

SHORT REPORT

Saccade velocity in idiopathic and autosomal dominant cerebellar ataxia

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Abstract

Slow saccades are often found in degenerative ataxia. Experimental studies have shown that horizontal saccades are generated in the paramedian pontine reticular formation and that lesions in this area produce slow saccades. Based on these findings, saccade slowing should be a frequent feature of olivopontocerebellar atrophy, a type of cerebellar degeneration with prominent involvement of the pons. To test this hypothesis, saccade velocity was measured in 31 patients with autosomal dominant cerebellar ataxia (ADCA) and 17 patients with idiopathic cerebellar ataxia (IDCA). Saccade velocity was reduced in most patients with ADCA whereas it was normal in IDCA although olivopontocerebellar atrophy occurred in both groups. Saccade velocities correlated with pontine size in ADCA but not in IDCA. The data disprove the hypothesis that saccadic slowing is a clinical hallmark of olivopontocerebellar atrophy. Instead, only patients with ADCA and morphological features of olivopontocerebellar atrophy have slow saccades.

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Keywords: saccade velocity; idiopathic cerebellar ataxia; autosomal dominant cerebellar ataxia; olivopontocerebellar atrophy

Slow saccades are often seen in patients with degenerative ataxia. Experimental studies in primates show that horizontal saccades are generated within the parapontine reticular formation.^{1,2} Postmortem studies disclosed degeneration of the paramedian pontine reticular formation in patients with ataxia with slow saccades.^{3,4} Based on these findings, saccade slowing should be a frequent feature in olivopontocerebellar atrophy, a type of cerebellar degeneration with prominent involvement of the pons, whereas saccade velocity should be normal in patients with pure cortical cerebellar atrophy. Both types of degeneration are found in dominantly inherited ataxia (autosomal dominant cerebellar ataxia, ADCA) and in late onset sporadic ataxia of unknown cause (idiopathic cerebellar ataxia, IDCA). Modern clinical classifications of ataxia further distinguish between ADCA with additional non-cerebellar symptoms (ADCA-I) and a pure cerebellar type of ADCA (ADCA-III).⁵ Genetic heterogeneity of ADCA-I has recently been shown with disease loci assigned to chromosome 6p (spinocerebellar ataxia 1, SCA1), 12q (SCA2), and 14q (SCA3).⁶⁻¹⁰ Similarly, IDCA is subdivided into a type with additional non-cerebellar symptoms (IDCA-P) and a pure cerebellar type (IDCA-C).¹¹ In vivo morphometric studies using MRI have shown that ADCA-I and IDCA-P are often associated with olivopontocerebellar atrophy, whereas patients with ADCA-III or IDCA-C usually have imaging findings compatible with cortical cerebellar atrophy.¹²

To test the hypothesis that olivopontocerebellar atrophy is associated with saccadic slowing we measured saccade velocity in 31 patients with ADCA and 17 patients with IDCA and evaluated the MRI of these patients to determine whether they had olivopontocerebellar atrophy or pure cortical cerebellar atrophy.

Patients and methods

We studied 48 patients with ADCA or IDCA and 30 age and sex matched healthy control persons (mean age (SD) 47.2 (16.5) years). The table gives a summary of the patient data. All diagnoses were made after exclusion of possible symptomatic causes (alcoholism, other toxic causes, malignancy, hypothyroidism,

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Clinical characteristics and neuropathological features

| | IDCA-C (n = 7) | IDCA-P (n = 10) | ADCA-III (n = 11) | ADCA-I (n = 20) |
|--|-------------------|--------------------|----------------------|--------------------|
| Age (y) (mean (SD)) | 53.7 (6.4) | 57.7 (9.1) | 48.6 (16.4) | 44.3 (15.5) |
| Frequency of neuropathological features: | | | | |
| Slow saccades (%) | 14.3 | 0 | 9.1 | 60 |
| CCA (%) | 57.1 | 10.0 | 81.9 | 20 |
| OPCA (%) | 0 | 80.0 | 0 | 75 |
| Atypical (%) | 42.9 | 10.0 | 18.2 | 5 |
| Frequency of extracerebellar symptoms (%): | | | | |
| Gaze palsy | 0 | 0 | 0 | 45 |
| Dementia | 0 | 0 | 0 | 25 |
| Pyramidal signs | 0 | 90 | 0 | 50 |
| Basal ganglia symptoms | 0 | 80 | 0 | 25 |
| Amyotrophy | 0 | 0 | 0 | 20 |
| Loss of proprioception | 0 | 10 | 0 | 60 |
| Bladder dysfunction | 0 | 80 | 0 | 30 |
| Orthostatic hypotension | 0 | 60 | 0 | 0 |

CCA = cortical cerebellar atrophy; OPCA = olivopontocerebellar atrophy.

