Journal of NeuroVirology (2000) 6, Suppl 2, S156–S159

www.jneurovirol.com

Grading brainstem involvement in multiple sclerosis – by means of electro-oculography

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One of the most frequent disorders of the brainstem in multiple sclerosis (MS) is internuclear opthalmoplegia (INO). The aim of this study is to show how it is possible to monitor the course of MS grading INO on the basis of electro-oculographic findings. We selected 130 patients with a diagnosis of clinically defined multiple sclerosis (78 males and 52 females, mean age 43.5 years) from a population of 354 MS patients. Both saccadic eye movements and spontaneous, vestibular (VOR), visuo-vestibular (VVOR) and optokinetich nystagmus (OKN) were assessed. Slowing of the adducting eye was considered as a sign of lesion of the interocular pathways. Statistical analyses showed that the most sensitive test was VVOR, the least sensitive being randomised saccades. An impairment of random saccades was always associated with abnormal results on all other tests. It seems thus possible to grade the involvement of the medial longitudinal fasciculi (MLF) in MS from an abnormality limited to the VVOR test up to an impairment of randomised saccadic movements. Grading brainstem involvement in MS is particularly important in therapeutic trials and during rehabilitation. *Journal of NeuroVirology* (2000) **6,** S156–S159.

Keywords: multiple sclerosis; internuclear ophtalmoplegia; electro-oculography

Internuclear opthalmoplegia (INO) is an easily recognisable disorder of horizontal eye movements and is a common finding in multiple sclerosis. INO is characterised by an impairment of the adduction of the eye on the side of the impaired medial longitudinal fasciculus (MLF).

INO is due to a reduction of the initial pulse of acceleration activity in the adducting eye with the loss of the pulse signals to ocular motor neurons and preservation of the step signals in the adducting eye during version eye movements (Gresty, 1977; Metz, 1976; Oliveri *et al*, 1997).

INO can be both unilateral and bilateral. While unilateral INO may be due to tumours and vascular diseases as well as to demyelinating lesions, bilateral INO is a pathognomonic sign of multiple sclerosis (MS) (Fischer, 1977; Kirkham and Katsarkas, 1977). Bilateral INO is therefore strictly connected to the problem of the diagnosis of this illness.

The best way to document INO in MS is by means of electro-oculographic recordings (EOG) of saccadic fast eye movements, elicited by the displacements of visual targets, and of gaze nystagmus. Recording patterns of both saccades and nystagmus are typical and they are characterised by a slowing of the adducting eye during saccades and nystagmus beats with hypermetric abducting movements (Thomke and Hopf, 1992).

While measurements of vertical saccades and of interocular timing differences provide no useful criteria for disturbances of binocular coordination in MS, the acceleration of the adducting eye is strongly reduced in patients with an INO, and this reduction is best identified by interocular comparison between binocular pairs of saccades.

Demonstration of INO is useful in the diagnostic staging of the disease but it does not provide information regarding the grading of the disease. Furthermore, interocular comparison of saccades is not sufficient for the follow-up of brainstem involvement of the patients.

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Thus, the aim of the paper is to present our experience regarding the use of EOG in detecting bilateral INO and in grading MLFs involvement, in order to define the evolution of the disease.

We used computerised direct current EOG (Nicolet Biomedical Nystar) and monocular horizontal electrodes. Eye movements were elicited by a semicircular LED screen. Random $6-32^\circ$ refixation saccades were studied. Although different parameters (accuracy, latency and maximum velocity) were available, INO diagnosis was based on the ratio between abduction and adduction peak velocities (versional disconjugacy index, VDI) for each eye, because it is the most sensitive and reliable parameter (Ventre *et al*, 1991).

Nystagmus was also evaluated:

- gaze nystagmus
- provoked nystagmus by sinusoidal rotation in the dark (vestibulo-ocular reflex, VOR) and in the light (visuo-vestibulo-ocular-reflex, VVOR) by the mean of a motorised rotatory chair (Racia Hl02)
- full field optokinetich nystagmus (OKN), elicited by the displacements of visual targets on the semicircular LED screen at 40°/s velocity, in the darkness.

For nystagmus evaluation the VDI was calculated comparing adducting and abducting mean slow phase velocities for each eye.

For both saccades and nystagmus, VDI was considered consistent with an adduction slowing when it was more than 1.13 (mean value$\pm$2 s.d., calculated in a group of 15 normal subjects).

