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Disturbance of Eye Movements in Huntington's Chorea*

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Summary. Eye movements were investigated in 14 patients with manifest Huntington's Chorea, 10 offspring and 10 normal subjects with electronystagmography (ENG) and during REM sleep. In choretic patients the following abnormalities were found:

1. Voluntary saccades were slowed in 10 of 14 patients and were more disturbed in the vertical than the horizontal direction.
2. Also, the velocity of the fast phase of optokinetic nystagmus was clearly reduced, especially in the vertical plane.
3. Horizontal, pendular pursuit movements are often superimposed by square wave opposite jerks.
4. Vestibular nystagmus was disturbed, too, especially in the fast phase.
5. During paradoxical sleep, rapid eye movements are less frequent.
6. In ten offspring, eight showed similar oculomotor disturbances.

Key words: Huntington's Chorea – Disturbed eye movements – REM sleep – Early detection.

Zusammenfassung. Bei 14 Patienten mit manifester Chorea Huntington, 10 Nachkommen und 10 Normalpersonen wurden Augenbewegungen im Nystagmogramm und während des REM-Schlafes untersucht. Bei Choreatikern fanden sich folgende Störungen:

1. Willkürsakkaden waren bei 11 von 14 Patienten vertikal stärker als horizontal deutlich verlangsamt.
2. Die Geschwindigkeiten der schnellen Phase des optokinetischen Nystagmus sind vertikal ebenfalls stärker gemindert als horizontal.
3. Horizontale Pendelfolgebewegungen sind häufiger als normal durch Gegenrucke überlagert.

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4. Auch der vestibuläre Nystagmus ist besonders in der schnellen Phase deutlich gestört.

5. Im paradoxen Schlaf sind rasche Augenbewegungen deutlich seltener.

6. Bei 8 von 10 Nachkommen von Huntington-Patienten zeigen sich zwei oder mehrere dieser Augenbewegungsstörungen, obwohl sie sonst phänotypisch gesund erschienen.

Schlüsselwörter: Chorea Huntington – Augenbewegungsstörungen – REM-Schlaf – Früherkennung.

Introduction

Disturbances of ocular movements in certain patients with Huntington's Chorea (H.C.) were reported for the first time by Dereux [7] and Andre-Thomas et al. [1] in 1945. These oculomotor abnormalities were explained as due to ocular apraxia in the earlier literature [4]. In the late course of Huntington's Chorea saccadic eye movements are highly impaired or may be totally absent during voluntary gaze, optokinetic stimuli, vestibular nystagmus, visual fixation, and REM sleep [21]. Avanzini et al. [3] constantly found significant reduction of saccadic velocity, especially for vertical movements. The pursuit movements were often jerky and the ability to perform repeated rhythmic movements was impaired.

As possible, early signs for clinical manifestations in offspring, the following were discussed: slightly disturbed ocular movements, especially in large vertical saccades; poor fixation; frequent blinking; an increased latency of ocular response [19].

All these results underline the selective defect of rapid eye movements as a characteristic feature of Huntington's disease.

The purpose of this study was to demonstrate that the impairment of saccadic and tracking eye movements can be detected at an early stage in offspring and measured by routine electronystagmogram (ENG) methods. The disturbance affects the whole oculomotor system and may also be seen in optokinetic or vestibular nystagmus and REM sleep.

Patients and Methods

Fourteen patients (25–51 years of age) with clinically manifest Huntington's disease were studied. The first choreic symptoms appeared 1 month to 20 years before admission to the hospital. Of these patients, six showed severe and seven only slight hyperkinesia; one showed a hypertonic rigid variant (Westphal type). In addition, ten offspring and ten normal subjects without obvious clinical symptoms were studied. One offspring reported only general inner nervousness that caused frequent clumsy movements.

