Multimodal Evoked Potential and Eye Movement Abnormalities in Myotonic Dystrophy

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Abstract

By means of multimodal evoked potentials (EPs) we evaluated the central nervous system (CNS) involvement in 25 subjects suffering from myotonic dystrophy (MD): brainstem auditory evoked potentials (BAEPs), middle-latency auditory evoked potentials (MLAEPs) and somatosensory evoked potentials (SEPs) from upper limb were performed on all the subject, whereas only the 19 patients, whose clinical ocular abnormalities were only slight, underwent pattern-electroretinograms (PERGs) and pattern visual evoked potentials (VEPs). In addition, we recorded saccade and smooth pursuit eye movements in 31 MD patients without clinically evident oculomotor deficits to establish the occurrence and the CNS or myogenic origin of subclinical oculomotor impairment.

PERGs were abnormal in 8/19 subjects, VEPs in 8/19 subjects (the two techniques were simultaneously abnormal in 8 eyes), BAEPs in 7/25 subjects, MLAEPs in 4/25 subjects (in one subject both BAEPs and MLAEPs were abnormal) and SEPs were abnormal in 1/25 subjects. 13/25 of our subjects showed at least one EP that revealed a CNS involvement.

On the basis of mean value comparisons, saccades were slower and hypometric and smooth pursuit eye movements performed worse in MD patients than in controls. On an individual basis, saccade duration was prolonged in 67.7%, saccades were hypometric in 19.4%, saccade latency was delayed in 9.7%, and the smooth pursuit performance index was decreased in 9.7% patients. We classified the oculomotor abnormalities detected as neurogenic in 11 MD patients and as myogenic in another 10, but in some subjects belonging to the second group concomitant CNS impairment is not to be excluded.

Key words: evoked potentials, eye movements, myotonic dystrophy.

Myotonic dystrophy (MD) is an autosomal dominant disease with variable penetrance; almost all patients show an unstable cytosine-thymine-guanine trinucleotide repeat, located within the MD gene located on chromosome 19 [24]. Skeletal muscles show a delayed relaxation after contraction (myotonia), progressive atrophy of the face, neck and extremities with distal preponderance.

MD involves a multisystem impairment to, inter alia, the Central Nervous System (CNS), as reported in several pathological, neuroradiological, neuropsychological and neurophysiological studies.

The latter include several studies [2, 10, 12, 13, 17, 21, 22, 23, 29] that have been performed by means of stimulus-related Evoked Potentials (EPs), but few of them adopted a multimodal approach [10, 12, 23, 29].

Despite the CNS dysfunction and the extraocular muscle impairment, which has been detected both by pathological [4, 7, 15, 18] and electromyographic studies [7, 19, 20, 26], MD patients rarely complain of or present with oculomotor symptoms or signs other than lid drop. By contrast, all studies based on eye movement recording were able to detect the subclinical involvement of the oculomotor system [1, 3, 9, 11, 14, 20, 26, 27, 28, 30, 33], but these studies do not agree as to the oculomotor abnormalities derive from a neurogenic or a myogenic dysfunction.

The aim of our study was therefore to evaluate, by means of multimodal EPs, the level of CNS involvement in patients with MD, with a particular emphasis on the location of the dysfunction along visual pathways. In addition, by means of eye movement recording we evaluated saccade and smooth pursuit alterations which were classified as myogenic or neurogenic on an individual basis.

Materials and Methods

Subjects

The patients were diagnosed as having MD on the basis of clinical and electrophysiological criteria [22].
We studied multimodal EPs in 25 MD subjects (21 families; 11 males, 14 females; mean age: 32.5 years; age range 20-58 years). We studied saccade and smooth pursuit eye movements in 31 MD subjects (26 families; 13 males, 18 females; mean age: 38.5 years; age range 15-63 years). Twenty-four patients underwent both to evoked potential and to eye movement recording.

All the subjects underwent fundoscopy and slit lamp examination and corrected visual acuity was ascertained: 19 showed only slight ocular abnormalities (i.e. visual acuity of 7/10 or more in both eyes, no clinical retinopathy and minimal lenticonular opacities). None of the subjects complained of diplopia or presented clinically evident disconjugate oculomotor alterations.

