SHORT REPORT

Saccade impairments in patients with fronto-temporal dementia

C Meyniel, S Rivaud-Péchoux, P Damier, B Gaymard

Background: Early diagnosis of fronto-temporal dementia (FTD) is often difficult because of the non-specific presentation. Saccadic eye movements, which are mainly controlled by the frontal areas, may provide a powerful tool for the analysis of frontal lobe dysfunction. The pattern of saccadic abnormalities has not previously been investigated in patients with FTD.

Objective: To study saccade tasks in a group of 23 patients with FTD and compare the results with aged matched healthy controls.

Methods: Triggering and inhibition of reflexive prosaccades were evaluated in a prosaccade and an antisaccade task, respectively, while the ability to withhold an antisaccade during a delay was explored in a delayed antisaccade task. Patients with progressive supranuclear palsy (PSP), in whom the pattern of eye movement deficit is well documented, were studied with the same protocol. To characterise the frontal lobe dysfunction in FTD more precisely, a battery of neuropsychological tests was carried out in these patients.

Results: Patients with FTD showed impaired reflexive saccade inhibition, similar to that observed in patients with PSP, and a decreased ability to withhold an antisaccade.

Conclusions: Inhibition of reflexive and voluntary saccades appears to be independently processed. A delayed antisaccade task could be useful for the early diagnosis of FTD.

Fronto-temporal dementia (FTD) is a neurodegenerative disorder affecting the frontal and temporal lobes. Its early diagnosis is often difficult, the initial symptoms tending to be restricted to non-specific behavioural disorders such as apathy or disinhibition. Various studies have shown that the analysis of saccadic eye movements may provide a useful tool for investigating neurological or psychiatric disorders in which the frontal lobe is impaired, as both saccade triggering and inhibition are mainly controlled by frontal cortical areas. Thus far, no oculomotor study has been undertaken in patients with FTD. We therefore tested various saccade paradigms in a group of patients with FTD, with special emphasis on inhibitory mechanisms. The same tasks were carried out in a group of healthy subjects and in a group of patients with progressive supranuclear palsy (PSP) in whom the pattern of saccadic impairments has been well described.

METHODS

Subjects
We recruited 23 patients with FTD meeting the Lund–Manchester criteria (mean (SD) age, 67 (9) years; duration of illness, 2.9 (2.0) years), along with 14 patients with PSP meeting Litvan’s criteria (mean age, 70 (6) years; duration of illness, 2.4 (1.6) years). We excluded patients with excessive neurological deterioration (mini-mental state examination (MMSE) score <20) or with a cerebral focal lesion assessed on magnetic resonance imaging (MRI) in the preceding two years, or both. Ten healthy subjects (mean age, 68 (9) years) with no history of neurological or psychiatric disorders served as a control group. All subjects gave their informed consent to be included in the study, which was approved by the local ethics committee.

Oculomotor tests
Eye movements were recorded by horizontal electro-oculography with our standardised protocol, as previously described. In the prosaccade task, subjects were asked to follow a target that jumped from a central position to an unpredictable 23˚ right or left location. A 200 ms gap was interposed between central target offset and lateral target onset. This task tests the ability to trigger a reflexive saccade. Only saccade latency was measured in this task. There were 24 trials per subject.

In the antisaccade task, the same stimulus condition was used as in the prosaccade task, but subjects were instructed to trigger a saccade as soon as possible in the opposite direction to the lateral target. This task tests the ability to inhibit a reflexive prosaccade. Correct antisaccade latency and the percentage of (uninhibited) prosaccades were measured in this task. There were 36 trials per subject.

In the delayed antisaccade task, a variable delay (3000, 3500, or 4000 ms) was interposed between lateral target presentation and central fixation point offset. Subjects were instructed to trigger an antisaccade at the end of the delay—that is, at the extinction of the central fixation point. Successful performance of this task required the ability both to inhibit a prosaccade and to withhold an antisaccade during the delay. Consequently, a trial in which at least one saccade was triggered during the delay was scored as an error, and any such saccade was considered to be an anticipatory prosaccade or antisaccade according to its direction. We therefore determined two scores: the percentage of anticipatory prosaccades and the percentage of anticipatory antisaccades. The latency of the anticipatory prosaccades and the anticipatory antisaccades with respect to target onset, and the latency of the correct antisaccade with respect to the fixation point offset. There were 24 trials per subject.

Saccade latencies were analysed by two way analysis of variance (ANOVA). Subsequent comparisons between groups were carried out with the Bonferroni correction. The percentage of responses was compared between the groups with a Mann–Whitney U test.

