Oculomotor abnormalities in myoclonic tremor: a comparison with spinocerebellar ataxia type 6

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In the present study, eye movements are recorded in two patient groups with an autosomal dominantly inherited cerebellar disorder, i.e. spinocerebellar ataxia type 6 (SCA6) and familial cortical myoclonic tremor with epilepsy (FCMTE). In SCA6 and FCMTE patients striking similarities with the extensive Purkinje cell changes in the cerebellar cortex were described, but the two disorders have a distinctive clinical picture. SCA6 is a late-onset cerebellar syndrome, with relatively minimal brain stem and cerebral cortex symptoms. In contrast, FCMTE is clinically characterized by cortical symptomatology with a distal cortical myoclonic tremor and infrequent epileptic attacks without cerebellar dysarthria and limb ataxia. Comparison of oculomotor function of six FCMTE patients, five SCA6 patients and 18 healthy controls demonstrated both in SCA6 patients and FCMTE patients square wave jerks, downbeat nystagmus (DBN) and a stronger reduced downward smooth pursuit gain than an upward smooth pursuit gain. Only in SCA6 patients horizontal smooth pursuit gain was reduced. Except for the downward direction mean saccadic gain in both patient groups was reduced. This is consistent with cerebellar cortical pathology in both disorders. Subsequently, both patient groups showed increase of DBN with hyperventilation. As a novel finding, only the FCMTE patients showed a significantly increased amount of express saccades in the pro-saccade paradigm.

Keywords: myoclonic tremor; spinocerebellar ataxia; SPEM; downbeat nystagmus; express saccades

Abbreviations: SPEM = smooth-pursuit eye movement; FCMTE = familial cortical myoclonic tremor with epilepsy; SCA6 = spinocerebellar ataxia type 6; SCA = spinocerebellar ataxias; SEP = sensory evoked potential; TMS = transcranial magnetic stimulation; AED = anti-epileptic drug; DMI = double magnetic induction; HV = hyperventilation; DBN = downbeat nystagmus; DLPPC = dorsolateral prefrontal cortex; SCI = superior colliculus inferior; SNr = substantia nigra pars reticulate; Vmax(20) = the estimated peak saccade velocity at 20 degrees


Introduction

In general, neurodegenerative disorders of brainstem and cerebellum are associated with a variety of eye movement abnormalities, for example, in patients with spinocerebellar ataxias (SCAs) (Zhuchenko et al., 1997; Buttner et al., 1998; Bürk et al., 1999; Yabe et al., 2003; Ying et al., 2005; Schols et al., 2008). Recently, patients with familial cortical myoclonic tremor with epilepsy (FCMTE), an autosomal dominantly inherited disorder, have been demonstrated to have oculomotor abnormalities. Although functional changes in this neurodegenerative disorder have been mainly located in the cerebral cortex, the neuropathological findings and eye movement abnormalities are specific for cerebellar pathology (van Rootselaar et al., 2007).

FCMTE is a genetically heterogenic disorder characterized by distal tremulous movements, infrequent epileptic attacks and electrophysiological signs of cortical hyperexcitability (van Rootselaar et al., 2005). The genetic cause of FCMTE is not known. Sensory evoked potential (SEP) and transcranial magnetic stimulation (TMS) studies have demonstrated involvement of the sensory motor cortex and abnormal disinhibition of the motor cortex in the generation of the tremulous movements (van Rootselaar et al., 2006, 2007). Although in FCMTE patients clinically cerebellar dysarthria and limb ataxia are absent as a rule, interestingly, post-mortem immunopathological investigations in two patients of a Dutch FCMTE pedigree revealed extensive Purkinje cell changes but no
abnormalities of the cerebral (sensorimotor) cortex (van Rootselaar et al., 2004). It was suggested that Purkinje cell degeneration in FCMTE leads to decreased cortical inhibition via the cerebellothalamic loop and clinically to cortical tremor and epileptic attacks (van Rootselaar et al., 2007).

