in mentalis showed a highly significant difference between patients with progressive supranuclear palsy and all other...
patient groups ($\chi^2$ test: $P < 0.001$ for all comparisons). Fig. 1 shows the responses obtained in one patient with multisystem atrophy and in one patient with progressive supranuclear palsy. The mean latency and peak amplitude of the responses were not different in patients and normal subjects (Table 2). Habituation was markedly reduced in patients in comparison with normal subjects. The amplitude of the orbicularis oculi response elicited by the third stimulus, expressed as percentage of that elicited by the first stimulus, was 8.5% ± 16% in normal subjects, 82% ± 12% in Parkinson’s disease patients, 89% ± 8% in multisystem atrophy patients, 64% ± 17% in corticobasal ganglionic degeneration patients and 48% ± 14% in patients with other (non-parkinsonian) neurological diseases ($t$ test: $P < 0.01$ for all comparisons). Similar figures were obtained for the mentalis response, which exhibited an abnormally reduced habituation (i.e. the amplitude of the response elicited by the third stimulus >50% of that elicited by the first stimulus).

![Fig. 1 Responses of the orbicularis oculi (upper traces) and mentalis (lower traces) muscles to median nerve stimulation in a patient with multisystem atrophy (A) and in a patient with progressive supranuclear palsy (B).](image-url)

**Table 2  Facial muscle responses to median nerve stimulation**

<table>
<thead>
<tr>
<th></th>
<th>Orbicularis oculi</th>
<th>Mentalis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency (ms)</td>
<td>Amplitude (µV)</td>
</tr>
<tr>
<td>Control subjects</td>
<td>57.3 ± 7.8</td>
<td>237 ± 88</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>57.9 ± 5.1</td>
<td>321 ± 54</td>
</tr>
<tr>
<td>Multisystem atrophy</td>
<td>60.1 ± 4.8</td>
<td>307 ± 78</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Corticobasal ganglionic degeneration</td>
<td>58.8 ± 8.3</td>
<td>292 ± 58</td>
</tr>
<tr>
<td>Other neurological diseases(^1)</td>
<td>51.6 ± 6.2</td>
<td>240 ± 70</td>
</tr>
</tbody>
</table>

Means ± SD are shown. *Recorded in only two persons. \(^1\)Non-parkinsonian.

Discussion

In the present study, we have found that an electrical stimulus to the median nerve elicited responses in two facial muscles in a few normal subjects and in most of the patients studied. The response elicited in mentalis was of a similar amplitude and latency in patients with progressive supranuclear palsy and in those with other parkinsonisms, while the response elicited in orbicularis oculi was absent in patients with progressive supranuclear palsy and present in all other patients examined. This observation has important clinical and physiological implications. Being a specific feature of patients with progressive supranuclear palsy, the absence of orbicularis oculi responses to median nerve stimuli can

**Trigemino-facial blink reflex and blink-reflex excitability recovery curve**

Blink-reflex responses to single supraorbital nerve electrical stimuli were present at a normal latency in all control subjects and patients (Table 3). There were no significant differences between patients with progressive supranuclear palsy and the other patient groups or the control subjects regarding latency and amplitude of the blink-reflex responses.

The percentage of excitability recovery of the blink reflex to paired stimuli at inter-stimulus intervals of 200 ms was higher in all patient groups except in those with corticobasal ganglionic degeneration when compared with normal subjects (unpaired $t$ test: $P = 0.0006$ for Parkinson’s disease patients; $P = 0.001$ for multisystem atrophy patients; $P = 0.0008$ for progressive supranuclear palsy patients; $P = 0.08$ for corticobasal ganglionic degeneration patients). The incidence of an excitability recovery >20% at the inter-stimulus interval of 200 ms was similar for patients with Parkinson’s disease (50%), progressive supranuclear palsy (42.8%), or multisystem atrophy (50%), but relatively low for patients with corticobasal ganglionic degeneration (16%).
contribute to their neurophysiological characterization when compared with other parkinsonian syndromes. Our finding shows that, in addition to the impairment of voluntary eyelid motility, patients with progressive supranuclear palsy may also have eyelid reflex disturbances. The observed dissociation between mentalis and orbicularis oculi responses implies that the activity elicited in these two muscles is generated by two separate reflex circuits, both triggered by the same stimulus.

