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DOTTORATO DI RICERCA TOSCANO IN NEUROSCIENZE

CICLO XXXIII

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Normal Tension Glaucoma Development in two years long-term evolution of in idiophatic Normal Pressure Hydrocephalus patients who received CSF shunting :follow up

Settore Scientifico Disciplinare MED/30

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1. INTRODUCTION

1.1 Glaucoma

1.1.1 Definition

The term “glaucoma” describes a group of ocular disorders of multi-factorial etiology united by a characteristic optic neuropathy with potentially progressive, clinically visible changes at the optic nerve head. All forms of the disease have in common a neurodegeneration of retinal ganglion cell axons, represented by focal or generalized thinning of the neuroretinal rim, with excavation and enlargement of the optic cup. To this corresponds a visual field loss, initially peripheric and arciform, but which can lead to complete loss of vision.

1.1.2 Classification

Glaucoma may be congenital or acquired. The most common types are open-angle glaucoma, closed-angle glaucoma and normal-tension glaucoma (NTG). Open-angle and angle-closure types are distinguished based on the mechanism by which aqueous outflow is impaired with respect to the angle configuration. Distinction is also made between primary and secondary glaucoma; in the latter a recognizable ocular or non-ocular disorder contributes to elevation of intraocular pressure (IOP).

1.1.3 Epidemiology

Glaucoma is the leading cause of global irreversible blindness. According to Bonomi et al., the prevalence of glaucoma is around 1,1%.[1] A review estimated that 67 million people globally, of whom 25 million live in Europe, are affected by glaucoma.[2] Primary open-angle glaucoma (POAG)

is the most common form in white, Hispanic/Latino and black individuals. On a worldwide basis, primary angle closure (PAC) constitutes up to half of cases and has a particularly high prevalence in Asian individuals.[3]

1.1.4 Anatomy

1.1.4.1 Aqueous production

Aqueous humour is produced from plasma by the ciliary epithelium of the ciliary body pars plicata, using a combination of active and passive secretion. A high-protein filtrate passes out of fenestrated capillaries (ultrafiltration) into the stroma of the ciliary processes, from which active transport of solutes occurs across the dual-layered ciliary epithelium. The osmotic gradient thereby established facilitates the passive flow of water into the posterior chamber. Secretion is subject to the influence of the sympathetic nervous system, with opposing actions mediated by beta-2 receptors (increased secretion) and alpha-2 receptors (decreased secretion). Enzymatic action is also critical – carbonic anhydrase is among those playing a key role.

1.1.4.2 Aqueous outflow

The trabecular meshwork (trabeculum) is a sieve-like structure at the angle of the anterior chamber (AC) through which 90% of aqueous humour leaves the eye. It has various components (Figure 1).

• The uveal meshwork is the innermost portion, consisting of cord-like endothelial cell-covered strands arising from the iris and ciliary body stroma. The intertrabecular spaces are relatively large and offer little resistance to the passage of aqueous.

• The corneoscleral meshwork lies external to the uveal meshwork to form the thickest portion of the trabeculum. It is composed of layers of connective tissue strands with overlying endothelial-like cells. The intertrabecular spaces are smaller than those of the uveal meshwork, conferring greater resistance to flow.

• The juxtacanalicular (cribriform) meshwork is the outer part of the trabeculum, and links the corneoscleral meshwork with the endothelium of the inner wall of the canal of Schlemm. It consists of cells embedded in a dense extracellular matrix with narrow intercellular spaces, and offers the major proportion of normal resistance to aqueous outflow.

The Schlemm canal is a circumferential channel within the perilimbal sclera. The inner wall is lined by irregular spindle-shaped endothelial cells containing infoldings (giant vacuoles) that are thought to convey aqueous via the formation of transcellular pores. The outer wall is lined by smooth flat cells and contains the openings of collector channels, which leave the canal at oblique angles and connect directly or indirectly with episcleral veins. Septa commonly divide the lumen into 2–4 channels.

