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Saccades in Huntington's disease: Slowing and dysmetria

A.G. Lasker, MS; D.S. Zee, MD; T.C. Hain, MD; S.E. Folstein, MD; and H.S. Singer, MD

Article abstract—Eye movements were recorded from 20 mildly affected patients with Huntington's disease (HD) who were divided into two groups, 10 patients with onset of symptoms before age 30 and 10 with onset of symptoms after age 30. In the younger onset group (HD < 30), peak saccade velocities were low (<255 deg/sec for 20-deg saccades) in six of the 10 patients, whereas none of the 10 patients in the older onset group (HD > 30) had peak saccade velocities lower than 300 deg/sec. Latencies for volitional saccades were greater than normal in the HD > 30 group, but were normal for the HD < 30 group. The ability to maintain steady fixation in the face of a distracting visual stimulus was decreased, to the same degree, in both groups of HD patients. In addition, 70% of the HD < 30 group had an affected father, while 70% of the HD > 30 group had an affected mother. These findings suggest that the pathophysiology of the slow saccades, initiation deficit, and excessive distractibility in HD are different.

Methods. The subjects sat in front of an arc (radius, 123 cm) that contained an array of light-emitting diodes (LEDs), located at 0 and at right and left 10, 20, and 30 degrees. Head movements were restricted by the use of a chin rest. Patients were in complete darkness except for the LEDs. Movements of the right eye were recorded with direct-current electro-oculography (EOG). The analog signals were low-pass filtered (40 Hz), digitized at a rate of 100 Hz on a PDP 11/73 microcomputer, and stored on magnetic tape for off-line analysis.

Testing paradigms. Saccades were elicited in three paradigms. For each paradigm the same cue signaled the time to initiate a saccade. The cue consisted of turning off the center fixation LED coupled with a nonlocalizable 100-msec auditory beep. In each paradigm, the trial began with fixation of an LED located at 0 degrees. At a random time (1,400 to 2,400 msec), direction (right or left), and amplitude (10, 20, or 30 deg), one of the peripherally located LEDs was illuminated. For each testing paradigm, 60 trials were elicited.

Paradigm NS (novel stimulus). The peripheral LED was illuminated, and simultaneously, the central fixation LED was extinguished and the beep sounded. This paradigm tested the ability of the patient to initiate saccades to a suddenly appearing visual stimulus.

Paradigm CS (continuous stimulus). The peripheral LED was illuminated, but the patient was instructed not to make a saccade to it until the cue occurred (1,000 to 1,800 msec). This paradigm tested the ability of a patient both to suppress a reflexive saccade to a suddenly appearing visual target and to make a saccade on command to a continuously visible target.

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Figure 1. Peak velocity for 20-degree saccades of the three groups of subjects for all three paradigms. \( n = 18 \) for the comparison group (C); \( n = 6 \) for each of the HD groups, HD < 30 (H₁) and HD > 30 (H₂). NS = novel stimulus; CS = continuous stimulus; and RS = remembered stimulus. Bars reflect the standard deviation for each group. H₁ shows slow saccades for all paradigms compared with either the comparison group or H₂.

Paradigm RS (remembered stimulus). This paradigm was identical to paradigm CS above, except that the peripheral LED was extinguished after it had been illuminated for 1,500 msec. Then, 1,000 to 2,000 msec later, the cue occurred. This paradigm tested the ability of a patient to both suppress a saccade to a suddenly appearing visual target and to make a saccade on command to the remembered location of a visual target.

Data analysis. We determined maximum saccade velocities, saccade amplitudes, and saccade latencies, using an interactive computer program that displayed each trial for review by the experimenter. The accuracy of the eye movement was expressed as a percentage, using the ratio of the amplitude of the initial eye movement to the amplitude of the target displacement and multiplying by 100. Each trial was individually calibrated to eliminate inaccuracy due to fluctuation in the amplitude of the corneoretinal potential. Peak velocity of saccades were determined by computer using a digital differentiator with a 0- to 40-Hz bandwidth. We determined latencies from the time of cue onset to the time of saccade initiation. All statistical comparisons were based on the Student’s t test.