ENG was used by the usual routine methods [11]. Pairs of Beckman silver chloride electrodes were affixed in the horizontal and vertical plane and coupled with a DC amplifier. The recordings were binocular for horizontal and vertical movements. The subject sat in a chair with the head stabilized manually. In the horizontal plane spontaneous eye movements with closed eyes were recorded as well as pendular pursuit movements at 0.5 and 0.3 Hz, optokinetic nystagmus at 30, 60, and 90 degree/s, vestibular postrotational, and caloric (cold water) nystagmus; in the vertical plane only optokinetic nystagmus was recorded.

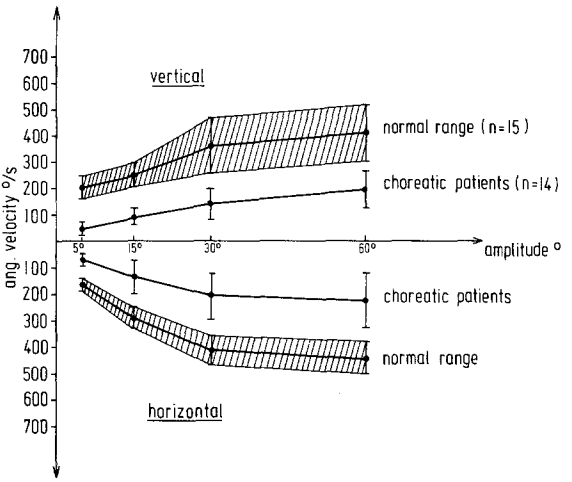

Fig. 1. Velocity of vertical and horizontal voluntary saccades in relation to their amplitudes

In addition, horizontal and vertical refixation saccades were elicited by alternatively illuminated spots at a distance of 5, 15, 30, and 60 degrees; voluntary saccades were also elicited by verbal command to look at different illuminated spots.

Polygraphic recordings during sleep included precentral and occipital EEG, the EMG of m. mentalis, and the recording of horizontal eye movements using paraocular electrodes.

During paradoxical or REM sleep characterized by low voltage, fast EEG, and decrease of muscle tone, frequency of eye movements per time period, the incidence of rapid eye movements per time period, and their percentage in relation to all the eye movements during REM sleep were calculated. Constant time intervals of 3 s each were examined, and the number of time intervals with eye movements and rapid movements were expressed in percentage of total number of time intervals. Only eye movements with an angle above 45° at a velocity of 15 mm/s of the registration paper were defined as *rapid.* Control recordings were performed for ten normal subjects.

Results

a) Vertical Saccadic Eye Movements. The most prominent finding in H.C. is the decreased velocity of vertical, voluntary saccades over the whole range of amplitudes studied between 5° and 60° (Fig. 1). This was found in 11 of 14 patients. Combined with this impaired velocity, prolonged latency up to 600 ms was regularly found.

This defect (though less distinct) could also be found in offspring without obvious clinical symptoms. Severity and duration of H.C. were not correlated to the degree of saccadic disturbance. Moreover, there were no differences related to sex and age.

Compared with voluntary saccades, vertical refixation saccades seemed to be faster but this trend was not significant. A similar difference was not detectable in the normal group.

Pendular vertical eye movements were not studied for technical reasons. Clinically the patients were unable to follow rapid, alternating movements in the vertical plane.