Abbreviations: DRS, dementia rating scale; FAB, frontal assessment battery; FTD, fronto-temporal dementia; MADRS, Montgomery and Asberg depression rating scale; MMSE, mini-mental state examination; PSP, progressive supranuclear palsy
Neuropsychological tests

Cognitive functions in both FTD and PSP patients were measured by the MMSE.7 Global frontal lobe functions were assessed by a frontal assessment battery (FAB) and the fronto-temporal behavioural scale of Lebert.8 9 Depression was measured by the Montgomery and Asberg depression rating scale (MADRS).10 In the FTD group, global frontal lobe functions were also evaluated by the Mattis dementia rating scale (DRS).12 As the orbitofrontal, dorsolateral, and fronto-median cortices may be affected differently in patients with FTD, we also studied three additional tests in this group. In the emotion related learning test of Rolls (orbitofrontal cortex), we measured “the number of reversals completed in the first 30 trials (R1) and the trial on which the last error occurred in the first reversal (R2) and in extinction (R3)” 11 In the spatial sequence generation task of Owen (dorsolateral cortex), we measured “the number of sequences generated, expressed as a percentage of 24 possible responses, and the percentage of sequences (after an error), that began with the same box used to begin the previous sequence”.14 Starkstein’s scale was used to quantify the level of apathy (fronto-median cortex).13 The performance of the FTD and PSP groups on neuropsychological tests was compared with a Mann-Whitney test. In the FTD group, the other results were analysed with respect to published reports.10 13 14

Correlations between neuropsychological scores and oculomotor variables were studied using the Spearman test.

RESULTS

Oculomotor tasks

Compared with the control group, saccade latency in the FTD group was increased in all three prosaccade (p<0.025), antisaccade (p<0.046), and delayed antisaccade tasks (p<0.015). Saccade latencies were not significantly different in the PSP and FTD groups (table 1).

In the antisaccade task, both FTD and PSP patients had an increased percentage of errors compared with control subjects (FTD, p<0.0001; PSP, p<0.0001); the results of the two patient groups were not significantly different. In the delayed antisaccade task, both PSP and FTD patients had an increased percentage of anticipatory prosaccades compared with controls (FTD, p<0.0001; PSP, p<0.004) (table 1). The percentage of anticipatory antisaccades was significantly increased in the FTD group compared with both the normal group (p<0.01) and the PSP group (p<0.014), but this percentage was normal in the PSP group (table 1).

Cognitive tests

Global cognitive functions (MMSE) were more affected in the FTD than in the PSP group (p<0.001). Frontal lobe functions were impaired in both FTD and PSP patients, but with no significant difference between the groups (FAB, p<0.182). The MADRS score was significantly higher in the PSP group than in the FTD group (p<0.041), but below the depression threshold in both groups. The results of the three regional frontal tests (Rolls, Owen, and scale of apathy) were abnormal in all FTD patients (table 1).

Correlations

Significant correlations were found between the percentage of errors in the antisaccade task and the results in the frontal lobe tests (FAB, r = -0.75, p<0.0001; Mattis DRS, r = -0.86, p<0.0001; Rolls R2, r = 0.69, p<0.007; Rolls R3, r = 0.55, p<0.004). No significant correlation was found between any of the three regional frontal tests and the percentage of anticipatory antisaccades in the delayed antisaccade task.

DISCUSSION

This is the first oculomotor study carried out on patients with FTD. Our main finding was that both FTD and PSP patients showed a decreased ability to inhibit reflexive prosaccades (antisaccade and delayed antisaccade tasks), but that only FTD patients were impaired in the ability to withhold voluntary saccades (delayed antisaccade task, fig 1A).
Reflexive prosaccade inhibition is abnormal in a broad spectrum of diseases in which the dorsolateral prefrontal cortex is damaged. Poor antisaccade performance is thus observed in patients with focal frontal lobe lesions, in neurodegenerative diseases such as PSP, Huntington’s disease, and Alzheimer’s disease, and in patients with schizophrenic or attention deficit/hyperactivity disorder. The high percentage of uninhibited prosaccades observed in FTD patients in both antisaccade and delayed antisaccade tasks thus suggests that the dorsolateral prefrontal cortex is affected in this disease. The correlation between the percentage of errors in the antisaccade task and the global frontal tasks (FAB, Mattis DRS) is consistent with an involvement of the dorsolateral prefrontal cortex in all these tasks. The correlation found between the percentage of errors in the antisaccade task and the Rolls test was unexpected. It could reflect the influence of motivation in the successful performance of the antisaccade task.

