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Abnormalities of ocular motility in myotonic dystrophy

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Summary

Are the oculomotor disturbances in myotonic dystrophy (MD), i.e. reduced smooth pursuit (SP) gain and reduced saccadic peak velocity (PV), of muscular or central origin? To answer this question the following two approaches were used. (i) The performance of SP was compared with the patient's ability to suppress the vestibulo-ocular reflex (VOR) visually (VOR suppression; VOR-S). In the latter task the SP system is involved, but the eyes hardly move within the orbits. A parallel impairment of SP and VOR-S would indicate a central dysfunction. (ii) Peak saccadic velocity was compared between two saccades performed to and fro in rapid succession. The intention was to measure any myotonic effect which might build up after the first saccade and slow down the second saccade. We studied 15 MD patients and 15 age-matched controls. Stimuli for slow eye responses consisted of sinusoidal horizontal rotations of the SP target and/or the vestibular rotation chair at frequencies between 0.1 and 0.8 Hz. Saccades were analysed in terms of PV, accuracy, duration and latency, comparing centripetal versus centrifugal saccades at short and long intersaccadic intervals (ISI; 400 ms and 900 ms, respectively). The SP gain was reduced in patients compared with the controls, the effect being most pronounced (32% less) at the highest stimulus frequency. Whereas VOR was normal in the patients, VOR-S was clearly impaired (50% worse at 0.8 Hz). Despite normal saccadic accuracy, peak saccadic velocity was significantly lower in the patient group (23% less for saccades of 12° amplitude), similarly for centrifugal and centripetal saccades; all these differences were independent of the ISI. Latency was normal with centrifugal saccades, but was considerably increased with centripetal saccades at short ISI (67% longer compared with controls). The observation of a parallel degradation of SP and VOR-S in the patients is interpreted in terms of a central deficit in the SP pathways. Thus, it appears that slow eye movements were not impaired by muscle dystrophy and myotonia to a considerable degree in our patients. The increase in saccadic latency for centripetal saccades at the short ISI also reflects a central deficit. However, the observed slowing of saccades might have a myopathic or neural origin; a distinction was not possible at present. A myotonic origin of the saccade slowing seems unlikely, because the effect was independent of the presaccadic activation of the relaxing (antagonistic) eye muscle.

Keywords: myotonic dystrophy; saccadic eye movements; smooth pursuit eye movements; vestibulo-ocular reflex; VOR suppression

Abbreviations: A = saccade amplitude; A_{63} = saccade amplitude at which peak velocity reaches 63% of its saturation value; ISI = intersaccadic interval; MC = myotonia congenita Thomsen; MD = myotonic dystrophy; PV = saccadic peak velocity; PV_{12} = peak velocity at 12°; PV_{MAX} = asymptotic maximum of peak velocity; SP = smooth pursuit; SQ = fixation suppression quotient; VOR = vestibulo-ocular reflex; VOR-S = VOR suppression

Introduction

Myotonic dystrophy is an autosomal dominant, multisystem disorder, characterized by a delay in muscle relaxation after active contraction (myotonia), dystrophic muscle changes, mild peripheral neuropathy and CNS involvement. Almost all MD patients show an unstable cytosine thymine guanine trinucleotide repeat, located within the MD gene on chromosome 19 (Brook *et al.*, 1992). Clinical manifestations of ocular involvement mainly include ptosis and cataract, and rarely diplopia or restriction of the range of eye movements (Miller, 1985). Furthermore, subclinical signs like a slowing of saccades and attenuation of SP gain have been described by means of oculographic recordings (Baloh *et al.*, 1975;

Oohira *et al.*, 1985; Ter Bruggen *et al.*, 1990; Bollen *et al.*, 1992; Koca *et al.*, 1992).

Although the decrease in saccadic velocity has been accepted in the literature as a subclinical feature of the disease, its pathophysiology (peripheral or central) has remained controversial to date. Some authors assume that it stems from dystrophic changes in the extraocular muscles (Oohira *et al.*, 1985; Ter Bruggen *et al.*, 1990). Dystrophic changes of the extraocular muscles have in fact been demonstrated histologically (Davidson, 1961; Kuwabara and Lessell, 1976). The finding of a 'warming-up' phenomenon for repetitive saccades was explained in terms of myotonia (Hansen *et al.*, 1993), which is known to involve the extraocular eye muscles (Oohira *et al.*, 1985; Ter Bruggen *et al.*, 1990). Still other authors suggested a central origin (Emre and Henn, 1985).

To address the question of a central versus peripheral origin for the oculomotor abnormalities in MD patients we studied both slow and fast eye movements. In particular, we compared their SP performance with their ability to suppress the VOR by visual fixation (VOR-S). The latter applies to a condition in which the subject fixates a visual target that is kept in fixed alignment with the head during whole-body rotation on a Bárány chair, so that the eyes hardly move within the orbit. It is generally assumed that the SP system is critically involved in this phenomenon (*see* Barnes, 1993). The effectiveness of the VOR-S is a powerful tool in evaluating the integrity of CNS function (Chambers and Gresty, 1983). Similar deficits observed for both SP and VOR-S would support a central mechanism for the SP impairment. In order to obtain an estimate of the SP signal used for VOR-S, the VOR was measured too.

With respect to saccadic eye movements, we compared horizontal centrifugal and centripetal saccades, the latter being performed with a short or a long ISI. Presaccadic activity of the pulling and the relaxing muscles that generate the saccade are different in the centrifugal versus the centripetal condition. Consider a centrifugal saccade of the right eye toward the right side. Prior to the saccade, the eye is in the primary position and both lateral and medial rectus muscles show a similar, intermediate state of activity. Following the saccade, the eye is deviated toward the right side, and activity in the lateral rectus muscle is high and that in the medial rectus muscle is low. This then represents the starting position for the centripetal saccade. Given that eye muscle myotonia is a relevant factor that affects eye motility, one would expect that the centripetal saccade is slowed down by a delayed relaxation of the lateral rectus muscle due to myotonia, possibly depending on the time interval between the centrifugal and centripetal saccade. A similar slowing of both centrifugal and centripetal saccades, by contrast, would suggest a myopathic, neural or brainstem origin of the deficit. In the saccade test, saccadic accuracy, duration and latency were also evaluated.

The results obtained from the MD patients were compared with those of normal controls and, for saccades only, with those of two patients with myotonia congenita Thomsen (MC). MC patients differ from MD patients, in that they show neither muscle dystrophy nor CNS involvement.