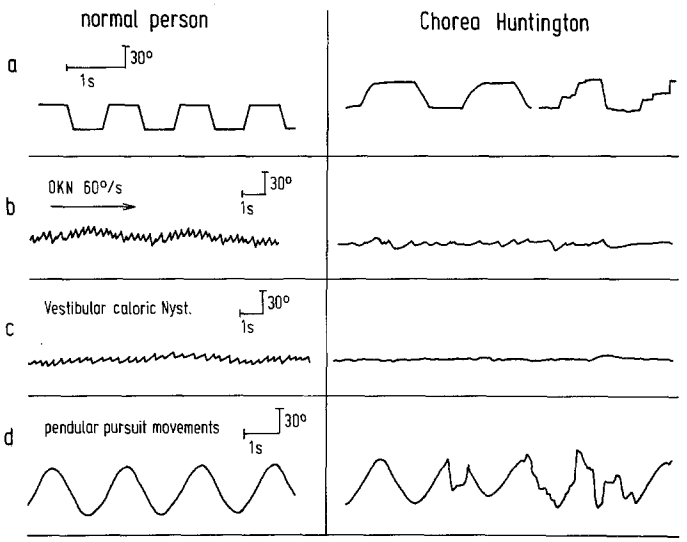

Fig. 2 a–d. Eye movements in normal subjects and in patients with Huntington's Chorea: **a)** voluntary saccades of 30°, **b)** horizontal optokinetic nystagmus at stimulus velocity of 60°/s, **c)** caloric nystagmus induced by cold water (20° C), and **d)** pendular pursuit movements

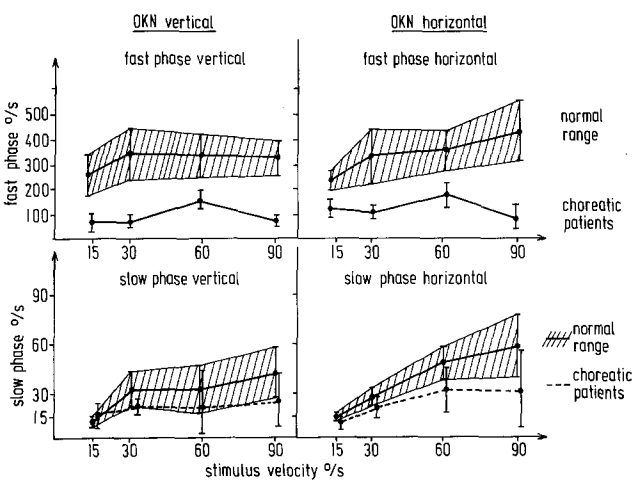

Fig. 3. Optokinetic nystagmus in normal subjects and patients with Huntington's Chorea

b) Horizontal Voluntary Eye Movements. In the horizontal plane, voluntary saccades were also slowed down significantly for all tested amplitudes, but less than in the vertical direction (Fig. 1). Latency was also prolonged. There was no clear difference between voluntary and refixational saccades. Often large saccades disintegrated into smaller corrective saccades (Fig. 2a).

c) The saccades of *optokinetic nystagmus* were clearly slower for the tested velocities of 30, 60, and 90 degree/s and more impaired for vertical than for

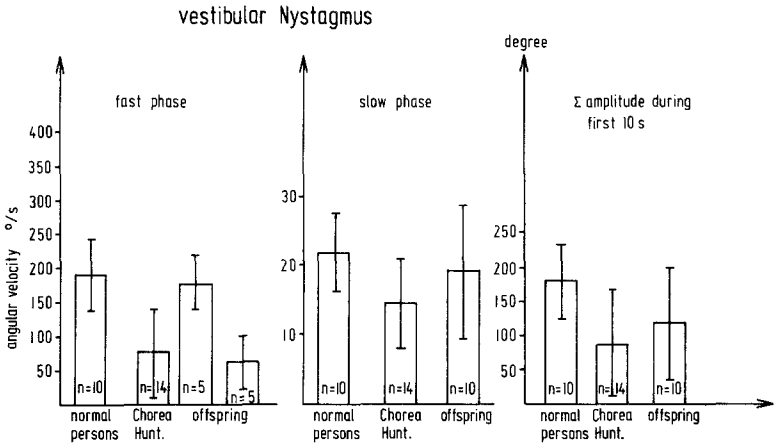

Fig. 4. Velocity of fast and slow phases and added amplitudes of over 10 s of vestibular nystagmus induced by caloric stimulation

