Optic nerve compression: the role of the lamina cribrosa and translaminar pressure

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Abstract

- AIM: To describe the morphological changes of the lamina cribrosa (LC) in patients with optic nerve compression.
- METHODS: Cross-sectional study. Twenty eyes with optic nerve compression, affected by Graves' ophthalmopathy (GO) were compared with 18 refractive error-matched healthy eyes. The following examinations were performed: best-corrected visual acuity (BCVA), intraocular pressure, optic nerve echography, visual field, SD-OCT including the retinal nerve fiber layer (RNFL), ganglion cell complex (GCC), and LC thickness and extent.
- RESULTS: A-scan revealed significant differences in the subarachnoid space (SAS) between the affected and control groups. LC thickness and LC area were 233 µm (SD 23) and 0.41 mm² (SD 0.19), respectively. Average GCC thickness (P=0.0005), LC thickness (P=0.001), MD (P=0.001) and PSD (P=0.001) differed significantly between the two groups; whereas LC area (P=0.2) and average RNFL (P=0.1) did not.
- CONCLUSION: Optic nerve compression reduces the SAS thereby altering the morphology of LC thickness and causing GCC damage.
- KEYWORDS: optic nerve compression; lamina cribrosa; translaminar pressure

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INTRODUCTION

Graves’ ophthalmopathy (GO) is the most common orbital disorder affecting between 25%-50% of patients with Graves’ disease. It is clinically characterized, in its moderate-severe form, by enlargement of the extra-ocular muscles (EOM) and by an enlarged orbital fat compartment resulting from a complex interaction between orbital fibroblasts, autoantibodies, immune cells, genetics and environmental factors[1]. Orbital compression seems to be sustained by thyroid-stimulating auto-antibodies that mimic the effect of thyrotropin. The orbital fibroblasts, through the thyrotropin receptor autoantigen (TSHR), differentiate into adipocytes thereby increasing the amount of adipose tissue in the orbit, which, in turn, increases TSHR expression[2]. Approximately 28% of GO cases present limited EOM motility associated to diplopia, exposure keratopathy, and optic neuropathy[3]. Moreover, EOM involvement produces orbital congestion of the superior ophthalmic vein and a crowded orbital apex, which leads to optic nerve compression[4].

Optic nerve compression is a common finding in patients affected by GO[5-9]. Its diagnosis is based on reduced mean perimetric sensitivities, visual field defects, changes in transverse echographic optic nerve diameters, tomographic damage of the retinal nerve fiber layer (RNFL) and of the ganglion cell complex (GCC; RNFL+ganglion cell layer + inner plexiform layer), even without changes in visual acuity in the early stages of the disease[10]. The lamina cribrosa (LC) is considered the cause of retinal ganglion cell axon damage. The net of LC separates the subarachnoid space (SAS) from the intraocular space, and is exposed to the differential translaminar pressure that exists across the two compartments, which contain cerebrospinal fluid (CSF) and aqueous humor, respectively. Elevated trans-lamina cribrosa pressure is associated to functional and anatomical optic nerve damage[11]. Given the same level of intraocular pressure, patients with elevated CSF pressure are protected against optic nerve damage, unlike patients with a low CSF pressure[12]. Our hypothesis is that in GO, the orbital apex compression reduces the CSF pressure in the retrobulbar space, thereby increasing the trans-laminar pressure that may induce morphological changes of the lamina cribrosa and consequent damage of the RNFL and GCC.

The aims of this study were to determine the morphological changes of the LC in patients affected by GO, and the functional and anatomical changes in patients affect by optic nerve compression. We also compared the findings of these patients with those obtained from 20 age-matched controls in order to investigate the most precocious signs of optic nerve damage.

**SUBJECTS AND METHODS**

**Study Design** Prospective cross-sectional study of 35 consecutive eyes affected by GO. We selected 21 eyes with optic nerve compression and compared them with 18 healthy age-matched eyes. All investigations and examinations conformed with the tenets of the Declaration of Helsinki 2013. The study was also approved by the Institutional Review Board Committee of the University of Naples “Federico II”.