Methods

Apparatus and stimuli

The subjects were seated on an electrically powered Bárány chair (Tönnies, Freiburg) in the centre of a cylindrical screen of 1.6 m radius. During presentation of the stimuli their heads were stabilized by means of a dental bite-board. A laser spot, subtending 0.2° of visual angle, could be projected onto the screen and horizontally rotated by means of a mirror galvanometer, the axis of which was collinear with that of the turning chair. The luminance of the laser was adjusted, by means of polarizing filters, to be well above subject's detection threshold for the spot.

Smooth pursuit and VOR runs

To elicit SP eye movements (i) the spot was rotated about the stationary subject, with the subject tracking the spot with his eyes. Horizontal VOR (ii) was elicited by rotating the turning chair in darkness, with the subject performing mental arithmetic to maintain a high vigilance level. For the testing of VOR-S (iii) the chair was rotated and the spot was presented so that it rotated in fixed alignment with the subject's head. The subject was instructed to fixate the spot. Stimuli consisted of sinusoidal rotations at frequencies of 0.2, 0.4, and 0.8 Hz with a PV of 20° s^{-1} (peak displacement, ±16°, ±8° and ±4°, respectively), and at 0.1 Hz (with a PV of 10° s^{-1}; peak displacement, ±16°). At each frequency 4–6 stimulus periods were dispensed. The order of stimulus conditions (i–iii) was randomized, whereas that of stimulus frequency within stimulus conditions was arranged in an ascending fashion (0.1–0.8 Hz).

Saccade runs

In these tasks the spot was initially presented as a fixation point located straight ahead with respect to the subject (eyes in primary position in orbit; presentation time 1500 ms). Then the spot was extinguished and, following an interval of 100 ms, it reappeared in a lateral eccentric location (8° or 16° on either the right or left side) as target for centrifugal saccades and then, again after a 100 ms gap, at primary position as target for centripetal saccades. The time interval between peripheral and second central target presentation was varied, yielding two different ISI (400 ms or 900 ms) for the centripetal saccades. The trial duration was 3 s. Target locations and ISI were randomized. Each subject performed 10 trials for each of the four target locations and each of the two interstimulus intervals (total, 80 trials).

During the recording session the subject was continuously monitored by means of an infrared camera system. The

experimenter repeatedly made verbal contact with the subject and allowed for appropriate pauses to avoid fatigue.

Eye movement measurements and data analysis

Eye movements were recorded using an infrared corneal reflection device (IRIS, Skalar Medical, Delft, The Netherlands) with a best spatial resolution of 2 arcmin. The system is linear within 3% for horizontal eye displacements of ±20°, and derives eye velocity by on-line electronic differentiation of the eye position signal. The position and velocity signals from both eyes, the position signals of the chair and the mirror galvanometer, together with the on–off signal of the laser beam, were sampled at 500 Hz and stored in a laboratory computer for off-line analysis.

Calibration of eye position was performed prior to, and after, each run. For calibration, subjects shifted their eyes repeatedly from the central fixation point towards targets at lateral locations of ±20°. A small calibration error with respect to VOR and SP, related to the fact that subjects' eyes were located ~9 cm in front of the rotation axes of the chair and the mirror galvanometer, was neglected (error ~5%).

For the analysis of the SP, VOR and VOR-S, eye movement recordings and smooth eye responses were separated from the compound responses by identifying the saccades and replacing them under visual control by linear segments, joining the corresponding beginning and end points. This was performed with the help of an interactive computer program. The smooth eye response signal and the stimulus signal which evoked the response were Fourier transformed and expressed in terms of gain and phase. Gain was defined as the amplitude ratio of the eye fundamental to the stimulus fundamental (SP gain, VOR gain, and VOR gain in the VOR-S condition: VOR-S gain). Phase was defined by the phase difference between the eye and stimulus fundamentals. To relate the VOR-S to the VOR amplitude, a fixation suppression quotient was calculated (SQ); [SQ = 1 – (VOR-S gain/VOR gain); *see* Koenig *et al.*, 1986; Johnston and Sharpe, 1994]. These values were calculated for three or four cycles of the sinusoidal stimulation, taking the median value for statistics. When analysing the data for leftward versus rightward eye movements no differences were noted for SP, VOR or VOR-S. The data were therefore lumped together across both directions.

The analysis of saccades was performed solely for the right eye. For this analysis, an interactive computer program was used which extracted saccade latency, duration, amplitude and maximum velocity. This was analysed separately for centrifugal and centripetal saccades, distinguishing between centripetal saccades at short (400 ms) and long (900 ms) interstimulus intervals. The dependency of the PV on amplitude was evaluated by fitting a curve to the peak velocity/amplitude data according to an exponential law of the type

$$PV = PV_{MAX}*[1 - \exp(- A/A_{63})],$$

(main sequence; Baloh *et al.*, 1975; Becker, 1989). In this equation A represents the amplitude of a saccade, PV_{MAX} the asymptotic maximum of PV as the amplitude tends towards infinity, and A_{63} is the amplitude at which PV reaches 63% of its saturation value. The ratio PV_{MAX}/A_{63} equals the initial slope of the function for small values of A. This analysis was applied to centrifugal saccades as well as to centripetal saccades with short and long ISI, including primary and secondary (corrective) saccades. Saccade accuracy was calculated for primary centrifugal saccades from the ratio of eye to target displacement. Statistical significance was assessed by analysis of variance.

Patients and controls

Fifteen MD patients aged 17–58 years (38.6±14.5, mean±SD), two MC patients aged 16 and 26 years, and 15 healthy subjects aged 16–61 years (35.1±12.3) gave their informed written consent to the study which was approved by the local Ethics Committee. General physical, neurological and ophthalmological examinations were performed on the patients.

The diagnosis of MD was based on the clinical picture with distal muscle weakness together with a myotonic reaction, which was related to the presence of typical 'dive bomber' discharges in EMG recordings. In most patients the symptoms began in early adulthood, with the duration of the disease since diagnosis ranging from 2 months to 16 years. The severity of MD was assessed by the Karnofsky index (Karnofsky and Burchenal, 1949); it ranged between 50% and 90% (mean 75%), i.e. most of the patients were capable of doing light work (selection criterion: Karnofsky index ⩾50%). Visual acuity was better than 0.6. Eleven patients had bilateral ptosis and one patient showed a limitation of left eye abduction with target eccentricity >40°. Routine clinical examinations of eye movements were otherwise normal. None of the patients showed signs of somnolence or decreased mental fatigue strength.

In two patients, typical clinical features with onset of myotonia in early childhood or infancy and subsequent gradual improvement, 'athletic' appearance with muscle hypertrophy instead of muscle wasting, lack of myopathic changes and presence of myotonic activity in the EMG and absence of the characteristic genetic MD abnormalities on DNA analysis (tested in only these two patients) suggested the diagnosis of MC. Other family members were similarly affected in one case, while the family history was negative in the other case.