In both FTD and PSP patients, anticipatory prosaccades in the delayed antisaccade task occurred shortly after target presentation (fig 1B). It might therefore be proposed that dorsolateral prefrontal cortex inhibitory functions are mainly exerted on reflexive, externally triggered movements—that is, during a short time window following target presentation. However, PSP patients were able to withhold voluntary saccades in the delayed antisaccade task (fig 1B). As the dorsolateral prefrontal cortex is the frontal area mainly affected in PSP, it does not seem to be essential for the suppression of non-reflexive internally triggered movements. An opposite pattern has been reported in patients with Gilles de la Tourette syndrome—that is, normal reflexive prosaccade inhibition but impaired ability to withhold voluntary saccades. These results are consistent with the hypothesis that inhibition of externally triggered movements and inhibition of internally triggered movements are processed independently. Hence, the markedly increased percentage of anticipatory antisaccades in FTD patients (delayed antisaccade task) probably resulted from a dysfunction lying outside the dorsolateral prefrontal cortex. The results of the neuropsychological tests indicate that frontal lobe dysfunction in our FTD patients was not restricted to the dorsolateral prefrontal cortex but extended to the orbitofrontal and fronto-median cortices as well. Inability to withhold voluntary saccades could therefore result from a dysfunction of these areas, individually or in association. Unfortunately, we did not find any correlation between the three regional frontal lobe tests and the percentage of anticipatory antisaccades. This negative result may be explained by an excessive sensitivity of these cognitive tests. Further investigation of this paradigm in patients with focal frontal lesions is therefore needed to clarify this issue.

In conclusion, our study suggests that oculomotor paradigms may be of interest for the study of FTD patients provided that this abnormality is present at an early stage of the disease.

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Authors’ affiliations
C Meyniel, P Damier, Service de Neurologie, CHU de Nantes, Nantes, France
S Rivaud-Pechoux, INSERM U679, Hôpital de la Salpêtrière, Paris, France
B Gaymard, Service d’Explorations Fonctionnelles du Système Nerveux, Hôpital de la Salpêtrière

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Correspondence to: Dr B Gaymard, INSERM U679 (formerly U289), Hôpital de la Salpêtrière, 75651 Paris Cedex 13, France; gaymard@ccr.jussieu.fr

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Figure 1  Delayed antisaccade task. (A) Typical eye movement recordings. The upper trace represents the paradigm. (B) Distribution of anticipatory prosaccade (PS) and anticipatory antisaccade (AS) latencies in the FTD and PSP groups. FP, fixation point; FTD, fronto-temporal dementia; PSP, progressive supranuclear palsy; T, target.
A 59 year old man with history of smoking, hypertension, diabetes mellitus, and hypercholesterolemia presented suddenly with numbness and weakness of both upper limbs. A few minutes after that he felt an intense and oppressive chest pain accompanied by profuse diaphoresis, severe hypotension, bradycardia, and low level of consciousness. No elevated damage cardiac markers or electrocardiographic changes were registered. Aortography ruled out an aortic dissection whereas coronary angiography showed a severe hypotension, bradycardia, and low level of consciousness.

An adequate neurological examination could be performed only after 48 hours, when the patient was extubated. He had a bilateral, predominantly proximal (MRC grade 2/5 versus 4/5 for the distal muscles), flaccid arm paresis, with absent reflexes. Muscular balance and deep tendon reflexes in both lower limbs were normal. All sensory modalities were preserved and there were neither autonomic abnormality nor Babinski sign.

Cranial MRI ruled out bilateral brain infarctions in the border zone between middle and anterior cerebral artery territories—the most frequent aetiology of acute man-in-the-barrel syndrome. Surprisingly, cervical MR demonstrated a spinal anterior artery territory infarction between C2 and C7 levels involving exclusively both anterior horns of the spinal cord (panels A and B), whose cells are known to have a spinal anterior artery territory infarction between C2 and C7 territories—the most frequent aetiology of acute man-in-the-barrel syndrome.

Prominent vegetative symptoms and chest pain at the onset provoked an initial misdiagnosis of acute myocardial infarction despite the absence of compatible biochemical and electrocardiographic changes, but they can be plausibly explained by a transient ischaemia of intermediate-lateral horns and of spinothalamic tracts at the lower segments of cervical cord, respectively. Magnetic angioresonance made evident a severe atheromatosis within the right vertebral artery (panel C).

Cervical cord infarction should be considered as a cause of acute bilateral arm paresis and included in the differential diagnosis of chest pain with accompanying neurological symptoms together with myocardial infarction and aortic dissection.

A Serrano-Pozo, G Sanz-Fernández, E Martínez-Fernández
Department of Neurology, University Hospital Virgen del Rocío, Seville (Spain)
J Nevado-Portero
Department of Cardiology, University Hospital Virgen del Rocío, Seville (Spain)
Correspondence to: Alberto Serrano Pozo, Plaza Ruiz de Alda n7 10 D, 41004 Seville (Spain); albsserrap@yahoo.es

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