Orbicularis oculi responses to nerve afferents from the limbs have seldom been reported in humans. They were elicited in normal subjects by single taps on muscles of the upper and lower limbs, and by electrical stimulation of the digital nerves of the third finger, when these stimuli were followed by a high intensity supraorbital nerve electrical stimulus (Valls-Solé et al., 1994). They were also reported by Miwa et al. (1995), to median nerve electrical stimuli, in patients with Miller–Fisher syndrome. These authors hypothesized that the orbicularis oculi response was mediated by circuits involving the brainstem reticular formation, and they advanced the possibility of the response being part of a somesthetic startle reaction. Generalized startle responses to median nerve electrical shocks were also reported by Matsumoto et al. (1992) in a few patients with hyperekplexia. We have found no other report in the literature describing consistent orbicularis oculi responses to median nerve stimulation in humans. In cats, startle-like facial responses are triggered by somatic afferent inputs (Tanaka et al., 1971; Gokin and Karpukhina, 1985). We believe that the human orbicularis oculi response to inputs from peripheral nerves is a form of startle response induced by somatic nerve afferents that, like other startle responses, could be mediated by structures of the brainstem reticular formation. Normally, this response would be suppressed or rapidly habituated, but it can be made apparent with techniques of conditioning (Valls-Solé et al., 1994), or in certain neurological disorders (Matsumoto et al., 1992; Miwa et al., 1995; the present study).

In striking contrast to all other patients examined in this study, our patients with progressive supranuclear palsy had no responses of the orbicularis oculi to high intensity electrical stimuli to the median nerve. This finding may be related to the reported observation, in the same patients, of absent or severely reduced orbicularis oculi responses to acoustic startling stimuli (Vidalhiet et al., 1992). Abnormality of the startle reaction in patients with progressive supranuclear palsy was attributed to lesions involving the nuclei of the pontine reticular formation, which is an important part of the circuit of the auditory startle in rats (Davis et al., 1982). Interestingly, the neurons of the caudal pontine reticular nucleus that are actually involved in generation of the startle reaction in the rat, the giant neurons, have a complex dendritic arbor that extend into the reticular formation and form a large membrane surface for integration of inputs from multiple modalities (Lingenohl and Frauf, 1992). Startle-related giant neurons of the pontine nuclei have been found not to be ‘dedicated’ exclusively to startle, but activated in relation to many movements (Wu et al., 1988). It is possible that some of these cells also respond to inputs from sensory modalities other than the auditory stimuli (Gokin and Karpukhina, 1985; Karpukhina et al., 1986). If such neurons integrate sensory inputs from multiple modalities before sending the information to the neurons in charge of execution of the startle reaction, their dysfunction would explain the absence of orbicularis oculi responses to both electrical stimulation of the median nerve and auditory stimulation in patients with progressive supranuclear palsy.

In this and previous studies (Vidalhiet et al., 1992), stimuli to the trigeminal nerve generated normal blink-reflex responses in patients with progressive supranuclear palsy. This suggests that the trigeminal and upper limb afferents follow different pathways to orbicularis oculi motorneurons. In the cat, trigemino-facial reflexes follow a relatively direct pathway through the lateral pontomedullary reticular formation (Inagaki et al., 1989). This circuit may not involve the nucleus reticularis pontis caudalis, which is located at a more medial and ventral position (Davis et al., 1982).