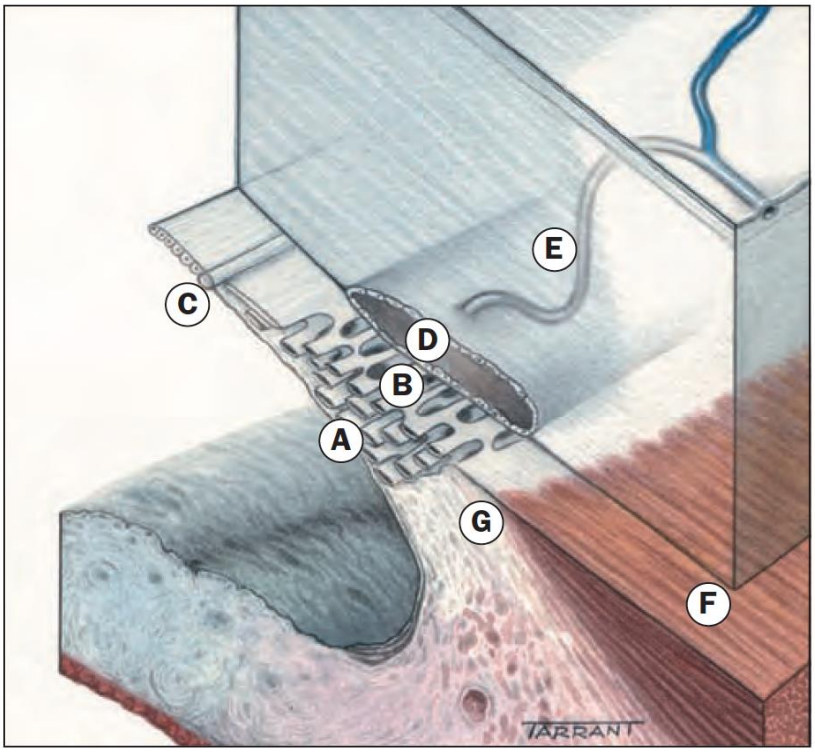

Figure 1. *Anatomy of outflow channels: A, Uveal meshwork; B, corneoscleral meshwork; C, Schwalbe line; D, Schlemm canal; E, connector channels; F, longitudinal muscle of the ciliary body; G, scleral spur*[3]

Aqueous flows from the posterior chamber via the pupil into the AC, from where it exits the eye via three routes (Figure 2).

• Trabecular outflow (90%): aqueous flows through the trabeculum into the Schlemm canal and then the episcleral veins. This is a bulk flow pressure-sensitive route so that increasing IOP will increase outflow.

• Uveoscleral drainage (10%): aqueous passes across the face of the ciliary body into the suprachoroidal space, and is drained by the venous circulation in the ciliary body, choroid and sclera.

• Iris: some aqueous also drains via the iris.[3]

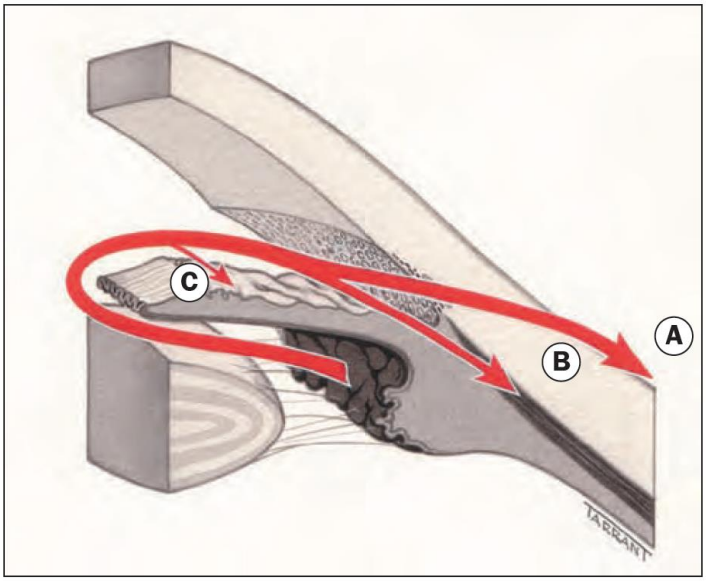

Figure 2. *Routes of aqueous outflow: A, trabecular; B, uveoscleral; C, iris*[3]

1.1.5 Evaluation of glaucoma

A complete evaluation of glaucoma includes:

• Measuring intraocular pressure (tonometry)

• Inspecting the drainage angle (gonioscopy)

• Testing for optic nerve damage with a dilated eye examination

• Imaging tests (pachymetry and optical coherence tomography)

• Checking for areas of vision loss (visual field test)

1.1.5.1 Intraocular pressure

Intraocular pressure is determined by the balance between the rate of aqueous production and its outflow, the latter in turn related to factors that include the resistance encountered in the trabeculum and the level of episcleral venous pressure.