The eye movement abnormalities in FCMTE patients show remarkable similarities to oculomotor disorders described in patients with spinocerebellar ataxia type 6 (SCA6), an autosomal dominantly inherited neurodegenerative disorder, caused by an abnormal expansion of a trinucleotide CAG repeat in exon 47 of the CACNA1A gene, which encodes the alpha1A subunit of the P/Q-type voltage-gated calcium channel (Gomez et al., 1997; Zhuchenko et al., 1997; Kordasiewicz and Gomez, 2007). Clinically SCA6 patients manifest with a picture distinctive from FCMTE. They have gait ataxia, dysarthria, truncal and appendicular ataxia and eye movement abnormalities. Eye movement recordings show dysmetric saccades, gaze-evoked nystagmus, rebound nystagmus, downbeat nystagmus (DBN), periodic alternating nystagmus, square wave jerks, reduced smooth pursuit gain and impaired vestibular ocular reflex. Saccade velocities are usually normal. Pathologically, in SCA6 patients neuronal loss is confined to Purkinje cells of the cerebellar cortex and selective atrophy of the cerebellum with the brain stem and the cerebral cortex relatively spared (Gomez et al., 1997).

In the present study, accurate eye movement recording and precise quantitative analysis of abnormalities of saccades, smooth pursuit and involuntary eye movements are compared between patients with FCMTE, patients with SCA6 and healthy controls. Abnormal eye movements in FCMTE and SCA6 were hypothesized to be similar.

**Materials and Methods**

**Patients and subjects**

Six definitely affected FCMTE patients with a median age of 40 years (range 20–60 years; either with typical cortical myoclonic tremor and epilepsy, or this typical tremor and a positive C-reflex and giant-SEP) belonging to a single Dutch pedigree and willing to participate in this study, were included. The clinical characteristics and use of anti-epileptic drugs (AEDs) are summarized in Table 1; the pedigree has been described in detail before (van Rootselaar et al., 2005). All patients had distal postural and action tremor as well as sporadic jerks in the arms and legs at rest. Patient FCMTE 3 was known with low visual acuity due to myopia and oscillopsia due to DBN. Three out of the six FCMTE patients used low-dose AEDs, but in none of the FCMTE patients gaze holding was abnormal and the mean smooth-pursuit eye movement (SPEM) gain, except for downward pursuit, was normal (see Results and Discussion sections).

Five genetically proven SCA6 patients with a median age of 61 years (range 55–70 years) were included. Clinical characteristics are summarized in Table 2. Three SCA6 patients had clinically both motor and ocular symptoms; one SCA6 patient had only

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### Table 1 Features of relatives of the Dutch FCMTE pedigree, and additional tests

<table>
<thead>
<tr>
<th>FCMTE # (pedigree)</th>
<th>Age</th>
<th>Gender</th>
<th>Symptoms (age at onset)</th>
<th>Ocular signs</th>
<th>AEDs</th>
<th>Electrophysiology</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tremor</td>
<td>Myocl Seiz</td>
<td>GTCS</td>
<td>nys</td>
</tr>
<tr>
<td>1 III:1</td>
<td>60</td>
<td>M</td>
<td>45</td>
<td>–</td>
<td>52</td>
<td>+</td>
</tr>
<tr>
<td>2 III:5</td>
<td>57</td>
<td>M</td>
<td>30</td>
<td>30</td>
<td>43</td>
<td>+</td>
</tr>
<tr>
<td>3 III:10</td>
<td>46</td>
<td>F</td>
<td>38</td>
<td>–</td>
<td>42</td>
<td>+</td>
</tr>
<tr>
<td>4 IV:1</td>
<td>34</td>
<td>M</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5 IV:2</td>
<td>33</td>
<td>F</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6 IV:8</td>
<td>20</td>
<td>F L</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Myocl seiz = myoclonic seizure; GTCS = generalized tonic clinic seizure; nys = nystagmus; osc = oscillopgia; sac = saccades during SPEM; EEG = electroencephalogram; g-SEP = giant sensory evoked potential; C-reflex = cortical reflex; M = male; F = female; L = left handed; 1 = valproic acid; 2 = oxcarbazepine; 3 = clonazepam; 4 = clobazam; s–w = spike–wave complexes; + = present; ++ = strongly present; – = not observed or none; ± = some, not specific; ? = not known; N = normal.