vitamin deficiency, inflammatory or vascular causes) using the following criteria:

Autosomal dominant cerebellar ataxia (ADCA; n = 31)

(1) Progressive, otherwise unexplained ataxia; (2) autosomal dominant inheritance. Families with ADCA were further subdivided into families with a pure cerebellar syndrome (ADCA-III, $n = 11$, mean age (SD) 48.6 (16.4) years) and families with additional non-cerebellar features such as optic atrophy, ophthalmoplegia, dementia, basal ganglia dysfunction, and amyotrophy (ADCA-I, $n = 20$, mean age (SD) 44.3 (15.5) years).⁵

Molecular genetic tests for SCA1, SCA2, and SCA3 were performed in all patients with ADCA as described elsewhere.⁶⁻¹⁰ The SCA1 mutation was identified in a single patient, whereas SCA2 was found in five patients and SCA3 in four.

Idiopathic cerebellar ataxia (IDCA; n = 17)

(1) Progressive, otherwise unexplained ataxia with disease onset after the age of 25 years; (2) family history without evidence of heredity or consanguinity of parents. Patients with IDCA were further subdivided into patients with a pure cerebellar syndrome (IDCA-C, $n = 7$, mean age (SD) 53.7 (6.4) years) and patients with additional non-cerebellar features such as parkinsonism, bladder dysfunction, dysphagia, spasticity, or orthostatic hypotension (IDCA-P, $n = 10$, mean age (SD) 57.7 (9.1) years). Patients with a disease duration of less than four years were excluded from this study.¹¹

For eye movement evaluation, normometric horizontal saccades were recorded by DC electrooculography (quasi-infinite time constant) using silver-silver chloride electrodes. Data were documented on strip charts. The measurement was done manually and taken from position records. Mean horizontal saccade velocity ($^{\circ}/s$) was calculated for 20 $^{\circ}$ horizontal saccades made to single light targets (average of four saccades, to the right and left, centrifugal and centripetal). Normal values were defined as the average control value ± 3 SD.

Brain MRI was performed with a superconducting system operating at 1.5 T field strength (Magnetom, Siemens AG, Erlangen, Germany) with a head coil of 30 cm diameter. Data were acquired and displayed on a 256 \times 256 matrix. A standard examination program was used with sagittal and axial T1 weighted images without gap (spin echo, TR = 600 ms, TE = 22 ms, slice thickness = 4 mm, two averages). The first axial image was located at the level of the dens, the last image apical to the lateral ventricles.

For quantitative evaluation we used an image analyser and a computerised interpretation program. For exact delineation of tissue areas the individual tissue signal intensity and the CSF signal intensity were determined so that within a region of interest all pixels with tissue signal intensity could be summed.^{12,13} The following areas were measured: the *basis pontis* was delineated by hand as an elliptic structure in the midsagittal slice with a dorsal border corre-

sponding to the medial lemniscus; the *cerebellar vermis* on the midsagittal plane; the *cerebellar hemispheres* on the first parasagittal plane lateral to the midsagittal plane, the *medulla oblongata* on the axial plane at the level of the inferior olives. The maximum diameter of the *middle cerebellar peduncle* was measured on an axial plane.

Results are given as pixel counts (basis pontis, cerebellar vermis, and hemispheres), mm (middle cerebellar peduncle), or mm² (medulla oblongata). To compensate for individual variations of head size we related the data for basis pontis, cerebellar vermis, and hemispheres to the total area of the posterior fossa (pixel \times 10 000/ pixel of the posterior fossa).^{12,13} The normal range was defined as the mean of the control group ± 2 SD. Two main patterns of atrophy were defined following classic neuropathological descriptions:¹²

Cortical cerebellar atrophy—(1) Pathological value for cerebellar vermis or hemispheres (2) No additional pathological values except for the fourth ventricle.

Olivopontocerebellar atrophy—(1) Pathological value for the cerebellar vermis or hemispheres. (2) At least two pathological values within the following anatomical structures: basis pontis, middle cerebellar peduncle, medulla oblongata.

Patterns of atrophy that did not fall into one of these categories were designated as *atypical* patterns.