The average IOP in the general population is around 16 mmHg on applanation tonometry, and a range of about 11–21 mmHg – two standard deviations either side of the average – has conventionally been accepted as normal, at least for a Caucasian population. However, some patients develop glaucomatous damage with IOP less than 21 mm Hg whilst others remain unscathed with IOP well above this level. Whilst reduction of IOP is a key modifiable element in essentially all types of glaucoma, additional incompletely understood factors are critical in determining whether a particular individual or eye develops glaucomatous damage. These include features influencing the IOP reading, such as corneal rigidity, and probably factors affecting the susceptibility of the optic nerve to damage, such as the integrity of its blood supply and structural vulnerability to mechanical stress at the optic nerve head.

Normal IOP varies with time of day (diurnal variation), heartbeat, blood pressure and respiration. The diurnal pattern varies, with a tendency to be higher in the morning and lower in the afternoon and evening. This is at least partially due to a diurnal pattern in aqueous production, which is lower at night. Glaucomatous eyes exhibit greater than normal fluctuation, the extent of which is directly proportional to the likelihood of progressive visual field damage, and a single reading may therefore be misleading. It is good practice always to note the time of day in conjunction with a recorded IOP.

1.1.5.2 Tonometry

Goldmann applanation tonometry (GAT) is based on the Imbert–Fick principle, which states that for a dry thin-walled sphere, the pressure (P) inside the sphere equals the force (F) necessary to flatten its surface divided by the area (A) of flattening (i.e. P = F/A). Theoretically, average

corneal rigidity (taken as 520 μm for GAT) and the capillary attraction of the tear meniscus cancel each other out when the flattened area has the 3.06 mm diameter contact surface of the Goldmann prism, which is applied to the cornea using the Goldmann tonometer with a measurable amount of force from which the IOP is deduced (Figure 3).

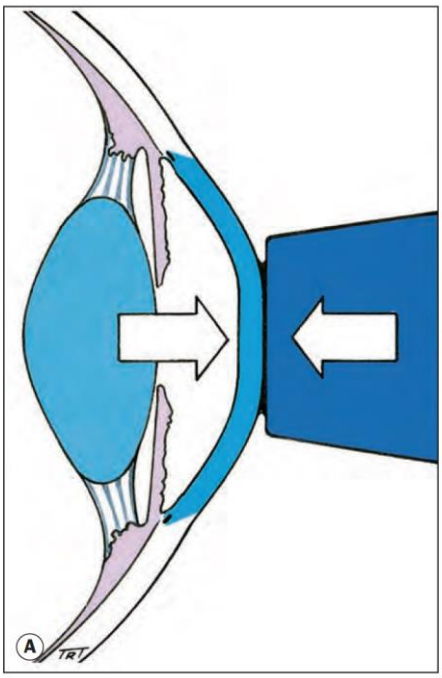

Figure 3. *Goldman tonometry, physical principle*[3]

Topical anesthetic and a small amount of fluorescein are instilled into the conjunctival sac. The patient is positioned at the slit lamp with his or her forehead firmly against the headrest and instructed to look straight ahead (often at the examiner's opposite ear). With the cobalt blue filter in place and illumination of maximal intensity directed obliquely (approximately 60°) at the prism, the prism is centered in front of the apex of the cornea. The dial is preset at 1 (i.e. 10 mmHg). The prism is advanced until it just touches the apex of the cornea (Figure 4A). Viewing is switched to the ocular of the slit lamp. A pattern of two green semicircular mires will be seen, one above and one below the horizontal midline, which represent the fluorescein-stained tear film touching the upper and lower outer halves

of the prism (Figure 4B). Care should be taken to horizontally and vertically center the mires so that as far as practically possible two centralized semicircles are observed. The dial on the tonometer is rotated to vary the applied force; the inner margins of the semicircles align when a circular area of diameter precisely 3.06 mm is flattened. The reading on the dial, multiplied by 10, gives the IOP; a version is available that shows IOP on a digital display.