### Table 2 SCA6 group, patient characteristics

<table>
<thead>
<tr>
<th>SCA</th>
<th>Gender</th>
<th>Age</th>
<th>Age at onset</th>
<th>Cerebellar symptoms</th>
<th>Cerebellar atrophy (MRI)</th>
<th>Drug</th>
<th>CAG repeats</th>
<th>Ocular signs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>motor</td>
<td>ocular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA6-1a</td>
<td>F</td>
<td>55</td>
<td>45</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1,2,3</td>
<td>+</td>
</tr>
<tr>
<td>SCA6-2</td>
<td>M</td>
<td>56</td>
<td>30</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>SCA6-3a</td>
<td>F</td>
<td>58</td>
<td>45</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>SCA6-4</td>
<td>M</td>
<td>70</td>
<td>56</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>SCA6-5</td>
<td>M</td>
<td>70</td>
<td>69</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

*Sisters.

1 = atenolol 25; 2 = imigran as needed; 3 = temazepam as needed; ND = not done.
motor symptoms and one SCA6 patient suffered from ocular symptoms. It cannot be excluded that benzodiazepine used by the sisters SCA6-1 and SCA6-3 may have affected the oculomotor response (see Discussion section).

Finally, 18 healthy controls (11 males and 7 females) without neurological disorders, and not using any medication known to act as a neurodepressant or neurostimulant, with a median age of 36 years (range 20–72 years) participated.

All subjects and patients gave their informed consent. The study was approved by the ethics committee of the Academic Medical Center, Amsterdam.

**Eye movement assessment**

Before electromagnetic eye movement recording all subjects were asked for visual complaints. Both visual inspection and video recordings of eye movements, including saccades, smooth pursuit and gaze stability, were performed. Subsequently, eye movements were recorded using the double magnetic induction (DMI) method developed by Bour and colleagues (1984, 2002). The subject’s head was positioned in a homogeneous alternating primary magnetic field with constant amplitude. Horizontal as well as vertical eye positions were derived from a secondary magnetic field picked up by a detection coil placed in front of the eye. Golden metallic rings placed onto the subject’s eye (anaesthetized with one droplet of 0.4% solution of oxybuprocaine hydrochloride) generated the secondary field and its strength was related to the rotation of the rings. Magnetic field strength was measured with a phase-locked amplitude technique (Robinson, 1963). Both horizontal and vertical eye positions of one eye were recorded, low-pass filtered (150 Hz, 12 dB/oct, 2nd order Bessel filter), sampled with a frequency of 500 Hz and computer stored. The visual target was a single, red, 0.5° of visual angle in diameter, circular laser-spot of 20 cd/m² luminance, projected on the rear of a white translucent screen by means of a scanning mirror device. Data calibration and analysis of saccades and smooth pursuit was performed off-line with a custom made interactive program, developed in the Department of Clinical Neurophysiology of the Academic Medical Center Amsterdam (Bour et al., 2000).

**Saccades**

For the test of rapid eye movements, subjects were instructed to fixate a central target. Immediately after the central target was switched off a peripheral target was presented with a variable interval (800–1500 ms) and a variable size (2–20°) and the subject was requested to make a pro-saccade. The peripheral target was presented in the horizontal or vertical plane on either side of the point of fixation. No gap paradigm was used. Quantitative analysis of saccade parameters, including saccade latency (difference between target onset and saccade onset), saccade duration (difference between saccade on- and off-set), saccade amplitude (change of eye position in degrees of visual angle between saccade on- and off-set), peak saccade velocity (maximum eye velocity in degrees/second between saccade on- and off-set), and saccadic gain (ratio between saccade amplitude and target amplitude) was performed by the interactive computer program. An automatic detection algorithm, based on a threshold detection of eye velocity larger than 50°/s, was used to mark saccade onset and saccade offset. Eye velocity was digitally calculated with a second-order low-pass (−3 dB at 65 Hz) differentiation algorithm (Usui and Amidror 1982), which allows a sufficient smoothing and a <5% reduction of the velocity profile (Chubb and Fuchs, 1982; van Opstal et al., 1985). If necessary, interactive corrections to the automatic saccade onset and saccade offset could be made. Anticipatory or spontaneous saccades (with latency <100 ms) were excluded from the analysis. The relationship between peak saccade velocity and saccade amplitude was estimated by fitting an exponential fit through the measured saccades for each direction (Bour et al., 1984). The estimated peak saccade velocity at 20° [V_{max}(20)] was calculated from the exponential curve.

