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● *Clinical Note*

TRANSBULBAR B-MODE SONOGRAPHY IN MULTIPLE SCLEROSIS: CLINICAL AND BIOLOGICAL RELEVANCE

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Abstract—Optic nerve sheath diameter quantification by transbulbar B-mode sonography is a recently validated technique, but its clinical relevance in relapse-free multiple sclerosis patients remains unexplored. In an open-label, comparative, cross-sectional study, we aimed to assess possible differences between patients and healthy controls in terms of optic nerve sheath diameter and its correlation with clinical/paraclinical parameters in this disease. Sixty unselected relapse-free patients and 35 matched healthy controls underwent transbulbar B-mode sonography. Patients underwent routine neurologic examination, brain magnetic resonance imaging and visual evoked potential tests. The mean optic nerve sheath diameter 3 and 5 mm from the eyeball was 22–25% lower in patients than controls and correlated with the Expanded Disability Status Scale ($r = -0.34$, $p = 0.048$, and $r = -0.32$, $p = 0.042$, respectively). We suggest that optic nerve sheath diameter quantified by transbulbar B-mode sonography should be included in routine assessment of the disease as an extension of the neurologic examination. (E-mail: dmsrrt@gmail.com)

Key Words: **Transbulbar B-mode sonography, Multiple sclerosis, Afferent visual pathway, Optic nerve, Visual evoked potentials, Brain magnetic resonance imaging.**

INTRODUCTION

Early subclinical involvement of the afferent visual pathway is described in most cases of multiple sclerosis (MS) (Mogensen 1990) and is considered a functionally eloquent system regarding the central nervous system (CNS), as well as a clinical model of the disease (Costello et al. 2006). The afferent visual pathway is made up of tissue-specific substrates that sustain visual function, including the retina, myelinated optic nerve, chiasm, tracts, optic radiations and Brodmann area 17 of the cerebral cortex. Apart from the retina, the optic nerve and other afferent visual pathway structures consist of myelinated axon fibers, similar to those forming white matter elsewhere in the brain, which makes them vulnerable to inflammatory demyelinating injury in MS. Thus, unlike the brain, the afferent visual pathway is regarded as "eloquent," because every lesion, however small, induces clinical and/or readily detectable instrumental abnormalities. Moreover, previous pathologic studies have reported that tissue-specific injury in the afferent visual pathway reflects global CNS effects in MS patients (Green et al. 2010). From this point of view, the optic nerve can be seen as a clinical model of MS.

Perivenular infiltrative T cells with axonal loss and reactive gliosis are common aspects involving the optic nerves, retina and cerebral hemispheres (Costello et al. 2006). Moreover, neuroinflammatory-dependent reduction in the retinal nerve fiber layer (RNFL) is correlated with brain and macular shrinkage, as well as optic nerve involvement (Green et al. 2010).

Optic nerve sheath diameter (ONSD) quantification by transbulbar B-mode sonography (TBS) is a non-invasive technique recently validated among the general

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population, making it an objective tool for neurologic examination (Bauerle et al. 2012, 2013). However, no application concerning MS is reported in the literature, so the predictive value of ONSD in this pathology is still unexplored. In this sense, the optic nerve is very interesting. Indeed, its derivation from the diencephalon (specifically from the quadrigeminal plate) and its oligodendroglial coating mark it as an external eversion of the central nervous system.

Optic nerve (ON) fibers are myelinated in the orbital part and the rest of the optic nerve, but they are unmyelinated in the lamina cribrosa, starting from the last 3 mm before their entry into the eyeball. The diencephalon is a central brain structure, delimited from the deep gray matter and crossed by sensitive and pyramidal/extrapyramidal tracts. Specifically, this strategic position near the internal capsule is responsible for the early enlargement of the third ventricle in MS, reflecting abiotrophic phenomena in distant structures of hemispheric white matter and the cortex (Minagar et al. 2013; Muller et al. 2013). To summarize, the involvement of the ON in MS can be considered an *experimentum naturae*, paradigmatic of diffuse pathologic processes in the CNS.