Normal values

For evoked potential parameters normal values were defined as the mean value ±2.5 standard deviation computed in an age- and sex-matched control group. For eye movement parameters normal values were defined as those between the 5th and 95th percentiles of an age- and sex-matched control group distribution.

Evoked Potentials

The stimulation, the recording and the analysis of the signals were performed with a Nicolet Pathfinder II system.

Pattern-Electroretinograms (PERGs) were obtained by monocular checkboard pattern-reversal stimulation, using a TV set (check size 60°; reversal rate 2.1/sec; contrast 75%); surface Ag/Cl recording electrodes were placed infraorbitally and at the ipsilateral temple (time-base 250 ms, bandpass 1-100 Hz; 2 series of 300 responses were averaged. PERGs were considered abnormal if b-wave was absent or delayed.

Visual Evoked Potentials (VEPs) were obtained by monocular checkboard pattern-reversal stimulation (check size 15°; reversal rate 2.1/sec; contrast 50%); recording electrodes were positioned at Oz-Cz (time-base 250 ms, bandpass 1-100 Hz); 2 series of 100 responses were averaged. VEPs were considered abnormal if P100 component was absent or delayed or if N70/P100 amplitude was reduced.

Brainstem Auditory Evoked Potentials (BAEPs) were obtained by alternating monaural click stimulation (rate 21, 1/sec, intensity 65 dBHL); click perceptual thresholds were obtained by using the method of ascending and descending limits [6]; the responses were recorded from electrodes positioned at Cz-ipsilateral ear lobe (time base 10 ms, bandpass 5-1500 Hz); 2 series of 2000 responses were averaged. BAEPs were considered abnormal if both Na and Pa or Pa wave alone was absent or delayed. We did not include Nb component in our abnormality criteria because in our experience, and in agreement with Deiber [6], this component is not stable enough to prevent the occurrence of false positives.

Somatosensory Evoked Potentials (SEPs) were obtained by unilateral median nerve stimulation of the right nerve at the wrist; square pulses (duration 0.1 ms) were delivered at a frequency of 3.3/sec with an intensity that slightly exceeded the motor threshold. Recording electrodes were positioned at C3, C7 and Erb point, with reference at linked-ears (time base 30 ms, bandpass 15-3000 Hz); 2 series of 500 responses were averaged. SEPs were considered abnormal if the N19 component was absent or delayed and/or the N13-N19 interval was delayed.

Eye movements

We recorded reflexive saccade and triangular ramp smooth pursuit eye movements by means of the bitemporal electrooculographic technique (EOG). The signal was filtered (bandpass: DC-40 Hz), sampled at a frequency of 250 Hz and stored for off-line analysis by specifically designed software [31, 32].

We elicited reflexive saccades by means of fifteen Light Emitting Diodes (LEDs) placed every 5° from +35° (right) to -35° (left) from the subject's midsagittal plane. The LEDs were then lit in a pseudo-random sequence (2 blocks of 29 trials). We considered the following parameters:

- amplitude - duration relationship: D = a + b * A, where D is the duration in ms and A is the amplitude in degrees. The relationship found for each subject was used for the computation of D20, which corresponds to the expected duration value as computed for a mid-range amplitude of 20°. For individual subject evaluation, D20 was considered abnormal (increased duration) if in excess of the 95th percentile of control distribution. We also computed the duration for both the 5° (D5) and the 35° (D35) amplitudes.

- precision: P = \frac{A}{TS}, where TS is the target step in degrees. For individual subject evaluation, the mean precision value was considered abnormal (hypometric saccades) if below the 5th percentile of control distribution.

- latency (L), the period of time from LED activation to the beginning of the saccade. For individual subject evaluation, the mean latency value was considered abnormal...
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In the following we will refer to D20, Vmax, P and L as "saccade parameters".

We elicited smooth pursuit eye movements by moving a target (LED) at a constant velocity and through a 60° amplitude (+30° and -30° back and forth). We used target velocities that ranged from 10 to 50°/s. Each subject performed 58 ramps. We considered the following relationship:

- target velocity - performance index relationship: \( PI = m - n \cdot V \), where \( PI \) is the performance index expressed as a percentage and \( V \) is target velocity in degrees/s.

