Eye Movements in Parkinsonian Syndromes

Marie Vidalhiet, MD, Sophie Rivaud, Neziha Gouider-Khouja, MD, Bernard Pillon, PhD, Anne-Marie Bonnet, MD, Bertrand Gaymard, MD, Yves Agid, MD, PhD, and Charles Pierrot-Deseilligny, MD

Eye movements were recorded in 14 patients with Parkinson’s disease (PD) in the “off” condition, 14 patients with striatonigral degeneration (SND), 10 patients with corticobasal degeneration (CBD), and 10 patients with progressive supranuclear palsy (PSP), with comparison with 12 control subjects. Vertical saccade paralysis was not observed in the PD, SND, and CBD groups but was present in 9 patients of 10 in the PSP group. In the PD and SND groups, horizontal reflexive visually guided saccade latency and accuracy were similar, and differed only slightly from those of controls. In the CBD group, saccade latency was significantly increased and correlated to an “apraxia score”; whereas, in the PSP group, saccade amplitude was significantly decreased. Thus, the abnormalities of both horizontal saccade parameters in the PSP group contrasted with those observed in the CBD group. The percentage of errors in the antisaccade task, an index of prefrontal dysfunction, was markedly increased only in the PSP group. The smooth pursuit gain was decreased in all groups but more severely in the PSP group. It may be concluded that saccade abnormalities are clearly different in SND, CBD, and PSP, and might help in early differential diagnosis in individual patients, but that SND cannot be differentiated from PD on the simple basis of eye movement abnormalities.


Eye movements have been extensively studied in Parkinson’s disease (PD) and progressive supranuclear palsy (PSP) but are less well known in striatonigral degeneration (SND) and corticobasal degeneration (CBD). In PD, only mild ocular motor abnormalities have been described, concerning in particular saccade latency [1] and the smooth pursuit gain [2, 3]. In contrast, in PSP [4], supranuclear vertical gaze paralysis is one of the cardinal signs of the disease [5], and horizontal visually guided saccades are markedly abnormal [6]. Little is known about eye movements in SND [7], which has been lumped together with Shy-Drager syndrome [8] and olivopontocerebellar atrophies into the group of multiple system atrophies (MSA) [9, 10]. Some ocular motor abnormalities have been reported in MSA, consisting of vertical gaze impairment [8, 9, 11] or square-wave jerks (SWJ) [12]. In CBD [13, 14], various ocular motor abnormalities have also been reported, with only clinical descriptions so far, including supranuclear gaze paralysis [15, 16]. Therefore, as in clinical practice, it is sometimes difficult to distinguish CBD from PSP, and, to a certain extent, SND from PSP or PD [17], in particular at an early stage of each disease, we studied eye movements with electrooculography (EOG) in these four diseases and compared the results with those of normal age-matched control subjects.

Patients and Methods

Patients

Four groups of patients and a control group of normal subjects were constituted.

The PD group comprised 14 consecutive patients (age, 61.5 ± 7.3 yr; disease duration, 11.3 ± 5.5 yr; stages II–IV [18]) (Table 1). The inclusion criteria were as follows: (1) parkinsonian syndrome responsive to levodopa (motor score improvement at least superior to 50%) and (2) without any sign atypical of idiopathic PD. Motor disability was evaluated using the motor subscale of the UPDRS scale [19]. The treated score was that at the time of maximum effect of levodopa, and the basal score that at the time of maximum disability without levodopa. The percentage of improvement in motor disability was calculated as follows: basal score — treated score/basal score × 100. PD patients were recorded in the “off” condition.

The SND group comprised 14 patients (age, 61.8 ± 9 yr; disease duration, 4.8 ± 2 yr) (see Table 1). Pathological diagnosis was obtained in 1 case (Patient 9). The inclusion criteria were (1) parkinsonian syndrome poorly responsive or unresponsive to levodopa (motor score improvement inferior to 50%, see below), (2) autonomic failure, i.e., genitourinary symptoms, with abnormal results of urological investigations, whether or not associated with orthostatic hypotension and abnormal autonomic test at electrocardiogram, (3) progressive evolution, and (4) absence of lesions on magnetic resonance imaging (MRI) or computed tomographic (CT) scan.
whom were right-handed (age, evolution, and with levodopa, (2) presence of at least a slight downward gaze 0 1 0 0 0 1 1 0 0 1 1 0 0
Upward gaze 3 3 3 0 3 1 2 3 3 2
Downward gaze 3 3 2 3 3 1 3 3 2 3

For details of scale, see text.