**Participants** A consecutive series of 21 eyes with diagnosis of optic nerve compression secondary to Graves’ disease were enrolled in the study. The status of the disease was evaluated with a modified version of the clinical activity score (CAS)\[13-14\]. To be enrolled in the study, patients had to be euthyroid for at least 3 mo during methimazole therapy with inactive phase of ophthalmopathy (CAS <2).

Graves’ ophthalmology was confirmed by computerized tomography, magnetic resonance imaging, and by increased thickness of the 4 EOM (superior, inferior, medial and lateral rectus) in zone IV (thickening of the muscle belly) at A-scan measurement. The study was conducted at the Department of Neurosciences, Reproductive Sciences and Dentistry, of the University of Naples “Federico II”. After receiving a detailed explanation of the study, patients underwent a comprehensive ophthalmologic examination. Informed consent was obtained from all participants. Exclusion criteria included eyes with preexisting retinal or optic nerve disease, intraocular pressure above 18 mm Hg, media opacity, diabetes mellitus or intraocular surgery performed less than three months earlier.

The following items were measured: best-corrected VA (BCVA), intraocular pressure, visual field, SD-OCT of macula area and optic nerve, A-scan measure of EOM and optic nerve.

**Functional Measurements**

**Visual acuity** The BCVA was measured with Early Treatment Diabetic Retinopathy Study charts, and analyzed by logarithm of the minimum angle of resolution (logMAR).

**Visual field** Static perimetry was performed with the Humphrey automated perimeter (Humphrey Instruments, Inc., Zeiss Humphrey, San Leandro, CA, USA) using the SITA 30-2 protocol with stimulus size III. For statistical analysis we took into account the mean deviation (MD) and pattern standard deviation (PSD). Mean deviation is the average differences versus age-matched normal eyes; the more negative the MD, the worse the visual field loss. Pattern standard deviation (PSD) is a measure of non-uniformity of visual field; the more positive the PSD, the more irregular is the visual field.

**Tomographic Measurements** The SD-OCT images were acquired with the Heidelberg Spectralis tracking laser tomography (Heidelberg Engineering, Carlsbad, CA, USA) for imaging of LC thickness, the LC area with enhance depth image mode. Spectralis OCT works by emitting a diode light with a wavelength of 870 nm through a dual beam SD-OCT and confocal laser scanning ophthalmoscope, and an infrared scan to simultaneously provide retinal images. The SD-OCT RTVue-100 (Optovue Inc., Fremont, CA, USA) was used to measure the RNFL and GCC parameters. This instrument uses a superluminescent diode with a wavelength of 840 nm. It can collect 26 000 A-scans per second with an axial resolution of 5 μm.

**Lamina Cribrosa Thickness and Area** The EDI OCT B-scans of the optic nerve head was scanned for 20-degrees by a 6-mm line (512 A-scans) with an interval of 50 μm. Thirty-five scan-frames were produced for each cross-sectional B-scan. The edges of the LC were measured from the line where the highly reflective region started to the line where it tended. We delimited the anterior and posterior laminar border between 2 horizontal lines. Lamina cribrosa thickness was defined as the distance between two points on the vertical line going through the center of the optic nerve that perpendicularly crosses the 2 previously drawn horizontal lines\[15\]. The anterior surface of the LC was measured on confocal scanning laser ophthalmoscopy images of the anterior laminar surface with improved contrast. The area was measured when the confocal scanning laser ophthalmoscopy image of the optic nerve was located on the LC pores in order to better identify the edges of the anterior surface of the LC\[16\].

The optic nerve head map protocol was used to obtain RNFL and GCC data. The thickness map was measured around a 3.45-mm-diameter circle centered on the optic disc. The macular region contains more than 50% of all retinal ganglion cells, therefore it is an ideal region on which to identify early cell loss over time. We recorded the average RNFL and GCC thicknesses\[17\].