\( PI \) is a way to represent smooth pursuit system performance after catch-up saccades have been removed [32]. The equation \( PI = 100 \), where \( m = 100 \) and \( n = 0 \), is intended to represent a perfect smooth pursuit which is able to match any target velocity and does not need the cooperation of saccades.

\( PI_{25} \) (i.e. mid-range \( V \) equal to 25 degrees/s) was computed in the same way as described for the amplitude - duration relationship, and was rated as abnormal (decreased \( PI \)) if below the 5th percentile of control distribution. In the following we will refer to \( PI_{25} \) as "smooth pursuit parameter".

Results

Evoked Potentials

All the patients underwent BAEP, MLAEP and SEP recording, whereas PERGs and VEPs were only performed in 19 patients, whose clinical ocular abnormalities were only slight.

PERG b wave was abnormal in 8 patients (42%, 5 bilaterally); it was absent in 8 eyes, and showed reduced amplitude in 5. In 8/19 subjects (42%, 7 bilaterally), VEPs revealed the following abnormalities: both latency delay and amplitude reduction in 6 eyes, latency delay in 3, reduced amplitude in 3. \( PI_{00} \) was absent in 3 eyes. Both PERGs and 15' VEPs were abnormal in 8 and normal in 18 eyes (Fig. 1); 7 eyes exclusively showed abnormal VEPs whereas abnormal PERGs alone were observed in 5 eyes.

BAEPs were abnormal in 7/25 subjects (28%) due to prolongation of I-V IPL (bilateral in 3) with delayed peak V (Fig. 2). Concomitant prolongation of I-III and III-V IPL, led us to locate the site of impairment twice at a caudal and 5 times at a rostral brainstem level. In addition, we registered an isolated bilateral delay of peak I once and an isolated delay of peak V 4 times.

Moreover, mean values for all peak and interpeak latencies, (with the exception of peak I) were longer than those obtained from our control group (Tab. 1).

MLAEPs were abnormal in 4 subjects (16%, 2 bilaterally) due to Pa wave delay (the Na component was always normal). The mean latencies of Na and Pa waves did not differ statistically from those of control subjects.

Both BAEPs and MLAEPs were abnormal once and normal 35 times, whereas BAEPs alone and MLAEPs alone were abnormal 9 and 5 times respectively; of the 25 subjects, 6 only demonstrated abnormal BAEPs, 3 only abnormal MLAEPs and 1 a concomitant BAEPs/MLAEPs abnormality; 15 subjects showed no BAEP or MLAEP abnormalities.

SEPs were abnormal in 1 subject (4%) due to a prolonged N13- N19 interval; in addition the cervical response N13 was undetectable in one patient whose N9-N19 interval was normal. In all the subjects N9 was well detectable and had a normal latency. Mean values for N9, N13 and N19 latencies and for N9-N13, N13-N19 and N9-N19 intervals did not differ statistically from those obtained for control subjects.

In conclusion, 13/25 (52%) of our subjects showed at least 1 EP that revealed a CNS involvement. 7 showed 2 EPs (VEPs + BAEPs: 4; VEPs + MLAEPs: 1; BAEPs + MLAEPs: 1; BAEPs + SEPs: 1) and 6 showed 1 EP (VEPs: 3; BAEPs: 1; MLAEPs: 2).
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Table 1. BAEP peak and IPL mean and standard deviation (sd) values in MD patients and in controls. The last column shows the probability (p) value derived from mean value comparison.

<table>
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<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
<td>mean</td>
</tr>
<tr>
<td>wave I</td>
<td>1.59</td>
<td>0.12</td>
<td>1.54</td>
</tr>
<tr>
<td>wave III</td>
<td>3.90</td>
<td>0.21</td>
<td>3.71</td>
</tr>
<tr>
<td>wave V</td>
<td>5.88</td>
<td>0.36</td>
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<tr>
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<td>4.29</td>
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</tr>
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</table>

Eye movements

The mean value comparisons (Tab. 2) show that reflexive saccades were slower (longer duration) and slightly hypometric but with normal latency as compared with controls.

