Localised wedge shaped defects of the retinal nerve fibre layer in glaucoma

Jost B Jonas, Dennis Schiro

Abstract
Glaucoma can be associated with a diffuse or localised loss of the retinal nerve fibre layer (RNFL). This study evaluated the wedge shaped localised RNFL defects. Red free wide angle RNFL photographs of 421 patients with glaucoma and 193 normal subjects were examined. Localised RNFL defects were described for one eye of the normal group and for 20% of the patients with glaucoma. They were usually located in the inferior temporal and superior temporal fundus regions. Within the glaucoma group, localised RNFL defects occurred most often (p<0.05) in normal pressure glaucoma, followed by primary open angle glaucoma, and finally secondary open angle glaucoma. They were positively associated with disc haemorrhages. The localised RNFL defects had a high specificity to indicate optic nerve damage. The nerve fibre layer defects occurring more likely in mild rather than advanced glaucoma, they were helpful in the diagnosis of early glaucoma. The association between localised RNFL defects and disc haemorrhages and the varying frequency of localised RNFL defects in different types of glaucoma may be important diagnostically and pathogenetically.


Glaucomatous changes of the retinal nerve fibre layer (RNFL) can be differentiated into localised defects and into a diffuse loss of retinal ganglion cell axons. The localised dropout of retinal nerve fibres is sharply demarcated and can more easily be detected than a disseminated decrease of the RNFL (Figs 1–3). The existence of both localised and diffuse patterns of retinal nerve fibre loss suggests that two or more different mechanisms may be responsible for optic nerve damage in glaucoma.

The purpose of this study was to evaluate the frequency and location of the localised defects of the RNFL and to investigate their association with other ocular and general parameters. We addressed the questions whether localised RNFL defects always indicate a pathological condition; whether they are helpful in the 'early' diagnosis of glaucoma; whether they occur preferentially in special fundus regions; whether they are correlated with other ocular and general glaucoma parameters; and whether they support the concept of different pathomechanisms in glaucoma.

Material and methods
The study included 609 eyes of 421 patients with glaucoma and 311 normal eyes of 193 subjects (Table 1). Only one randomly selected eye per patient and subject was taken for statistical analysis. The patients and subjects were part of an ongoing prospective study on the biomorphometry of the optic nerve involving all those patients coming to the hospital with an optic nerve anomaly or disease. Eyes with a myopic refractive error exceeding −8 dioptres were excluded because of a differing optic disc morphology. Criteria for the diagnosis of glaucoma, each of which had to be fulfilled, were an elevated intraocular pressure to readings of more than 21 mm Hg with the exception of eyes with normal pressure glaucoma; glaucomatous changes of the intraripillary region of the optic nerve head such as an unusual small neuroretinal rim area in relation to the optic disc size, an abnormal form of the neuroretinal rim and cup to disc ratios being vertically greater than horizontally; and glaucomatous visual field defects. The latter comprised nasal steps of at least 10 degrees, paracentral isolated or confluent scotomata, and a mean visual field defect exceeding 2 dB or a loss variance of more than 6 units as examined by the Octopus perimeter. The subjects of the control group came to the eye clinic or hospital for an ophthalmic check up, prescription of glasses, or diseases of the contralateral eye that was not included in the study. These diseases—for example, perforating corneal injuries, did not primarily affect the optic nerve.

The total glaucoma group was divided into (i) eyes affected by primary open angle glaucoma with no obvious reason for the elevated intraocular pressure, (ii) eyes with normal pressure glaucoma with intraocular pressure readings of 20 mm Hg or less, and (iii) eyes with secondary open angle glaucoma (Table 1). In the latter, the

<table>
<thead>
<tr>
<th>Table 1 Composition of the control and glaucoma group (mean (SD))</th>
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<tr>
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<tr>
<td>Number of subjects/patients</td>
</tr>
<tr>
<td>Males/females</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Refractive error</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

POAG = primary open angle glaucoma; NPG = normal pressure glaucoma; SOAG = secondary open angle glaucoma.
The localised RNFL defects (white arrows).

Figure 1  Retinal nerve fibre layer photography of a normal eye. Black arrowheads: slit-like pseudodefects.

Figure 2  Retinal nerve fibre layer (RNFL) photograph of an eye with glaucoma. Diffuse loss of RNFL visibility compared with Figure 1.

Figure 3  Retinal nerve fibre layer (RNFL) photograph of an eye with glaucoma. Note: localised RNFL defects (white arrows).

elevation of the intraocular pressure was attributed to causes such as pseudoxfoliation of the lens, pigment dispersion syndrome, and traumatic anterior chamber angle recession. For the diagnosis of normal pressure glaucoma the intraocular pressure had to be measured in at least two 24 hour pressure profiles with at least four measurements between 5 pm and 7 am. Neurological, neuroradiological, and general medical examination did not reveal any reason for optic nerve damage other than glaucoma.