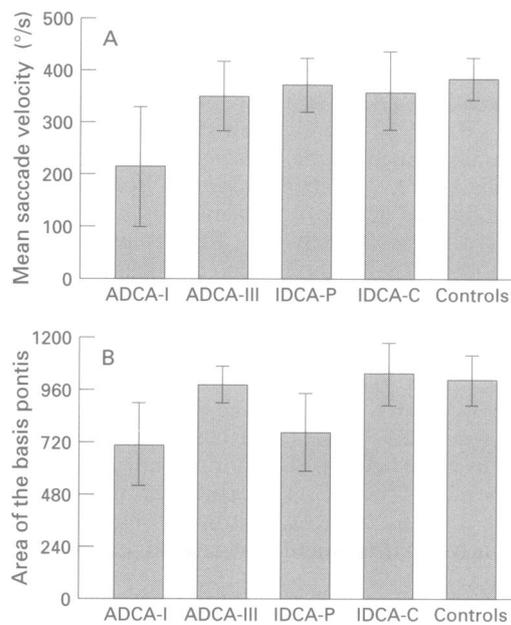
One way analysis of variance (ANOVA) with the fixed factor group was used to statistically analyse the results of saccade velocity and pontine size measurements. Differences were considered significant at $P < 0.05$. Post hoc analysis was done using the Tukey test. For correlation studies we used the Pearson correlation coefficient (r).

Results

There were highly significant differences between the groups with respect to both, saccadic velocity ($F(17, 174)$, $P < 0.0001$) and pontine size ($F(16, 457)$, $P < 0.0001$). Mean saccade velocity was significantly reduced in ADCA-I compared with controls ($P < 0.0001$) and with all other patient groups ($P < 0.0001$). Mean saccade velocities of the other patient groups were the same as that of the control group (figure, A). By contrast, pontine size was significantly reduced in both ADCA-I ($P < 0.0001$) and IDCA-P ($P < 0.0001$), but not in the other patient groups (figure, B). For the individual data, 60% of the patients with ADCA-I, but only one patient with IDCA-C and one with ADCA-III, had slow saccades. Saccade slowing in these two patients was mild (saccade velocity $> 200^{\circ}/s$) compared with patients with ADCA-I (25% had saccade velocities $< 100^{\circ}/s$). The patient with SCA1 and all patients with SCA2 had slow saccades, whereas saccade velocity was normal in three of four patients with SCA3. No patient with IDCA-P had slow saccades (table).

The morphological criteria for olivopontocerebellar atrophy were fulfilled in most patients with ADCA-I (75%) and patients with

Mean saccade velocity ($^{\circ}/s$) (A) and area of the basis pontis (B) in ADCA-I ($n = 20$), ADCA-III ($n = 11$), IDCA-P ($n = 10$), IDCA-C ($n = 7$), and controls ($n = 30$). The area of the basis pontis was measured planimetrically on midsagittal MRI. For statistical evaluation see results. ADCA = autosomal dominant cerebellar ataxia; IDCA = idiopathic cerebellar ataxia.



IDCA-P (80%). All patients with SCA2, one patient with SCA1, and two patients with SCA3 presented with olivopontocerebellar atrophy. By contrast, most patients with ADCA-III (81.9%) and IDCA-C (57.1%) had cortical cerebellar atrophy (table). In a minority of patients we found atypical patterns of atrophy.

To further study the relation between saccade velocity and pontine size we correlated saccade velocity and pontine size in ADCA and IDCA. Whereas both variables were positively correlated in ADCA ($r = 0.659$) there was no correlation in IDCA ($r = -0.056$).

Discussion

Saccades are generated by burst neurons in the paramedian pontine reticular formation, the final premotor area for all types of rapid eye movements including quick phases of vestibuloocular and optokinetic reflexes.¹² Saccade slowing has been reported in neurodegenerative disorders such as Huntington's chorea,¹⁴ progressive supranuclear palsy,¹⁵ and olivopontocerebellar atrophy,¹⁶⁻²⁰ a type of cerebellar degeneration primarily involving the pons.

We found saccade slowing in most patients with ADCA-I but not in patients with IDCA-P despite olivopontocerebellar atrophy with severe pontine atrophy in both conditions. Saccade velocity and pontine size were positively correlated in ADCA, whereas there was no such relation in IDCA. These findings disprove the opinion that saccade slowing is a characteristic sign of olivopontocerebellar atrophy and suggest that pontine degeneration involves the paramedian pontine reticular formation in ADCA-I but not in IDCA. Postmortem studies in Indian families with ataxia and slow saccades have shown degeneration of the paramedian pontine reticular formation.³

Recently, it has been found that saccade velocity is severely reduced in SCA2 whereas it is usually normal in SCA3 and intermediate in SCA1.²¹ The underlying genotype in ADCA-I

was defined in 10 patients: all patients with SCA2 and one patient with SCA1 showed considerable saccade slowing, whereas three of four patients with SCA3 had normal saccades.

Apart from differential involvement of the saccadic system in ADCA and IDCA there are additional neuropathological and clinical differences between these conditions. For example, glial intracytoplasmatic inclusion bodies are found in the brains of patients with IDCA-P but are not a typical feature of ADCA.²² These differences in conjunction with the present findings indicate that ADCA and IDCA are distinct disorders even if they share certain macroscopic neuropathological features which are usually subsumed under the label of olivopontocerebellar atrophy.

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