

CHAPTER 1

General introduction

General Introduction

1. Glaucoma

The number of people with glaucoma has been estimated at 66.8 million, with 6.7 million suffering from bilateral blindness.¹ This makes glaucoma the second leading cause of irreversible blindness worldwide. Glaucoma is a progressive optic neuropathy characterized by loss of retinal ganglion cells. It has a multifactorial origin with an elevated intraocular pressure (IOP) as the most important risk factor.² The hallmark of the disease is the typical excavation of the optic nerve head as seen on ophthalmic examination.³ When left untreated, glaucoma results in visual field loss and eventually blindness. The course of events that leads to death of the retinal ganglion cell (RGC) is not exactly known. Roughly, there are two theories that explain how the RGC is affected in glaucoma: direct mechanical damage by elevated intraocular pressure and/or indirect damage by disturbances in ocular blood flow.⁴ In considering the diagnosis of glaucoma, the physician will evaluate the IOP, the optic nerve head and the visual field. This seems to be a straightforward diagnostic process but, unfortunately, all three signs have their shortcomings as diagnostic criteria.

2. Intraocular pressure (IOP)

Epidemiological data show that glaucoma is a multifactorial disease with elevated IOP as the most important risk factor.² Other risk factors include age, black ethnic origin, positive family history, myopia, diabetes, migraine and cardiovascular disease.² Glaucoma patients tend to have an elevated IOP, but not all patients have this sign. Conversely, not all people with an elevated IOP also develop glaucoma. This is illustrated by reports in which an abnormal IOP was defined as > 21 mm Hg. The sensitivity for detecting glaucoma was 44% to 59%, at specificity levels between 92% to 95%.⁵⁻⁷ The condition of elevated IOP without evidence of glaucoma is called ocular hypertension. Thus, although the IOP adds to an individual's risk profile for glaucoma, its sensitivity is too low to serve as a diagnostic criterion. In addition, the IOP is typically measured once during an ophthalmic visit, whereas large (undetected) fluctuations of the IOP during the day and also during the night may exist.⁸ Finally, the IOP measurement may vary with corneal thickness.⁹

3. Morphology of the optic disc

Glaucomatous cupping of the optic disc is the hallmark of the disease: with increasing loss of retinal ganglion cells, the optic disc becomes more and more excavated (or cupped). Traditional ophthalmoscopic judgement of the optic disc is subject to moderate inter- and intra-observer reproducibility,^{10,11} and lacks a quantitative nature. Better reproducibility of judgement is obtained with stereophotographs of the optic disc,^{12,13} but the results in terms of sensitivity and specificity for detecting glaucoma still vary widely between investigators. This may be, in part, due to practical problems with image acquisition. For a true stereographic (rather than a pseudo-stereographic) image, one needs to take two simultaneous images with a fixed parallax. Even more important is the need for fully dilated pupils and clear media in the patient. As a result of this, a part of the patient population is unsuited for imaging. In a recent report, 13% of the test population could not be successfully imaged.¹⁴ All in all, stereophotographs have never become widespread in glaucoma diagnosis.

As glaucoma progresses, it is accompanied by progressive visual field loss in the patient. The assessment of the (damaged) visual field of the patient is called perimetry. It is an indispensable diagnostic test because of all tests, it most closely relates to the visual (dys)function of the patient. The Humphrey Field Analyzer (HFA, Zeiss Humphrey Systems, Dublin, CA, USA) is a widely used perimeter, both clinically and scientifically. Despite its value for glaucoma diagnosis, it has a number of drawbacks that preclude its use as a criterion for glaucoma. A considerable part of the test population fails to produce a reliable¹⁵ test result. In one study, the sensitivity and specificity of the Glaucoma Hemifield Test (a much examined test parameter) was 94% and 90%, respectively.¹⁶ However, these good results were obtained after exclusion of 31.5% of that part of the test population that had failed to produce a reliable test result. This may be explained by fatigue (as a result of the long test duration) or inability to understand the instructions during testing. Also, when subjects are performing perimetry for the first time, a learning effect has to be considered.¹⁷ In many trials where long term perimetric data is analyzed, such as the recent Ocular Hypertension Treatment Study (OHTS), a perimetric baseline is routinely repeated.¹⁸ Even when the subject is familiar with perimetry, the reproducibility of measurements may be poor. At some point in the OHTS, subjects whose visual field had become abnormal were re-tested. On the repeated test the abnormality was reproduced in only 14.1%.¹⁹ Also, there is no consensus on the exact definition of the glaucomatous visual field, nor on its perimetric progression, despite the many efforts towards standardization.²⁰⁻²² Finally, histopathologic evidence suggests that 25-50% of all RGCs have to be damaged before visual field defects become apparent.^{23,24}

4. Visual field loss

Of all the risk factors that play a role in glaucoma, the IOP is presently the only one that can be altered therapeutically. This can be done pharmaceutically (eye drops or oral medication) or surgically (laser surgery, filtering surgery or implant surgery). For a long time, unequivocal reports in the literature existed on the benefit of treating patients with ocular hypertension.²⁵⁻³² More recently, the Ocular Hypertensive Treatment Study (OHTS) set out to provide a definite answer to the dilemma.³³ It documented a delay or prevention of onset of glaucoma in the group that received topical hypotensive treatment as compared to the control group.

