Original Article

Capsula Eburnea

OCULAR MANIFESTATIONS OF MULTIPLE SCLEROSIS: EVALUATION OF THE RETINAL NERVE FIBER LAYER ATROPHY

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SUMMARY

Multiple sclerosis (MS) is the most common and complex neurological disease in young adults, characterised by demyelination and axonal loss. Many neuro-ophthalmological manifestations can occur during the course of the illness, and Optic neuritis (ON) is both the most frequent and the best known. The research herein presented has highlighted, through the execution of instrumental exams, that people with MS and with episodes of ON, show a reduction in the medium depth of the nerve retinal fibres (a datum which is already present in literature). It has also been shown that people with MS without previous episodes of ON present a sectorial reduction in the depth of the retinal nerve fibers. The discovery of this alteration could shed light on the pathology prognosis and also enhance the patient's quality of life.

Introduction

Multiple Sclerosis (MS) is a chronic recurring and remitting demyelinating pathology of the central nervous system (CNS) with autoimmune pathogenesis and represents the most common cause of neurological disability amongst young adults. Demyelization frequently involves the visual apparatus and manifests itself through a variety of neurological-ophthalmological symptoms. It has been highlighted in international literature that patients, suffering from MS with episodes of ON, show a reduction in the medium depth of the nerve fibres.

The aim of this research is to assess, in patients suffering from MS, but who have never had episodes of ON, the presence of alterations in the nerve fibres of the optic nerve; this is easier today thanks to modern semiological techniques, such as the OCT (Optic Coherence Tomography) and the HRT (Heldelberg Retina Tomograph). The confirmation of the presence of these alterations in the optic nerve fibres could have a predictive value not only as regards the possible onset of an ON but also as in terms of the impairment of the central nervous system. Indeed, this could play an important role in the pathology prognosis and in the patient's quality of life.

Impairment of the visual apparatus is quite common and in many cases could represent the only clinical sign at the onset of the pathology. The demyelization process can involve any portion of the visual apparatus, establishing distinctive neuro-ophthalmologic pictures which manifest themselves with ocular motion disorders as well as sensory visual disorders. Among the ocular motion disorders the most common are: nystagmus and internuclear ophtalmoplegy. Nystagmus is a form of involuntary eye movement, which is the result of the typical alterations caused by the disease and which are present in the marrow and the cerebellum. It is characterized by two opposite cyclical phases.

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Internuclear ophtalmoplegy, however, is characterized by the weakening of ocular adduction, although convergence is generally normal, it is often associated to lateral medial fascicle damage. Divergent eye movement blocks the binocular fusion with consequent visual confusion, diplopia, reading troubles and loss of stereopsis [1].
As regards sensory visual disorders the most frequent clinical onset is the ON which often represents the first clinical onset of MS. This term is generally used to suggest any optic neuropathy regardless of its etiopathogenesis, but it often implies an acute pathology of the optic nerve which is assignable to a focal inflammation associated to a demyelization, a typical MS process. Even if the age of onset is extremely variable, most of the patients suffering from ON are young, with an age ranging from 20 to 50. There is a clear difference between the two genders, indeed, women's chances of developing an ON are three times higher than men.
In MS, it is possible for the degenerative process to involve the entire optic nerve. The anterior portion is less frequently affected, giving rise to a clinical picture known as papillitis, a higher incidence is instead observed in the back tract, resulting in a retrobulbar ON [2]. The objective analysis is different in the two aforementioned cases, in the anterior form, the optic papilla comes with a roughly definite edema while in the second case the papilla doesn't present any alterations, showing a normal aspect. In the two forms of ON, although the clinical picture shows some differences, the symptomatology is perfectly superimposable. Patients constantly complain about a sudden, more or less serious vision reduction, managing to perceive light only, within a period between one to two weeks [1]. Improvement in visual acuity can usually be obtained within a few weeks from the beginning of the symptomatology, often with a complete remission, although in some cases it can remain seriously at risk [3]. Functional symptomatology can be preceded and often comes with an upper back orbital pain which gets worse with ocular movements; we can also observe alterations in chromatic sense and in contrast sensitivity.
Ocular motion disorders, caused by a paralysis of the cranial nerves, can often involve the III nerve (oculomotor nerve) with the impairment of the iris sphincter muscle, the extrinsic eye muscles like the superior, inferior and lateral rectus, the inferior oblique and the elevator palpebrae superior, or the VI nerve (abducens nerve) which involves the external rectus muscle [4]. The Visual Field (VF), if it is possible to perform due to often seriously damaged vision, is characterized by a central or centrocecal scotoma, with the enlargement of the blind spot; and in some cases we can also observe quadrantic VF defects and hemianopsia. In the study of the visual evoked potentials (PEV), the typical alteration is represented by an increase in the central conduction time with a growth in the latency, sometimes associated to a decrease in the amplitude. They are altered in around 90% of patients with manifest ON.
ON diagnosis, especially in the chronic phase, is based on the exclusion of other pathologies such as chronic glaucoma in which the papilla has a typical aspect and presents itself as hollow or with an infiltration process etc. [5].
Despite the serious impairment of vision which characterizes neuritis during MS, recovery is often optimal and excellent, even without treatment, however, it is possible that there may be some subsequent relapses.
Several studies have confirmed the risk of developing MS even after a single episode of ON, with an incidence ranging from 11% to 85%. Poor predictive factors are: visual acuity, ocular clinical picture (papillitis or retrobulbar neuritis), presence/absence of ocular pain, PEV, age of onset, gender, bilateralism of the ON, ON recurring episodes, HLA phenotype and ON beginning period. The presence of cerebral alterations at the NMR is the most important diagnostic factor and must, therefore, be present before submitting patients with ON to an NMR [6].