**Smooth pursuit**

Subjects were asked to track the laser target, which moved with a constant velocity of 10°/s from left to right and vice versa. Extreme target positions were at ±10°. By means of the automatic saccade detection, smooth pursuit data were separated in a smooth and a saccadic component. For each 2 s track from left to right or vice versa samples starting 250 ms from the turning point until 250 ms before the next turning point were included to calculate the smooth pursuit gain, defined as the ratio between target velocity and eye velocity of the smooth component. The mean smooth pursuit gain for each direction (left, right, upward and downward) was calculated from at least 16 tracks of pursuit.

**Fixation/hyperventilation**

Eye movements were examined with eyes open while fixating a stationary laser spot and whilst looking straight ahead in darkness. During the latter condition, subjects were asked to hyperventilate (HV). Recordings were made before (10 s), during (30 s) and after (60 s) HV. Subjects were also asked to fixate an eccentric placed target at 15° of visual angle both horizontally and vertically.

**Statistics**

Group statistics were carried out using SPSS v. 12 (Chicago, IL). Differences between patients and controls for mean smooth pursuit gain and saccade amplitude were assessed with a Mann–Whitney U-test.

**Results**

**History and visual inspection**

Three patients (FCMTE 1–3) had visual complaints caused by vertical oscillopsia, especially when watching television and in traffic. Oculomotor abnormalities that were clinically observed in the FCMTE patients and SCA6 patients are listed in Tables 1 and 2, respectively. The healthy normal control group had no oculomotor abnormalities.

**Saccades**

The first four columns of Table 3 show the means of saccadic gain of all three groups. Compared to the FCMTE group, the SCA6 group contained more elderly people (Tables 1 and 2). Age dependency of saccadic gain was investigated with a general linear model for the controls (Fig. 1A). Saccadic gain in all four directions did not significantly depend on age (P>0.35). Group comparisons applying the two-tailed non-parametric Mann–Whitney test, showed in all directions no significant differences.
between the two patient groups for saccadic gain \((P > 0.05)\). Only for saccadic gain in the upward direction no significant differences between healthy controls and the SCA6 patient group \((P = 0.23)\) and the FCMTE patient group \((P = 0.27)\) were found. For all the other directions of saccades significant reduction \((P < 0.01)\) in mean gain was found between the control group and the two patient groups.

Since no significant differences were found between saccadic latency distributions for different directions within the normal control group and the two patient groups, latencies of saccades in all directions were pooled per group. First, comparison of latency distributions of the FCMTE group and the SCA6 group with the control group showed that the patient groups had a prolonged tail, i.e. there was a considerable increased amount of saccades with longer latencies. Whereas in the control group 4.4% \((44/996)\) of the saccades had latencies longer than 280 ms, this was the case for 24% \((75/313)\) and 21% \((70/337)\) of the saccades in the SCA6 and the FCMTE group, respectively (Fig. 2A–C).

The latency distribution of visually elicited horizontal and vertical saccades (no gap paradigm) in the FCMTE group clearly showed a double peaked latency distribution with an ‘express’ peak at 135 ms, which almost equalled in amplitude the ‘normal’ peak at 190 ms (Fig. 2A). The SCA6 group showed a main peak at 200 ms and at 290 ms there was a second much smaller peak in the latency distribution (Fig. 2B). The control group showed a single peak at 180 ms (Fig. 2C). Whereas in the control group 5.5% \((55/996)\) of the saccades had latencies less than 150 ms, this was the case for 1% \((2/313)\) and 18% \((62/337)\) of the saccades in the SCA6 and the FCMTE group, respectively.

For all directions \(V_{\text{max}}(20)\) of every patient in the FCMTE group was within the 5–95% limit of the normal control group \((> 350^\circ/s)\). However, in the SCA6 group the \(V_{\text{max}}(20)\) in all directions was within the 5–95% normal limit for only one patient. In one patient this was the case only in the horizontal direction (Fig. 3). The remaining three patients had significantly low velocities in all directions. For the SCA6 group particularly, the upward saccades were too slow \([\text{mean } V_{\text{max}}(20) = 276^\circ/s, \text{SEM} = 35^\circ/s]\). For the downward saccades in the SCA6 group the mean value \(V_{\text{max}}(20)\) was 304\(^\circ/s\) and the SEM 47\(^\circ/s\). \(V_{\text{max}}(20)\) for horizontal saccades was not significantly lower in the SCA6 group \((P = 0.052)\) than in the FCMTE group, however, for upward saccades \(V_{\text{max}}(20)\) was significantly slower \((P = 0.047)\).

