PAPER

Ocular motility and Wilson's disease: a study on 34 patients

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Background: Wilson's disease is an autosomal recessive genetic disorder resulting from an abnormality of copper metabolism. The excessive accumulation of copper in the brain induces an extrapyramidal syndrome. Oculomotor abnormalities occur in most extrapyramidal disorders but have rarely been studied in Wilson's disease.
Objective: To evaluate the ocular motility manifestations of Wilson's disease.
Methods: A prospective study of 34 patients affected by Wilson's disease who were recruited and their ocular motility recorded by electro-oculography (EOG).
Results: Vertical smooth pursuit was abnormal in 29 patients (85%). Vertical optokinetic nystagmus and horizontal smooth pursuit were impaired in 41% and 41% of patients, respectively. No MRI abnormality was found in the lenticular nuclei of seven patients who manifested ocular motility abnormalities.
Conclusion: Vertical eye movements, in particular vertical pursuits, are impaired in Wilson's disease, more often than vertical optokinetic nystagmus and vertical saccades. EOG abnormalities can be found in patients who do not yet exhibit anatomical lesions on MRI.

Wilson's disease is due to mutations in the ATP7B gene,[1] which is responsible for the production of a copper transporting protein which has a major role in the mitochondrial respiratory chain.[2] Excessive accumulation of copper in the brain or the liver induces the main neurological and hepatic manifestation of the disease. The prevalence of this disease was estimated to be 1.7 cases per 100 000 in Ireland.[3] Early diagnosis is often difficult but certainly very important in order to start the lifelong treatment as early as possible and prevent irreversible lesions.[4] In the brain, the basal ganglia seem most vulnerable to mitochondrial dysfunction; other cerebral structures such as the cerebellum and white matter can also be affected.[5] The basal ganglia play a major role in ocular motility,[6] and ocular motor abnormalities have been reported in Wilson's disease.[7–10]

Because we believe that the identification of ocular motility abnormalities can appreciably help in the diagnosis of the neurological form of Wilson's disease, we regularly perform ocular motility recordings in our patients.

In order to assess the ocular motor abnormalities that could occur in Wilson's disease, various types of eye movements were studied in our reported patient series.

MATERIALS AND METHODS

Thirty-four patients, affected by Wilson's disease, were prospectively recruited between 1991 and 2002. The diagnosis of Wilson's disease was proved through biological tests: low serum copper, low ceruloplasmin and increased urinary copper excretion.

Each patient was classified as having either the neurological or hepatic form of the disease. The neurological form was defined by the presence of one or several of the following signs: tremor, involuntary movements, abnormal speech, sialorrhoea, dysphagia, gait abnormality, change in handwriting or psychiatric symptoms. The hepatic form was defined by abnormalities of the following liver function tests: alkaline phosphatase, bilirubin, transaminases, cholinesterase, gamma glutamyl transferase and albumin. All patients in the study had been receiving treatment for variable periods of time.

Electro-oculography (EOG) was performed to record ocular movements: nine Beckmann-type electrodes were placed on the skin: one electrode was placed in the middle of the forehead; two were placed by the inner and outer canthi of each eye; and two electrodes were placed at the upper and lower orbital margins of each eye. The electrodes were then connected to a preamplifier, itself connected to an amplifier. The Metrovision Company software was used. Eye fixation was first recorded. Then, various stimulations were performed to study horizontal pursuit (distance 40°; track speed 30°/s), horizontal saccades (distance 40°), vertical pursuit (distance 30°; track speed 30°/s), horizontal saccades (distance 40°), horizontal optokinetic nystagmus (OKN) in both left–right or right–left directions and vertical upward and downward OKN. Fixation was defined as abnormal in the presence of square waves or nystagmus. Horizontal smooth pursuit was defined as abnormal if recovery saccades occurred: slightly saccadic (one or two recovery saccades) or saccadic (more than two recovery saccades). The horizontal saccades were analysed depending on their morphology, amplitude and speed. They were qualified as normal or abnormal. The horizontal OKN was analysed depending on its morphology, amplitude and frequency. Abnormal horizontal OKN could be defined as atypical, asymmetric (if better in one direction of rotation), with some jerks or present but with weak amplitude. Abnormal vertical smooth pursuit was qualified as slightly saccadic (one or two recovery saccades) or saccadic (more than two recovery saccades). The vertical saccades were analysed depending on their morphology, amplitude and speed. The vertical OKN was analysed depending on its morphology, amplitude and frequency. Abnormal vertical OKN was differentiated into three groups: not present, asymmetric (best high speed phase upward) or atypical.

