Glaucoma care optimised in an ageing population

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CHAPTER 1

General Introduction

With an estimated number of 64.3 million people having the disease worldwide, glaucoma is the leading cause of irreversible blindness.[1] Glaucoma is defined by the World Glaucoma Association as "*a group of eye diseases that cause progressive damage of the optic nerve at the point where it leaves the eye to carry visual information to the brain. If left untreated, most types of glaucoma progress (without warning nor obvious symptoms to the patient) towards gradually worsening visual damage and may lead to blindness. Once incurred, visual damage is mostly irreversible*" (http://www.worldglaucoma.org/what-is-glaucoma). From this definition some the key features of glaucoma can be extracted, being: (1) Glaucoma is a disease of the optic nerve; (2) Glaucoma affects the visual field; (3) Glaucoma is a progressive disease; (4) Damage due to glaucoma is irreversible; and (5) Glaucoma can be present or progress without the patient noticing it. Note that intraocular pressure and other related factors are not defining criteria for glaucoma.

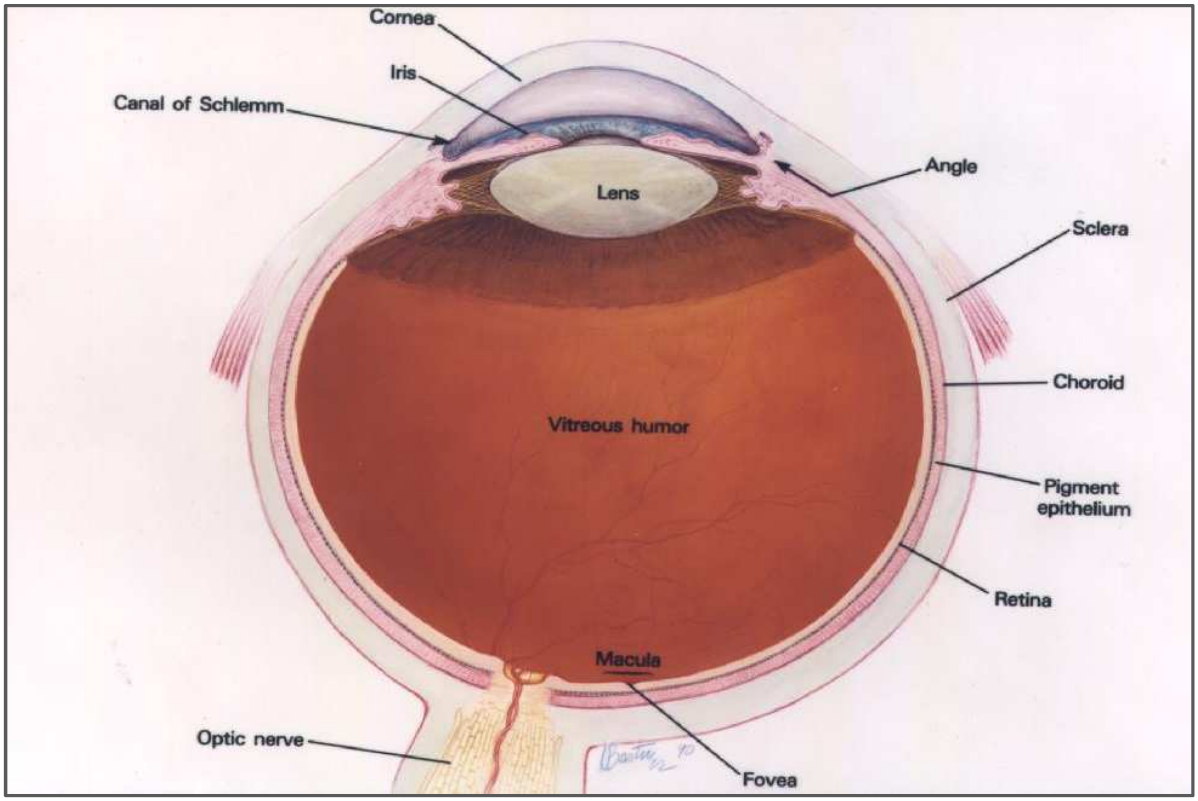

Figure 1.1. *Drawing of the Eye. (with permission from: The National Eye Institute; https://nei.nih.gov)*