**Smooth pursuit**

The last four columns of Table 3 show the means of SPEM gain, for the four different directions, for the three groups.

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**Table 3** Mean gain for saccades to the right (Gsac R), to the left (Gsac L), upward (Gsac U) and downward (Gsac D) for the three groups are shown. Also the mean gain for SPEM to the left (Gspem L) to the right (Gspem R), upward (Gspem U) and downward (Gspem D) are listed.

<table>
<thead>
<tr>
<th></th>
<th>Gsac R</th>
<th>Gsac L</th>
<th>Gsac U</th>
<th>Gsac D</th>
<th>Gspem R</th>
<th>Gspem L</th>
<th>Gspem U</th>
<th>Gspem D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.90 ± 0.06</td>
<td>0.88 ± 0.06</td>
<td>0.83 ± 0.08</td>
<td>0.87 ± 0.09</td>
<td>0.92 ± 0.09</td>
<td>0.93 ± 0.09</td>
<td>0.85 ± 0.10</td>
<td>0.83 ± 0.13</td>
</tr>
<tr>
<td>SCA6</td>
<td>0.78 ± 0.04 *</td>
<td>0.80 ± 0.03 **</td>
<td>0.69 ± 0.11 *</td>
<td>0.99 ± 0.24</td>
<td>0.60 ± 0.11 **</td>
<td>0.57 ± 0.17 *</td>
<td>0.58 ± 0.08 *</td>
<td>0.31 ± 0.25 *</td>
</tr>
<tr>
<td>FCMTE</td>
<td>0.80 ± 0.06 *</td>
<td>0.74 ± 0.06 **</td>
<td>0.61 ± 0.10 *</td>
<td>0.80 ± 0.13</td>
<td>0.82 ± 0.33 **</td>
<td>0.76 ± 0.22</td>
<td>0.72 ± 0.12 *</td>
<td>0.57 ± 0.24 *</td>
</tr>
</tbody>
</table>

* \(P < 0.05\), Mann–Whitney between control and SCA6 or between control and FCMTE.
** \(P < 0.05\), Mann–Whitney between SCA6 and FCMTE.
With the two-tailed non-parametric Mann–Whitney test, group comparison showed that SPEM gain of the FCMTE group compared to the healthy controls was significantly different for the SPEM in downward ($P = 0.04$) and upward direction ($P = 0.017$). The SPEM gain in the SCA6 group compared to normal controls was significantly impaired in all directions ($P < 0.001$). In addition, the means of the SPEM gain in all directions of the SCA6 group were also decreased compared to the means of the FCMTE group. Except for the SPEM to the right ($P = 0.017$), this was not significantly different between the two patient groups ($P > 0.05$). In general, with respect to smooth pursuit, the SCA6 group, compared to the FCMTE group, was more severely affected. Figure 4 clearly shows the asymmetry in vertical pursuit in Patient 1 of the FCMTE group with a predominant reduction of velocity gain for downward pursuit. This is due to the effect that the downward pursuit is opposed to the spontaneous upward drift. There is also a slight asymmetry in horizontal direction. A small amplitude DBN can be observed during horizontal SPEM.

**Fixation/hyperventilation**

Accurate eye movement recordings during fixation straight ahead revealed, in four out of six patients of the FCMTE group, a DBN accompanied with square wave jerks with a frequency varying between 1.5 and 3 Hz and an amplitude varying between $0.2^\circ$ and $3^\circ$. In these patients horizontal jerks occurred simultaneously with the downbeat resulting in a so called bow-tie nystagmus. In these four patients after HV in the dark the DBN increased in amplitude by at least a factor 2. One patient had an upbeat nystagmus which changed with HV in darkness to a DBN. The other patient demonstrated only DBN in darkness with HV. None of the FCMTE patients had gaze-holding deficits in the horizontal direction.