The CBD group comprised 10 consecutive patients, all of whom were right-handed (age, 66.5 ± 6.8 yr; disease duration, 3 ± 1.2 yr) (see Table 1). The inclusion criteria were (1) parkinsonian syndrome without any response to levodopa, (2) apraxia, (3) clear asymmetry of abnormal signs (9 in the right upper limb, 1 in the left upper limb), (4) progressive evolution, and (5) absence of focal lesions on MRI or CT scan.

The PSP group comprised 10 consecutive patients (age, 62.5 ± 5.5 yr; disease duration, 2.1 ± 0.56 yr) (see Table 1), of whom 4 were subsequently confirmed pathologically (Patients 2, 4, 5, and 8). The inclusion criteria [20] were (1) parkinsonian syndrome without significant improvement with levodopa, (2) presence of at least a slight downward saccade impairment, determined from recordings (Table 2), (3) falls, (4) pseudobulbar palsy or dysarthria, (5) frontal lobe-like signs, (6) progressive course of the disease, and (7) absence of focal lesions on MRI or CT scan.

Severe intellectual deterioration was a criterion for exclusion in each patient group. Evaluation of intellectual deterioration and frontal lobe dysfunction was performed according to procedures described elsewhere [21]. A global frontal score was calculated and expressed as a percentage of the best value obtained in normal subjects. Absence of apraxia was clinically determined in PD, SND, and PSP patients. In the CBD group, because apraxia is characteristic of the disease, we analyzed this abnormality with three tests of motor and gestural functions, i.e., ability to copy finger position [22], to use real or mimed objects [23, 24], and to perform symbolic gestures at command or by imitation [23]. For each patient of the CBD group, left and right "apraxia scores" were expressed as the sum of the scores in these three tests (maximum score, 50).

A control group of 12 right-handed subjects (age, 63.9 ± 8.3 yr) was studied with the same paradigms as the patients. They had no history of neurological disorders and were normal on neurological examination.

Eye Movement Recordings
Eye movements were recorded by direct-current EOG in darkness with four electrodes (two horizontal temporal, because eye movements were always conjugate in our patients, and two vertical on one eye). The bandwidth of the recording amplifiers was from 0 to 100 Hz, and the system had a resolution of 1 degree. The patient's head was immobilized.

Horizontal reflexive visually guided saccades were studied with two paradigms. In the gap task, disappearance of the central fixation point was followed after an interval (gap) of 200 msec by the onset of a luminous lateral target located 25 degrees to right or left of the central point. The subject was instructed to fixate the central point and then look at the lateral target as soon as it appeared. The target was presented randomly right or left, with unpredictable timing. Target eccentricity was limited to 25 degrees to make the task easier to perform. All measurements were made by hand. Left and right saccade latencies were calculated for each subject by averaging 20 measurements made in each direction. These calculations excluded saccades with latencies of <75 msec, probably corresponding to anticipatory movements [25], and those with latencies >800 msec, probably resulting from inattention. Saccade accuracy was determined by the saccade gain (amplitude of the first saccade over apparent eccentricity of the target). In the antisaccade task, the procedure was the
same as in the gap task except that the subject was asked to look in the opposite direction to the suddenly appearing lateral target. The percentage of misdirected saccades (beginning in the direction of, or reaching, the target) was determined for each lateral direction.

In horizontal foveal smooth pursuit, the subject was instructed to follow a target with a sinusoidal displacement and peak velocity of 20 degrees/sec (0.15 Hz). The pursuit gain (peak eye velocity over peak target velocity) was measured by hand, rightward and leftward.

Vertical eye movements cannot be analyzed quantitatively with EOG. Therefore, the impairment of vertical saccades was scaled as follows: 0, when saccade was normal; 1, when velocity was decreased but still permitted the target (20 degrees' eccentricity) to be reached by one or usually several hypometric saccades, i.e., when there was only a slight saccade impairment; 2, when there was both a decrease in saccade velocity and a reduction in the final amplitude of the movement, i.e., when there was a moderate saccade impairment; 3, when the eyes remained on the midline during attempted saccades, i.e., when there was saccade paralysis. Vertical oculocephalic reflexes were tested by moving the subject's head and analyzed qualitatively.