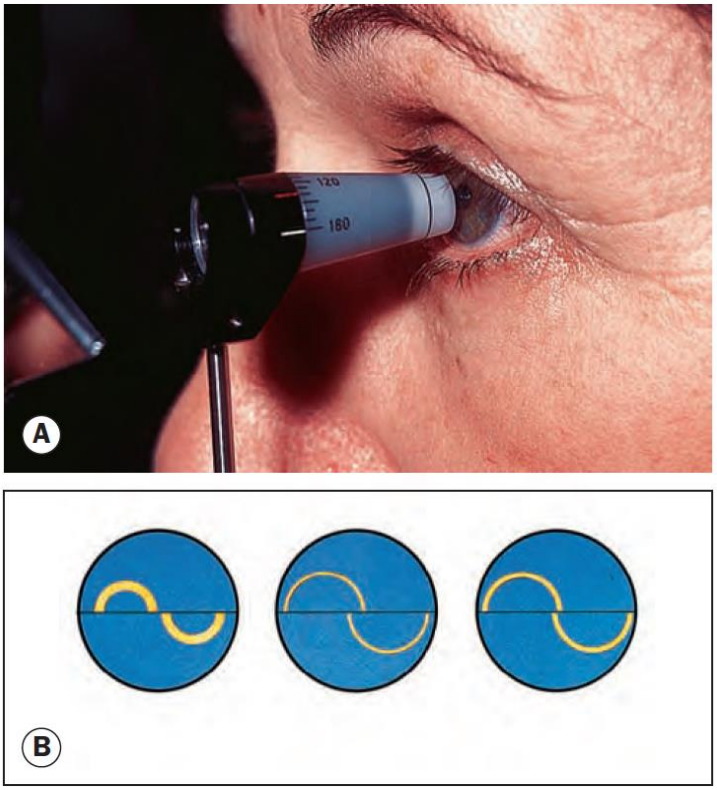

Figure 4. *Applanation tonometry. (A) Contact between the tonometer prism and the cornea; (B) fluorescein-stained semicircular mires – the diagram at right shows the correct end-point*[3]

Possible sources of error in applanation tonometry can be:

• Inappropriate fluorescein pattern. Excessive fluorescein will result in the mires being too thick, with consequent overestimation of IOP; insufficient will make the semicircles too thin, with consequent underestimation (see Figure 4B, left and center).

• Pressure on the globe from the examiner's fingers, eyelid squeezing or restricted extraocular muscles (e.g. thyroid myopathy) may give an anomalously high reading.

• Central corneal thickness (CCT). Calculations of IOP by GAT assume that central corneal thickness is 520 μm, with minimal normal variation. If the cornea is thinner, an underestimation of IOP is likely to result, and if thicker, an overestimation. Corneas tend to be thicker than average in individuals with ocular hypertension, and thinner in normal-tension glaucoma; following refractive surgery procedures the cornea is both thinner and structurally altered such that IOP is likely to be underestimated.

• Astigmatism, if significant, may give distorted mires as well as leading to mechanically induced errors. If over 3 dioptres, the average reading of two can be taken with the prism rotated 90° for the second, or optimally the prism is rotated so that the red line on the tonometer housing is aligned with the prescription of the minus axis.

• Other factors include corneal oedema, incorrect calibration of the tonometer, wide pulse pressure, a tight collar and breath-holding, both of which obstruct venous return and can raise IOP.

Other forms of tonometry are also available:

• Pneumotonometry is based on the principle of applanation, but the central part of the cornea is flattened by a jet of air rather than a prism. The time required to sufficiently flatten the cornea relates directly to the level of IOP. Contact is not made with the eye and topical anaesthesia is not required, so it is particularly useful for screening in the community. Accuracy is improved if an average of at least three readings is taken.

• Portable applanation tonometry (Perkins) uses a Goldmannprism in conjunction with a portable light source. It is hand-held, and can therefore be used in bed-bound or anaesthetized patients.

• Dynamic contour tonometry (DCT) uses a solid state sensor and a corneal contour-matching surface, with the aim of measuring IOP relatively independently of corneal mechanical factors such as rigidity. It is mounted on a slit lamp in similar fashion to the Goldmann tonometer, and IOP is shown on a digital display. Studies comparing DCT and GAT IOP readings

with manometric intracameral IOP seem to confirm DCT as providing a more physiological measurement.

