Oculomotor Testing in the Differential Diagnosis of Degenerative Ataxic Disorders

Karl Wessel, MD; Carsten Moschner, MD; Klaus-Peter Wandinger, MD; Deflef Kömpf, MD; Wolfgang Heide, MD

Background: Oculomotor abnormalities have been reported in patients with degenerative ataxic disorders.

Objective: To assess the diagnostic sensitivity and specificity of oculomotor deficits in patients with Friedreich ataxia (FA), cerebellar atrophy (CA), and olivopontocerebellar atrophy (OPCA).

Setting: Neurology clinic at a university hospital in Lübeck, Germany.

Patients: Seven patients with FA, 9 with CA, and 10 with OPCA were studied. These patients were selected from an ongoing follow-up study.

Main Outcome Measures: Eye movements were recorded by electro-oculography; an extensive battery of quantitative tests was used.

Results: A proven CAG repeat expansion on chromosome 6 or 14 was significantly associated with reduced saccadic eye velocity and vertical gaze palsy (P < .001, Mann-Whitney U test). All 6 patients with OPCA and slow saccades had an autosomal-dominant inheritance; 4 of them were proved to have spinocerebellar atrophy type 1. In 9 of these patients (4 with FA, 1 with CA, and 4 with OPCA), the genetic defect could not be identified. Saccadic dysmetria, impairment of smooth pursuit and optokinetic nystagmus, deficient suppression of the vestibulo-ocular reflex by either visual or otolith input, and pathological nystagmus were attributed to degenerative lesions in different parts of the cerebellum. However, these symptoms failed to clearly distinguish between the different groups of patients, whereas decreased vestibulo-ocular reflex gain, slow saccades, and vertical gaze palsy pointed to an extracerebellar manifestation of the degenerative disease, occurring only in patients with OPCA and FA.

Conclusions: In this prospective study, oculomotor disturbances were mainly related to cerebellar dysfunction. Only a few of them were caused by extracerebellar manifestations of the disease, such as slowing of saccades, which was characteristic for patients with OPCA of autosomal-dominant inheritance.

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As a result of recent advances in molecular genetics, the hereditary ataxic disorders can now be classified partly on the basis of the genotype of the family. The issue is complicated by the fact that 1 clinical subtype, eg, autosomal dominant cerebellar ataxia (ADCA) 1, includes cases with lesions on different genes, for example on chromosome 6p (spinocerebellar atrophy type 1 [SCA 1]), on chromosome 14q (SCA 3; Machado-Joseph disease), or on chromosome 12q (SCA 2). Furthermore, only about half of the cases with ADCA can now be classified on the basis of a neurogenetic analysis, because in the rest the gene locus is still unknown or at least speculative. On the other hand, cases with idiopathic cerebellar ataxia also belong to the clinical group of the degenerative ataxic disorders. Therefore, many patients with progressive cerebellar ataxia still have to undergo diagnosis based on medical history, clinical features, neurophysiological tests, and neuroradiological examination.

Several attempts have been made to determine whether there are specific oculomotor abnormalities in degenerative ataxic disorders; the results were somewhat controversial. Therefore, in this study, the sensitivity and specificity of oculomotor deficits in Friedreich ataxia (FA), cerebellar atrophy (CA), and olivopontocerebellar atrophy (OPCA) were compared by means of an extensive battery of quantitative tests. Although we were aware that OPCA represents a heterogeneous category, both genetically and clinically, and that its usefulness has been questioned, these 3 diagnostic cat-

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SUBJECTS AND METHODS

SUBJECTS

During standardized testing procedures, the eye movements of 26 patients who showed clinical and radiological signs of progressive cerebellar degeneration and 17 healthy subjects (8 female and 9 male; age [mean ± SD], 41.1 ± 17.6 years) were recorded by electro-oculography. All participants gave informed consent in accordance with the guidelines of the local ethics committee and showed a corrected visual acuity of at least 0.7 (20/30). On the basis of family history, repeated clinical examinations during a period of at least 3 years, and neuroradiological findings (computed tomography or magnetic resonance imaging), all patients matched the criteria for FA, pure CA, or OPCA (patients with predominant CA and additional extracerebellar findings).

The FA group included 7 patients (mean age, 39.3 years) with autosomal recessive inheritance. Four of the 7 patients had an unstable GAA trinucleotide expansion in the first X25 intron on chromosome 9q13.