5. Treatment of glaucoma

There is good evidence that, once glaucoma has been established, IOP lowering treatment slows down progression of the disease. This has been shown for pharmaceutical treatment,³⁴⁻³⁶ and for surgical treatment (Advanced Glaucoma Intervention Study).³⁷ Since glaucomatous damage is irreversible, patients will benefit from early detection and early initiation of treatment. This is important for patients who already have glaucoma (to slow down progression) and for subjects with a high risk profile for glaucoma (to prevent or delay the onset of glaucoma).

With no generally agreed upon criteria, diagnosing glaucoma can be quite a challenge, even to the experienced glaucoma specialist. Today, there is still no measure that relates to the nature of the disease (the retinal ganglion cell), that is quantitative, objective, well reproducible, fast and patient friendly to obtain, and, above all,

6. Glaucoma as a clinical challenge

highly sensitive and specific for glaucoma. This explains why a lot of research of the last decade has focussed on finding such a measure. One field of this research is called imaging.

7. Imaging

Along with the fast rise in laser technology and quality of optical components, various instruments were developed to assess structures that contain RGCs. Well-known imaging techniques include Scanning Laser Topography, commercially available as the Heidelberg Retina Tomograph³⁸⁻⁴¹ and the Topographic Scanning System.^{42,43} This technique provides quantitative, three-dimensional information on the morphology of the optic disc. Retinal Thickness Analysis⁴⁴ provides quantitative data on the thickness of the retina and is not primarily a tool for glaucoma diagnosis. Optical Coherence Tomography⁴⁵⁻⁴⁷ and Scanning Laser Polarimetry provide quantitative data on the thickness of the peripapillary retinal nerve fiber layer. The latter technology is studied in this thesis.

8. Scanning Laser Polarimetry (SLP)

The first scanning laser polarimeter (Laser Diagnostic Technologies, San Diego, CA, USA)⁴⁸⁻⁵⁰ came to the market in 1993 as the Nerve Fiber Analyzer. Extensive hardware revisions lead to the Nerve Fiber Analyzer II, which was later upgraded to the Nerve Fiber Analyzer/GDx (in short: GDx). The GDx features statistical software that compares an individual's data to a normative database.

The GDx is a confocal scanning laser ophthalmoscope that assesses retinal nerve fiber layer (NFL) thickness in the peripapillary retina. The NFL is made up of axons from the RGCs. The working principle of polarimetry is based on the retinal NFL being the most form-birefringent structure in the retina. A polarized 780-nm laser beam is aimed at the peripapillary retina. As the laser light passes through the NFL, a phase shift in the state of polarization occurs. This phase shift is called retardation and is thought to arise at the level of the axonal microtubules.⁵¹ The polarization is relatively unaltered by the remaining structures in the retina. After reflection by the retinal pigment epithelium, the light passes through the retina again, and is captured by the detector in the instrument where the amount of retardation is measured. The highest retardation values are found around the 12 o'clock and 6 o'clock position, and correspond to known locations of the superior and inferior NFL bundle.⁵²⁻⁵⁴ It was found in a monkey model that the retardation linearly correlated with NFL thickness.^{54,55} One degree of retardation corresponded to 7.4 microns of NFL thickness with a 514-nm laser.⁵⁵ Instead of a 514-nm laser, the current instrument uses a 780-nm laser source. Correcting for the wavelength, the manufacturers have chosen a conversion factor of 3 microns for every degree of retardation (Zhou Q, Laser Diagnostic Technologies, written communication). Unfortunately, this correlation has never been histopathologically validated in humans.

In about 0.7 seconds, the peripapillary retina is scanned at 65,536 locations, and a retardation image of 256x256 pixels is constructed. This image is color-coded: a continuous scale from yellow to red to blue represents areas from high to low retardation. A retardation image of a healthy eye (fig 1-1, p. 102) has red and yellow colors at the 12 and 6 o'clock position, corresponding to the superior and inferior arcuate

bundle. The image is typically blue in the nasal and temporal area. On the printout (fig 1-2) there is also a reflectance image that is constructed from the intensity of the backscattered light. Since it is an image constructed from monochromatic information, it lacks the usual detail of conventional optic disc photographs and clinicians should resist the urge to judge the optic disc from it. On the GDx printout, the reflectance image holds value as a reference image for the retardation data. In this image, the operator will typically position a circle or ellipse on the margin of the optic nerve head. A second one with 1.75 times the diameter of the first is displayed automatically. It allows the calculation of the parameters from those pixels that sit peripherally to it. The second circle is also the inner circle of a 10-pixel wide band, displayed on the retardation image. The retardation values under the band are displayed in the so-called double hump graph. This curve represents a cross section of the two arcuate bundles with the nasal and temporal areas in between.