• Electronic indentation/applanation tonometry is a hand-held electronic contact tonometer. The probe tip contains a transducer that measures applied force. Besides portability, its main advantage is the facility to measure IOP reasonably accurately in eyes with distorted or oedematous corneas, and through a soft contact lens.

• Other forms of tonometry are ocular response analyser, rebound tonometry, indentation (impression) tonometry, implantable tonometers.

1.1.5.3 Gonioscopy

Gonioscopy is a method of evaluating the anterior chamber angle and can be used therapeutically for procedures such as laser trabeculoplasty and goniotomy. Other means of angle assessment such as anterior segment optical coherence tomography (OCT) and high-frequency ultrasound biomicroscopy (UBM) offer advantages in some aspects of angle analysis, but current clinical opinion suggests they should supplement rather than replace visual gonioscopic analysis.

The angle of the AC cannot be visualized directly through the intact cornea because light from angle structures undergoes 'total internal reflection' at the anterior surface of the precorneal tear film. When light travels from a medium of higher to one of lower refractive index (such as cornea to air) it will be reflected at the interface between the two unless the angle of incidence is less than a certain 'critical angle' dependent on their refractive index difference (46° for the tear film–air interface). Because the refractive index of a goniolens is similar to that of the cornea, it eliminates total internal reflection by replacing the tear film–air interface with a tear film–goniolens interface. Light rays can then be viewed as they exit the contact lens, directly or indirectly.

Indirect goniolenses use a mirror to reflect rays from the angle such that they exit the goniolens at much less than the critical angle. They provide a mirror image of the opposite angle and can be used only in conjunction with a slit lamp. Non-indentation gonioscopy is very common in

clinical practice. The classic Goldmann lens consists of three mirrors (Figure 5A), one of which is specifically for gonioscopy; some goniolenses have one (Figure 5B), two or four mirrors. It is essential that the examination takes place in a room in which the ambient illumination is very low – completely dark if possible. The size and intensity of the slit beam should be reduced to the absolute minimum compatible with an adequate view, in particular avoiding any of the beam being directed through the pupil. The patient is seated at the slit lamp and advised that the lens will touch the eye but will not usually cause discomfort; the forehead must be kept against the headband and both eyes should remain open. A drop of local anaesthetic is instilled. A drop or two of coupling fluid is placed on the contact surface of the lens. The patient is asked to look upwards and the lens is inserted rapidly so as to avoid loss of the coupling fluid. The patient then looks straight ahead. Excessive pressure with a non-indentation lens narrows the angle appearance. Excessive pressure also causes folds in the cornea that compromise the clarity of the view. In some eyes, suction on the cornea from the lens may artificially open the angle; awareness of the need to avoid retrograde, as well as anterograde, pressure on the lens will tend to prevent inadvertent distortion. Lenses must be cleaned between patients to remove any particulate matter and then sterilized.

Indentation (dynamic, compression) gonioscopy is also possible. Goniolenses are four-mirror gonioprisms. The contact surface of the lenses has a curvature flatter than that of the cornea, negating the need for a coupling substance. The lenses do not stabilize the globe and are relatively unsuitable for laser trabeculoplasty. A common criticism is that it is easy to inadvertently open the angle, giving a misleadingly reassuring impression, especially if inexperienced.