Materials and Methods

The present research involves 140 subjects, divided into three groups:
Group 1: (MS) composed of 58 subjects with an age ranging from 24 to 35, affected by MS at its initial stage, and with no signs of ON, with VF and PEV within the norm; everyone has a vision of 10/10 and intraocular pressure within the norm (medium IOP = 14 mmHg).
Group 2 : (MS + ON) composed of 32 subjects with an age ranging from 22 and 34,

affected by MS, with visual acuity of 10/10 and intraocular pressure within the norm (medium IOP=14 mmHg), but with previous ON pressure; some subjects presented alteration in the VF.
Group 3: (healthy control) composed of 50 healthy subjects with an age ranging from 26 to 35, with medium visual acuity of 10/10 and intraocular pressure within the norm (IOP =13 mmHg).
In all the subjects the following examinations were carried out:
Measuring of the nerve fibre depth with OCT, through a scanning program, Fast RNFL thickness (3.4), with circular scannings around the optic papilla of 3,4 mm diameter.
Assessment of the optic papilla morphological parameters with HRT;
VF, carried out with Humphrey 750 perimeter, 30-2 program.
The OCT is a recent diagnostic method, which is not invasive and allows transversal retinal sections to be displayed at high resolution and at around 7 micron with OCT 3. OCT obtains retinal transversal section images at high resolution, by measuring the optical reflectivity of several scans carried out with a ray of near infrared light (845 nm).
HRT system is a tomographic confocal scanning laser which allows for the acquisition and analysis of tridimensional images of the back segment and the topographic analysis of the optic nerve head. It uses a diode laser with a wavelength of 679 nm.
For each parameter, the values of the 3 groups have been compared with the Anova test. In case of significance, a comparison between 2 groups with the Student T-test has been carried out.

Results
The subjects with previous episodes of ON, compared to the healthy subjects, presented a reduction in the medium depth of the nerve fibre ($p < 0.001$); the reduction was located in particular in the superior quadrant ($p < 0.001$) and nasal quadrant ($p = 0.001$). Compared to the subjects affected with MS but without previous ON episodes, a reduction in the medium depth was found ($p = 0.028$), with a localized reduction particularly in the superior quadrant ($p = 0.021$) and nasal quadrant ($p = 0.029$). The subjects without previous optic neurits episodes presented a significant difference in the depth of the nerve fibre layer compared to the healthy subjects in other sectors (nasal sector $p = 0.006$) (see table I).
The subjects with previous episodes of ON, compared to the healthy ones, presented a significant increase in the Rim Area ($p = 0.003$), a reduction in the Linear C/d ($p = 0.001$), in the Mean Cup Depth ($p < 0.001$), in the Maximum Cup Depth ($p < 0.001$). No important difference was present among the subjects with MS but with previous episodes of ON and in the healthy subjects. The subjects with sclerosis and neuritis compared to the subject with sclerosis but without previous episodes of neuritis

Table 1: Depth of the retinal nerve fibre layer, measured with OCT3.

OCT		AVERAGE	QUADRANTS (90°)			
			UPPER	NASAL	LOWER	TEMPORAL
MS + ON n = 32	Media St Dev	83 24	107 19	57 19	109 29	59 18
MS n = 58	Media St Dev	98 15	124 22	68 24	121 20	69 19
Healthy n =50	Media St Dev	103 13	130 13	83 18	122 19	70 12
MS + ON Vs healthy MS + ON Vs MS Healthy Vs MS		<0.001 0.028 Ns	<0.001 0.021 Ns	0.001 0.029 0.006	Ns Ns Ns	Ns Ns Ns

presented minor Linear C/D (p = 0.023), Mean Cup Depth (p = 0.001) and Maximum Cup Depth (p < 0.001) (see table II).
Subjects with MS and ON compared to the subjects of the other two groups presented a significant alteration in the parameters of the considered VF (MD and PSD, for both groups p = 0.001). No significant difference was present among the subjects with MS but without previous episodes of neuritis and the healthy subjects (see table III).

