Ocular microtremor (OMT): a new neurophysiological approach to multiple sclerosis

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Abstract
Using a piezoelectric transducer, the frequency and pattern of ocular microtremor (OMT) between 50 normal subjects and 50 patients with multiple sclerosis were compared. Controls were age matched. All records were analysed blindly. The frequency of OMT in the normal group was 86 (SD 6) Hz, which was significantly different from that of the multiple sclerosis group (71 (SD) 10 Hz, p<0.001). Those in the multiple sclerosis group with clinical evidence of brain stem or cerebellar disease (n=36) had an average OMT frequency of 67 (SD 9) Hz (p<0.001) compared with normal (n=86), whereas those with no evidence of brain stem or cerebellar involvement (n=14) had a frequency of 81.2 (SD 6) Hz (p<0.05, n=64). The differences between the two multiple sclerosis groups were also significant (p<0.001, n=50). At least one abnormality (frequency and pattern) of OMT activity was seen in 78% of patients with multiple sclerosis. In the presence of brain stem or cerebellar disease 89% had abnormal records whereas in the absence of such disease 50% had abnormal records. This is the first report of the application of this technique to patients with multiple sclerosis. The results suggest that OMT activity may be of value in the assessment of multiple sclerosis.

Keywords: multiple sclerosis; ocular microtremor; brain stem; physiological tremor; piezoelectric; neurophysiology

The diagnosis of multiple sclerosis is fundamentally a clinical one, requiring the demonstration of characteristic symptoms and signs of lesions disseminated within the CNS, both in time and space. The most commonly used diagnostic criteria are those of the Poser Committee. Brain MRI is the single most useful diagnostic investigation in multiple sclerosis. Serial MRI shows new lesions and exacerbation of old lesions in patients who are clinically stable. The exact relation between plaques and disability, however, is unclear, and the cost of MRI is considerable.
OMT records and all subjects underwent MRI of the head.

Informed consent was received from all patients and volunteers. The study was approved by the federated Dublin voluntary hospitals ethics committee.

METHODS

Ocular microtremor was recorded using the piezoelectric strain gauge technique developed by Bengi and Thomas. The piezoelectric element was mounted in a perspex rod and its tip was covered in silicone rubber. The perspex rod was mounted on a head frame and lowered directly to the scleral surface which was anaesthetised with 1% proxymethacaine hydrochloride solution. The subject was asked to keep the head still throughout the recording but no means of head restraint were used. Probe placement was judged by visual inspection and by listening to the signal being recorded, using audio cassette headphones. The eye lids were retracted using adhesive tape.

During recording the subject lay supine, looking straight ahead in a normally lit room. The signal generated was amplified and stored on magnetic tape for later retrieval and analysis on an ECG tape analyser (Reynolds Medical (RM) Pathfinder 3 and RM TP-Thermal Printer). All records were made at the patients’ bedside or in the outpatient clinic.

A recording of between 30 seconds and one minute of OMT activity was taken. As with previous series no adverse reactions to the test procedure were reported from either patients or volunteers. After a recording session the probes were soaked in sodium hypochlorite (concentration 500 ppm) for 10 minutes, for sterilisation purposes, before being used again.

RECORD ANALYSIS

The OMT activity was assessed in terms of the frequency of the tremor and the tremor pattern. Normal OMT has a distinct pattern consisting of an irregular baseline tremor superimposed on which are sinusoidal episodes of regular activity, termed bursts. The bursts are easily distinguishable, possessing a greater amplitude than the rest of the microtremor and a packet-like appearance against the baseline tremor. In the absence of such a normal regular pattern a record was declared abnormal, whether or not the overall frequency was within the normal range. Previous studies by Bolger have shown a correlation coefficient of reliability of 0.84 and 0.97 for mean peak count frequency and for pattern analysis respectively by different observers. Analysis of records was by visual inspection by an investigator who was unaware of the clinical status of the subject. The peaks occurring per unit time on a printed record are counted. This provides a good estimate of the high frequency component of any random signal, particularly OMT.

Results

ANALYSIS OF FREQUENCY

The results of the frequency analysis for the healthy controls and patients with multiple sclerosis are given in the table and the figure. The mean frequency of OMT in the control group was 86.15 (SD 6.3) Hz. The mean frequency of OMT in patients with multiple sclerosis was 71.3 (SD 10.53) Hz, which is significantly less than the controls (p<0.001). If only those subjects with evidence of brain stem or cerebellar disease are considered the difference is more marked (p<0.001), the mean frequency of these subjects being 67.09 (SD 8.9) Hz. Comparison of the frequencies of OMT between the normal controls and patients with multiple sclerosis without brain stem or cerebellar disease are considered the difference is more marked (p<0.001), the mean frequency of these subjects being 67.09 (SD 8.9) Hz. Comparison of the frequencies of OMT between the normal controls and patients with multiple sclerosis without brain stem or