In the SCA6 group, four out of five patients showed DBN accompanied with square wave jerks (bow-tie) with a frequency varying between 1.5 and 2.5 Hz and amplitudes varying between $0.2^\circ$ and $3^\circ$. In these four patients the amplitude of the nystagmus was dependent on gaze and in one of these patients (SCA6-5) DBN increased considerably.
by looking to the left and to the right (Fig. 5). Also in these patients the intensity of nystagmus increased with HV. In the fifth SCA6 patient (SCA6-3) only a DBN was observed in upgaze and it did not increase with HV. One patient (SCA6-1) had a continuous drift of the eyes to the left, which was corrected by rightward saccades. One patient (SCA6-4) had eccentric gaze-holding deficit to the left and one patient (SCA6-5) had a gaze-holding deficit both to the left and to the right and a rebound nystagmus (Fig. 5).

**Discussion**

In the current study, we compared oculomotor function of 6 FCMTE patients, 5 SCA6 patients and 18 healthy controls, including smooth pursuit, saccades and spontaneous eye movements with and without HV. Similar, although somewhat less severe to SCA6 patients, FCMTE patients demonstrated significantly decreased mean saccadic gain in horizontal and upward direction, reduced mean smooth pursuit gain in vertical directions, square wave jerks.
and DBN. FCMTE patients demonstrated increase of DBN with HV, which also was found in SCA6 patients. All FCMTE patients had normal peak saccade velocities both in horizontal and vertical direction, whereas in the SCA6 group, compared with the FCMTE group, vertical saccades particularly in upward direction were slow. Another very interesting new finding is that, unlike SCA6 patients and normal controls, FCMTE patients showed a significantly increased amount of express saccades in the pro-saccade paradigm both in horizontal and vertical direction.

Downbeat nystagmus, observed in both the SCA6 and FCMTE patients, almost exclusively points to cerebellar cortical pathology (Zee et al., 1974; Baloh and Spooner, 1981) particularly of the Purkinje neurons in the vestibular cerebellum (Zee et al., 1974, 1981; Chubb and Fuchs, 1982; Pierrot-Deseilligny and Milea, 2005). Impaired inhibition of the cerebellar Purkinje cells to the superior vestibular nucleus in the brainstem creates an imbalance of the structures which are responsible for upward and downward smooth movement of the eyes, resulting in a slow upward drift, which is compensated by a fast downward component (Yabe et al., 2003; Marti et al., 2005a, b; Pierrot-Deseilligny and Milea, 2005). The asymmetry of mean vertical saccadic gain, i.e. downward saccadic gain is strongly reduced compared to upward saccadic gain, and the asymmetry of mean vertical SPEM gain, i.e. upward SPEM gain being much less impaired than downward SPEM gain, observed in both patient groups, is in line with the vertical gaze imbalance, and again indicates cerebellar cortical involvement (Yabe et al., 2003; Marti et al., 2005a, b; Pierrot-Deseilligny and Milea, 2005). Increase of DBN with HV, which has been observed in both SCA6 and FCMTE patients, may suggest a channelopathy (Walker and Zee, 1999). However, genetic testing up until now has excluded the presence of CAG repeat in the Dutch FCMTE family described (van Rootseelaar et al., 2005).

Striking is the synchronous occurrence, also in darkness, of square wave jerks and DBN resulting in a bow-tie nystagmus in the majority of SCA6 and FCTME patients. Bow-tie nystagmus in this case is associated with DBN and upward drift, instead of a downward drift with an upbeat nystagmus (Leigh and Zee, 2006). The origin of these square wave jerks concurrent with DBN is not clear.

Gaze-holding deficits in the horizontal direction were observed in three out of five SCA6 patients and in none of the FCMTE patients. Furthermore, mean smooth pursuit gain in all directions was more reduced in the SCA6 patient group than in the FCMTE patient group. These findings suggest that the cerebellar deficits were less severe in the FCMTE group.