We selected 130 (78 males and 52 females, aged 43.5 years) clinically defined chronic progressive multiple sclerosis (MS) patients out of a consecutive 354 patients. In these patients, at least one of the performed tests was consistent with a bilateral impairment of adduction.

Adduction was differently involved in saccadic and nystagmus tests. While saccades demonstrated bilateral slowing of adduction in 56 patients (43.2%), OKN was disconjugated in 71 patients (54.6%), gaze nystagmus in 88 patients (67.6%), VOR in 98 (75.4%), and VVOR in 103 patients (79.2%).

Statistical analysis was performed by Pearson cross-tabulation for significance. Pearson correlations were:

- saccades/OKN: 0.008
- VVOR/VOR: 0.007
- VOR/OKN: 0.04
- OKN/gaze nystagmus: 0.03

The most sensitive test is VVOR while the least sensitive is saccade. VVOR detects INO in 36% of patients more than saccades. Impairment of saccades is always associated with abnormal results in all the other tests. In this way the following grading of involvement of MLFs results:

- VVOR
- VOR
- Gaze Nystagmus
- OKN
- Saccades

Brainstem is one of the most important site of integrations of sensorial inputs and motor outputs involved in the control of eye movements. Vestibular lesions are frequent in MS both at onset of the disease and during the course of the disease itself, (Brown, 1988; Gass and Hennerici, 1997).

Usually, neurologists adopt auditory evoked potentials (ABR) to investigate brainstem pathways involvement in MS (Alonso *et al*, 1992). Our previous researches (Alpini *et al*, 1994) demonstrated that the sensitivity of ABR is about 40% while vestibular investigations increase detection of brainstem lesions up to 80%. INO is well recognisable and can be considered a specific sign of MS. In this way grading the impairment of MLFs is correlated to the grading of brainstem involvement.

INO has been generally classified on the basis of gaze clinically detected nystagmus by Cogan (1970) in anterior and posterior INO, accordingly if slowing regards the adducting (anterior INO) or the abducting (posterior INO) eye. This classification is not useful to grade MLFs involvement. In the same way, the classification of complete or uncomplete INO according to the complete or not paresis of the adducting eye, based on clinical evaluation, it is not useful in detecting early involvement of MLFs lesions.

Flipse *et al* (1997) attempted to increase the sensitivity for detection of abnormal binocular saccadic eye movements calculating the ratios between peak acceleration and velocities of saccades pairs (abducting eye/adducting eye). A much sharper distinction between normal and patients with INOs was found by considering this ratio. In fact, since it eliminates much intra- and interindividual variability, had a narrow range in normals, and all values for INOs were outside of this range. In this way patients without clinically manifest INO, were easily separated in subjects with normal eye functions and in patients with subclinical MLFs impairments.

In this paper we attempt to increase sensitivity of EOG in detecting and grading MLFs impairments combining saccades evaluation with nystagmus investigation. The typical clinical pattern of INO is in fact abduction nystagmus with hypermetric abduction saccades, due to an increased phasic innervation adjusted to the adduction paresis.

We adopted the Versional Disconjugacy Index (VDI, Ventre *et al*, 1991) also to calculate nystagmus impairment. Statistical analyses showed that the most sensitive test is VVOR, the least sensitive being randomised saccades (VOOR detects INO in 36% of cases more than saccades). An impairment of random saccades was always associated with abnormal results on all other tests. These results indicate that the sole clinical evaluation of nystagmus (gaze nystagmus) is not sufficient to diagnose INO. Thus, EOG is the specific tool to investigate conjugation pathways.

Abduction nystagmus reflects an adaptive process that helps overcome the adduction weakness of the opposite eye. This response operates under the constraints of Hering's law of equal innervation: any attempt to increase the innervation to a weak muscle in one eye must be accompanied by a commensurate increase in innervation to the yoke muscle in the other eye. In this way, abduction nystagmus, a manifestation of a normal adaptive response in patients with INO, may be present or not according to intensity of adduction paresis (Herishanu and Sharpe, 1983; Muri and Meienberg, 1985; Zee *et al*, 1987).

In our experience, abducting gaze nystagmus can be present even if no adducting slowing of saccades is detectable. Thus, abducting nystagmus is not always an adaptive phenomenon but it may reflect another site or extension of the demyelinating processes. According to Reulen *et al* (1983), demyelination in the patients manifesting INO may not be restricted exclusively to one or both medial longitudinal fasciculi, but may extend to other brainstem structures which are functionally involved in the programming of saccades, like vestibular nuclei and reticular formation.