The response of the mentalis muscle in patients with progressive supranuclear palsy was not different from that in the patients with other disorders examined in the present study. An electrical stimulus to the median nerve has been used to reproduce the palmaromental reflex electrophysiologically (Reis, 1961; Dehen et al., 1975). In the standardized neurological examination of our patients, the palmaromental reflex was found in about one half of the progressive supranuclear palsy patients, a proportion that did not differ from that found in the other patients with parkinsonism. The effects of a mechanical stroke in the thenar eminence may not be the same as those of a median

### Table 3 Blink reflex to supraorbital nerve electrical stimulation (R1, R2 and R2c components)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Latency (ms)</th>
<th>Amplitude (µV)</th>
<th>Recovery (%) at 200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R2c</td>
</tr>
<tr>
<td>Control subjects</td>
<td>11.3 ± 6.0</td>
<td>34.6 ± 3.6</td>
<td>35.2 ± 2.6</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>11.5 ± 1.1</td>
<td>32.7 ± 3.4</td>
<td>36.0 ± 4.1</td>
</tr>
<tr>
<td>Multisystem atrophy</td>
<td>10.9 ± 1.1</td>
<td>31.2 ± 2.8</td>
<td>35.8 ± 6.6</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>11.1 ± 0.7</td>
<td>30.6 ± 3.6</td>
<td>34.1 ± 3.3</td>
</tr>
<tr>
<td>Corticobasal ganglionic degeneration</td>
<td>10.7 ± 0.9</td>
<td>33.1 ± 2.8</td>
<td>33.7 ± 3.4</td>
</tr>
</tbody>
</table>

Means ± SD are shown. *Recovery of the response to the second (test) stimulus with paired stimuli given 200 ms apart. **P < 0.05.
nerve electrical stimulus and, therefore, responses to electrical and mechanical stimuli might have different central circuits. The higher incidence of mentalis muscle responses detected electromyographically to electrical stimulation of the median nerve, in comparison with clinical observation, agrees with the results reported by other authors. For instance, Reis (1961) reported that all subjects showed electromyographic responses, provided the electrical stimuli were of sufficiently high intensity. The central circuits of the palmomental reflex are not known. A theory on a long circuit involving the cerebral cortex is based on the contiguity between the chin and thumb sensori-motor representations (Dehen et al., 1975), but this theory is weakened by the fact that integrity between the brainstem and the cerebral hemispheres is not required for the observation of the reflex (Reis, 1961). It was suggested that in parkinsonian patients (Maertens de Noordhout and Delwaide, 1988), the palmomental reflex may result from suppression of inhibition of the reflex circuits, usually exerted by the striatal projections to the thalamus. One way by which the basal ganglia could influence movement is by gating sensory influences into motor areas (Schneider et al., 1982). Therefore, lesions of the striatum may liberate motor responses of brainstem reflex circuits. In progressive supranuclear palsy there is a loss of large neurons, and a presence of neurofibrillary tangles, in the thalamus, the inner part of the globus pallidus and many other subthalamic nuclei (Lantos, 1994). As a consequence, disinhibition of brainstem reflex responses related to abnormal striatal output is likely to occur in patients with progressive supranuclear palsy, as well as in other parkinsonian syndromes.

The dissociation between mentalis and orbicularis oculi responses indicates that limb afferents project onto specific facial motoneurons following different paths. It has been demonstrated in the monkey that lower facial motoneurons receive innervation predominantly from the cortico-nuclear tract, while the direct cortical innervation of upper facial muscles is scant (Jenny and Saper, 1987). We suggest that limb afferents may project onto the lower facial motoneurons innervating mentalis through the cortico-nuclear tract. The reflex path for the mentalis response would be functionally preserved, and enhanced, in patients with progressive supranuclear palsy as well as in those with other neurological disorders. Conversely, the orbicularis oculi response is likely to be mediated by circuits of interneurons in the brainstem reticular formation, which are selectively damaged in patients with progressive supranuclear palsy (Hirsch et al., 1987; Zweig et al., 1987; Malessa et al., 1991).

Brainstem histological lesions may be responsible for many clinical signs found in patients with progressive supranuclear palsy, including those involving eyelid movements. Clinically evident dysfunction of voluntary eyelid movements is a characteristic feature of patients with progressive supranuclear palsy. The present observation of absent orbicularis oculi responses to median nerve electrical stimuli inducing mentalis responses adds to the spectrum of eyelid movement abnormalities and, together with the reported finding of abnormal startle responses (Vidailhet et al., 1992), reflects the impairment of reflex brainstem function. The abnormality reported in the present study constitutes a distinctive neurophysiological derangement in patients with progressive supranuclear palsy.

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