None of the patients or the controls took any drugs at the time of the eye movement measurements.

Results

Smooth pursuit

Figure 1A gives an example of SP in a MD patient at 0.2 Hz stimulus frequency. Composite eye displacement ('eye

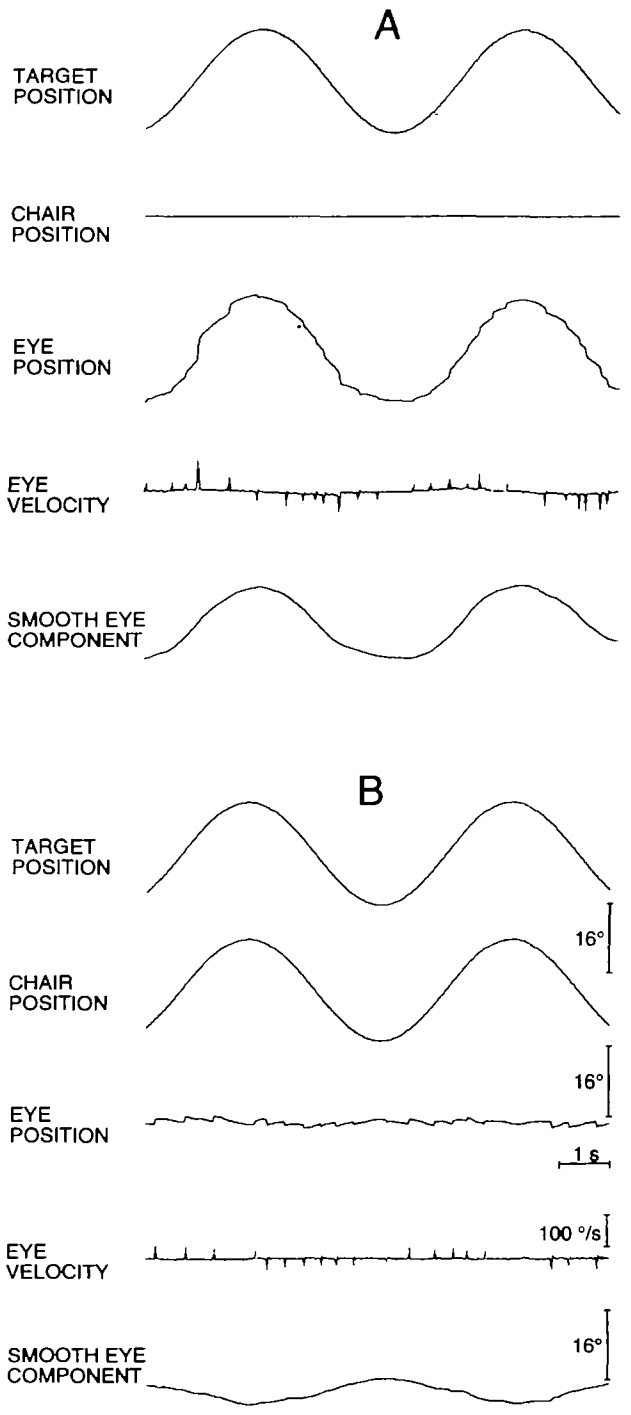

Fig. 1 (**A**) Example of impaired SP eye movement in a patient with MD. The target moves sinusoidally at 0.2 Hz with a 32° peak-to-peak amplitude, while the rotation chair is stationary. The eye position signal contains catch-up saccades, which are especially prominent in the eye velocity signal below. After the removal of the saccades from the eye position trace, the smooth component is obtained. (**B**) Example of VOR-S. The patient (same as in **A**) tries to fixate the eyes on the target which is rotated in fixed alignment with the chair (0.2 Hz; 32°). Note that VOR-S is incomplete.

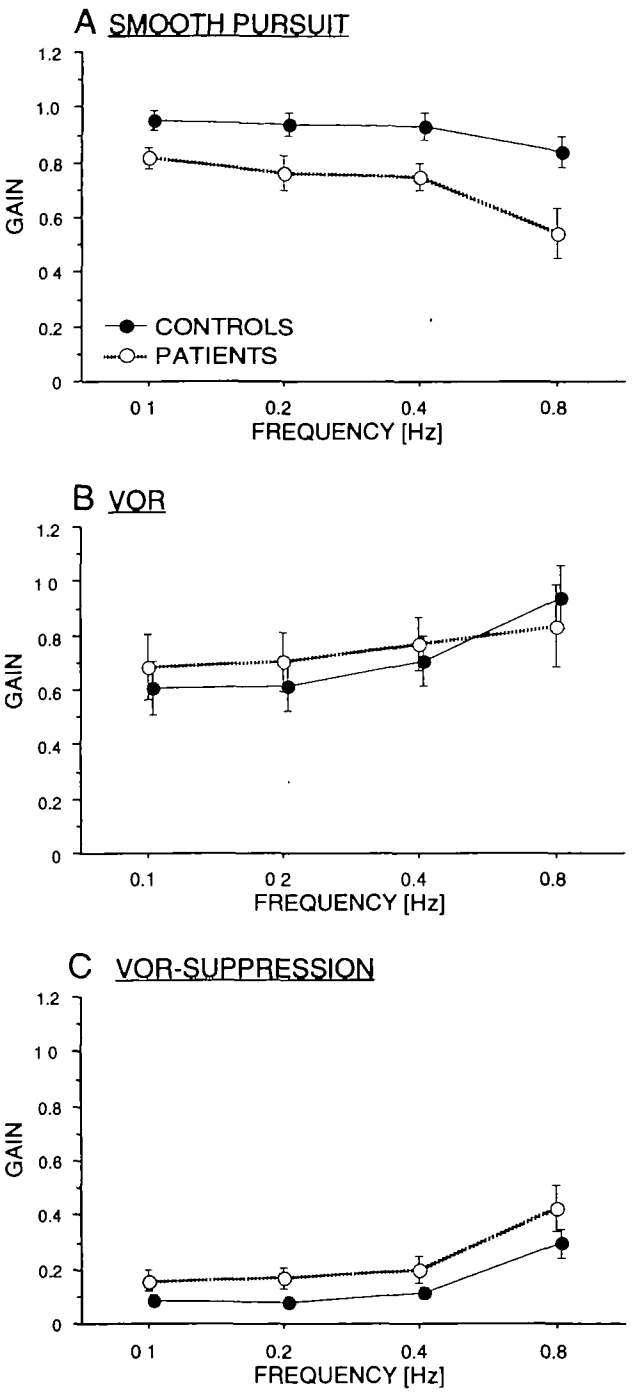

Fig. 2 Gain of slow component of (**A**) smooth pursuit, (**B**) VOR in complete darkness and (**C**) VOR-S from MD patients (n = 15, open circles) and controls (n = 15, filled circles). Mean gain values (±95% confidence intervals) are plotted as a function of stimulus frequency.