The existence or absence of SWJ was studied at the beginning of the recording session, during a period of 10 seconds while the subject attempted to fixate the central point. The percentage of patients presenting SWJ was determined in each group.

Statistical Analysis
Lateral saccade latency and amplitude, and the smooth pursuit gain, in each patient group, were compared with the control group by analysis of variance, and multiple comparisons were made using the Newman-Keuls procedure. The percentage of errors in the antisaccade task, in each patient group, was compared with the corresponding values of the control group using the Kruskal-Wallis test. The frontal scores in the CBD and PSP groups were compared using the Mann-Whitney test. A nonparametric correlation test (Spearman test) was used to determine a possible relationship between saccade latency in the gap task and the apraxia score in the CBD group, and between the percentage of errors in the antisaccade task and the frontal score in the PSP group.

Group results are expressed as the mean ± standard deviation (SD).

Results
Vertical eye movements were qualitatively normal in the PD and SND groups. There was no paralysis of downward or upward saccades in the CBD group (see Table 2). Downward saccades were qualitatively slightly impaired in 3 patients of 10, and upward saccades slightly or moderately (i.e., with restricted final amplitude) impaired in 7 patients of 10. In 3 patients, vertical eye movements appeared to be normal. Impairment of downward saccades was required for inclusion in the PSP group, but saccade paralysis or a restricted final amplitude was not necessary. In fact, such slight impairment existed in only 1 patient (see Table 2). In 2 others, there was restricted final amplitude of downward saccades and, in the remaining 7 patients, downward saccade paralysis. Finally, vertical gaze paralysis (upward or downward) existed in 9 patients of 10 in the PSP group. Vertical oculocephalic reflexes resulted in full vertical eye deviation in all patients, suggesting the supranuclear feature of vertical gaze impairment, when this impairment was present.

Mean results of lateral horizontal eye movements are given in Table 3. In the PD and SND groups, saccade latency was slightly increased bilaterally, com-

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### Table 3. Mean Horizontal Eye Movement Values

<table>
<thead>
<tr>
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<th>Visually Guided Saccades</th>
<th>Antisaccades</th>
<th>Smooth Pursuit</th>
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<tr>
<td></td>
<td>Latency (msec)</td>
<td>Gain (%)</td>
<td>Gain (%)</td>
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<td></td>
<td>(Mean ± SD)</td>
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<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
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<tr>
<td>Controls (n = 12)</td>
<td>203 ± 30</td>
<td>198 ± 20</td>
<td>0.95 ± 0.04</td>
</tr>
<tr>
<td>PD group (n = 14)</td>
<td>248 ± 67</td>
<td>258 ± 67</td>
<td>0.87 ± 0.1</td>
</tr>
<tr>
<td>SND group (n = 14)</td>
<td>251 ± 71</td>
<td>246 ± 64</td>
<td>0.84 ± 0.13</td>
</tr>
<tr>
<td>CBD group (n = 10)</td>
<td>355 ± 94b</td>
<td>382 ± 97b</td>
<td>0.90 ± 0.08</td>
</tr>
<tr>
<td>PSP group (n = 10)</td>
<td>183 ± 101</td>
<td>224 ± 72</td>
<td>0.54 ± 0.2b</td>
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</tbody>
</table>

Comparisons between each patient group and the control group are given.

*p < 0.05; *p < 0.001; **p < 0.01. For other comparisons and statistical methods used, see text.

PD = Parkinson's disease; SND = striatogral degeneration; CBD = corticobasal degeneration; PSP = progressive supranuclear palsy.

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Fig 1. Eye movement recordings in corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). (A) Horizontal saccades in the gap task. (B) Horizontal foveal smooth pursuit. a = control subject; b = CBD patient; c = PSP patient; L = left; M = midline; R = right; s = stimulation; t = lateral target. The arrow indicates the extinguishing of the central fixation point (gap = 200 ms).

score and saccade latency was studied (Fig 2); in this group, the mean right and left apraxia scores were 27.4 (range, 0–45) and 32.4 (range, 9–50), respectively. There was a significant correlation for leftward values (Spearman’s $r = 0.786, p < 0.05$) but not for rightward values.