Glaucoma is a disease of the optic nerve

The pathophysiologic change in glaucoma is at the level of the retinal ganglion cells, which are central nervous system neurons. There are approximately 1.2 million of these cells in the human eye.[2] Together they form the optic nerve which

carries visual information from the eye to the brain (**figure 1.1**). The common denominator in all types of glaucoma is a decrease in the number of retinal ganglion cells (RGCs) beyond the normal physiological loss that comes with advancing age (**figure 1.2**). Ganglion cell death leads to structural changes of the retinal nerve fiber layer (RNFL) and at the level of the optic disc, being loss of the neuroretinal rim and enlargement of the optic disc cup. The structural changes are most profound on the superior and inferior pole of the optic disc and RNFL. There have been several theories explaining these changes, among which mechanical damage, vascular (ischemic) injury, and combined theories.[3] None of these fully reveal the exact mechanism of glaucomatous neuropathy. The RNFL and the optic disc can be visualized and analyzed with ophthalmoscopy and imaging modalities like (stereo)photography, confocal laser-scanning ophthalmoscopy, scanning laser polarimetery, and ocular coherence tomography.

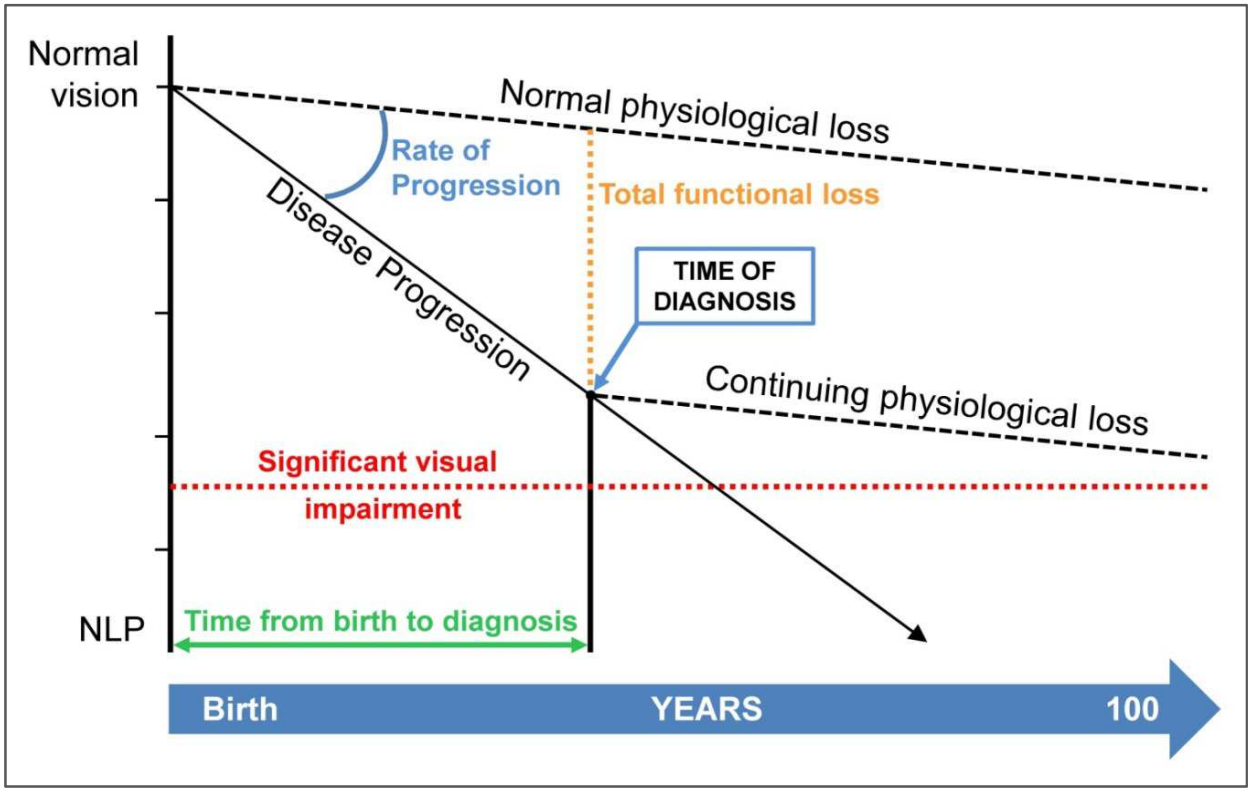

Figure 1.2. *Schematic of the course of glaucoma. In this graph the visual function of an eye or individual is placed on the y-axis and the time of life on the x-axis. The black dashed line at the top represents a normal physiological loss of visual function, and the continuous line represents pathologic loss of visual function. The red dashed line represents the amount of visual function under which the patient experiences visual impairment. (adapted from European Glaucoma Society. The Terminology and Guidelines for Glaucoma, 4th edition. Savona: Svetprint d.o.o., 2014)*