position') corresponds quite well to target displacement, whereas its smooth component is considerably smaller, a fact which is compensated for by saccades (so-called catch-up saccades). Mean SP gain is shown in Fig. 2A as a function of stimulus frequency, separately for the MD patients and the normal controls. Normal subjects show an essentially constant gain of almost unity at 0.1–0.4 Hz and a slight gain attenuation

at 0.8 Hz. The patients' gain is lower by about 0.15 at 0.1 Hz, with the difference becoming larger with increasing frequency, amounting to 0.27 at 0.8 Hz. Statistically, these effects were significant with respect to the two factors, group and frequency [group: $F(1,112) = 89.9$, $P < 0.0001$; frequency: $F(3,112) = 25.9$, $P < 0.0001$]. Furthermore, there was a significant interaction between the two factors; the difference between patients and controls was larger at high compared with low frequency [$F(3,112) = 3.28$; $P = 0.02$].

The phase developed a slight lag with increasing stimulus frequency, from −1° at 0.1 Hz to −12° at 0.8 Hz (not shown), similarly in both the patient and the control group (statistically no significant difference). There was no obvious relationship between the SP gain and the Karnofsky index.

Vestibulo-ocular reflex

Figure 2B shows the VOR gain as a function of stimulus frequency for the patients and the control subjects. There was no statistically significant effect with respect to the factor group, but there was an effect for the factor frequency [$F(3,112) = 9.17$; $P < 0.0001$]; it is well known that VOR gain is slightly higher at high compared with low frequency.

Similarly in both subject groups the VOR phase was essentially ideal, i.e. the phase of the VOR slow component was almost perfectly compensatory with respect to chair displacement at 0.2, 0.4 and 0.8 Hz (not shown). Only at 0.1 Hz did the VOR exhibit a slight phase lead in the patients (8°±10.5°), unlike that in the controls (0°±8.3°).

Vestibulo-ocular reflex suppression

Neither the patients nor the controls perfectly cancelled their VOR during fixation of the head-fixed spot. An example from a MD patient is given in Fig. 1B. Mean VOR-S gain (Fig. 2C) in normal controls was 0.09 at 0.1 Hz and increased slightly with increasing frequency, reaching 0.24 at 0.8 Hz. In the patient group gain was higher by 0.04 at 0.1 Hz, with the difference becoming slightly larger with increasing frequency. Statistically, there were significant effects for the factors group [$F(1,112) = 47.4$; $P < 0.0001$] and frequency [$F(3,112) = 59.3$; $P < 0.0001$], while there was no significant interaction between these factors. When analysing the SQ there were again significant effects for the factors group and frequency.

Scatter of phase values in this stimulus condition, in which the response showed only small amplitudes, was large in both patients and controls. Therefore, an analysis of these phase data was omitted.

Saccadic PV, duration and accuracy

Figure 3 gives examples of a centrifugal saccade followed by a centripetal saccade at short and long ISI. Figure 4 shows PV as a function of saccade amplitude in terms of the fitted exponential function (main sequence; *see* Methods),

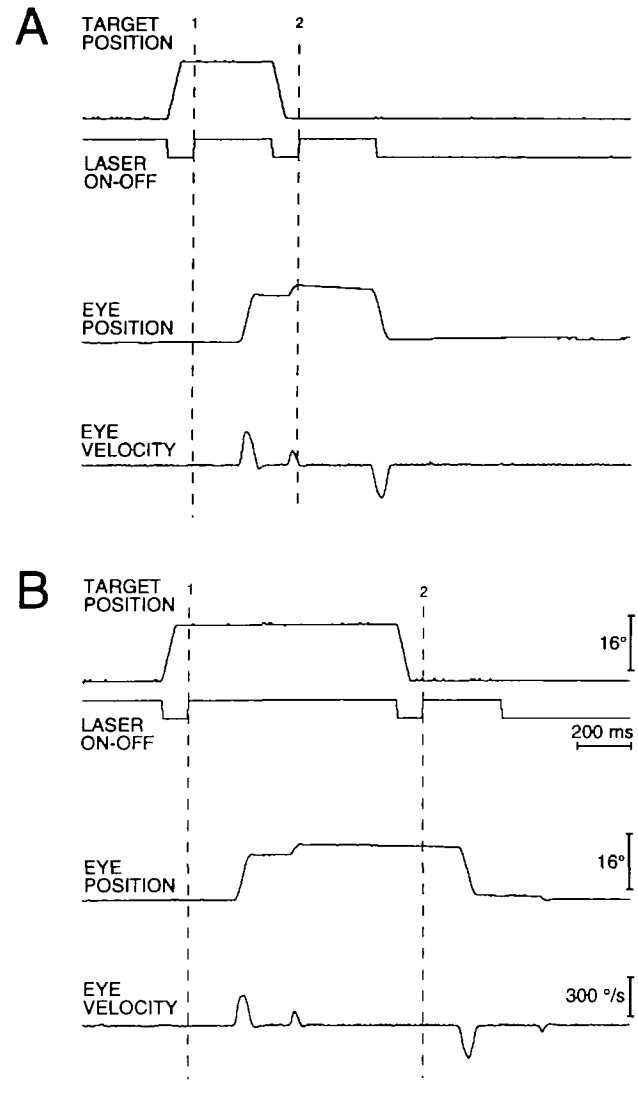

Fig. 3 Examples of visually-guided saccades from an MD patient. (**A**) Trial with a short ISI (400 ms). (**B**) Trial with a long ISI (900 ms). The patient first fixates the target at the primary position, which is then is extinguished for a 100 ms interval/gap and reappears at 16° to his right as target for a centrifugal saccade (vertical lines: 1). After a presentation time of 300 ms (**A**) or 800 ms (**B**) and a further gap of 100 ms the spot reappears at its primary position as the target for a centripetal saccade (vertical lines: 2).

separately for the centrifugal saccades and the centripetal saccades at short and long ISI. When comparing mean error sums of squares as a measure of fit quality across patients and controls, no statistically significant difference was found ($P = 0.6$). In normal subjects the exponential curves for centrifugal saccades tended towards a PV_{MAX} of 474° s^{-1}, which is in accordance with the literature (Becker, 1989). The PV_{MAX} values for centripetal saccades with short and long ISI were considerably higher (584° s^{-1} and 533° s^{-1}, respectively). The corresponding PV_{MAX} values in the MD patients were lower than in the normal controls (381° s^{-1}, 405° s^{-1}, and 398° s^{-1}, respectively), without showing a considerable difference between the three saccade conditions,