**A-scan Measurements**

Echographic measurements were obtained with an A-scan standardized echograph (Cine Scan S, Quantel Medical SA, Le Brezet, France) and with an 8 mHz probe. The transverse optic nerve diameter (arachnoid-arachnoid) was measured at its passage through the orbital apex. The 30-degree test was performed to differentiate between the dry and wet optic nerve\[18\]. In this test the optic nerve is measured by A-scan in primary gaze (wet optic nerve) and then re-measured after the patient abducts the eye about 30 degrees after 3 min of exercise (dry optic nerve). This exercise forces the CSF out of the SAS, so that the optic nerve is “dry” (the diameter is reduced). Three minutes later, the optic nerve is measured under normal conditions with the gaze at 0°, and returns to being “wet” (same diameters as baseline, with the CSF in the SAS) whereas under optic nerve compression, the...
CSF slowly returns to the SAS due to the compression at the orbit apex, therefore the arachnoid-arachonid diameter remains reduced and the optic nerve is “dry”.

**Statistical Analysis** We performed the non-parametric Kruskal-Wallis 1-way test of variance for parameters not normally distributed for comparisons between the optic nerve compression group and control group. Student t test was used for normally distributed parameters. We performed regression analysis to compare functional measures [BCVA and visual field (VF)], tomographic findings (LC area, LC thickness, RNFL and the GCC), and ultrasound A-scan measures (optic nerve measurements) were performed to correlate functional and anatomical measures. P≤0.05 denoted statistical significance. All analyses were conducted using the SPSS software version 3.1 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Tomographic Outcomes** As shown in Table 1, the mean LC area did not differ significantly between the optic nerve compression group and the control group 0.41 mm² (SD 0.19) and 0.48 mm² (SD 0.15), respectively. The difference between the groups was not statistically different (P=0.2). The LC thickness was significantly lower (P=0.01) in the optic nerve compression group, 233.83 µm (SD 23.7) than in the control, 350 µm (SD 21) (Figure 1). The average of GCC (including the RNFL, ganglion cell layer and inner plexiform layer) was significant lower (P=0.0005) in the optic nerve compression group, 90.86 µm (SD 5.2) than in the control, 98.89 µm (SD 4.65), whereas neither the foveal loss volume (FLV) nor the global loss volume (GLV) differed between the optic nerve compression and control group: FVL [1.24 (2.9) vs 1.4 (2.8), P=0.8], and GLV [8.24 (4.9) vs 9.2 (4.6), P=0.5]. The average RNFL thickness was lower, albeit not significantly so, in the optic nerve compression group [102.85 µm (SD 6.7)] than in the control group [109.77 µm (SD 19.5)], and the difference was not statistically different (P=0.1) (Figure 2).

We also recorded the dynamics of SAS including the measure at 0° in primary position, and again at 0° in primary position after three minutes exercise at 30°.

At baseline, the optic nerve diameters in primary gaze did not differ between the two groups, i.e. 3.99 mm (SD 0.24) vs 4.12 mm (SD 0.18), P=0.06, whereas it was significantly (P<0.01) reduced in the optic nerve compression group, namely 3.31 mm (SD 0.22) vs control 4.07 mm (SD 0.15) after the 30-degree test, showing optic nerve compression at the orbit apex (Figure 3).

**Functional Outcomes** The BCVA was respectively 0.85 (0.15) logMAR and 1.0 (0.1) logMAR in optic nerve compression group and controls group. The difference of MD was statistically different between the groups -1.60 (1.0) vs 0.08 (1.13); P=0.001. The PSD was statistically (P=0.001) higher in optic nerve compression group 2.2 (SD 0.8) compared with control group 1.42 (SD 0.6).