Glaucoma affects the visual field

The normal field of view extends 100 degrees laterally, 60 degrees medially, 60 degrees upward, and 75 degrees downward.[4] The normal human visual field has the highest sensitivity to light in its center. This sensitivity gradually decreases to the periphery, forming the classical hill of vision. With advancing age the visual field undergoes a global but relatively mild decrease in light-sensitivity, lowering the hill of vision slightly. In contrast, glaucoma starts with focal defects in the visual field, corresponding to the affected axons. This causes "valleys" within the hill of vision, classically in an arcuate form, called arcuate or Bjerrum scotoma (**figure 1.3**). Other forms of defects, like paracentral scotoma, altitudinal defects, or a nasal step are not uncommon. As the structural changes are most profound on either the superior or inferior side of the horizontal meridian, so are the visual field defects. Mostly, the central part of the visual field is spared until the late phases of the disease, but – disabling – exceptions exist.

The visual field can be measured using a perimeter. Perimetry measures the ability of the subject to distinguish a light stimulus from a uniform background. Automated perimetry has become the standard form of perimetry in glaucoma today. It uses white static stimuli on a white background and measures a fixed number of test location within the central 24 or 30 degrees of the visual field (Standard Automated Perimetry; SAP). The threshold sensitivity for all test location is determined and then compared to an age corrected normative database. Any deviations are displayed on a printout as Total Deviations (TD; **figure 1.3**). A global index of these deviations is calculated by the perimeter (Mean Deviation; MD). The MD ranges from approximately 0 dB in a normal visual field to around -30 dB in a blind visual field, and is a key parameter in many chapters.

Glaucoma is a progressive disease

As stated above, the number of retinal ganglion cells in patients with glaucoma decreases beyond the physiological loss that comes with advancing age, leading to visual field loss. This is demonstrated in **figure 1.2**, where a patient's life span is placed on the x-axis and the visual function is placed on the y-axis. The dashed red line represents the amount of visual function damage at which there is significant visual impairment. It can be seen that a normal physiological decay in visual function will not result in impairment. If the decay is pathologically fast, however, the patient's visual function will intersect the line representing visual