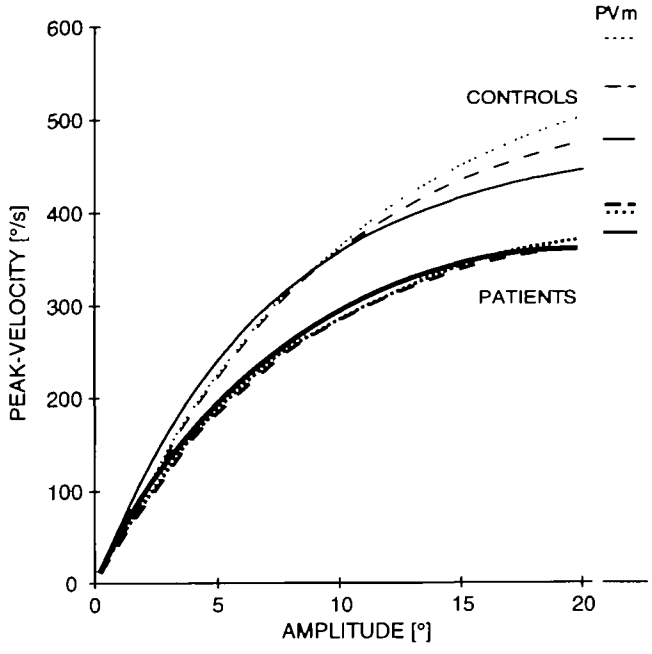

Fig. 4 Exponential fits of the PV as a function of saccade amplitude in MD patients (thick curves) and normal controls (thin curves). The fits are plotted separately for the centrifugal saccades (solid lines) and for the centripetal saccades at short and long ISI (dotted and dashed lines, respectively). The asymptotic maxima of PV (PV_{MAX}) are given on the right hand side (*see* PVm).

however. Statistical analysis was restricted to a saccade amplitude of 12° in the fitted curves, thus remaining well within the range of the actual measured amplitudes. The corresponding mean values for PV at 12° (PV_{12}) and the quotient PV_{MAX}/A_{63} are given in Table 1, separately for the three saccade conditions. For PV_{12}, statistics revealed a significant effect for the factor group [F (1,84) = 37.2; P = 0.0001], but no significant effect for that of saccade condition. Corresponding results were obtained for the quotient PV_{MAX}/A_{63} (factor group: P = 0.0018).

The reduction of PV in patients suggests that, in order to reach a given amplitude, saccade duration has to be increased. This assumption held true; mean duration for 12° centrifugal saccades was 58±8 ms in normal subjects, while the corresponding value in patients amounted to 72±16 ms [F (1,28) = 9.80; P = 0:004]; values were taken from the regression line of the duration-amplitude function. Saccade duration in patients did not depend on saccade condition, which is in line with the fact that saccade slowing was similar in the three conditions (*see* above). In contrast, saccadic accuracy of the centrifugal saccades was similar in the MD patients (0.83±0.09) compared with the normal subjects (0.87±0.11; statistically no significant difference). The same applied to the centripetal saccades with short and long ISI.

Saccadic latency

The saccadic latencies of normal subjects and of MD patients are plotted in Fig. 5 as frequency histograms, separately for the centrifugal saccades and the centripetal saccades with short and with long ISI. The distributions for the centrifugal saccades are similar across normal subjects and patients (mean latencies: 209±36 ms and 228±47 ms, respectively) and are in accordance with previous studies on visually guided saccades (Becker, 1989). For centripetal saccades with short ISI, the distribution in normal subjects remains similar to that for centrifugal saccades (200±48 ms), whereas the distribution for the patients becomes different; apart from a small initial peak (present in five of the 15 MD patients), there is a pronounced broadening of the distribution, which is reflected in a considerable increase in mean latency (334±138 ms).

For the centripetal saccades with long ISI, the distributions in normal subjects and patients become more similar again, in that both show some anticipatory saccades (latencies: −200 to +100 ms) and the mean latencies become shorter (normal subjects: 137±21 ms; patients: 191±60 ms). Still, there remains a difference between normal subjects and patients with respect to a clearly broader distribution in the patients. Statistically, there were significant effects for the factors group [F (1,84) = 22.4; P = 0.0001] and saccade condition [F (2,84) = 16.7; P = 0.0001], and a significant interaction between the two factors, in the sense that the latencies for the centripetal saccades were longer in the patients than in the control subjects [F (2,84) = 5.4; P = 0.006]. Neither for the patients nor for the control group was there a relationship between the latency at short ISI and the corresponding trial-to-trial variation in PV (taken as the ratio of the actual PV of a saccade and the one predicted by the exponential fit).

Saccade parameters in MC patients

The measures used to characterize PV as a function of saccade amplitude (PV_{12}, PV_{MAX}/A_{63}) for the two MC

Table 1 *Peak saccadic velocity* (° s^{-1})

	Controls		MD patients		MC patients	
	PV_{12}	PV_{MAX}/A_{63}	PV_{12}	PV_{MAX}/A_{63}	PV_{12}	PV_{MAX}/A_{63}
Centrifugal saccades	381±72.6	69.4±10	306±76.4	58.8±12.9	407±76.4	66.6±14.2
Centripetal, short ISI	397±66.4	63.4±13.6	301±59.8	54.8±13.9	431±21.2	56.7±24.2
Centripetal, long ISI	380±64.9	66.4±16	291±64.8	56.6±18.1	421±28.3	66.9±9.5

