Ocular microtremor in patients with idiopathic Parkinson’s disease

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Abstract
Abnormalities in the oculomotor control mechanism of patients with idiopathic Parkinson’s disease are well recognised. In this study the effect of Parkinson’s disease on tonic output from oculomotor nuclei was studied by using oculomicrotremor as an index of such output. Oculomicrotremor readings were taken from 22 Parkinsonian patients and 22 normal healthy volunteers using the piezoelectric strain gauge technique. There was a slower overall tremor frequency, baseline, and burst frequency in the parkinsonian group. There was also a significant increase in the duration of baseline, with a decrease in the number of bursts a second and a decrease in average duration of bursts in the patient group compared with the normal group. One patient, whose medication was withdrawn, showed a marked decrease in mean frequency and baseline frequency with a decrease in number of bursts and increase in baseline duration compared with readings taken when treatment recommenced. These results suggest that variables measured in oculomicrotremor are altered compared with normal subjects, reflecting altered tonic output from oculomotor nuclei in patients with idiopathic Parkinson’s disease.

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Abnormalities in the oculomotor control mechanisms of patients with idiopathic Parkinson’s disease are well recognised. The abnormalities described would seem to be broadly compatible with the more general disorder of motor control seen in this condition. These include the loss of the ability to programme coordinated eye-head movement. In patients with mild to moderate idiopathic Parkinson’s disease saccades are normal when directed to a novel target (reflexive saccades) or even to the mirror image of the target location (antisaccade). However, patients exhibit a reduction in the amplitude of memory guided and predictive saccades, as well as multistepting hypometria in these cases. Indeed the spatial error of parkinsonian saccades does not invariably take the form of hypometria when part of a rapid sequence of eye movements and they can be hypermetric relative to the target location. Abnormalities in a smooth pursuit gain have also been documented.

Oculomotor units exhibit continuous activity even when the eye is at rest or in the primary position. Constant oculomotor unit activity produces a fine high frequency eye tremor recordable at the eye surface. This neurologically generated tremor (oculomicrotremor) is constantly present in all subjects and is entirely involuntary. Tonic activity in the frontal eye fields is in part responsible for the constant output from the oculomotor units, and activity in this state is known to be affected by dopamine depletion in Parkinson’s disease.

The purpose of this research was firstly to investigate the effect of Parkinson’s disease on tonic output from oculomotor nuclei, by using oculomicrotremor as an index of such output, and secondly, to investigate the possibility of using oculomicrotremor as an objective measure of neuronal activity in these patients.

Methods

PATIENTS
Twenty-two patients with idiopathic Parkinson’s disease were studied (mean age 68 (SD 10.45) years). All of the patients were being treated with dopaminergic drugs and none were taking psychotropic or tranquillising agents. None of the patients had any evidence of oculomotor dysfunction on clinical examination. At the time of recording, patients were subjected to a full neurological examination including a mini mental state examination (none scoring below 28). They were also scored on the bradykinesia subsection of the Webster scale. Patients with a score of 0 or 1 were considered “on” while those with a score of 2 or 3 were considered “OFF”. Twelve patients were “on” (mean age 67 (SD 11) years) and 10 patients were considered “off” despite medication (mean age 70 (SD 10) years). Clinical examinations of the patients were repeated fully at each recording session.

CONTROL GROUP
Twenty-two neurologically normal healthy volunteers were included for study (mean age 68 (SD 10.21) years). The group consisted of 12...
men and 10 women. All were free from medication and had no evidence of concurrent disease.

RECORDING SESSION

Ocular microtremor was recorded using the piezoelectric strain gauge technique first developed by Bengi and Thomas. This technique is described in detail elsewhere and has been shown to provide a reliable estimate of ocular microtremor activity. Briefly, the piezoelectric element is mounted in a Perspex rod and its tip is coated with silicone rubber. The subject lies supine with the eyes in the primary position in a normally lit room. The Perspex rod is mounted on a headframe and lowered directly on to the scleral surface, which has been anaesthetised with 0.5% proxymethacaine hydrochloride solution. The eyelids are retracted with adhesive tape. Probe placement is judged by visual inspection and by listening to the signal being recorded, using audio cassette headphones.

The signal from each probe is passed to a conditioning unit and amplified (differential amplifier with 40 dB common mode rejection ratio, flat (within 1dB) frequency response between 20 and 150 Hz) and stored on audiotape using an adapted Sony Walkman for later retrieval and analysis. This system has a signal/noise ratio of >23 dB and the resolution is <1% of the dynamic range, or 25 nm. The frequency response is flat between 20 Hz -150 Hz with <2dB deviation from peak response.

OMT records were analysed by visual inspection by an investigator who was unaware of the clinical status of the subject. Normal eye tremor activity consists of an irregular baseline tremor superimposed on which are regular sinusoidal episodes of activity termed bursts. The OMT record is analysed visually and the bursts are easily distinguishable, possessing a greater amplitude than the rest of the microtremor and a packet-like appearance against the baseline tremor. Studies have shown that the bursts are of a near sinusoidal oscillation at a frequency of 80 Hz (range 75 Hz-115 Hz). The baseline pattern is irregular with the frequency being 92 Hz (range 70 Hz-126 Hz). The mean interval between the bursts is in the order of 70 ms. Seven indices of OMT activity were analysed. These were overall frequency, the percentage of the record occupied by baseline activity, the frequency of baseline activity, the number of bursts occurring per second, the frequency content of those bursts, the average duration of a burst, and the average duration of the baseline (interburst period).