Clinical data. We studied 20 patients with HD and a comparison group of 18 subjects. All the HD patients were minimally to mildly affected with respect to both cognition and motor performance. The HD population was divided into two groups based on the patient’s age at the onset of symptoms. These symptoms were determined by interviews with a family member living with the patient at the time of onset. Using this family informant, we documented the year of onset of any movement disorder. To increase the accuracy of estimating onset, we used a semistructured interview that helped the informant put symptoms in the context of documented life events.

The younger onset group (HD < 30) consisted of 10 patients (mean age at onset 22.8 yrs ± 4.8 yrs [SD]; range, 16 to 29 yrs). The older onset group (HD > 30) also consisted of 10 patients (mean age at onset 50.6 yrs ± 8.9 yrs [SD]; range, 36 to 63 yrs). The durations of illness for the two groups were similar; for the younger group, 4.5 yrs ± 4.3 yrs (SD), range 1 to 15 years; and for the older group, 3.1 yrs ± 2.9 yrs (SD), range 1 to 10 yrs. At the time of recording, the age range of the younger onset group was 17 to 36 years, while the range of the older onset group was 36 to 65 years. Seventy percent of the younger onset group had an affected father, while 70% of the older onset group had an affected mother. The degree of severity of HD in both patient groups was also comparable. There were no statistically significant differences in the Quantitative Neurological Examination (QNE), Activities of Daily Living (ADL), or the Mini-Mental Status Examination. Three of the patients with HD were taking phenothiazine medication,
Results. Figures 1, 2, and 3 compare the peak velocities, latencies, and accuracies of 20-degree saccades for the three groups for each of the three paradigms. The HD groups consisted of six patients each, for whom we had data for all three paradigms. The table summarizes the means and standard deviations for all 20 HD patients in whom data for just the NS and CS paradigms were available.

Peak velocity. The mean value for peak saccade velocity progressively decreased from paradigm NS to RS for each group (figure 1). However, for all paradigms, HD patients who acquired their symptoms prior to the age of 30 (HD < 30 (H₁)) had significantly lower (p < 0.01) peak velocities than those of the older HD patients or the comparison group. The patients who acquired their symptoms after the age of 30 (HD > 30 or H₂) had peak velocities that did not differ significantly from the comparison group.

Four were taking tricyclic antidepressants, and one was taking baclofen. The number of HD patients taking medications was divided equally between the two age groups.

The comparison group consisted of 10 normal individuals, four subjects with developmental dyslexia, and four patients with Gilles de la Tourette’s syndrome, two of whom were taking neuroleptic medications. The mean age of the comparison group was 36.2 years ± 18.6 years (SD), with a range of 14 to 69 years.

Table. Velocity, latency, and accuracy of all HD patients (n = 20) and the comparison group in the novel stimulus (NS) and continuous stimulus (CS) paradigms

<table>
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<tr>
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<th>HD &lt; 30*</th>
<th>HD &gt; 30*</th>
<th>Comparison†</th>
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<tr>
<td>Velocity</td>
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<tr>
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<td>420</td>
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<tr>
<td>SD</td>
<td>89</td>
<td>51</td>
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<td>47</td>
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<td>Accuracy</td>
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<tr>
<td>SD</td>
<td>12.0</td>
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<td>3.9</td>
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* (n = 10), † (n = 18).

Figure 3. Accuracy for all three groups of subjects for whom data were available for all three paradigms. n = 18 for the comparison group (C); n = 6 for each of the HD groups, HD < 30 (H₁) and HD > 30 (H₂). NS = novel stimulus; CS = continuous stimulus; and RS = remembered stimulus. Bars reflect the standard deviation for each group. The accuracy of the saccades made by the HD groups are essentially the same for the NS and CS paradigms, but differ significantly for the RS paradigm.
controls ($p < 0.005$). There was no significant difference between the percent errors for the HD < 30 (19.4%) and HD > 30 (27.7%) group.

A comparison of both the HD and the Tourette's syndrome patients failed to find any relationship between use of medications and the velocity, latency, or accuracy of their saccades.