**DISCUSSION**

The lamina cribrosa, which lies at the base of the optic cup, a is a collagenous beam structure characterized by pores through which the ganglion cell axons and retinal blood vessels go beyond. It is the principal site of ganglion cell axon injury in patients affected by optic nerve damage secondary to glaucoma[18], as the macular ganglion cell analysis showed

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**Table 1 Comparison of anatomical outcomes between patients of optic nerve compression group and control group**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Optic nerve compression (21 eyes)</th>
<th>Control (18 eyes)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.68 (13.73)</td>
<td>46.7 (9.43)</td>
<td>0.6</td>
</tr>
<tr>
<td>AXL</td>
<td>22.02 (0.91)</td>
<td>22.6 (1.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>IOP</td>
<td>16.67 (1.59)</td>
<td>16.0 (0.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>LC thickness</td>
<td>233.83 (23.7)</td>
<td>350 (21)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LC area</td>
<td>0.41 (0.19)</td>
<td>0.48 (0.15)</td>
<td>0.2</td>
</tr>
<tr>
<td>Avg RNFL</td>
<td>102.85 (6.7)</td>
<td>109.77 (19.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>Sup Avg</td>
<td>100.54 (6.6)</td>
<td>122.1 (16.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inf Avg</td>
<td>105.16 (9.5)</td>
<td>124.1 (17.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Avg GCC</td>
<td>90.86 (5.2)</td>
<td>98.89 (4.65)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Sup GCC</td>
<td>90.58 (5.3)</td>
<td>92.3 (2.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>Inf GCC</td>
<td>91.15 (5.7)</td>
<td>94.5 (2.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>FLV</td>
<td>1.24 (2.9)</td>
<td>1.4 (2.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>GLV</td>
<td>8.24 (4.9)</td>
<td>9.2 (4.6)</td>
<td>0.5</td>
</tr>
<tr>
<td>Optic nerve thickness 0°</td>
<td>3.99 (0.24)</td>
<td>4.12 (0.18)</td>
<td>0.06</td>
</tr>
<tr>
<td>Optic nerve thickness 0° E</td>
<td>3.31 (0.22)</td>
<td>4.07 (0.15)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

AXL: Axial length; IOP: Intraocular pressure; LC: Lamina cribrosa; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; FLV: Focal loss volume; GLV: Global loss volume.
Thanks to advances in imaging technology, it is now possible to examine the LC \textit{in vivo}. In particular, EDI SD-OCT produces cross-sectional images of the LC including the posterior and anterior LC surface with laminar pores even below the neuroretinal rim. Lamina cribrosa imaging with EDI OCT was reported to be significantly more reliable and have a better interobserver and inter-visit reproducibility than standard imaging procedures\cite{15}. The LC has become a landmark of interest consequent to the finding that CSF pressure is involved in the pathogenesis of various eye diseases. As a thin anatomical area, LC undergoes to a differential pressure (translaminar pressure gradient) separating two differentially pressurized compartments such the orbital SAS (where is present the CSF) and the intraocular space. The CSF pressure largely is responsible for retrolaminar tissue pressure acting on LC independently from IOP\cite{22}. The early morphological changes of glaucomatous cupping includes posterior migration of LC insertion into the sclera and collapse and thinning of LC\cite{21}. Morphology changes of LC are described in primary open angle glaucoma (POAG) and in NTG showing that the structural changes of LC are not induced just by a mechanical stress of IOP\cite{15}. Park \textit{et al}\cite{15} reported that LC thickness was significantly thinner in NTG and in POAG eyes than in the control group, and even thinner in presence of disc hemorrhage. It has been also reported that in pathologic myopia the LC is anatomically thinner than in ametropic eyes and therefore more susceptible to CSFP with increased translaminar pressure gradient. This finding may also explain the increased risk of optic nerve damage in highly myopic eyes.