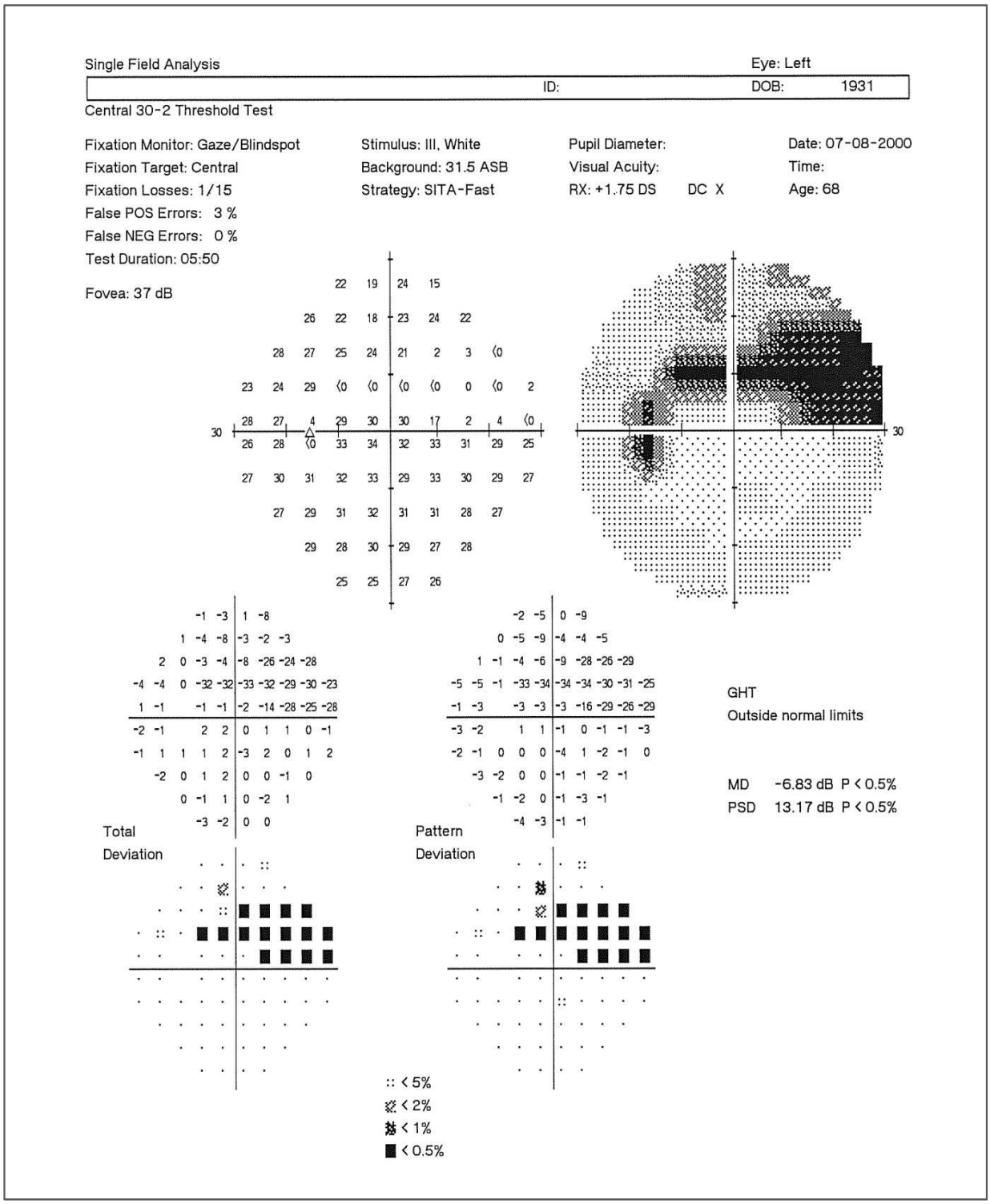

Figure 1.3. *Printout of a Standard Automated Perimetry visual field examination in a 68 years old glaucoma patient with a Bjerrum scotoma of the left eye. On the top, patient information is displayed. The top-left plot shows the numeric light sensitivities of all test points. These are graphically represented in the top-right plot, called the grayscale plot. On the left side on the bottom half of the printout, two small plots are displayed, one above the other, labeled Total Deviation (TD). The numeric values in the upper portion represents the difference in decibels between the patient's test results and the age-corrected normal values. The lower TD plot translates the values from the upper plot into shaded symbols indicating the statistical significance. The Mean Deviation (MD) is displayed on the far right side.*

impairment. If glaucoma is diagnosed before this point and the disease progression can be slowed down to (ideally) a physiological amount, then the patient can be spared from visual impairment. Lowering the intraocular pressure is essentially the only proven way to lower the glaucoma progression rate.[5-10]

The rate of progression is defined as the difference between the normal physiological loss and the disease progression velocity. This rate of progression is an important variable in glaucoma care. The guidelines from the European glaucoma society for instance state: "treatment must be individualized to the needs and rate of progression of each patient". Hence, it is important to carefully evaluate the glaucoma patient's visual field and ganglion cell status longitudinally, providing a quantification of the rate of progression. It also underlines the importance of longitudinal studies in the field of glaucoma.

Damage due to glaucoma is irreversible

There is some evidence that with the lowering of the intraocular pressure (IOP), a small improvement in structural or functional parameters can be observed.[11-14] This may be the result of RGCs that were on the verge of cell death that are just salvaged by lowering the IOP. Besides this effect, glaucoma is irreversible. This means that all consequences for the visual field and thus for the impact on the patients quality of life are irreversible as well.

As stated in the first paragraph, glaucoma is a leading cause of blindness. In a recent review of retrospective studies, it was calculated that up to 24% of glaucoma patients met criteria for unilateral blindness at the end of life and 10% met criteria for bilateral blindness at the end of life.[15] Risk factors for blindness in this review were fourfold: (1) worse disease stage at baseline (time of diagnosis); (2) worse IOP parameters; (3) longer duration from baseline to death; and (4) coexistence other ocular pathology.