Nine patients with CA (mean age, 51.8 years) showed the characteristic signs of a pure cerebellar lesion. Their cranial computed tomographic scans or magnetic resonance images demonstrated moderate to severe atrophy of the cerebellum but otherwise normal brain structures. In 3 patients the disease had an autosomal dominant inheritance; 1 of them had an unstable and expanded CAG trinucleotide repeat on chromosome 14q3. Nine patients with CA (mean age, 51.8 years) showed the characteristic signs of a pure cerebellar lesion. Their cranial computed tomographic scans or magnetic resonance images demonstrated moderate to severe atrophy of the cerebellum but otherwise normal brain structures. In 3 patients the disease had an autosomal dominant inheritance; 1 of them had an unstable and expanded CAG trinucleotide repeat on chromosome 14q13.

Ten patients (mean age, 43.2 years) were diagnosed as having OPCA; 8 cases had an autosomal dominant inheritance. Four of the latter cases had a CAG repeat expansion on chromosome 6p (SCA 1). Besides cerebellar ataxia and dysarthria, all patients had additional extracerebellar features, including vertical gaze palsy, extrapyramidal signs, spasticity, mild dementia, or autonomic failure.

Results

Mean latencies of primary visually guided saccades were significantly prolonged in all 3 patient groups (Table 1). The average peak velocity of primary saccades was significantly lower in the OPCA group than in the control group (Mann-Whitney U test; P < .05 for all OPCA cases; P < .001 for the 6 cases with OPCA of autosomal dominant inheritance). This difference was more prominent for centripetal saccades. In the OPCA group, slow saccades occurred in 50% of the patients with centripetal and in 60% with centripetal saccades. Figure 1, B, gives an example of markedly slowed saccades. In 5 of 6 patients with OPCA, slow horizontal saccades were accompanied by mild or moderate vertical gaze paresis, predominantly concerning upgaze, which was limited to eccentricity below 20° to 30°. Horizontal saccade velocity was slightly below the normal range in 2 patients with FA (Table 1).

The mode of inheritance or the proof of a repeat expansion had a significant influence only on saccade velocity in patients with OPCA. This has to be interpreted carefully because of the relatively small number of cases with either hereditary or sporadic disease in each of our 3 patient groups. All 6 patients with OPCA and slow saccades (see Table 1) had an autosomal dominant inheritance (ADCA); 4 of them were proved to have SCA 1. These 4 had the lowest peak velocities of horizontal saccades, ranging from 170° to 240° per second for amplitudes of 20°. Except for saccade velocity, there were no other differences in oculomotor variables between the 4 cases with SCA 1 and the whole patient group; there were also no differences between the 4 patients with FA with a proved GAA trinucleotide expansion and those in whom this mutation was not found. Because the mode of inheritance did not have any influence on all other oculomotor tests, we did not further subdivide patients according to neurogenetic criteria.

The mean (±SD) amplitude gain of primary saccades amounted to 0.95 ± 0.05 in the healthy control group, 0.92 ± 0.25 in patients with OPCA, 0.92 ± 0.10 in patients with CA, and 0.96 ± 0.19 in patients with FA. Although intergroup differences were not statistically sig-
To assess saccadic dysmetria, the amplitude gains of all primary saccades were calculated. Only primary saccades with an amplitude gain of less than 0.85 were defined as being hypometric and saccades with an amplitude gain of more than 1.05 as hypermetric. In an alternative procedure, we analyzed the frequency and direction of up to 3 corrective saccades. Possible first-, second-, and third-order corrective saccades directed toward the target step direction were classified as on saccades, and saccades directed in the opposite direction were classified as off saccades.

Pathological Nystagmus and Fixation Instability

The presence of spontaneous nystagmus was tested during rest with the subject's eyes closed and during active fixation of a real target in the center position. Gaze-evoked nystagmus was diagnosed if it occurred during eccentric fixation at ±10°, 20°, 30°, or 40° during a period of at least 10 seconds. Rebound nystagmus was assessed after the return to center position from 40° eccentric fixation. In addition, we measured the frequency of square-wave jerks during fixation of a stationary target.

Optokinetic Nystagmus and Smooth Pursuit

Optokinetic nystagmus (OKN) was tested by means of a pattern of vertical black and white stripes projected on a semispherical screen. The pattern was rotated in the horizontal plane with a constant velocity of ±30° or ±90° per second. The OKN gain was calculated on the basis of the maximum slow-phase velocity. During smooth-pursuit tests, subjects were instructed to track a laser dot that moved sinusoidally in the horizontal plane (frequency, 0.2 Hz; amplitude, ±20°). The mean velocity gain was calculated as the ratio of the cumulative change in eye position divided by the time needed for this change. To assess performance of the smooth pursuit without saccades, all segments with eye velocities of more than 35° per second were excluded.