For a quantitative approach to the retardation image, several automated parameters are available to the user. First, areas of blood vessels are automatically eliminated from analysis since they are a source of noise.^{56,57} Next, the retardation image is divided into 4 sectors: a 120 deg superior sector, a 50 deg nasal sector, a 120 deg inferior sector and a 70 deg temporal sector. Finally, 14 parameters are calculated automatically. For example, the superior maximum parameter is the average of the 1500 thickest pixels in the 120 deg superior sector, and reflects the thickness of the superior nerve fiber bundle. All parameters that are calculated by the software are used to calculate a summary parameter called 'the Number'. The Number ranges from 1-99. The higher the Number, the higher the probability of glaucoma. The Number is calculated by a proprietary algorithm that was developed with the help of a neural network.

After having used the GDx for some time, we found that images in some patients reproduced poorly. This turned out to be caused by eye movements during imaging, resulting in what we called "motion artifacts". In *chapter 2* we have determined the effect of motion artifacts on the retardation values and have illustrated how motion artifacts can be recognized. Also, this has led to the definition of 4 criteria for image quality.

9. Clinical studies in SLP

In *chapter 3*, the reproducibility of measurements of high quality images was assessed. Weinreb *et al.*⁵⁶ had already reported a coefficient of variation of 4.5% for measurements with the NFA I. We argued that a coefficient of variation is of limited clinical value. We wanted to know how much a GDx output parameter from two consecutive measurements was allowed to change before it became statistically significant. The limits of agreement, first described by Bland and Altman,⁵⁸ is such a measure. We calculated the limits of agreement for all available GDx parameters, and for normal subjects and glaucoma patients separately.

In the normal eye, the NFL is thickest around the 12 and 6 o'clock position: the superior and inferior nerve fiber bundle. This was also found with the GDx.⁵⁴ Some patients, however, had an abnormal NFL pattern. These subjects were otherwise without abnormalities on ophthalmic examination, especially without evidence for

glaucoma. We called this variability in NFL orientation a “split bundle”. In *chapter 4*, a definition for split bundles is proposed, and the prevalence is determined in a large number of healthy eyes.

In *chapter 5*, we assessed NFL thickness in eyes with strabismic amblyopia. Although the amblyopic eyes had a poor visual acuity, we found no differences in NFL thickness when compared to the fellow, healthy eye. Clinically, this means that the standard normative database can also be used for amblyopic eyes under evaluation for glaucoma.

The NFL is also subject to other diseases than glaucoma. One such a disease is an anterior ischemic optic neuropathy (AION) where decreased perfusion of the anterior part of the optic nerve results in ischemic damage and visual loss. *Chapter 6* describes images of an eye that suffered from an AION. We found that the NFL had considerably decreased in thickness 3-4 weeks after the onset of the insult.

In *chapter 7*, four new GDx parameters have been examined. In addition to the parameters that are available on the GDx printout, several authors had developed new parameters, to better discriminate between normal subjects and glaucoma patients. The Ellipse Standard Deviation, developed by Choplin *et al.*,⁵⁹ is the standard deviation around the mean of the values contained in the measuring ellipse. The Normalized Superior Area developed by Xu *et al.*,⁶⁰ is the area under a 90 deg sector of the double hump graph with the highest retardation in the superior region. The Normalized Inferior Area is defined likewise, only for the inferior region. The fourth parameter is called the Discriminant Analysis, which is identical to the Linear Discriminant Function developed by Weinreb *et al.*⁶¹ It is calculated by an algorithm that uses three existing parameters: average thickness, ellipse modulation and ellipse average. The new parameters had not been previously validated on a population other than the one from which they were derived. We imaged 263 normal subjects and 241 glaucoma patients and determined sensitivity and specificity values for detecting glaucoma of the four new parameters. Sensitivity values were calculated again for early, moderate and advanced glaucoma separately.

While working with the GDx, we found that printouts generally contained more useful information than was reflected by the parameters. We gradually developed a standardized interpretation protocol for GDx printouts. We found that other ophthalmologists found this protocol useful as well, and that initiated a series of instruction courses known as The Rotterdam GDx Course. In *chapter 8*, we evaluated the application of this interpretation protocol. We tested it against the Number, which was the current best parameter, and found that the sensitivity and specificity of subjective judgement was considerably better.

In *Chapter 9*, the general discussion of this thesis is presented. *Chapter 10* contains the summary of the main findings. The CD-ROM version of the Rotterdam GDx course can be found in the appendix.

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