On the basis of mean value evaluation the abnormal duration and peak velocity is detectable both for small (see D5) and, to a greater extent, for large saccades (see D35). Figure 3 compares the respective tracings of a 35° saccade from an MD patient and a normal subject.

Although mean m and n parameters differed very little between MD patients and controls, the significantly reduced P125 mean value shows smooth pursuit as impaired (Tab. 2). The degree of impairment was less for smooth pursuit than for saccades.

On the basis of individual patient evaluation, D20 was prolonged in 21 (67.7%) patients. Precision was abnormal in 6 (19.4%) patients, all of whom presented with hypometric saccades, and latency was delayed in 3 (9.7%) patients. In 11 patients, D5/D35 dissociation, namely a normal D5 combined with an abnormal D35, was detectable (Tab. 2).

The smooth pursuit performance index was reduced in 3 (9.7%) patients; moreover, in one of these the performance index values were very low for all target velocities, and the performance index - target velocity relationship was not computable.

Hypometric saccades were invariably associated with a prolonged saccade duration and a reduced peak velocity, in 2/6 patients with D5/D35 dissociation, and in one patient with a reduced smooth pursuit performance index.

Saccade latency delay combined with an abnormal saccade duration in one patient, with the abnormality of all saccade parameters in another patient and with the abnormality of all saccade and smooth pursuit parameters in a further patient.

Table 2. Saccade and smooth pursuit parameter mean and standard deviation (sd) values in MD patients and in controls: The last column shows the probability (p) value derived from mean value comparison. a and b are the amplitude-duration relationship coefficients, D20 is saccade duration value computed for 20° saccade, P is mean saccade precision, L is mean saccade latency, m and n are the target velocity-performance index relationship coefficients, PI25 is the smooth pursuit performance index when target velocity is 25%.

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<tr>
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<td>26.08</td>
</tr>
<tr>
<td>b</td>
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</tr>
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<td>53.28</td>
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<tr>
<td>P</td>
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<td>0.07</td>
<td>0.95</td>
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<td>L</td>
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<td>248.45</td>
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<tr>
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<tr>
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<td>0.25</td>
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<tr>
<td>PI25</td>
<td>69.38</td>
<td>12.52</td>
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Figure 3. A 35° saccade position (up) and velocity tracings (bottom) from a control (left) and a MD patient (right).
Finally, the reduction of smooth pursuit performance was associated in all the patients with D5/D35 dissociation. Eighteen patients showed normal smooth pursuit and abnormal saccades.

**Evoked potentials and eye movement correlations**

Six of the 7 patients with abnormal BAEP also showed an abnormal saccade duration, but this figure did not prove to be significant on account of high occurrence of prolonged saccade duration.

The average value of P100 latency did not correlate significantly with saccade latency.

**Discussion**

We underline the frequent involvement of visual pathways detected by means of PERGs (42%) and VEPs (42%). However, these figures are lower than those previously reported in the literature [13, 17, 21, 22, 23] as a consequence of the greater stringency of our selection criteria (visual acuity of 7/10 or more in both eyes, no clinical retinopathy and minimal ocular opacities). We sought to prevent our results from being hampered by peripheral visual impairment and to identify a reliable way of detecting visual pathway involvement at a CNS level, i.e. a post-retinal defect. On the basis of our abnormal PERG/VEP data it is possible to suggest that the visual impairment was located at a retinal level (ganglion cell layer) in 5 eyes (abnormal PERG, normal VEP) and at a post-retinal level in 7 eyes (normal PERG, abnormal VEP). It is difficult to decide where the abnormality is located in the remaining 8 eyes, due to the concomitant alteration of both PERGs and VEPs; a simple explanation for this could be the coexistence of both a retinal and a post-retinal impairment [21]. However, since none of our patients showed a maculopathy [16], a low amplitude PERG may derive from a visual pathway axonal loss, as detected by a low amplitude N70-P100, by means of a retrograde degeneration mechanism that affects the retinal ganglion cell layer [5]. In other words, a reduced amplitude of both PERG and VEP may be explicable in terms of a post-retinal impairment. Accordingly, the following localization hypotheses can be proposed (Tab. 3): in 4 eyes post-retinal impairment (low amplitude b-wave coupled with low amplitude P100 wave, which, moreover, was also and always delayed); in 2 eyes the coexistence of retinal and post-retinal impairment (absent PERG with delayed, but normal amplitude, P100 wave). Finally, no hypothesis can be expressed for 2 eyes (PERG and VEP both absent [16]).