To assess each subject's ability to compensate for a pursuit deficit by adequately sized "catch-up" saccades, a second so-called global tracking gain was measured, based on the total cumulative change in eye position including saccades and smooth-pursuit segments.

Vestibular Nystagmus

During tests of vestibulo-ocular reflex (VOR) function, the subject's chair was rotated around a vertical axis in the dark, first sinusoidally at 0.1 Hz with a peak velocity of ±90° per second, second after acceleration from zero velocity to a constant rotational chair velocity of 90° per second within 1 second, and third after deceleration from a constant velocity of 90° per second to zero within 1 second. During sinusoidal VOR stimulation, subjects were additionally asked to fixate a head-stationary target to measure the VOR fixation suppression (VOR fix). Generally, calculation of VOR gain was based on the ratio of the fastest VOR slow-phase velocity to the corresponding change of chair velocity. Additionally, the time constant (τ) of VOR, defined as the decay of 37% of maximum slow-phase velocity, was approximated to one third of the duration of prerotatory and postrotatory nystagmus while the head was kept in an upright position. To test VOR tilt suppression, subjects were asked to bend their heads 90° forward 4 seconds after the chair had stopped. The effect of this change in otolith input on VOR was estimated by comparing postrotatory VOR time constants with the head in an upright position and with the head tilted.

Normal ranges of quantitative measurements were given as the mean ± 2 SDs of the pooled corresponding measurements in healthy controls. We statistically compared results in different groups by means of the Mann-Whitney U test or the χ² test with a minimum level of significance of 5%.

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**Table 1. Saccadic Latency and Peak Velocity**

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>FA</th>
<th>CA</th>
<th>OPCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (target steps of 20°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means±SD latency, ms</td>
<td>205±22</td>
<td>325±88†</td>
<td>275±22†</td>
<td>269±37†</td>
</tr>
<tr>
<td>No. (%) of patients with increased latency (&gt;249 ms)</td>
<td>NA</td>
<td>6 (86)</td>
<td>6 (67)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Velocity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means±SD peak velocity of 20° saccades</td>
<td>368±38</td>
<td>349±76</td>
<td>385±48</td>
<td>321±134†</td>
</tr>
<tr>
<td>Means±SD peak velocity of 40° saccades</td>
<td>476±57</td>
<td>421±98</td>
<td>474±64</td>
<td>369±137†</td>
</tr>
<tr>
<td>No. (%) of patients with slow centripetal saccades (&lt;304%/s)</td>
<td>NA</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>No. (%) of patients with slow centrifugal saccades (&lt;287%/s)</td>
<td>NA</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>

* FA indicates Friedreich ataxia; CA, cerebellar atrophy; OPCA, olivopontocerebellar atrophy; and NA, not applicable.
† Significantly prolonged (Mann-Whitney U test; P<.05).
‡ Saccades in response to target steps of 20°. Percentages were identical for steps of 40°.

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centrifugal direction (Table 2). In these patients, the amount of dysmetria was dependent on relative initial eye position.

A first corrective saccade in off-direction, often followed by a second or more corrective saccades, characterizing the typical hypermetric pattern, was present in all patient groups. The average frequency of this pattern ranged from 12% in patients with CA to 25% in patients with FA. Hypometric patterns of at least 2 corrective saccades in on-direction were found in 6% of all saccadic responses made by patients with CA and in 3% of those made by patients with OPCA. Patients with FA, however, generally used only 1 on-saccade to correct for hypometria of primary saccades.

Abnormalities of visual fixation were found in each group of patients. Spontaneous nystagmus during steady fixation was generally restricted to the vertical plane, presenting as downbeat nystagmus in 1 patient in each group and as upbeat nystagmus in 1 patient with CA. One patient with FA showed a typical periodic alternating nystagmus. The percentage of cases with gaze-evoked nystagmus ranged between 33% in the CA group and 50% in the OPCA group. The occurrence of rebound nystagmus was restricted to patients who showed gaze-evoked nystagmus during eccentric fixation. It was found in 2 CA patients, 1 with OPCA and 1 with FA. Repeated square-wave jerks were more common in FA (57%) than in OPCA (10%) (P<.05, χ² test); in the CA group they occurred in 33% of the cases.