<table>
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<th>No</th>
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<th>Frequency</th>
<th>SD</th>
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<tr>
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<td>50</td>
<td>41.8</td>
<td>71.3***</td>
<td>10.53</td>
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<tr>
<td>MS with evidence of brain stem disease</td>
<td>36</td>
<td>42.9</td>
<td>67.09*</td>
<td>8.9</td>
</tr>
<tr>
<td>MS without evidence of brain stem disease</td>
<td>14</td>
<td>39.8</td>
<td>81.98*</td>
<td>5.7</td>
</tr>
</tbody>
</table>

*p<0.05; ***p<0.001.

MS=Multiple sclerosis.

Figure 1 Scattergram of the ocular microtremor frequency in normal controls (n), Patients with multiple sclerosis with evidence of brain stem or cerebellar disease (MS1) and patients with multiple sclerosis without evidence of brain stem or cerebellar disease (MS2). The 2 and 3 SD levels refer to the control population.
Ocular microtremor (OMT) dysfunction. In about 20% to 50% of patients with multiple sclerosis, and 67% of patients with clinically definite multiple sclerosis. Somatosensory evoked potentials (BAEPs) were abnormal in 80% of patients.6

ANALYSIS OF PATTERN
Thirty six of 50 patients with multiple sclerosis were judged to have an abnormal tremor pattern (72%). Of those patients with clinical evidence of brain stem or cerebellar disease 29 (of 36) had an abnormal tremor pattern (80%) and seven of 14 without brain stem or cerebellar disease had an abnormal pattern (50%). One of the 50 normal subjects had an OMT record that was labelled abnormal on blind analysis (2%).

COMBINED ANALYSIS
At least one abnormality of OMT activity was seen in 39 of 50 patients with multiple sclerosis (78%). Of those 36 patients showing clinical evidence of brain stem or cerebellar disease 32 had OMT abnormalities (89%) and of the 14 patients with no evidence of such lesions seven (50%) demonstrated abnormalities of tremor activity. By contrast, only one of 50 normal records was considered abnormal (2%).

No significant association between abnormal eye tremor and disease or disability could be demonstrated that was independent of the effects of brain stem or cerebellar disease.

Discussion
In this study, the identification of abnormality in 78% of all our patients, and in 89% of those patients with clinical evidence of brain stem or cerebellar disease compares favourably with other neurophysiological techniques. When applied to patients with clinically definite multiple sclerosis, visual evoked potentials have been reported to be abnormal in 85% of patients with clinically definite multiple sclerosis and 37% of those with probable or possible multiple sclerosis.15 Brain stem auditory evoked potentials (BAEPs) were abnormal in 67% of patients with clinically definite multiple sclerosis, 41% with probable multiple sclerosis, and 30% with possible multiple sclerosis, and in about 20% to 50% of patients in all categories with no clinical signs of brain stem dysfunction.16 A recent study by Soustiel et al17 found abnormal BAEPs in 72% of patients with definite multiple sclerosis. Somatosensory evoked potentials may be abnormal in up to 80% of patients.6

The analysis of physiological tremor provides sensitive information on the activity of the motor units generating that tremor.21 Because tonic oculomotor unit activity is dependent on the numerous tonic inputs to the motor units, lesions in any of these inputs may effect the recorded tremogram.4 The high frequency nature of the tremor should also enhance its sensitivity when assessing patients with multiple sclerosis as demyelinated nerves exhibit a particularly impaired ability to respond to rapid stimulation.21

The recording of ocular microtremor provides a new neurophysiological technique for the assessment of patients with multiple sclerosis. Only one of the control subjects was thought to have an abnormal OMT pattern on blind analysis of his record. This subject had a normal clinical examination and had no evidence of neurological disease. He was, however, the oldest tested, at 70 years of age. The same subject also had the lowest OMT frequency recorded from a normal subject (70 Hz). In more recent studies on 105 normal volunteers we have shown a significant fall in OMT frequency after 70 years of age.22 In this study 206 OMT recordings were made and in no case were adverse effects seen. Unlike other electrophysiological methods the technique is rapid and requires a minimum of patient cooperation. Including time for setting up; a recording session takes 10 minutes with 30 seconds of tremor record being required for analysis.14 The equipment is portable and recordings may be made at the patients’ bedside as easily as in the laboratory.

The results presented here are encouraging. The extent of the abnormalities detected would indicate that this method may be of value in assessing patients with apparently single lesions. However, for this technique to be applied clinically further studies are required to assess patients in “clinically possible” or “clinically probable” groups who then go on to develop clinically definite disease. More information may be derived from the application of frequency spectral analysis to patient records and this is being studied.