To summarize, our neurophysiological investigations revealed visual pathway impairment in 20 eyes. In 18/20 of these eyes, we located impairment in 5 (2 subjects) at a retinal level, in 11 (5 subjects) at a post-retinal level and in 2 (one subject) at both levels. The last subject showed

<table>
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<th>Patient</th>
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<th>PERG</th>
<th>VEP</th>
<th>Alteration</th>
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<tr>
<td>A</td>
<td>*</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>?</td>
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<td>retinal + post-retinal</td>
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<tr>
<td>B</td>
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<td>0</td>
<td>L</td>
<td>retinal + post-retinal</td>
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<td>A</td>
<td>N</td>
<td>RETINAL</td>
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</table>

Table 3. Hypothesized location of visual impairment in the 6 patients presenting with both PERG and VEP abnormal in a given eye. The Alteration - Eye column suggests the location of the alteration for that eye. The Alteration - Global column suggests the location of the alteration for that patient. *: eye with both PERG and VEP abnormal. °: fellow eye with either a normal PERG or a normal VEP. N: normal response; O: absent response. A: reduced amplitude. L: delayed latency. ?: no reliable hypothesis.
an anomalous pattern with impairment located at differing levels in the two eyes.

As regards BAEPs, an abnormal I-V response occurred in 28% of the subjects; this is slightly below the values reported in the literature [10, 23, 29]. One subject with abnormal BAEPs also showed abnormal MLAEPs and three additional subjects showed an auditory pathway impairment detectable by MLAEPs but not by BAEPs. It follows that auditory impairment in MD is mainly located at a brainstem level but, in a few cases, MLAEPs enable the detection of an alteration located between the brainstem and the auditory cortex.

Finally, SEPs were abnormal in one subject, which is similar to the occurrence of SEP abnormalities reported in all previous reports [10, 29] with one exception [23] in which this occurrence is higher. Thus, in 5 of the 19 subjects in which all EPs were performed, it is possible to discover CNS impairment that involves 2 sensory pathways (always visual + auditory); in 6 of the subjects the involvement of one sensory pathway is discernible (3 visual, 3 auditory).

Considering now eye movement abnormalities, we detected a very high occurrence of abnormal saccade parameters: 67.7% of the patients showed at least one abnormal parameter that invariably included a prolonged saccade duration. These figures are in keeping with those reported previously by other authors [1, 3, 9, 14, 20, 26, 27, 30].

Differences in analytical design possibly explain why there is less agreement about the occurrence of smooth pursuit abnormalities. Values in the literature range from 100% [33] to 0% [30] of patients; the latter case series excluded patients with any other visual or oculomotor deficit that might have been responsible of the smooth pursuit impairment. On the basis of mean value comparison, smooth pursuit has variably been reported as similar to [3] and different from control values [26]. Our results on smooth pursuit lie in the middle. Our patients showed a slight but significant reduction in PI25 mean values. However, on an individual basis, only 3 (9.7%) of them proved to be abnormal.

Differences in opinion about the origin of oculomotor impairment in MD partly stem from the controversy about smooth pursuit impairment. The reports by von Noorden et al. [33] (abnormal smooth pursuit and normal saccade latency and accuracy), Bollen et al. [3] (abnormal smooth pursuit and normal saccade latency and fixation), Anastasopoulos et al. [1] (reduced mean smooth pursuit gain that paralleled the capacity to suppress the vestibulo-ocular reflex by means of visual stimuli, normal vestibulo-ocular reflex, normal saccade accuracy, decreased saccade peak velocity, a delayed latency for centrifugal saccade with short interstimulus interval and normal saccade accuracy) favor the "neurogenic hypothesis". The "neurogenic hypothesis" is also supported by the case report by Emre and Henn [11] (in this subject smooth pursuit eye movements were normal and horizontal saccades were lost) and by Di Costanzo et al. [9] (reduced saccade velocity and normal saccade accuracy and latency, smooth pursuit not investigated).