Results

The table gives the mean results for both the control and Parkinson’s disease groups. The mean overall frequency in the control group was 67.68 (SD 10.75), range 43–84, median 73.78 (SD 5.55) (U=25.0, df=8, p<0.0036), whereas that in the “on” group was 10.35 (SD 4.50) whereas that in the “on” group was 70.50 and this difference was significant (U=54.0, df=21, p<0.00001). This difference is reflected in a reduction in the frequency of both baseline and burst components of overall frequency in the parkinsonian group (U=105.0, df=21, p<0.0013, U=155.5, df=21, p<0.042 respectively). There was also a significant increase in the amount of record occupied by baseline activity in the parkinsonian group (U=21.0, df=1, p<0.00001). This is reflected in both a significant reduction in the number of bursts occurring per second (U=30.5, df=21, p<0.0001) and a decrease in the average duration of the bursts that were present (U=82.0, df=21, p<0.0002). There was a corresponding decrease in the average period between bursts (duration of baseline) (U=33.0, df=21, p<0.00001). Thus, not only do parkinsonian patients exhibit an eye tremor which is significantly slower than that seen in normal subjects, but this tremor also has an abnormal pattern (figure).

EYE TREMOR RECORD AND CLINICAL STATUS

Abnormalities of eye tremor activity in parkinsonian patients are subject to the influence of the clinical state of the patient. Those judged to be “off” are significantly different from patients who are “on”. Patients who are “off” have a significantly lower eye tremor frequency than those judged to be “on”. The mean peak count frequency in the “off” group was 58.88 (SD 10.35) whereas that in the “on” group was 73.78 (SD 5.55) (U=12.0, df=8, p<0.0019).

This is explained by a reduction in the frequency content of burst activity alone (U=15.0, df=8, p<0.0036), there being no significant effect on baseline frequency content. In addition, there was a significant increase in the amount of record occupied by baseline activity (U=25.0, df=8, p<0.025). It should by noted that although there is a marked abnormality of the eye tremor activity in the “off” group, the
“on” group exhibits indices of oculomicrotremor activity which remain markedly different from those seen in normal subjects.

WITHDRAWAL OF MEDICATION
In one patient medication was withdrawn to investigate a coincident problem of hypertension. Oculomicrotremor records were obtained from this patient on two occasions. The first record was obtained 48 hours after the cessation of dopamine treatment and the second 24 hours after recommencement of treatment. In that period, the patient’s clinical state changed from being “off” to being “on”.

The first record of oculomicrotremor activity was markedly abnormal with an overall frequency of 66.5 Hz. This was reflected in a marked decrease in baseline frequency. He also had an abnormally large percentage of his record occupied by baseline activity (77%) with a reduced number of bursts (4 bursts per second) and an increase in the mean period between bursts (171 ms). However, 24 hours later, corresponding to 24 hours after recommencement of treatment, the overall frequency had increased to 78.5 Hz, with a decrease in the percentage of his record occupied by baseline activity (55.8%), an increase in the number of bursts (8.5 bursts per second), and a decrease in the mean period between bursts (171 ms).

Discussion
It is well established that parkinsonism is associated with oculomotor control abnormalities. Recent electro-oculographic studies on these patients show abnormalities of vestibular and oculomotor systems which are not correlated with clinical features. Deficits in the caloric nystagmus induced in these patients cannot be explained on the basis of an inability to initiate voluntary movement. Although a good correlation exists between the extent of oculomotor and peripheral motor dysfunction in Parkinson’s disease, many differences exist between the oculomotor and peripheral motor systems in terms of physiology. Analysis of oculomicrotremor in parkinsonian patients has disclosed major differences between these patients and normal healthy volunteers. This reflects abnormalities of oculomotor function in these patients. The finding of such abnormalities shows that oculomotor dysfunction in parkinsonian patients cannot be purely explained on the basis of problems with the initiation of voluntary movement which would support the finding of abnormalities in the caloric system. It is unclear whether or not this finding shows a direct striatal effect on the oculomotor system as other authors have concluded or whether the effect of dopamine depletion on other areas of the CNS known to have a tonic output to the oculomotor neurons such as the frontal eye fields are responsible for this change. A distinct anatomical connection exists between the frontal eye fields and the basal ganglia and this may provide a pathway for mediation of the effects of dopamine depletion, although the basal ganglia may have a more direct input to oculomotor areas.
An interesting aspect of the work to date has been the demonstration of the sensitivity of movement abnormalities to dopamine concentrations. Dopamine sensitivity has been shown by both direct administration of levodopa and by alterations in the movement abnormalities seen with the “on/off” phenomenon, this phenomenon being due to fluctuation in dopamine concentrations in the striatum. In MPTP-induced Parkinson’s syndrome, abnormalities of the saccadic system are reversible with levodopa, both in humans and in primates. Abnormalities of the saccadic system seen in idiopathic Parkinson’s disease are also dopamine responsive and vary with the “on/off” syndrome. However, dopamine sensitivity of smooth pursuit abnormalities has been less clearly seen with conflicting effects of the “on/off” phenomenon being reported. The differences reported here between distinct clinical groups of patients are broadly supportive of evidence that oculomotor dysfunction fluctuates in patients with the “on” and “off” syndrome and therefore that abnormalities in the oculomotor system may be directly related to striatal dopamine concentrations. Our study of dopamine withdrawal in one patient shows a marked response of oculomotor abnormalities to levodopa administration. The increase in oculomotor activity cannot be explained on the basis of day to day variation as overall frequency, frequency content of baseline, and average burst duration have been shown to have no significant day to day variation. Whereas these results are being reported in a comparatively few patients, particularly the patients with adequate records is portable. This work was supported by the Health Research Board, Ireland.