The differences in age between the normal and glaucomatous eyes were significant. Since the visibility of the RNFL depends on age,11 a control group matched for age with the glaucoma group was formed. This control group consisted of 99 subjects with a mean age of 57.8 (8.2) years and a mean refractive error of +0.5 (1.8) dioptres.

For 262 patients with primary open angle glaucoma, for 79 patients with secondary open angle glaucoma, and for all patients with normal pressure glaucoma the intraocular pressure had been measured in 24 hour pressure profiles containing at least four measurements between 5 pm and 7 am. The five highest values and the five lowest values were recorded. The mean maximal intraocular pressure was significantly the highest in the secondary open angle glaucoma subgroup (24.2 (6.0) mm Hg), p<0.001; Mann-Whitney test) followed by the primary open angle glaucoma subgroup (21.8 (5.5) mm Hg). It was the lowest in the eyes with normal pressure glaucoma (16.6 (2.4) mm Hg). Accordingly, the mean minimal intraocular pressure readings were significantly the lowest in the normal pressure glaucoma group (11.1 (2.8) mm Hg, p<0.05; Mann-Whitney test), followed by the eyes with primary open angle glaucoma (12.2 (3.0) mm Hg), and finally the secondary open angle group (12.9 (3.2) mm Hg).

For all eyes 60 degree red free photographs of the retinal nerve fibre layer had been taken as already described.12 We used a Canon 60 degree fundus camera, a high power illumination, a blue filter, and a low sensitive film with high resolution. Instead of paper prints diapositives were developed. These slides were projected with a magnification of 15 times after maximal defocusing of the projector. The area of the blurred image of the optic disc was covered, then the projector refocused and the RNFL evaluated. A localised defect was defined as a wedge shaped and not spindle-like defect, running towards or touching the optic disc border for not more than 60 degrees of the optic disc circumference (Figs 1–3). Its location was noted as the region where the localised RNFL defect reached or would reach the optic disc border. Its depth was estimated as the difference in the RNFL visibility in the area of the localised RNFL defect compared with the neighbouring sectors. For that purpose a grade of visibility of the retinal nerve fibre bundles was assigned. This grading was a subjective one, ranging from '0' for 'no fibre bundles detectable' to '8' for 'abundant nerve fibre bundles visible'. A pseudodefect was defined as a spindle-like but not wedge shaped narrow dark area in the RNFL (Fig 1).

The nerve fibre layer photographs were asses-
Table 2 Frequency of localised RNFL defects in different stages of glaucoma defined by decreasing neuroretinal rim area (SD)

<table>
<thead>
<tr>
<th>Glaucoma stage</th>
<th>No.</th>
<th>Neuroretinal rim area (mm²)</th>
<th>Localised RNFL defects (%)</th>
<th>Localised RNFL defects (numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99</td>
<td>1.80 (0.41)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>170</td>
<td>1.53 (0.37)</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>II</td>
<td>76</td>
<td>1.37 (0.32)</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>III</td>
<td>87</td>
<td>0.87 (0.26)</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>IV</td>
<td>77</td>
<td>0.54 (0.38)</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>V</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Glucoma stage 0 = normal eye. RNFL = retinal nerve fibre layer.

Results

In the normal group, localised RNFL defects were seen in one subject (1/193 or 0.5%). In the control group age-matched with the glaucoma group no localised RNFL defects were observed. Slit-like pseudodefects (Fig 1) were found most often in the inferior temporal and superior temporal fundus regions.

In the glaucoma group, the frequency of the localised RNFL defects increased from an 'early' glaucoma stage to an intermediate stage of advanced glaucomatous optic nerve atrophy and decreased again at a late stage of optic nerve damage (Table 2). In eyes with absolute glaucoma, no localised RNFL defects were detected. The dependence of the frequency of localised RNFL defects on the degree of glaucomatous optic nerve damage was found in the total glaucoma group as well as in the subgroups with primary open angle glaucoma and secondary open angle glaucoma. The subgroup with normal pressure glaucoma was too small to be subdivided further.

Corresponding to the total count of localised RNFL defects, the number of localised RNFL defects per eye increased from an early glaucoma stage to a stage with medium advanced optic nerve damage and decreased again towards absolute glaucoma.