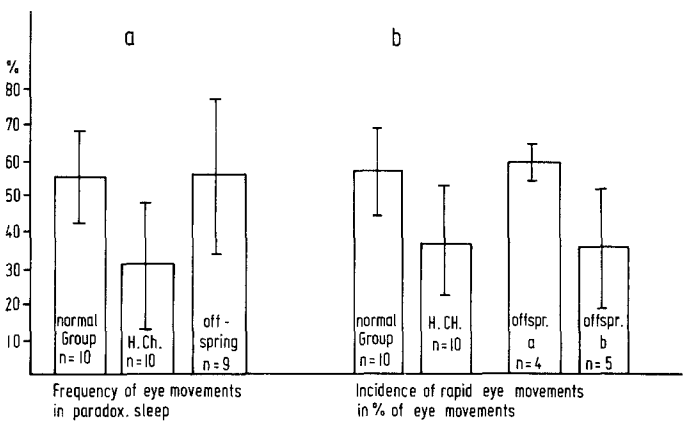

Fig. 5a and b. Eye movements in paradoxical or REM sleep. **a)** Incidence of all eye movements in paradoxical sleep. **b)** Relative incidence of *rapid* eye movements in percentage of all eye movements (see Patients and Methods)

horizontal movements. Also, the velocity of the slow phase was clearly reduced (Fig. 3) but without any significant difference between vertical and horizontal nystagmus.

d) Horizontal pendular pursuit movements were always smooth, at least during some periods, but could show irregular hyperkinetic jerks of changing amplitudes and impredictable direction as well, as was encountered in six of ten patients. This typical abnormality appeared more often with higher pendular frequencies, but only in patients with manifest chorea (Fig. 2 d).

e) Vestibular Nystagmus. By vestibular caloric or rotational stimulation only an irregular nystagmus of small amplitude could be evoked. While the velocity of the slow components did not decrease very much, saccades were clearly impaired in

velocity (Fig. 4). In five patients with highly reduced saccades, only tonic eye deviations were evoked.

f) Eye Movements During REM Sleep. The mean incidence of eye movements in REM sleep was reduced to 31% ± 18 compared to 54% ± 13 in normals (Fig. 1b). In addition, a decrease of *rapid* eye movements from 30% ± 11 in normals to 12% ± 8 in H.C. was found. Only 37% ± 16 of eye movements were rapid compared to 54% ± 12 in normals. One-half the offspring showed relatively normal incidence of rapid eye movements; in the other half, incidence was significantly reduced, comparable to that in H.C. (60% ± 5 compared to 34% ± 17).

g) Convergence Paresis. Of 14 patients, 9 showed more or less pronounced inability to converge the eyes, mostly related to clinically obvious impairment of optokinetic upward nystagmus.

h) Eye Movements in Offspring. Of the ten offspring examined without manifest clinical symptoms, eight showed oculomotor abnormalities in at least two of the five measured criteria as seen in following Table 1.

Table 1

Name	Pendular pursuit with square wave opposite jerks	Slowed vertical voluntary saccades (30°)	Slowed fast phases vertical OKN (60°)	Slowed fast phases of vestibular nystagmus	Reduced rapid eye movements during REM sleep
K.K. (♀)	+	+(118)°/s	+ (109)°/s	+ ∅	+ (5)°/s
C.B. (♀)	+	+(202)°/s	+ (142)°/s	+ (58)°/s	no investigation
M.J. (♀)	+	+(221)°/s	(+)(216)°/s	+ (103)°/s	+
R.H. (♀)	–	–	–	+ (78)°/s	(+) 48°/s
H.G. (♂)	–	–	+ (195)°/s	–	+ 45°/s
A.B. (♀)	+	–	+ (173)°/s	–	–
H.S. (♂)	–	–	(+)(177)°/s	(+)(148)°/s	+(39)°/s
A.M. (♀)	+	–	–	+ (123)°/s	–
W.Sch. (♂)	–	–	–	–	–
C.D. (♀)	–	–	–	–	–

Discussion

Eye movements are controlled by functionally different mechanisms. In voluntary gaze and optokinetic nystagmus a saccadic and smooth pursuit or tracking system work together in both the horizontal and vertical direction. Besides these two gaze-controlling mechanisms, a fixation system is also responsible for position maintenance. Furthermore, the oculomotor system is under the ascend-

ing influence of vestibulo-ocular and cervico-ocular reflexes from the lower brain stem. Finally, eye movements occur during sleep, showing all the characteristics of saccadic and slow tracking eye movements and demonstrating that endogenous mechanisms, probably of pontine origin, may evoke different eye movements.