By contrast the "myogenic hypothesis" is supported by Oohira et al. [20] on the basis of a particular pattern of saccade peak velocity slowing (this point will be discussed in the following), and by ter Bruggen et al. [26] who detected normal smooth pursuit with normal saccade latency and precision, but with reduced peak velocity.

Finally, Verhagen et al. [30] made an extensive investigation of the oculomotor, vestibular and auditory systems. Individual basis evaluation showed saccade slowing in 77% of the 13 patients, whereas smooth pursuit was normal in all patients but two; these latter also presented poor visual acuity, divergent strabismus and convergence paralysis. The authors stated that the abnormalities could derive from a central or peripheral dysfunction.

As to the origin of oculomotor impairment, none of our patients complained of diplopia, nor did any of them show the classical pattern of oculomotor impairment that is attributable to an ocular nerve palsy. Accordingly, we apply the "neurogenic" label to CNS oculomotor impairment and the "myogenic" label to myopathic impairment of oculomotor muscle.

Oohira et al. [20] reported that saccade slowing in ocular myopathies involves both small and large amplitude saccades and not large saccade alone as in oculomotor palsies. The latter situation corresponds to the D5/D35 dissociation. In 33 patients suffering from multiple sclerosis and presenting with slow saccades the D5/D35 dissociation occurred in 78.78% patients, but not in the other 21.22% patients most of which showed a very severe saccade duration impairment. Taken together these data suggest that D5/D35 dissociation occurs both in peripheral and in central nervous system diseases leading to saccade slowing, whereas, according to Oohira et al. [20], the lack of dissociation stands for a myogenic impairment. However, the lack of dissociation is to be considered cautiously as a feature of myogenic saccade slowing because it also occurred in some multiple sclerosis patients. In case of lack of D5/D35 dissociation, the combination with saccade hypometria would support the hypothesis of a myogenic impairment.

D5/D35 dissociation was detectable in 11 patients, who we classify as "neurogenic". This group included the 3 patients with reduced PI25 and 2 other patients with a saccade latency delay. Saccade latency delay invariably derives from CNS impairment which involves either the structures concerned with saccade programming or the projections of such structures to the burst generator.

The other 10 patients with prolonged saccade duration but without D5/D35 dissociation should be labeled as having a "myopathic" oculomotor deficit. However, the MD patients without D5/D35 dissociation also showed significantly prolonged saccade duration (137.86 ms) in comparison with those without the dissociation (107.85 ms), and we know from MS patients that in this situation
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the lack of D5/D35 dissociation should be interpreted cautiously.

In four patients without D5/D35 dissociation, saccades were also hypometric, and this combination (slow saccades of restricted amplitude) strengthens the "myogenic" hypothesis. In the other patients, the "myogenic" hypothesis is weaker, and a concomitant CNS involvement cannot be excluded. For instance, one patient showed a saccade latency delay, and another 2 patients showed a prolonged BAEP I-V IPL. In all the patients without D5/D35 dissociation, smooth pursuit eye movements were normal and this finding would suggest both a sparing of oculomotor muscles and a saccadic system impairment located at a CNS level [11]. This argument too is inconclusive, however, since saccades are a more demanding task for extraocular muscles than is smooth pursuit, and it is possible that MD affects the global layer fibers which are more involved in saccade than it does the orbital layer fibers which are more involved in smooth pursuit [25, 26].

In conclusion, MD patients frequently show a CNS impairment detectable by means of multimodal EPs. The CNS impairment mainly affects the visual and auditory systems and in some patients it also leads to saccade and smooth pursuit abnormalities. However, eye movement abnormalities may also originate from an extraocular muscle dysfunction and in some patients the combination of both a neurogenic and myogenic oculomotor dysfunction cannot be excluded.

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