**Discussion.** Relationship of age at onset and saccade abnormalities in HD. The age at onset of HD appeared to influence the type of saccade abnormalities shown by our patients. Increased saccade latencies were present primarily in the HD > 30 group, especially for the CS and RS paradigms, while slow saccades were present only in the HD < 30 group. In our mildly affected patients, age at symptom onset, not duration of the illness, determined whether or not latencies or velocities were abnormal. This is not to say that older people do not develop slow saccades eventually. They do; but our results indicate that patients who are only mildly affected with HD and who have slow saccades are likely to be young. On the other hand, increased distractibility was present in all HD patients and did not appear to be age related. These findings suggest that the pathophysiology of the slow saccades, of the initiation deficits, and of the excessive distractibility shown by patients with HD are different.

Why might age at onset influence the nature of the saccade abnormalities in HD? It is unlikely that age per se is the explanation. Rather, some common genetic factor probably accounts for both the differences in the age at onset and the type of eye movement deficit. For example, Myer and his group found a correlation between the age at onset of symptoms and the gender of the affected parent. Persons who showed symptoms of HD at an early age were more likely to have inherited the gene from the father, those later in life from the mother. This was true in our patients; 70% of the younger group inherited HD from their father and 70% of the older group inherited HD from their mother. Clinical differences between the younger and the older onset groups may also be related to differences in the patterns of biochemical abnormalities and distribution of loss of nerve fibers described for each group.

**Mechanism of slow saccades in HD.** We have argued previously that the defects in saccade initiation and the excessive distractibility in HD reflect abnormalities in the frontal lobes or basal ganglia, or both. The origin of the saccade slowing is less clear. Slow saccades have usually been attributed to abnormalities in the brainstem reticular formation and in particular the burst cells that generate the immediate premotor commands for saccadic eye movements. There is, however, recent evidence that slow saccades may also be caused by abnormalities in higher level circuits that trigger the brainstem networks that generate saccades. In addition, some patients with HD who had documented slow (vertical) saccades in life showed no pathologic abnormalities, other than a mild gliosis, in the regions of the brainstem where the burst neurons for vertical saccades are located. Finally, Hikosaka and Wurtz have shown that slow saccades occur with pharmacologic lesions—either with lidocaine or muscimol—of the superior colliculus. Administration of the latter, which
appears to mimic excessive inhibition of the superior colliculus by the substantia nigra pars reticulata, leads to slowing of all types of saccades and to dysmetria of volitional saccades, especially those made to the remembered location of a target. Our younger patients with HD showed just this combination of deficits.

How might disturbances of supranuclear control of burst neurons lead to slow saccades? Abnormal inputs to pontine pause neurons might lead to slow saccades.22 Normally, pause cells act to inhibit burst neurons. When a saccade is called for, pause neurons must cease discharging to disinhibit burst neurons and permit them to generate a saccade. Accordingly, slow saccades could occur if only a fraction of the pause cells were inhibited, thereby allowing only a fraction of the burst cells to discharge. Alternatively, if a portion of the direct, cerebral, or collicular projections to burst neurons are affected in HD, slow saccades might occur because only a fraction of the burst neurons might be recruited during the saccade. Of course there also may be nonspecific higher-level tonic influences upon brainstem neurons which, if lost, could account for a decrease in the sensitivity of burst neurons to supranuclear inputs and consequently lead to slow saccades. In any case, the initial cause of the slow saccades in HD may not be due to direct involvement of brainstem burst neurons, although the exceedingly slow saccades that ultimately develop in some patients may reflect a combination of disturbed supranuclear inputs and direct involvement of the burst neurons in the paramedian reticular formation of the brainstem.

Saccade dysmetria in HD. Our patients showed nearly normal accuracy of saccades. Only saccades to remembered targets were inaccurate and then only by a small amount. Experimental lesions in the basal ganglia and superior colliculus do lead to saccadic dysmetria which is greatest for saccades to remembered targets.20,21 The dysmetria shown by our patients may be the clinical correlate of this finding.

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References

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