Medication used by some patients may have caused gaze-holding deficits and reduction of SPEM gain (Leigh and Zee, 2006). Although three out of six FCMTE patients used low-dose AEDs, gaze holding in none of the patients

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**Fig. 5** Gaze holding in patient SCA6-5. From top to bottom are shown, horizontal eye position of right (Hod) and left (Hos) eye and vertical position of right (Vod) and left (Vos) eye. For horizontal traces down is left and for vertical traces down is down. The eye movement during a blink is indicated by B. The dotted line indicates straight ahead horizontal position. Patient is looking from 15° left to 15° right and then back to straight ahead position. DBN is continuously present but almost disappears when the patient looks straight ahead again. Also note the rebound nystagmus when the patient changes fixation from right to straight ahead.
was abnormal. Compared to the control group, mean SPEM gain in all directions of the FCMTE patients also was normal except for downward pursuit. This selective impairment of SPEM gain is not expected from medication but is consistent with the DBN and the Purkinje cell pathology causing the upward drift of the eyes. Only two SCA6 patients (SCA6-1 and SCA6-3) used a low-dose benzodiazepine that to some extent may have affected the gain of SPEM, the gain of saccades and the saccade latency (Wang et al., 2005). However, oculomotor abnormalities were also found in the other four SCA6 patients.

Except for the downward direction, compared to the normal control group, hypometria of saccades was present in both the SCA6 and the FCMTE group, which in general is symptomatic of cerebellar cortical dysfunction (Chubb and Fuchs, 1982; Robinson and Fuchs, 2001). The absence of hypometria of saccades in the downward direction is compatible with the slow upward drift inducing the DBN as well as an overshoot of downward saccades. Hypometria of saccades (Rottach et al., 1996; Bhidayasiri et al., 2001) as well as positionally induced DBN has been reported also in other neurodegenerative disorders including multiple system atrophy with dominant cerebellar features (MSA-C) (Wessel et al., 1998; Bertholon et al., 2002). In contrast to our SCA6 group and MSA-C patients reported in the literature, slowing of saccades in our FCMTE group could not be demonstrated suggesting that pathology of burst neurons in the reticular formation of the brain stem in FCMTE seems unlikely.

In contrast to these similarities between the SCA6 and FCMTE group, the FCMTE patients show a significantly increased amount of express saccades compared with the control group and the SCA6 group, during the pro-saccade task. This indicates in FCMTE patients a disturbed suppression of visually guided saccades and may originate from a dysfunction within the fronto-striatal pathways, but also through projections to the brainstem reticular formation subsequently causing disinhibition of saccades. This is a remarkable finding since in healthy subjects the amount of express saccades is normally significantly increased only when the gap paradigm is being used, i.e. a 200 ms dark interval is present between the disappearance of the fixation target and the appearance of the peripheral target (Fischer and Ramsperger, 1984, 1986). Considering the current finding during the pro-saccade paradigm, it is interesting to extend the study of saccade latencies with the gap paradigm in the FCMTE group.

Lesions of the dorsolateral prefrontal cortex (DLPFC) are likely to reduce the ability of subjects to suppress reflexive pro-saccades (Guitton et al., 1985; Ploner et al., 2005). Munoz and Everling (2004) have demonstrated that frontal and prefrontal areas (DPLFC) control the fixation behaviour via projections to the intermediate layers of the superior colliculus inferior (SCI). Fixation neurons are located in the SCI that are tonically active during visual fixation and pause during saccades. Drop in fixation activity of these cells leads to a disinhibition of the saccadic system through projections to the brainstem reticular formation. The authors hypothesize that dysfunction of prefrontal cortex and/or substantia nigra pars reticulate (SNr) influence the ability to recruit saccadic suppression signals, making it more difficult to inhibit reflexive saccades. A significantly increased amount of express saccades also has been demonstrated in patients with Parkinson’s disease (Roll et al., 1996; Chan et al., 2005; Gurvich et al., 2007). In these studies consistency is suggested with dysfunction within fronto-striatal and prefrontal-collicular pathways influencing suppression and selection of eye movements. Alternatively, the abnormal occurrence of express saccades in FCMTE patients also can be hypothesized to find its origin in abnormally reduced cerebellar inhibition of fixation neurons in the SCI (Fischer et al., 1995; Biscaldi et al., 1996). In SCA6 patients with comparable cerebellar pathology, however, no excessive amounts of express saccades have been demonstrated.

In conclusion, the current study supports the pathologic similarities in FCMTE and SCA6 patients with mainly cerebellar abnormalities. The additional increase of the amount of express saccades in FCMTE, in contrast to SCA6 patients, supports the cortical functional changes in FCMTE.

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References


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