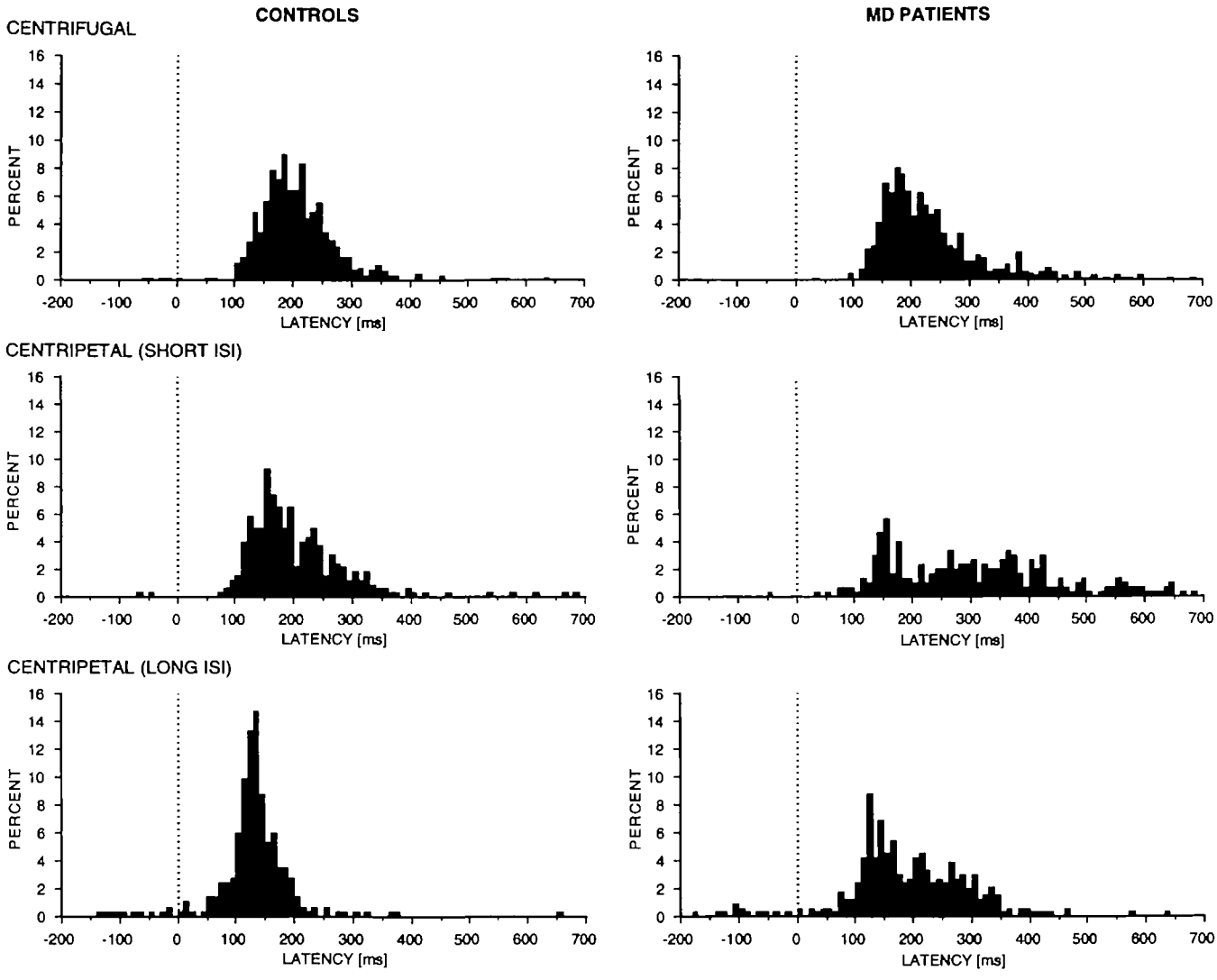

Fig. 5 Frequency histograms of saccadic latencies from MD patients and normal controls, for centrifugal and centripetal saccades at short and long ISI (bin width = 10 ms).

patients are also shown in Table 1. Their data fall well into the normal range. Furthermore, saccadic accuracy of the centrifugal saccades in the MC patients (0.88±0.01) was similar to that in normal subjects. Finally, the latencies of centrifugal saccades (208±52 ms) and the centripetal saccades at short ISI (167±38 ms) and at long ISI (141±8 ms) of MC patients were also normal.

Discussion

Smooth pursuit and VOR-S

There is considerable physiological evidence that SP makes a major contribution to VOR-S (Barnes *et al.*, 1978; Robinson, 1982; *see* Barnes, 1993). Evidence also comes from studies investigating the effect of cerebellar lesions on SP and VOR-S (Dichgans *et al.*, 1978; Zee *et al.*, 1981; Waterston *et al.*, 1992). Furthermore, in a large population of 52 patients selected on the basis of a SP deficit, all patients also showed a deficit in VOR-S (Büttner and Grundei, 1995).

Our results, showing a degradation of SP gain in MD patients, confirm the findings of a number of previous authors (von Noorden *et al.*, 1964; Burian and Burns, 1967; Bollen *et al.*, 1992). Furthermore, our results show that the patients' SP deficit can be differentiated from the performance of normal controls better at high than at low stimulus frequency (or acceleration, since this covaried with frequency in our experiments). In contrast, VOR was normal in our patients, which excludes the possibility that peripheral deficits might significantly affect their performance of slow eye movements. The normal VOR gain together with normal latencies of centrifugal saccades (*see* below) also indicates that our patients' level of vigilance was not degraded. In line with this notion was the finding that SP phase was normal in our patients. Furthermore, a normal SP phase at high stimulus frequencies suggests that the patients' capability of predicting periodic stimuli is essentially preserved (*see* Waterston *et al.*, 1992).

Our patients' ability to suppress the VOR was impaired;

VOR-S gain was significantly higher than in the control subjects. This held true when we analysed the SQ, which takes into account subjects' VOR gain. However, the impairment of VOR-S was slightly less than that of SP. This is similar to earlier findings in patients with cerebral lesions, and applies to both the horizontal (Chambers and Gresty, 1983) and the vertical (Ranalli and Sharpe, 1988) planes. The phenomenon is generally related to the fact that VOR-S involves, in addition to SP, non-visual mechanisms. For instance, it may be enough that a subject imagines a head-fixed visual target in order to suppress the VOR (Barr *et al.*, 1976), and suppression of the VOR can start prior to SP (Johnston and Sharpe, 1994).

Taken together, we assume that the parallel degradation of SP and VOR-S in our MD patients reflects a central deficit. A cerebral involvement in MD is well established in the literature. Several studies have demonstrated cognitive impairments (*see* Censori *et al.*, 1994). Furthermore, NMR imaging has revealed considerable white matter lesions in the cerebral hemispheres (Huber *et al.*, 1989; Damian *et al.*, 1993). Diffuse loss of myelin in the deep white matter has been described in a neuropathological case report (Abe *et al.*, 1994). We used NMR with three of our patients, and all three showed white matter lesions of the kind described in the previous studies. This raises the question, whether the patients' SP deficit is related to a general mental impairment, or to a more specific one that involves visuo-motor functions. As already mentioned above, the finding of a normal VOR and of normal latencies of centrifugal saccades speak against the assumption that the SP deficit results from a diffuse cerebral impairment. Furthermore, there was no correlation between SP gain and the Karnofsky index. We therefore conceive that the SP deficit stems from a specific involvement of cerebral visuo-oculomotor pathways. It has been shown that the lesions in MD show a preponderance for the periventricular white matter (Glantz *et al.*, 1988). We suggest, in accordance with Bollen *et al.* (1992), that the patients' SP deficit might be related to lesions of fibres descending from visual association areas, which in monkey have been shown to pass through posterior periventricular regions (Tusa and Ungerleider, 1988). Lesions of the parieto-occipital visual association areas are known to affect SP gain, especially at high stimulus frequencies/accelerations (Leigh and Tusa, 1985).