The primary aim of this study was to assess any differences between patients with MS and healthy control subjects in terms of ONSD and, secondarily, to investigate any correlation between ONSD and neurophysiological, morphometric and clinically relevant parameters in a random MS population.

METHODS

In an open-label, comparative, cross-sectional study, we investigated 60 unselected relapse-free MS patients and 35 sex- and age-matched healthy control subjects, for totals of 120 and 70 eyes, respectively. All patients underwent TBS, which in patients was part of their clinical examination. Within 24 h, brain magnetic resonance imaging (MRI) was conducted on the diseased patients, and visual evoked potentials were measured. TBS was carried out personally by the primary author of this work, a neurophysiologist certified by the Italian neurosonology society (Italian Society of Neurosonology and Brain Haemodynamics [SINSEC]).

A Vivid 7 GE US system (GE Vingmed Ultrasound AS, Horten, Norway) was used in accordance with Bauerle et al. (2013, 2012). Briefly, with the 2.5- to 10-MHz linear probe placed on the temporal part of the closed upper eyelid, the optic nerve was depicted in a transverse plane, revealing the papilla and the optic nerve in its longitudinal course at 3 and 5 mm behind the eyeball bilaterally. The distance between the external borders of the hyperechoic area surrounding the ON was quantified as ONSD.

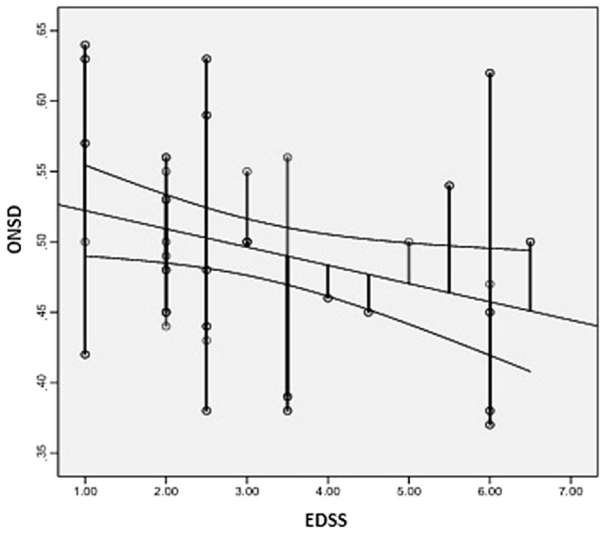

Fig. 1. Significant inverse correlation between optic nerve sheath diameter (ONSD) measured at 5 mm from the eyeball and Expanded Disability Status Scale score in patients with multiple sclerosis.

P100 latency (P100 L) and amplitude (P100 A) were calculated in accordance with Odom's pattern-reversal standard protocol. Briefly, visual evoked potentials (VEPs) are visually evoked electrophysiologic signals extracted from the averaged electroencephalographic activity in the visual cortex, recorded from the scalp using an active occipital electrode placed near the visual cortex. The standard pattern stimulus is a high-contrast black and white checkerboard with a square element size of $1 \pm 20^{\circ}$ per side. For the pattern-reversal protocol, the black and white checks change phase abruptly and repeatedly at a specified frequency (about two reversals per second) evoking the P100 wave, whose amplitude and latency reflect the functional integrity of the visual system, including the retina, optic nerve, optic radiations and occipital cortex.

All patients were positioned and imaged with a 1.5-T Philips MR apparatus (180 mT/m) (Achieva, Philips Medical Systems, Best, Netherlands), in accordance with international guidelines (Miller et al. 1991). Briefly, the acquisition sequence types were SE T1–TSE T1 MT–BRAIN VIEW FLAIR 3-D; acquisition time 2.17′–3.07′–4.14′; field of view 230 × 183 mm AX–250 × 250 FLAIR SAG–180-200 × 180 mm COR MT; orientation: TRA–COR–TRA; alignment: TRA–COR–TRA; and voxel size: 0.89/0.88/4–0.56/0.56/4–0.31/0.31/0.6, respectively. TR was 450–614–4800; TE was 15–12–307; and TI was –/–/1660. The flip angle was 69°–90°–/, and the NEX was 1–2–2. SENSE parallel imaging method and contrast enhancement (Gadovist single dose, 10 min post-administration) were used.