Thus, saccades evaluation is not sufficient although it can be used as routine investigation. In fact if saccades are dissociated, further tests could be unnecessary, but if they are normal, diagnosis is not complete. The involvement of interocular conjugacy pathways regards especially eye movements provoked by visuo-vestibular stimulation (rotation of the patient in the light). In this way a stress of oculomotor connections is induced. The first level of interaction between different ocular-motor networks is represented by the visuo-vestibular interaction. For a long time it was difficult to recognise the anatomical pathways connecting visual and vestibular informations. Now, vestibular afferences to the visual system have been demonstrated. They pass through the superior colliculus and reach the visual cortex. Visual afferences reach also the vestibulo-cerebellum especially the nodulus and the flocculus, and both cortical vestibular areas and vestibular nuclei: the vestibular neurons are thus activated either from the displacement of the visual field in a direction or from the displacement of the head in the opposite direction. Convergence of visual informations on the vestibular neurons ameliorates sensitivity and neural responses during contemporary variation of visual and vestibular stimulations, especially when they are not congruent. This convergence allows either a correct ocular motor response during the movement of the head, and/or the body, under natural circumstances, or a correct selection of the most appropriate sensorial information during constant stimulations. The ocular response provoked by simultaneous and congruent visual and vestibular stimulation is the so-called visuo-vestibular-reflex (VVOR).

Visuo-vestibular connections have been well demonstrated regarding labyrinth stimulations. In the cat and in the rat have been demonstrated also visuo-otolitithic convergences aimed to the contemporary control of eye movements and posture. Convergence of visual inputs on vestibular nuclei pass through the cerebellum, especially the flocculus, by a polisynaptic pathway which regards also the inferior olive and the accessory optic tract. Another pathway regards pretectal nuclei, the prepositus hypoglossi nucleus and the reticular tegmenti pontis nucleus. Convergence of visual and otolithic informations is aimed to ameliorate the tachimethric function elaborating information regarding the velocity of the head, independently from the informations concerning the acceleration and the frequence of head movements.

These multiple connections between visual pathways, vestibular nuclei, reticular formation and cerebellum, seem to be connected with the higher sensitivity of VVOR in detecting disturbances in eye movements conjugation. The difference between VVOR and VOR is not significant. Thus, it is probable that the most delicate signal elaboration regards vestibular information rather than visual inputs. This seems to be confirmed by the lower sensitivity of optokinetich nystagmus.

Optokinetich nystagmus is a particular expression of the visuo-vestibular interaction. When the environment moves wider than the visual field, vestibular and visual pathways cooperate in order to produce a complex eye movement constituted by a slow pursuit phase and a rapid resetting phase. It has been demonstrated that the integrity of the vestibular nuclei (and labyrinth) is necessary to produce a correct optokinetich nystagmus. It is now clear that generation of the optokinetich nystagmus is not a simple fast pursuit eye movement. It represents a primitive way to stabilise the visual field when the displacement of the environment is much too large. The first part of the movement is philogenetically ancient and it is realised in the brainstem, involving principally the vestibular nuclei, and it is elicited by a stimulation of the peripheral retina. The second part of the optokinetich phenomenon, is due to the stimulation of the foveal retina and it involves visual cortex and the pathways of the smooth pursuit. This component provides the beginning of the movement with velocities of the eyes until 35–40°/s while the vestibular component realises the faster part of the movements with velocities until 50–60°/s. Optokinetich stimulation stress interocular conjugacy pathways more than saccades stimulation but less than rotation in the light.

A complete EOG battery is thus necessary because it is possible to graduate diagnosis of INO. Saccades involvement represents the worse condition which means a more extensive lesion, while VVOR and VOR involvement may be referred to the mildest form of INO, due, in our opinion, to a smaller demyelinating process.

In fact, the saccadic system is simpler than the vestibulo-ocular system, in which correct eye-head coordination requires a very fine tuning of oculomotor signals. In this way, small demyelination of the oculomotor pathways may be 'amplified' and it is able to induce oculomotor dissociation.

Our findings confirm the value of standardised objective examination of eye movements in the detection and clarification of subclinical lesions in the central nervous system especially for patients with an early diagnosis of MS.

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