Discussion

ON is often the first clinical onset of the MS. An undulant progression with alterations in the VF and the PEV are typical of the pathology.
Parisi et al. [7] have conducted a study which correlates the morphological alterations with electro-functional examinations. In these patients a significant reduction of the nerve fibre depth (p < 0.01) was evident, both in the medium total value and in the temporal sector, compared to the healthy patients. A correlation with the pattern electroretinogram (PERG), but not with the PEV, was also observed. The reduction in the depth of the retinal nerve fibre layer was confirmed by other research [8], and was noted in the contralateral eye [9], and in the eyes of patients with MS without episodes of ON [10].
Trip et al. [11] have also noticed a significant reduction in the retinal volume. Zangwill et al. [12] have highlighted that RNFL depth, measured with OCT, decreases when the damage to RNFL, highlighted through a picture with monochromatic red light, is higher and the MD noticed in the computed perimetry is significantly associated to the depth of the retinal nerve fibre layer.
Various studies have pointed out that the reduction in the retinal nerve fibre depth is correlated to other ocular and systemic alterations such as: VF alteration [13], with the normalized cerebral volume, T1 volume of white substance lesions and the normalized volume of the white substance [14], physical and cognitive disability [15]. This element would be not predictive of which subjects affected by ON would develop distributed MS [16]. Even though our results showed a reduction in the medium depth of the nerve fibre, the localization of the damage is variable in relation to the extreme variability of the lesions, typical of MS. The reduction in the retinal nerve fibre

Table 2: Morphological parameters of the optic papilla, measured with HRT-II.

HRT		DISK AREA	CUP AREA	RIM AREA	CUP VOLUME	RIM VOLUME	LINEAR C/D	Mean Cup depth	Maximum Cup depth	Cup Share measue	Height Var Contour	Mean RNFL thick	RNFL Cross area
MS + ON n = 32	Media	2.03	0.31	1.70	0.08	0.68	0.18	0.15	0.28	-0.16	0.41	0.27	1.41
	Dev st	0.53	0.09	0.53	0.00	0.30	0.03	0.03	0.08	0.05	0.16	0.13	0.51
MS n = 58	Media	1.92	0.40	1.58	0.08	0.59	0.29	0.19	0.51	-0.18	0.42	0.28	1.36
	Dev st	0.31	0.22	0.62	0.07	0.18	0.09	0.10	0.08	0.03	0.04	0.09	0.28
Healthy n = 50	Media	1.95	0.41	1.51	0.05	0.61	0.39	0.23	0.52	-0.17	0.45	0.26	1.28
	Dev st	0.27	0.10	0.22	0.01	0.22	0.09	0.10	0.09	0.03	0.04	0.09	0.28
MS + ON Vs Healthy		Ns	Ns	0.003	Ns	Ns	0.001	<0.001	<0.001	Ns	Ns	Ns	Ns
MS + ON Vs MS		Ns	Ns	Ns	Ns	Ns	0.023	0.001	<0.001	Ns	Ns	Ns	Ns
Healthy Vs MS		Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns

layer is caused by the loss of the axons which form the optic nerve head, as confirmed also by recent neuropathology research about the histological preparation of patients affected by MS. Hence the retrogressive degeneration could lead to morphological changes in the optic nerve head. In patients with MS but with no episodes of neuritis, we have noticed statistically significant alterations compared to the healthy subjects in some sectors. As regards the morphology of the optic nerve head, in patients with MS and positive anamnesis to the ON, signs of papillary edema (increase of the papilla diameter and rim, excavation reduction) were noticed. Initial signs of edema (increase of the papilla dimension and rim) were found in patients with MS but without previous episodes of neuritis. This preliminary evidence deserves to be investigated further.

Conclusions

MS is a disease which often presents episodes of ON either as initial onset or after. The results of this research, which assessed the morphology of the optic nerve head and the depth of the retinal nerve fibre layer, has shown a reduction in the depth of the retinal nerve fibres and some signs of papillary edema in subjects with previous episodes of ON. In the subjects with MS without previous episodes of ON, further research should investigate the presence of alterations, which could actually be highly evident during the active phase of the disease and diminish in the remission phase or be indicative of a predisposition to an involvement of the optic nerve. It should also be mentioned that alterations to the retinal nerve fibre layer could be indicative of actual damage to the central nervous system or its precursor.

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Table 3: Parameters of Visual field (measured with Humprey 750, program 30-2).

VISUAL FIELD 30-2		MEAN DEFECT	PATTERN STANDARD DEVIATION
MS + ON n = 32	Media Dev st	-5.75 2.52	4.77 1.77
MS n = 58	Media Dev st	-2.27 1.59	2.68 1.04
Healthy n = 50	Media Dev st	-2.14 1.37	2.26 0.81
MS + ON Vs Healthy MS + ON Vs MS Healthy Vs MS		0.001 0.001 Ns	0.001 0.001 Ns

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