In the PD, SND, and CBD groups, the rightward and leftward saccade gains were close to that of the control group (with no significant difference). In the PSP group, the gain was markedly and significantly decreased compared with that of the control group ($p < 0.001$ for each lateral direction). This gain was also significantly lower than that observed in each of the other patient groups ($p < 0.001$ for each lateral direction, in each comparison). Therefore, several small successive saccades were required to reach the 25-degree target in PSP (see Fig 1).

In the antisaccade task, the percentage of errors in the PD, SND, and CBD groups did not differ from.
that in the control group. In the CBD group, the rightward percentage of errors was moderately but not significantly increased. In the PSP group, the percentage of errors was markedly and significantly increased, compared with that of the control group ($p < 0.001$ for each direction). This percentage of errors was also significantly higher than that existing in the SND group ($p < 0.001$ for each direction) or the PD group ($p < 0.01$ for each direction) but not significantly different from that existing in the CBD group.

A significant correlation existed for right values between the percentage of errors in the antisaccade task and the frontal score (Spearman's $r = 0.808$, $p < 0.01$), and significance was nearly reached for left values (Spearman's $r = 0.597$, $p < 0.06$). Last, it should be noted that the frontal score was significantly lower in the PSP group than in the CBD group ($p < 0.01$), suggesting a more marked frontal dysfunction in the former.

The smooth pursuit gain was significantly decreased in the PD and the SND groups ($p < 0.05$ for the rightward movement), in the CBD group ($p < 0.01$ for the rightward movement and $p < 0.05$ for the leftward movement), and in the PSP group ($p < 0.001$ for each direction), in which the impairment was the greatest, compared with that of the control group.

SWJ were present in 18% of PD, 7% of SND, 20% of CBD, and 60% of PSP patients.

Discussion

The results observed in the patient groups may have clinical implications for the early diagnosis of these diseases, and some physiopathological hypotheses are suggested to account for such results.

Clinical Aspects

The overall results of this study concerning saccades were as follows: (1) in the PD and SND groups, very slight or no saccade impairment; (2) in the CBD group, markedly increased lateral saccade latency; and (3) in the PSP group, markedly decreased lateral saccade amplitude, combined with a high percentage of errors in the antisaccade task and vertical gaze paralysis. Furthermore, the lateral smooth pursuit gain was decreased and SWJ were present in all patient groups, but these two abnormalities were much more marked in the PSP group than in the others. Because it may be difficult in clinical practice to differentiate between certain of these diseases at an early stage of their evolution, in particular atypical PD versus SND, SND versus PSP, and PSP versus CBD, we will review how eye movement abnormalities may help in such diagnosis problems.

PD versus SND. Many authors have already drawn attention to the difficulty in clinically distinguishing atypical PD from SND [10, 26]. In our study, the age at disease onset was approximately the same in the PD and SND groups. Parkinsonian disability was also similar in both groups (see Table 1), but the disease duration in the SND group was less than half that of the PD group, suggesting more rapid aggravation in the former. Response to levodopa could be observed at an early stage of evolution in the SND patients and usually lasted <1 year, whereas in the PD patients it had been maintained for at least 11 years on average. Besides the parkinsonism and autonomic failure, required for inclusion, SND patients had also a postural instability, dysarthria, and pyramidal signs, none of which were observed in PD patients. These relatively nonspecific signs indicated more widespread damage in SND patients than in PD patients.

Similar eye movements were observed in the PD and SND groups, with nearly normal saccade latency and accuracy, normal percentage of errors in the antisaccade task, moderately decreased smooth pursuit gain, and the presence of SWJ in some patients. Slight or no saccade and antisaccade impairment in PD is consistent with previously reported results in this disease [1, 2, 27, 28]. Finally, this study, which is the first to analyze in detail eye movements in SND, shows that the abnormalities found in this disease cannot help in the differential diagnosis of SND and PD.