Cerebral MRI was performed only in a subcohort of our patient group. In the 27 patients who had cerebral MRI, we investigated the possible correlation between the ocular motility abnormality and high signal intensity at the level of the lenticular nuclei.

RESULTS

Thirty-four patients with Wilson's disease were studied (mean age at first EOG was 29 (SD 9.8) years; range 14–55) (table 1).

Abbreviations: EOG, electro-oculography; OKN, optokinetic nystagmus

Table 1 Patient characteristics

Patient No	Age (y)	Sex	EOG results	Neurological signs	MRI
1	20	M	Abnormal	Yes	Abnormal
2	18	M	Abnormal	Yes	No MRI
3	42	M	Abnormal	Yes	Abnormal
4	15	M	1 element	Yes	Abnormal
5	44	F	1 element	Yes	Normal
6	18	F	Normal	Yes	Abnormal
7	41	F	Abnormal	No	Normal
8	37	M	Normal	No	No MRI
9	42	M	1 element	No	Normal
10	55	M	Abnormal	Yes	No MRI
11	25	F	Abnormal	No	No MRI
12	29	F	Abnormal	Yes	Abnormal
13	29	F	1 element	Yes	No MRI
14	31	M	Abnormal	Yes	Abnormal
15	25	F	Abnormal	Yes	No MRI
16	33	M	Abnormal	Yes	Abnormal
17	38	F	Abnormal	Yes	Abnormal
18	25	F	Abnormal	Yes	Abnormal
19	22	M	Abnormal	Yes	Abnormal
20	26	F	Abnormal	Yes	No MRI
21	30	F	Abnormal	Yes	Abnormal
22	29	M	1 element	No	Abnormal
23	23	M	Abnormal	Yes	Abnormal
24	30	M	Abnormal	No	Normal
25	29	M	Normal	Yes	Normal
26	35	M	1 element	Yes	Abnormal
27	14	M	1 element	Yes	Abnormal
28	16	M	Abnormal	Yes	Abnormal
29	24	F	Abnormal	No	Normal
30	31	M	Abnormal	No	Normal
31	17	F	Abnormal	Yes	Abnormal
32	18	M	1 element	Yes	Abnormal
33	45	M	1 element	Yes	Normal
34	32	F	1 element	Yes	Abnormal

EOG, electro-oculography.

Twenty patients were male and 14 were female (sex ratio 1.43). Twenty-four patients had predominantly neurological manifestations and nine predominantly hepatic manifestations. One patient was asymptomatic but had a relative with symptomatic Wilson's disease. Three patients had completely normal ocular motility and 31 patients had one or more abnormalities of ocular motility (91% of the study cohort).

Ten patients had only one ocular motility abnormality (9/10 had abnormality of vertical smooth pursuit, which was either saccadic or slightly saccadic). Abnormalities of vertical smooth pursuit were the most salient finding in the above results as they appeared in 85% of the cohort (table 2). Vertical OKN abnormalities and impairment of horizontal smooth pursuit represented the second most common abnormality: 41% and 41%, respectively. Among the nine patients with the hepatic form of the disease, 89% showed more than one abnormal eye movement. Among the 24 patients with predominantly neurological manifestations of Wilson's disease, only two had a normal EOG. Thirteen patients had an abnormal EOG, and one abnormal eye movement was found in the remaining nine patients (ie, 21 of 24 patients (87.5%) with predominantly the neurological form of the disease had at least one abnormal eye movement). The patient with an asymptomatic form of the disease had an abnormal EOG. Among the population of 27 patients having had an MRI performed, no abnormality of the lenticular nuclei or brainstem was found in seven patients, despite ocular motility abnormalities.

DISCUSSION

It must be emphasised that our patients were recruited mostly from a neurology department, which implies that in our cohort, possibly neurological forms of the disease were more represented than hepatic forms. As expected, the majority of patients with the neurological form of the disease had an abnormal EOG. It was noteworthy that most patients with the hepatic form also presented with an abnormal EOG.