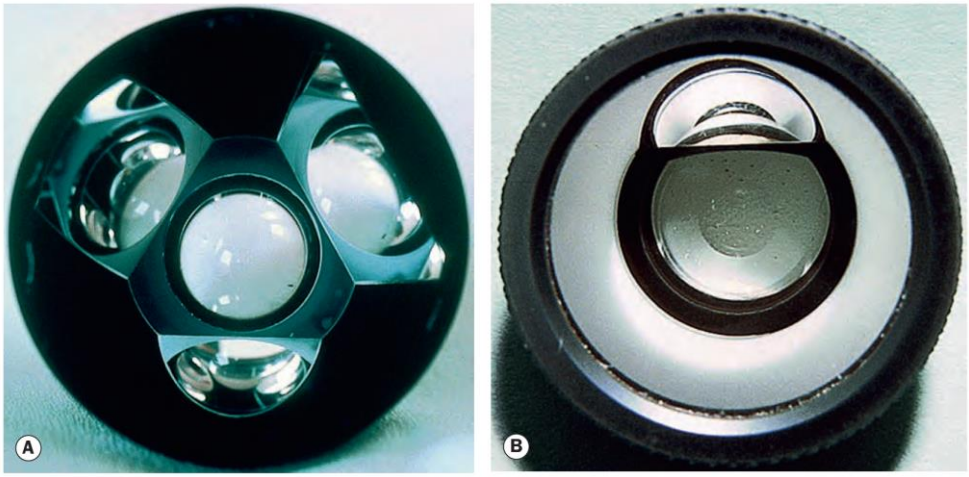

Figure 5. *Goldmann goniolens. (A) Three mirrors; (B) single mirror*[3]

Moreover, a direct gonioscopy also exists. Direct goniolenses work by constructing the viewing surface of the lens in a domed or slanted configuration such that exiting light rays strike the contact lens/air interface at a steeper than critical angle so that they will pass through to the observer. This approach is called 'direct' because light rays from the angle are viewed directly, without reflection inside the lens. They do not require a slit lamp and are used with the patient in the supine position, typically under general anaesthesia in the evaluation and surgical treatment of infantile glaucoma.

In practice, the angle width is graded by many practitioners simply according to the number of structures visible, together with qualifying comments relating to the width of the iris approach; many angles are narrowest superiorly, though this difference may be reduced by decreasing the ambient illumination. The Shaffer system records the angle in degrees between two imaginary lines tangential to the inner surface of the trabeculum and the anterior surface of the iris about one-third of the distance from its periphery. The system assigns a numerical grade to each quadrant of the angle:

• Grade 4 (35–45°) is the widest angle, characteristic of myopia and pseudophakia; the ciliary body can be visualized without tilting the lens.

• Grade 3 (25–35°) is an open angle in which the scleral spur is visible.

• Grade 2 (20°) is an angle in which the trabeculum but not the scleral spur can be seen.
• Grade 1 (10°) is a very narrow angle in which only the Schwalbe line and perhaps the top of the trabeculum can be identified.
• Slit angle is one in which there is no obvious iridocorneal contact but no angle structures can be identified.
• Grade 0 (0°) is closed due to iridocorneal contact.

1.1.5.4 Evaluation of the optic nerve head

The neuroretinal rim (NRR) is the orange-pink tissue between the outer edge of the cup and the optic disc margin. The inferior rim is the broadest followed by the superior, nasal and temporal (the 'ISNT' rule); this has high sensitivity for glaucoma but is not very specific, i.e. eyes without glaucoma often do not respect the rule.

The cup/disc (C/D) ratio indicates the diameter of the cup expressed as a fraction of the diameter of the disc; the vertical rather than the horizontal ratio is generally taken. Small diameter optic discs have small cups and vice versa; only 2% of the population have a C/D ratio greater than 0.7. In any individual, asymmetry of 0.2 or more between the eyes should also be regarded with suspicion, though it is critical to exclude a corresponding difference in overall disc diameter.

Optic disc size is important in deciding if a C/D ratio is normal and is also a prognostic indicator. Large discs are believed to be more likely to sustain damage, particularly in NTG. This may be the result of the larger diameter conferring relative mechanical weakness and hence greater vulnerability to IOP-induced displacement of the lamina cribrosa; the lamina cribrosa has been found to be thinner in eyes with NTG. Disc size varies on average between racial groups and is largest in black individuals. Imaging can objectively measure disc area, but vertical diameter is the parameter most frequently used clinically; normal median vertical diameter (for non-glaucomatous discs) is 1.5–1.7 mm in a white population.

In many cases it is not possible to be certain whether an individual optic disc is glaucomatous. The clinical findings and results of investigation should be considered together to guide management.

Glaucomatous damage results in characteristic signs involving
(a) the optic nerve head,
(b) the peripapillary area and
(c) the retinal nerve fibre layer.

Optic nerve head

Pathological cupping is caused by an irreversible decrease in the number of nerve fibres, glial cells and blood vessels. A documented increase in cup size is always significant. If an eye with a small optic disc and correspondingly small cup develops glaucoma, the cup will increase in size, but even in the presence of substantial damage may still be smaller than that of a large physiological cup.