The averaged velocity gain of OKN and pure smooth pursuit was markedly impaired in all patient groups (Figure 2 and Figure 3, A). Impairment of OKN was generally more obvious during fast stimulation with 90° per second than during slower stimulation with 30° per second (Figure 2). Although the averaged OKN gain tended to be higher in FA than in CA or OPCA, the relative number of patients with abnormal low OKN gain was about the same in all 3 groups of patients (Table 3). Patients’ average gain for pure smooth pursuit was 0.77 in the CA and OPCA groups and 0.79 in the FA group (Figure 3, A). Because of the effect of compensatory catch-up saccades, the so-called global tracking gain in the FA and CA groups showed normal values of 0.96 and 0.98 (Figure 3, B). Only in OPCA, the global tracking gain of 0.88 remained below the normal limit. The inability of patients with OPCA to compensate for their low pursuit gain by using catch-up saccades was related to the slowing of saccades, as mean peak saccadic velocities correlated positively with their global tracking gain (multiple regression analysis, P<.05).

Average gain of rotatory VOR was increased in CA (Mann-Whitney U test; P<.05), whereas mean VOR gain in patients with OPCA and FA was not significantly different from that in controls (Figure 4, A). This was also true for rotatory VOR gain with ramp stimuli. Standard deviations were much higher in patients with OPCA and FA than in controls, indicating abnormally low or high VOR gain in single cases.
About 40% of patients with FA and OPCA but none of the patients with CA showed an abnormally low VOR gain (Table 3). An abnormal increase of VOR gain occurred in 44% in the CA group, in 14% in the FA group, and in 22% in the OPCA group.

Fixation suppression of the VOR during sinusoidal rotation was markedly impaired in all 3 patient groups. Half of the patients in each group were unable to suppress VOR gain (Table 3). In the CA group, the average VOR fix gain was significantly increased (Mann-Whitney test; P<.05), and a similar statistical trend was found in patients with FA and CA (P<.1) (Figure 4, B).

Measurements of the mean time constant of the postrotatory VOR with the head in upright position disclosed no significant differences (Figure 4, C). In controls, head tilt led to a significant reduction of the postrotatory VOR time constant (Wilcoxon rank test; P<.05). However, none of the patient groups demonstrated a significant effect of head tilt on the VOR time constant (Figure 4, D), ie, the otolith input did not significantly affect the discharge (“dumping”) of the velocity storage mechanism of the VOR. 25,26 Evaluation of individual data showed that in only 1 patient of each group head tilt reduced the time constant to less than 70% of the initial
hitory projections to neurons in the underlying fasti-
gial nuclei. In summary, saccadic dysmetria, impair-
ment of smooth pursuit and OKN, deficient suppression of the VOR either by visual or otolith input, and pathological nystagmus can be attributed to degenerative lesions in different parts of the cerebellum.

Other oculomotor findings reported in this study are, at least in part, the result of an extracerebellar manifestation of the degenerative disease. Pathological decreased VOR gain measurements were exclusively found in patients with FA or OPCA. Decreased VOR gain might be caused by retrograde degeneration of neurons in the vestibular nuclei resulting from the disconnection of their projections to the cerebellum.37

The prominent slowing of saccades, mainly found in OPCA, is likely caused by degenerative lesions outside the cerebellum. Slowing of saccades in patients presenting with hereditary as well as sporadic OPCA has previously been reported; however, the underlying defect has not yet been clearly identified because of the lack of neuropathological data. In at least some patients with OPCA who have slow saccades, the paramedian pontine reticular formation, site of the “saccadic burst generator,” was found to be relatively well preserved in post-mortem studies,13,38 and it has been assumed that slow saccades in these cases were caused by atrophy of rostral midbrain structures or the substantia nigra.59

Abnormally frequent square-wave jerks were present in all 3 patient groups, although they were most frequent in FA.17 However, ocular flutter and frequent square-wave jerks are not specific for cerebellar degeneration; they also occur with progressive supranuclear palsy as well as other cerebral lesions and neurological disorders,10 and it has been argued that their presence in patients with cerebellar degeneration is the result of accompanying brainstem lesions involving certain neurons of the saccadic generator.