Saccades

Saccadic accuracy (amplitude) as well as latency of centrifugal saccades in our MD patients were similar to those in the controls. These findings are in agreement with earlier results of Ter Bruggen *et al.* (1990) and Bollen *et al.* (1992). Other authors, in contrast, have reported hypometric saccades in MD patients (Koca *et al.*, 1992; Hansen *et al.*, 1993). We assume that the patients in these studies were more severely affected by the disease than our patients (*see* Selection criterion in Methods). Yet, the saccades of our patients were affected with respect to peak eye velocity and duration and, as a novel finding, to the latency of centripetal saccades. Since we take for granted that the latency increase also represents a central deficit, we consider this finding first, before dealing with PV.

The saccadic task used was specific, in that the timing of the central target presentation (for centripetal saccades) was randomized (either 400 ms or 900 ms). The subjects could not predict whether the target would appear at the short interval or not, whereas if no target came up at 400 ms, subjects would 'know' that the interval was long. Normal subjects drew profit from this situation, in that their mean latency for the centripetal saccade at the long interval was considerably shorter than that for the centripetal saccade at the short interval and that for the centrifugal saccades (mean values: 137, 200, and 209 ms, respectively). In contrast, our MD patients showed only a minor difference between long interval centripetal saccades and the centrifugal saccades (191 ms versus 228 ms). The most impressive finding, however, was a pronounced increase in latency for the short interval centripetal saccades (334 ms). Obviously, this increase is not related to myopathic or myotonic muscle changes, since PV (as well as saccadic amplitude and duration) was similar across the three saccade conditions. For the same reason one would not assume a neural or brainstem dysfunction, either. The deficit certainly stems from a hemispherical dysfunction. Considering the fact that the latency for centrifugal saccades was essentially normal in our patients, we exclude a major impairment of visual pathways as reported by other authors, who observed an increase of saccade latency associated with a prolonged VEP latency in their MD patients (Ter Bruggen et al. 1990). Rather, we consider that our MD patients had difficulties in programming the saccades, a function which we would localize mainly in the parieto-occipital visual association areas (Braun *et al.*, 1992; Pierrot-Deseilligny *et al.*, 1992).

Functionally, saccadic peak eye velocity reflects a high-frequency burst of oculomotor neurons and a rapid contraction of the eye muscles, necessary to overcome inertia of the eye ball and viscous-elastic properties of the soft tissues in order to generate a rapid (saccadic) eye displacement (*see* Becker, 1989). Conceivably, myopathic and myotonic eye muscle changes, which are observed in MD (Burns, 1969; Kuwabara and Lessell, 1976; Ter Bruggen *et al.*, 1990) and which do not impair slow eye movements, might well become functionally relevant with the extreme of activity during saccades. We shall consider mainly the question whether the slowing of saccades which we observed in accordance with previous authors (Baloh et al., 1975; Oohira et al., 1985; Emre and Henn, 1985; Ter Bruggen *et al.*, 1990; Koca *et al.*, 1992; Hansen *et al.*, 1993) is dependent on myotonia, as suggested by Hansen *et al.* (1993), or may occur independently of it.

As previously mentioned, myotonia is due to a delay in muscle relaxation or, in other words, to prolonged involuntary muscle activity which vanishes over time. In myotonia

therefore, a sequence of two antagonistic movements should lead to prolonged activity in the muscle performing the first movement, thus impairing/slowing the second movement. This effect should be stronger at shorter intervals between these two movements. In our experiments, however, PV was independent of the particular saccade condition, i.e. whether the saccade was centrifugal or centripetal, and whether the centripetal saccade was performed at a short or a long interval after the centrifugal saccade. We therefore conclude that myotonia does not play a role in our experiments.

Hansen *et al.* (1993) found, in a group of three MD patients, that peak saccadic velocity and amplitude was subnormal when tested after 1 min of ocular rest. However, the a mplitude built up to normal when patients performed a sequence of saccades at 0.5 Hz or 1.0 Hz. In parallel, PV increased, but never reached normal values. The amplitude and velocity deficit as well as the 'warming up phenomenon', which is reminiscent of that seen in the skeletal muscles of myotonic patients, was no longer found when patients were on treatment with a membrane-stabilizing agent (tocainide). We would assume, however, that this analogue of 'myotonic stiffness' plays no role in the patients' everyday life. Normally, ISI are of the order of 200 ms to a few seconds, thus the extraocular muscles would normally be 'warmed up'. In our experiments we tested subjects under these real world conditions and, as mentioned above, did not find any significant myotonic effect. In line with this notion, saccade amplitudes were normal in our patients, who performed at least two saccades per trial (trial duration, 3 s). Despite normal amplitudes in our study, the PV was decreased, and this decrease was essentially constant throughout the testing. Furthermore, we observed no glissade-like saccade trajectories in our patients, although they were briefly mentioned in the study of Hansen *et al.* (1993).

A second, related finding in the study of Hansen *et al.* (1993) was that the subnormal PV increased slightly as a function of stimulus frequency (1.15 Hz compared with 0.18 Hz) in two patients of a second group of four patients. However, it remained clearly subnormal at 1.15 Hz in three of the four patients. Furthermore, the frequency effect was also present in the normal control data of these authors. Thus, the effects observed in both parts of their study, which the authors attribute to myotonia, do not fully explain the decrease of PV. As already mentioned, the decrease of PV in our patients did not depend on the amount and duration of presaccadic activity in the eye muscles. Finally, in our two MC patients, in whom myotonia is the predominant symptom, PV was normal.

Instead, we suggest that the slowing of saccades in our MD patients is due to a moderate eye muscle paresis of myopathic and/or neural (nerve or brainstem) origin. A differentiation between muscular and neural origin was attempted by Oohira *et al.* (1985), who found that PV of large saccades, unlike that of small saccades, is decreased in patients with ocular nerve paresis, whereas it is decreased for both small and large saccades in patients with ocular myopathy and, to a less degree, in patients with MD. In our patients the initial slope of the PV-amplitude function (given by PV_{MAX}/A_{63} in Table 1) is indeed consistently decreased in all three saccade conditions. But the effect is so weak that we cannot take it as an indication of a myopathic contribution, at present.

Taken together, moderately impaired MD patients show discrete oculomotor symptoms which may, in part, be of muscular or neural origin (saccade slowing), whereas other symptoms (deficit of SP and VOR-S; increase in latency of saccades at short ISI) appear to stem from central lesions. Myotonia, in contrast, apparently does not lead to a significant functional deficit under normal conditions.