Glaucoma can be present or progress without the patient noticing it

Only one quarter of glaucoma patients will have eye symptoms at the time of diagnosis. Of this quarter, only one fourth has symptoms related to their glaucoma, whereas the remainder has symptoms related to another disorder. This means that less than 10% of patients had eye symptoms related to their glaucoma at the time of diagnosis.[16] Furthermore, it has been calculated that about 50% of newly

diagnosed glaucoma patients have moderate or advanced visual field defects to start with.[17] Since 50% is by far more than 10%, moderate or advanced glaucoma can be present in patients without any recognized glaucoma related symptoms. In other words: patients progressed to moderate or advanced stages without the patient being aware of having the disease.

Intraocular pressure and other risk factors for glaucoma

Intraocular pressure is regarded the most important risk factor for glaucoma. Numerous studies showed increased prevalence and incidence with increasing IOP[18-21] or decreased the risk of glaucomatous progression with lowering of the IOP.[5-10] Nevertheless, there is considerable overlap in IOP in people with and people without glaucoma.[22] There is no single value at which the intraocular pressure is too high. Sir Duke-Elder defined a high intraocular pressure in his System of Ophthalmology as: *"The degree of raised pressure which assumes a pathological significance is impossible to define"*.

Other risk factors for glaucoma can be subdivided into ocular, systemic and demographic. Ocular risk factors for glaucoma are myopia, smaller central cornea thickness, and pseudoexfoliation.[23-25] Demographic risk factors include a family history of glaucoma and age.[20,26-29] There are also racial differences as well. In Africans, Africa descended people and Hispanics the prevalence of open angle glaucoma is higher than in whites.[27,30-33] No convincing relations are found between systemic factors such as diabetes, blood pressure, smoking, or diet.[34]

Groningen Longitudinal Glaucoma Study

Cornerstone for the current thesis is Groningen Longitudinal Glaucoma Study (GLGS), a cohort study in a clinical setting. The study started at the 1st of July 2000 and is still ongoing. All patients attending the glaucoma service of our outpatient department were included from this day until the 30th of June 2001. Patients who provided informed consent were included in an institutional review board-approved observational prospective follow-up using conventional perimetry, frequency doubling perimetry (FDT; Carl Zeiss Meditec AG, Jena, Germany) and laser polarimetry (GDx; Laser Diagnostic Technologies, San Diego, CA, USA). The GLGS taught us the sensitivity and specificity of GDx and FDT for detecting patients with glaucomatous visual field defects.[35] It also showed that confirming an abnormal FDT test resulted in a better diagnostic performance.[36] Furthermore, it

appeared that FDT and GDx test results were helpful for identifying glaucoma suspect patients at risk of developing glaucomatous visual field loss.[37]

Outline of this thesis

This thesis is about optimizing the ophthalmic care for the glaucoma patient. How should the available tests be used and interpreted? Can visual field testing be improved or perhaps replaced by tests that are more easily performed? And since glaucoma is mainly a disease of the elderly: can the intensity of glaucoma care safely be reduced if patients are in the fall of their lives?

Detecting visual field progression in a series of visual field tests of a single glaucoma patient can be challenging. **Chapter 2** describes the visual field follow-up of the patients enrolled in the GLGS. In this chapter it is determined which patients showed visual field progression and at what speed the fields deteriorated. A novel algorithm for detecting glaucomatous visual field progression that can be easily used in clinical practice is presented. It is compared to an existing algorithm that is commercially available in perimeters or visual field software. In clinical practice it is useful to know which glaucoma patients are most likely to show progressive glaucoma. **Chapter 3** presents the results of univariate and multifactorial risk factor analysis for glaucomatous visual field progression. Three different statistical approaches are compared. **Chapter 4** covers the suitability of using FDT and GDx for detecting glaucoma progression in a clinical setting. For this, the ability of standard automated perimetry, FDT and GDx in detecting glaucoma progression is compared. Furthermore, the longitudinal signal-to-noise ratios of the three testing modalities are compared to further gain insight in the test characteristics. Perimetry can be tiresome and trying for some glaucoma patients. The possibility of optimizing the perimetric test strategy is the topic of **chapter 5**. It is explored if it is safe to ignore blind parts of the visual field in future tests. In **chapter 6 and 7**, it is calculated at what age it can be reasonably said that a glaucoma patient will not be blind at the time of death. For these calculations, the residual life expectancy is determined, being life expectancy, corrected for the age already reached. Furthermore, gender, current visual field status and visual field progression velocity are taken into account in calculating whether a glaucoma patient will go blind. The certainty of the predictions is calculated.

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