SND versus PSP. In contrast, the comparison between SND (or PD) and PSP patients showed several clear differences. There was no vertical gaze paralysis in SND patients, whereas 9 of 10 patients with PSP presented upward or downward saccade paralysis, despite a shorter disease duration. It should be noted that vertical gaze paralysis was frequently found in the PSP group, though only slight downward saccade impairment (visible on recordings) was required for inclusion in this group. Both horizontal saccade parameters were almost normal in the SND group, whereas severe impairment of saccade amplitude existed in the PSP group. The percentage of errors in the antisaccade task was normal in the SND group, but markedly abnormal in the PSP group. Thus, SND (or PD) and PSP result in noticeably different findings concerning saccades, which may help in differential diagnosis in some patients.

The smooth pursuit gain was decreased in both groups, but impairment was greater in the PSP group. SWJ were much more frequent in the PSP group (60% of patients) than in the SND group (7% of patients). The frequency in the latter appears much lower than that observed in the MSA and “Parkinson plus” groups of patients previously reported [12]. However, in this recent report, because patients with Shy-Drager syndrome and olivopontocerebellar degeneration were included with SND patients, valid comparisons between
the two studies are not possible. Thus, smooth pursuit impairment and SWJ appear to be less useful for the differential diagnosis of SND and PSP.

PSP versus CBD. The eye movement abnormalities observed in the CBD group were relatively homogeneous from one patient to another. The main disturbances concerned vertical and lateral saccades, and allowed us to distinguish clearly between the CBD and PSP groups. For vertical saccades, it should be noted that there was no paralysis in the CBD group but rather a slight or moderate impairment, clearly predominating in upward gaze. In contrast, in the PSP group, vertical saccade paralysis existed in almost all patients despite a shorter disease duration in this group and the fact that such paralysis was not required as an inclusion criterion (see above). Thus, although it cannot be ruled out that vertical saccade paralysis may also occur in CBD at a late stage of the disease, it can be concluded from our study that such paralysis is not usually observed at an early stage, whereas it appears frequent at this stage in PSP. Furthermore, in the CBD group, horizontal saccade latency was significantly and markedly increased, but accuracy was normal. In the PSP group, the results obtained for both saccade parameters were contrary to those observed in the CBD group. It should be noted that horizontal saccades in CBD were also different from those in SND or PD. Saccade latency may be significantly increased in PD, but only at a later stage of the disease, in the off condition [1].

Results in the antisaccade task were significantly abnormal only in the PSP group. However, the rightward percentage of error was moderately increased in the CBD group. The smooth pursuit gain was also impaired in both groups but more severely in the PSP group. Last, SWJ were more frequent in the PSP than in the CBD group. Therefore, these last three ocular motor abnormalities appear to be less discriminatory for the diagnosis of each disease than those of vertical and lateral saccades.

From this clinical discussion, it appears that the study of saccades may contribute to early diagnosis of PSP and CBD. Each of them includes a relatively specific saccadic syndrome compared with saccade abnormalities of the other parkinsonian syndromes. In contrast, PD and SND cannot be differentiated purely on the basis of eye movement abnormalities.

Physiopathological Aspects
These points concern saccades in the CBD and PSP groups, in which the abnormalities of eye movements are the most useful for clinical diagnosis.

In the PSP group, vertical saccade paralysis, and the decrease in horizontal saccade amplitude could be explained by damage to the basal ganglia and the premotor structures controlling vertical and lateral saccades [29, 30]. The marked increase in reflexive horizontal saccade latency was the main eye movement abnormality observed in the CBD group. Latency of the same saccades was also increased bilaterally in patients with unilateral focal lesions affecting the posterior parietal cortex, in contrast to patients with frontal lesions, in whom saccade latency was not severely disturbed [31]. Parietal damage in CBD is supported by several other arguments, such as the existence of apraxia. It should be noted that, at least for left values, a correlation was found between the apraxia score and saccade latency. This merely unilateral correlation could be explained by the asymmetrical feature of apraxia. Such a correlation could simply mean that damage was widespread in the parietal lobe.

The percentage of errors in the antisaccade task was moderately increased unilaterally in the CBD group, and more markedly increased in the PSP group, bilaterally (see Table 3). It was correlated to the frontal score on one side in the latter group. Disturbances in the antisaccade task appear to be related to frontal cortex dysfunction [32], especially of the prefrontal cortex [31]. In PSP patients, frontal impairment is essentially due to bilateral deafferentation from the subcortical structures, as shown by metabolic [20, 33] and anatomical [34] studies; whereas, in CBD patients, the frontal cortex may be asymmetrically affected [13, 35].

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