Comparing the three glaucoma subgroups with each other, the area of the neuroretinal rim was not significantly different (Mann-Whitney test). The eyes with normal pressure glaucoma showed a significantly larger optic disc area than the other eyes (Mann-Whitney test) (Table 3). Localised RNFL defects were found most often in the eyes with normal pressure glaucoma, followed by the eyes with primary open angle glaucoma (p<0.05; χ² test). They were least common in the eyes with secondary open angle glaucoma (Table 3). Within each glaucoma subgroup, the frequency of the localised RNFL defects was independent of the optic disc area, sex, and right or left eye. Similar to the localised RNFL defects, optic disc haemorrhages were more common in the eyes with normal pressure glaucoma (2/34 or 5.9%) than in eyes with primary open angle glaucoma (13/306 or 4.3%) in which they were more frequent than in eyes with secondary open angle glaucoma (1/81 or 1.2%). Accordingly, the optic disc haemorrhages were significantly more common in eyes with localised RNFL defects (7.1%) than in eyes without localised RNFL defects (2.1%) (p<0.05; χ² test).

The localised RNFL defects were significantly (p<0.05; McNemar test) more often located in

Table 3 Frequency of localised RNFL defects and papillomorphometric data

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>p Value</th>
<th>Normals (age-matched)</th>
<th>p Value</th>
<th>Glaucoma</th>
<th>p Value</th>
<th>POAG</th>
<th>p Value</th>
<th>NPG</th>
<th>p Value</th>
<th>SOAG</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects/patients</td>
<td>193</td>
<td>NS</td>
<td>99</td>
<td>421</td>
<td>306</td>
<td>2.61 (0.54)</td>
<td>&lt;0.001</td>
<td>3.07 (0.77)</td>
<td>&lt;0.001</td>
<td>2.50 (0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic disc area (mm²) (SD)</td>
<td>2.72 (0.64)</td>
<td>NS</td>
<td>2.73 (0.63)</td>
<td>NS</td>
<td>2.64 (0.58)</td>
<td>NS</td>
<td>2.61 (0.54)</td>
<td>&lt;0.001</td>
<td>3.07 (0.77)</td>
<td>&lt;0.001</td>
<td>2.50 (0.48)</td>
<td></td>
</tr>
<tr>
<td>Neuroretinal rim area (mm²) (SD)</td>
<td>1.86 (0.42)</td>
<td>NS</td>
<td>1.80 (0.41)</td>
<td>&lt;0.001</td>
<td>1.04 (0.53)</td>
<td>NS</td>
<td>1.03 (0.56)</td>
<td>0.95 (0.34)</td>
<td>NS</td>
<td>1.15 (0.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of localised RNFL defects</td>
<td>0-5%</td>
<td>NS</td>
<td>0%</td>
<td>&lt;0.001</td>
<td>20%</td>
<td>NS</td>
<td>19%</td>
<td>&lt;0.05</td>
<td>47%</td>
<td>&lt;0.05</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Number of localised RNFL defects</td>
<td>1</td>
<td>NS</td>
<td>0</td>
<td>&lt;0.001</td>
<td>84</td>
<td>NS</td>
<td>58</td>
<td>&lt;0.05</td>
<td>16</td>
<td>&lt;0.5</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

p Value indicates the significance of the difference between the two values adjacent to each other in the same line.

RNFL = retinal nerve fibre layers; POAG = primary open angle glaucoma; NPG = normal pressure glaucoma; SOAG = secondary open angle glaucoma; NS = not significant.
Table 4  Frequency (%) and position of localised retinal nerve fibre layer defects when touching the optic disc border; position 1 hour to 12 hour clockwise counted in left eyes and counted anticlockwise in right eyes (3 hours = temporal horizontal; 9 hours = nasal horizontal)

<table>
<thead>
<tr>
<th>Position</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>6-2</td>
</tr>
<tr>
<td>2-3</td>
<td>4-0</td>
</tr>
<tr>
<td>4-5</td>
<td>3-3</td>
</tr>
<tr>
<td>5-6</td>
<td>7-1</td>
</tr>
<tr>
<td>6-7</td>
<td>8-1</td>
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<tr>
<td>7-8</td>
<td>1-4</td>
</tr>
<tr>
<td>8-9</td>
<td>0-2</td>
</tr>
<tr>
<td>9-10</td>
<td>0-0</td>
</tr>
<tr>
<td>10-11</td>
<td>0-2</td>
</tr>
<tr>
<td>11-12</td>
<td>1-0</td>
</tr>
<tr>
<td>12-1</td>
<td>4-5</td>
</tr>
</tbody>
</table>

Discussion
The ophthalmoscopic evaluation of the retinal nerve fibre layer has increasingly gained interest since its first description by Vogt in 1913 and 1917 and its 're-discovery' by Hoyt, Frisén and coworkers in 1972 and 1973. Sommer, Quigley, Airaksinen, Schwartz, Iwata and other investigators repeatedly reported on glaucomatous changes of the RNFL and on the importance of the RNFL evaluation for the diagnosis of glaucoma. The RNFL alterations were differentiated into a diffuse loss and a localised dropout of retinal nerve fibre bundles. In the present study, we examined the localised RNFL defects and evaluated their value for glaucoma diagnosis.