In our GO patients, the average RNFL thickness was greater in the inferior quadrant (105.16 μm) than in the superior quadrant (100.54 μm). This finding is in accordance with a recent study by Danesh-Meyer \textit{et al}\cite{24}, devoted to the differentiation between compressive and glaucomatous optic neuropathy; in fact they found that the inferior RNFL average thickness was thinner than the superior RNFL average thickness in the open-

\begin{table}[h]
\centering
\caption{Correlation between anatomical and functional findings in patients affected by optic nerve compression}
\begin{tabular}{|l|l|l|l|}
\hline
Parameters & LC area & LC thickness & AVG GCC \\
\hline
BCVA & R=-0.6 & R=0.49 & R=0.6 \\
& P=0.025 & P=0.09 & P=0.03 \\
AVG RNFL & R=-0.11 & R=0.21 & R=0.6 \\
& P=0.7 & P=0.49 & P=0.01 \\
AVG GCC & R=-0.93 & R=0.07 & 1 \\
& P=0.7 & P=0.8 & \\
LC thickness & R=0.6 & 1 & R=0.07 \\
& P=0.03 & & P=0.8 \\
Optic nerve thickness 0° E & R=0.2 & R=0.2 & R=0.1 \\
& P=0.5 & P=0.4 & P=0.9 \\
VF MD & R=0.42 & R=0.43 & R=0.65 \\
& P=0.16 & P=0.15 & P=0.02 \\
VF PSD & R=0.56 & R=0.31 & R=0.21 \\
& P=0.054 & P=0.31 & P=0.94 \\
\hline
\end{tabular}
\end{table}

BCVA: Best corrected visual acuity; AVG: Average; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; LC: Lamina cribrosa.

Although the LC imaging has been described as a useful diagnostic tool, even more than peripapillary RNFL thicknesses, for diagnosis of NTG, especially in early glaucomatous changes\cite{21}. Recently, LC defects have been associated with glaucomatous visual field progression; in fact, the visual field progression rate was significantly faster in eyes with focal LC defects that in eyes without focal LC defects \((P=0.009)\)\cite{20}.
angle glaucoma group (77.2 vs 89.5 μm), whereas the opposite occurred in the compressive optic neuropathy group (81.5 vs 81.1). In our study, also the GCC were thicker in the inferior (91.15 μm) than in the superior quadrant (90.58 μm). In addition, in 5 out of 21 eyes (24%) the RNFL average thickness was thinner in the inferior than in the superior quadrant, as reported for glaucomatous eyes. Taken together, the above findings support the hypothesis that both compressive and glaucomatous damage is present in the early phases of GO. We suggest that swelling of the EOM belly induces optic nerve at the orbitapex. This compression exerts a “valve effect” on SAS. Ocular movements empty the SAS from the CSF thereby leading to a “dry” optic nerve, which, as shown by A-scan, results in smaller diameter. In the presence of compression, the CFS slowly flow back into the SAS leading to a reduced CSF pressure, which in turn, alters translaminar pressure. In this context, Jonas et al[23], based on population of 3468 individuals of the Beijing Eye Study 2011, found that the translaminar pressure gradient was better correlated than IOP with glaucoma markers[24]. The authors calculated the CSF pressure as follows: CSF pressure=0.44×Body Mass Index kg/m^2)+0.16×Diastolic Blood Pressure (mm Hg) - 0.18×Age (y) - 1.91. The translaminar pressure was calculated as the difference between IOP and CSF pressure[25].

In our study the reduced CSF pressure was confirmed by the positive 30 degrees test, measuring the A-scan arachonoid-arachnoid spikes. The reduction of CSF pressure was due to the orbital apex compression induced by EOM swelling. The EOMs of GO patients are the preferred target of inflammation that most often induces changes in reflectivity, structure, and thickness of orbital muscle. The consequences include apical compression on the SAS at the orbital apex that reduces the CSF pressure in the retrolaminar space[26]. In line with previous studies[7-8], we also found that, in patients affected by GO with optic nerve compression, the reduction of SAS and LC morphology were correlated with damage of GCC and RNFL. Such changes are detectable with EDI SD-OCT. We believe that LC morphology and GCC and RNFL thicknesses could be useful diagnostic tools for the early detection of optic nerve damage induced by GO. Furthermore, morphologically detectable changes of LC may precede clinically significant functional damage.

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Translaminar Pressure in Optic Nerve Compression