There are different subtypes of glaucomatous damage. Four 'pure' glaucomatous disc appearances have been described, and although the majority of discs are unclassifiable the descriptions encompass a useful overview of patterns of glaucomatous damage, and may provide clues to underlying pathological processes.

• Focal ischaemic discs (Figure 6A) are characterized by localized superior and/or inferior notching and may be associated with localized field defects with early threat to fixation.

• Myopic disc with glaucoma (Figure 6B) refers to a tilted (obliquely inserted), shallow disc with a temporal crescent of parapapillary atrophy, together with features of glaucomatous damage. Dense superior or inferior scotomas threatening fixation are common. This morphology is most common in younger male patients.

• Sclerotic discs (Figure 6C) are characterized by a shallow, saucerized cup and a gently sloping NRR, variable peripapillary atrophy and peripheral visual field loss. The peripapillary choroid is thinner than in other disc

types. Patients are older, of either gender, and there is an association with systemic vascular disease.

• Concentrically enlarging discs are characterized by fairly uniform NRR thinning (Figure 6D) and are frequently associated with diffuse visual field loss. IOP is often significantly elevated at presentation.

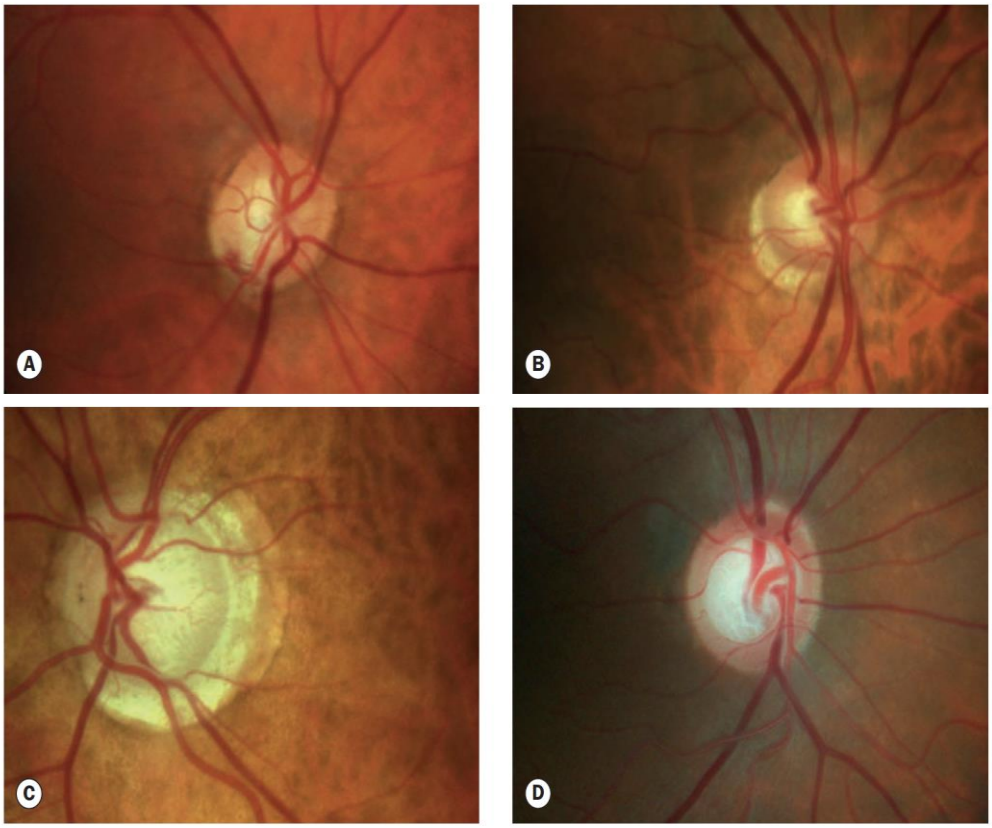

Figure 6. *Classic subtypes of glaucomatous damage. (A) Focal ischaemic – inferior notch and disc haemorrhage; (B) myopic; (C) sclerotic; (D) concentrically enlarging*[3]

Non-specific signs of glaucomatous damage include:

• Disc hemorrhages often extend from the NRR onto the retina, most commonly inferotemporally. Their presence is a risk factor for the development and progression of glaucoma. They are more common in NTG, but can also occur in healthy individuals as well as patients with systemic vascular disease.