DO LOCALISED RNFL DEFECTS ALWAYS INDICATE A PATHOLOGICAL CONDITION?
Since localised RNFL defects were very rarely observed in the normal eyes of this masked study, they had a high specificity (proportion of normal eyes without localised RNFL defects) to indicate optic nerve damage. It shows that localised RNFL defects almost always indicate an optic nerve abnormality. According to their prevalence in the glaucoma group, the localised RNFL defects had a sensitivity (proportion of glaucoma eyes with localised RNFL defects) of only 20%. It indicates that in the presence of localised RNFL defects optic nerve damage is very likely, and that the absence of localised RNFL defects does not contradict optic nerve atrophy. The localised RNFL defects should not be confused with slit-like or spindle shaped pseudodefects (Fig 1). Similar to the localised RNFL defects, the slit-like pseudodefects were found most often in the superior temporal and inferior temporal fundus regions corresponding to the thickest retinal nerve layer and the best ophthalmoscopic RNFL visibility in these regions in normal eyes. 

ARE LOCALISED RNFL DEFECTS HELPFUL IN THE 'EARLY' DIAGNOSIS OF GLAUCOMA?
The detection of localised RNFL defects is helpful in the 'early' glaucoma diagnosis because the RNFL changes were present in eyes with only slight glaucomatous optic nerve damage (Table 2). This is in agreement with the literature. Airaksinen et al found localised RNFL defects more often in ocular hypertensive subjects than in glaucoma patients with visual field defects. Sommer et al reported that 60% of ocular hypertensive eyes showed RNFL changes six years before visual field defects developed. Quigley et al described RNFL changes to be more sensitive to indicate early optic nerve damage than optic disc changes. Although the reported RNFL changes were not only localised RNFL defects, it indicates that one should look for localised RNFL defects during every ophthalmoscopic examination especially in eyes of ocular hypertensive subjects.

DO LOCALISED RNFL DEFECTS OCCUR PREFERENTIALLY IN SPECIAL FUNDUS REGIONS?
The localised RNFL defects were found most often in the inferior temporal and superior temporal fundus regions, followed by the temporal horizontal sector. They were least common in the nasal part of the fundus (Table 4). This sequence of regions correlates with several other parameters: the histology of the retinal nerve fibre layer that is thicker in the inferior and superior peripapillary areas than in the temporal and nasal peripapillary regions; the visibility of the retinal nerve fibre bundles that are best detectable in the inferior temporal fundus region following by the superior temporal sector, the nasal superior area, and the nasal inferior fundus region; the shape of the neuroretinal rim that is wider in the inferior and superior disc regions compared with the nasal and temporal disc sectors; and the morphology of the lamina cribrosa with the largest pores in the inferior and superior disc regions and the smallest pores in the temporal and nasal areas.

The question arises whether the localised RNFL defects were more often observed in the inferior temporal and superior temporal sectors because these regions have a high RNFL visibility in normal eyes or because the fibres coming from the superior temporal and inferior temporal fundus regions are preferentially lost by a circumscribed damaging mechanism. Corresponding with their frequency, the depth of the localised RNFL defects was largest in the temporal inferior and temporal superior fundus regions. It can be explained by the histology of the retinal nerve fibre layer. It is normally thickest and thus ophthalmoscopically best visible in the temporal inferior and temporal superior fundus sectors. Consequently a localised RNFL defect can be much deeper in these regions compared with the temporal horizontal or nasal fundus regions where the retinal nerve fibre layer is much thinner.

ARE LOCALISED RNFL DEFECTS CORRELATED WITH OTHER OCULAR AND GENERAL GLAUCOMA PARAMETERS?
The localised RNFL defects were more common in eyes with normal pressure glaucoma compared with eyes with primary open angle glaucoma or eyes with secondary open angle glaucoma (Table 3). One has to take into consideration that this varying frequency of the localised RNFL defects in the different glaucoma subtypes may be the result of bias in referral of patients. Eyes with normal pressure glaucoma might have been transferred mainly to
due to abnormal optic disc parameters such as high cup to disc ratios, and patients with second-
ary open angle glaucoma may be the result of localised RNFL defects. This can explain the decreased fre-
quency of localised RNFL defects in eyes with far advanced or even absolute glaucoma com-
pared with eyes with medium advanced optic nerve atrophy (Table 2). The presence of both a diffuse type of RNFL loss as shown by Tuulonen and Airaksinen and a localised type of RNFL loss in the eyes with early glaucoma or medium advanced nerve damage shows, however, that the localised and diffuse RNFL changes might indicate different mechanisms in the glauco-
matous process.


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