The saccadic system is localized in the paramedian pontine reticular formation in the region of the abducens nucleus and probably works with a rather complex neuronal network [9]. It is depressed early in the development of intoxication [2] and can be impaired rather selectively in the course of some degenerative disease such as supranuclear palsy, Wernicke encephalopathy, and hereditary ataxia [19, 20, 23].

In contrast, the pursuit system seems less sensitive. Slow eye movements induced either by visual or vestibular stimuli are found even in those cases where saccades are absent. Moreover, in comatose patients pendular movements occur spontaneously or may be evoked by caloric stimulation or by the oculocephalic reflex [23].

The observation of impaired saccadic eye movements, especially in the vertical direction as is found in manifest H.C. and less frequently and pronounced in healthy offsprings, too, confirms and expands earlier results [1, 3, 7, 19, 20, 21]. Moreover, no comprehensive study exists on rapid eye movements during paradoxical sleep in a large number of choreic patients.

Both these studies emphasize the early alteration of rapid and saccadic eye movements. In contrast to the report of Avanzini et al. [3], this disturbance may occur early in the course of the disease. The changes are independent of the severity and duration of H.C. This fact may be illustrated by one offspring in our series who was healthy except for the most severe alteration of fast eye movements found in this study. Therefore, there may be a special oculomotor type of H.C.

Impaired voluntary saccades was the most prominent defect and was regularly found. This alteration could not always be observed during clinical examination, but velocity measurements always revealed it. Voluntary saccades were more impaired than those evoked by displacement of a target, but this difference was only marked in the vertical direction and is not a general finding as reported elsewhere [3].

According to these data, a serious alteration of the saccadic system in Huntington's disease must be considered. Horizontal and vertical saccadic eye movements are probably generated in the paramedian pontine reticular formation [6, 9]. Although neuropathological degeneration is not a condition for functional disturbance, which can be found in the early stage of this disease, it is interesting that neuropathologically only slight degeneration and diffuse gliosis are reported in the brain stem [4, 5, 8, 17].

Impaired saccadic velocity, the disturbance of the vestibulo-ocular reflex, and rapid eye movements all favor our hypothesis: impaired oculomotor function mainly bound to the brain stem. In view of the slight neuropathological findings in the brain stem, this oculomotor dysfunction may also be due to disequilibrium of neurotransmitters.

Higher structures may modulate these lower oculomotor mechanisms. In this context, the atrophy of the frontal lobe that occurs early in H.C. was discussed as responsible for impairment of voluntary saccades [3, 10, 13, 20]. Similarly, with regard to the main neuropathological finding of degeneration in the striatum, Starr [21] only explained the saccadic alteration by dysfunction of the caudate nucleus.

This hypothesis is corroborated by stimulation experiments in the caput nuclei caudati to evoke rapid eye movements on the contralateral side [14]. In bilateral stereotactic lesions of the caudate nucleus in cats, spontaneous eye movements were less frequent [18].

Reduced occurrence of eye movements and decreased mean velocity of rapid eye movements in paradoxical sleep also calls attention to the disintegration of reticular oculomotor structures. REM sleep does not seem to be dependent on cortical structures, as demonstrated in mesencephalic cats [16, 22].

The ability to produce smooth pursuit movements is generally preserved, but compared to normals it is more frequently superimposed by square wave opposite jerks (Gegenrucke). Similar changes are knwon from cerebellar lesions [12]. Cerebellar degeneration of the dentate nucleus and loss of Purkinje's cells as reported in H.C. [15, 17] could support cerebellar and pontine origin of this alteration.

Since oculomotor abnormalities are encountered in a high percentage of offspring nystagmographic and REM recordings may be valuable in preclinical diagnosis of the disease, especially for genetic counseling. Only a follow-up study can prove whether this presumption is true.

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