Our study confirms the pervasiveness of ocular motility abnormalities in patients with Wilson's disease. Pursuits are more affected than saccades and it is the vertical smooth pursuit which is mostly affected, assuming that the vertical smooth pursuit is the most ''sensitive'' element or the earliest ocular motility functional disorder. The study of ocular motility disorders in Wilson's disease had not been extensively studied to date. Decrease in saccade velocity and abolition of the OKN slow phase were reported by Kirkham and Kamin.[7] Goldberg and Van Noorden described the abolition of recovery saccades.[8]

Table 2 EOG analysis on 34 patients affected by Wilson's disease

	Fixation (%)	Horizontal pursuit (%)	Horizontal saccades (%)	Horizontal OKN (%)	Vertical pursuit (%)	Vertical saccades (%)	Vertical OKN (%)
Normal	31 (91)	20 (59)	29 (85)	25 (7.5)	5 (15)	24 (70)	20 (59)
Abnormal	3 (9)	14 (41)	5 (15)	9 (26.5)	29 (85)	10 (30)	14 (41)

EOG, electro-oculography; OKN, optokinetic nystagmus.

Hypermetric saccades and upward gaze paralysis have also been reported.[9 10] In 1989, Lennox and Jones presented the case of a woman with neurological symptoms, later diagnosed with Wilson's disease, who was unable to fix her gaze for more than 2 s and not attracted by other peripheral targets.[11] Abnormality in near synkinesis was reported.[12] Patel and Bozdech presented the case of a patient with Wilson's disease who exhibited hypometric saccades and whose brain MRI showed hyperintense signal in the basal ganglia and thalamus.[13] Takahashi *et al* described the case of a patient in which only saccadic movements were affected, and in this case, MRI revealed bilateral pontine tegmental lesions.[16]

It is now recognised that pursuits, saccades and OKN originate in specific neuronal networks. While the brainstem, particularly the pons, is involved in smooth pursuit, the saccades are controlled by the pontine tegmentum. In 1991, Snow *et al* suggested that the nigrostriatal pathway is involved in the neurological form of Wilson's disease[17] and this assumption was confirmed by positron emission tomography scan which revealed dopaminergic presynaptic lesions in the putamen of four patients with Wilson's disease.[18] Despite many clinical observations, the influence of the extrapyramidal system on ocular motility performance is not well understood.[19] Nevertheless, it seems that the extrapyramidal fibres originating from the striated nucleus and the pallidum play a role of relay in the Cajal and Darkschewitsch nuclei, providing afferent fibres to the ocular motor nuclei through the medial longitudinal fasciculus that constitutes the third main element.

In our patients, we found that EOG could be abnormal despite normal brain MRI findings. EOG detects functional alterations, whereas MRI detects anatomical lesions. Even if MRI were not always contributory, it would be useful to attempt to establish a correlation between the precise localisation of the abnormality assessed by the imaging and the functional abnormalities of ocular motility, as is attempted for other clinical features of the disease.[19 20] MRI studies performed in patients with Wilson's disease have shown the presence of hyperintense signals in the lenticular nucleus, dentate nucleus, white matter, cerebellum and/or the brainstem, as well as hypointense signals in the putamen and cerebral atrophy zones.[21] As the basal ganglia (the caudate nucleus and particularly the pars reticulata of the substantia nigra) as well as the thalamus send information to the superior colliculus, a structure known to play a role in the control of ocular motility,[22, 23] their alteration in Wilson's disease could be responsible for the ocular motility disorders identified in our study. Additional work is necessary to better understand the relationships between the functional alterations and MRI lesions. We are currently conducting a follow-up study of ocular motility in this cohort of patients. Preliminary results demonstrate that generally the ocular motor abnormalities lessen with treatment but in some cases they may worsen with chelation therapy. These results will be published at a later date.

It would also be worthwhile to perform future studies on patients with predominantly the hepatic form of Wilson's disease, in order to better quantify the value of the EOG test in the early diagnosis of neurological disorders.

Ocular motility recording is of major interest for physicians working with patients suspected of having Wilson's disease and such testing could become important diagnostic criteria for diagnosis, particularly regarding the neurological form of the disease.

CONCLUSION

Our study confirmed that the ocular motor system is affected in Wilson's disease: pursuits are more affected than saccades, and vertical movements are more affected that horizontal ones. We demonstrated the usefulness of performing electrophysiological tests such as the EOG which is a functionally simple, non-invasive and reliable method, in order to assess subclinical functional disorders (ie, to assess a neurological form of the disease, even when other neurological signs are lacking or when the cerebral MRI results are normal). Moreover, this technique can be an objective method to assess the effectiveness of the treatment in patients with Wilson's disease.

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