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References

Abe K, Fujimura H, Toyooka K, Yorifuji S, Nishikawa Y, Hazama T, et al. Involvement of the central nervous system in myotonic dystrophy. J Neurol Sci 1994; 127: 179–85.

Baloh RW, Konrad HR, Sills AW, Honrubia V. The saccade velocity test. Neurology 1975; 25: 1071–6.

Barnes GR. Visual-vestibular interaction in the control of head and eye movement: the role of visual feedback and predictive mechanisms [Review]. Prog Neurobiol 1993; 41: 435–72.

Barnes GR, Benson AJ, Prior AR. Visual-vestibular interaction in the control of eye movement. Aviat Space Environ Med 1978; 49: 557–64.

Barr CC, Schultheis LW, Robinson DA. Voluntary, non-visual control of the human vestibulo-ocular reflex. Acta Otolaryngol (Stockh) 1976; 81: 365–75.

Becker W. Metrics. In: Wurtz RH, Goldberg ME, editors. The neurobiology of saccadic eye movements. Amsterdam: Elsevier, 1989. 13–67.

Bollen E, den Heyer JC, Tolsma MHJ, Bellan S, Bos JE, Wintzen AR. Eye movements in myotonic dystrophy. Brain 1992; 115: 445–50.

Braun D, Weber H, Mergner T, Schulte-Mönting J. Saccadic reaction times in patients with frontal and parietal lesions. Brain 1992; 115: 1359–86.

Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member [published erratum appears in Cell 1992; 69: 385]. Cell 1992; 68: 799–808.

Burian HM, Burns CA. Ocular changes in myotonic dystrophy. Am J Ophthalmol 1967; 63: 22–34.

Burns CA. Ocular histopathology of myotonic dystrophy. Am J Ophthalmol 1969; 68: 417–22.

Büttner U, Grundei T. Gaze-evoked nystagmus and smooth pursuit deficits: their relationship studied in 52 patients. J Neurol 1995; 242: 384–9.

Censori B, Provinciali L, Danni M. Chiaramoni L, Maricotti M, Foschi N, et al. Brain involvement in myotonic dystrophy: MRI features and their relationship to clinical and cognitive conditions Acta Neurol Scand 1994; 90: 211–7.

Chambers BR, Gresty MA. The relationship between disordered pursuit and vestibulo-ocular reflex suppression. J Neurol Neurosurg Psychiatry 1983; 46: 61–6.

Damian MS, Bachmann G, Herrmann D, Dorndorf W. Magnetic resonance imaging of muscle and brain in myotonic dystrophy. J Neurol 1993, 240. 8–12.

Davidson SI. The eye in dystrophia myotonica. Br J Ophthalmol 1961; 45: 183–96.

Dichgans J, von Reutern GM, Römmelt U. Impaired suppression of vestibular nystagmus by fixation in cerebellar and noncerebellar patients. Arch Psychiatr Nervenkr 1978; 226: 183–99.

Emre M, Henn V. Central eye movement disorder in a case of myotonic dystrophy. Neuro-ophthalmology 1985; 5: 21–5.

Glantz RH, Wright RB, Huckman MS, Garron DC, Siegel IM. Central nervous system magnetic resonance imaging findings in myotonic dystrophy. Arch Neurol 1988; 45: 36–7.

Hansen HC, Lueck CJ, Crawford TJ, Kennard C, Zangemeister WH. Evidence for the occurrence of myotonia in the extraocular musculature in patients with dystrophia myotonica. Neuro-ophthalmology 1993; 13: 17–24.

Huber SJ, Kissel JT, Shuttleworth EC, Chakeres DW, Clapp LE, Brogan MA. Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy [see comments]. Arch Neurol 1989; 46: 536–40 Comment in. Arch Neurol 1990; 47: 253–4.

Johnston JL, Sharpe JA. The initial vestibulo-ocular reflex and its visual enhancement and cancellation in humans. Exp Brain Res 1994; 99: 302–8.

Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. Evaluation of chemotherapeutic agents. New York: Columbia University Press, 1949: 191–205.

Koca MR, Horn F, Korth M Alterations of saccadic eye movements in myotonic dystrophy. Graefes Arch Clin Exp Ophthalmol 1992; 230: 437–41.

Koenig E, Dichgans J, Dengler W. Fixation suppression of the vestibulo-ocular reflex (VOR) during sinusoidal stimulation in humans as related to the performance of the pursuit system. Acta Otolaryngol (Stockh) 1986; 102: 423–31.

Kuwabara T, Lessell S. Electron microscopic study of extraocular muscles in myotonic dystrophy. Am J Ophthalmol 1976; 82: 303–9.

Leigh RJ, Tusa RJ. Disturbance of smooth pursuit caused by infarction of occipitoparietal cortex. Ann Neurol 1985; 17: 185–7.

Miller NR. The muscular dystrophies. In: Walsh FB, Hoyt WF, editors. Walsh and Hoyt's clinical neuro-ophthalmology, Vol. 2. 4th ed. Baltimore: Williams and Wilkins, 1985: 794–811.

Oohira A, Goto K, Ozawa T. Slow saccades in myogenic and peripheral neurogenic ophthalmoplegia. Neuro-ophthalmology 1985; 5: 117–24.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of reflexive visually-guided saccades. Brain 1991; 114: 1473–85

Ranalli PJ, Sharpe JA. Vertical vestibulo-ocular reflex, smooth pursuit and eye-head tracking dysfunction in internuclear ophthalmoplegia. Brain 1988; 111: 1299–317

Robinson DA. A model of cancellation of the vestibulo-ocular reflex. In: Lennerstrand G, Zee DS, Keller EL, editors. Functional basis of ocular motility disorders. Oxford: Pergamon Press, 1982: 5–13.

Ter Bruggen JP, Bastiaensen LAK, Tyssen CC, Gielen G. Disorders of eye movement in myotonic dystrophy. Brain 1990; 113: 463–73.

Tusa RJ, Ungerleider LG. Fiber pathways of cortical areas mediating smooth pursuit eye movements in monkeys. Ann Neurol 1988; 23: 174–83.

Van Noorden GK, Thompson HS, Van Allen MW. Eye movements in myotonic dystrophy: an electro-oculographic study. Invest Ophthal 1964; 3: 314–24.

Waterston JA, Barnes GR, Grealy MA. A quantitative study of eye and head movements during smooth pursuit in patients with cerebellar disease. Brain 1992; 115: 1343–58.

Zee DS, Yamazaki A, Butler PH, Gücer G. Effects of ablation of flocculus and paraflocculus of eye movements in primate. J Neurophysiol 1981; 46: 878–99.

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