ROLE OF OCULOMOTOR FINDINGS IN THE DIFFERENTIAL DIAGNOSIS

Some oculomotor signs of (para)flocular dysfunction occur in almost all cases with CA but also with FA and OPCA during the course of the disease. Accordingly, gain of OKN and pure smooth pursuit were markedly reduced in most patients; pathological nystagmus (mainly gaze-evoked nystagmus) tended to occur less frequently. The number of patients with abnormal VOR suppression by visual fixation ranged from 50% in FA to 77% in CA. Generally, oculomotor findings related to a flocular lesion are commonly found in ataxic patients irrespective of whether they are classified as having FA, CA, or OPCA. Our study did not clearly support the previous suggestion that flocular function is less affected in FA than in conditions such as CA or OPCA.21

Previous studies20,21 failed to find distinct patterns of saccadic dysmetria in different degenerative ataxia syndromes. We reevaluated their results, including an analysis of corrective saccade patterns and a more detailed subanalysis of factors such as right-left asymmetry and effect of relative initial eye position. We found a significantly greater number of patients with pure hypometric pri-
mary saccades in OPCA. On the other hand, hypermetria was most common in FA. However, none of the patient groups showed an exclusive pattern of dysmetria, irrespective of whether primary or corrective saccades were analyzed. Instead, various combinations of hypometria and hypermetria occurred in all patient groups. Separate analysis of centrifugal or centripetal saccades was found to be useful in identifying patients with mild dysmetria, where hypermetria became significant only in centripetal saccades or hypometria only in centrifugal saccades. This influence of initial eye position on saccadic dysmetria has previously been described in patients with acute or subacute cerebellar lesions. In conclusion, measurements of saccade accuracy clearly demonstrated cerebellar dysfunction in the majority of the patients in this study but failed to distinguish between different patient groups.

So far, saccadic slowing has been reported in ataxic syndromes with additional brainstem involvement (eg, OPCA). On the other hand, saccade velocity has been found to be unaffected in CA and FA. Only 1 study, by Fetter et al, found slowing of saccades to be equally distributed among patients with the clinical diagnosis of CA and OPCA. Wadia originally proposed that OPCA with extremely slow saccades was a homogeneous entity with autosomal dominant inheritance (eg, SCA 2), but later studies also found slowing of saccades with sporadic or autosomal recessively inherited OPCA. In our study, 6 of 10 patients with OPCA showed slow saccades. All of them had autosomal dominant inheritance, genetically proven as SCA 1 in 4 cases. The reduction of saccadic peak velocity was less severe than in the cases reported by Wadia. As expected, slowing also affected small catch-up saccades during smooth pursuit, resulting in decreased global tracking gain in these patients with OPCA. Saccade velocity was also mildly decreased in 2 patients with FA, whereas it remained normal in all patients with CA. Thus, this study generally supports the view that analysis of saccade velocity provides a useful tool to distinguish between CA and OPCA. Slowing of saccades seems to be a marker for autosomal dominant inheritance, occurring also in cases with SCA 1.

According to Moschner et al, VOR function tests can provide further differential clues. Increased VOR gain has typically been found in patients with a pure cerebellar lesion, but not in FA or OPCA. On the other hand, decreased VOR gain points to an additional extracerebellar lesion in the brainstem or the peripheral vestibular system. Consistent with this, decreased VOR gain has been observed in patients with FA and, to a lesser extent, in OPCA. In this study, a comparative examination of VOR tilt suppression was included for the first time. In contrast to findings in normal controls, the time constant of postrotatory VOR was unaffected by head tilt in most patients. Thus, the rapid discharge (dumping) of the eye velocity storage mechanism by otolith input was severely impaired. This pathological feature was found equally in all 3 patient groups, being a sensitive sign of cerebellar degeneration, but not contributing to the differential diagnosis.

In conclusion, our study in patients with different degenerative ataxic diseases classified as FA, CA, and OPCA showed that most oculomotor disturbances are sensitive signs of cerebellar dysfunction. Among these, saccadic dysmetria and impaired tilt suppression of VOR indicate dysfunction of the posterior and inferior cerebellar vermis with high topodiagnostic specificity. Deficits of smooth pursuit or OKN gain or impaired fixation suppression of VOR are sensitive signs of the degenerative cerebellar disease, but of no topodiagnostic specificity. Some other oculomotor findings are specifically caused by extracerebellar manifestations of the degenerative disease, such as abnormally low VOR gain and slowing of saccades. All patients with slow saccades showed autosomal dominant inheritance (ADCA), genetically proved as SCA 1 in 4 cases. Thus, this study generally supports the view that measurements of saccade velocity and VOR gain are a useful tool to distinguish between CA and OPCA. Slowing of saccades seems to be a relative characteristic finding for cases with ADCA, but it is not a specific finding for the SCA 2 subtype.

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Reprints: Wolfgang Heide, MD, Department of Neurology, Medical University, Ratzeburger Allee 160, D-23538 Luebeck, Germany (e-mail: heide_w@neuro.mu-luebeck.de).

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