• Baring of circumlinear blood vessels is a sign of early thinning of the NRR. It is characterized by a space between the neuroretinal rim and a superficial blood vessel.

• Bayoneting is characterized by double angulation of a blood vessel. With NRR loss, a vessel entering the disk from the retina may angle sharply backwards into the disk and then turn towards its original direction to run across the lamina cribrosa.

• Collaterals between two veins at the disc, similar to those following central retinal vein occlusion, are relatively uncommon. They are probably caused by chronic low-grade circulatory obstruction. Retinal vascular tortuosity may also occur. Loss of nasal NRR is a sign of moderately advanced damage; a space may develop between the NRR and the central retinal vasculature.

• The laminar dot sign occurs in advancing glaucoma. Grey dot-like fenestrations in the lamina cribrosa become exposed as the NRR recedes. The fenestrations sometimes appear linear, and this itself may be a sign of advanced damage, indicating distortion of the lamina. The dots may be seen in normal eyes.

• 'Sharpened edge' or 'sharpened rim' is a sign of advancing damage. As NRR is lost adjacent to the edge of the disc, the disc margin contour assumes a sharper angle backwards. Bayoneting of vessels is often seen at a sharpened edge. This should not be confused with a 'sharpened nasal polar edge', which refers to the sharp angulation of the NRR at the nasal margin of a focal vertical polar notch.

Peripapillary changes

Peripapillary atrophy (PPA) surrounding the optic nerve head may be of significance in glaucoma (Figure 7), and may be a sign of early damage in patients with ocular hypertension.

• Alpha (outer) zone is characterized by superficial retinal pigment epithelial changes. It tends to be larger and possibly more common in glaucomatous eyes.

• Beta (inner) zone is characterized by chorioretinal atrophy; it is distinct from the scleral rim, the white band of exposed sclera central to the beta zone. The beta zone is larger and more common in glaucoma, and is a risk factor for progression; the location of beta-zone PPA seems to indicate the orientation of likely visual field loss.

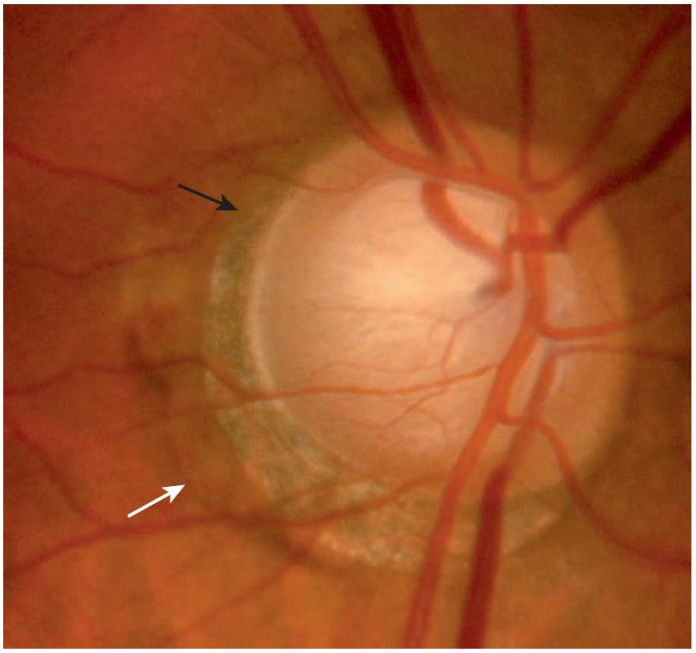

Figure 7. *Parapapillary changes. Alpha zone (white arrow) and beta zone (black arrow)*[3]

Retinal nerve fibre layer

In glaucoma subtle retinal nerve fibre layer (RNFL) defects precede the development of detectable optic disc and visual field changes; their onset often follows disc haemorrhages. Two patterns occur: localized wedge-shaped defects and diffuse defects that are larger and have indistinct borders. Defects are sometimes evident following disc haemorrhages (Figure 8A). Red-free (green) light increases the contrast between normal retina and defects on slit lamp biomicroscopy or fundus photography (Figure 8B) and typically makes identification easier. OCT and scanning laser polarimetry are highly effective means of quantifying the RNFL. It

should be noted that RNFL defects are not specific to glaucoma, and can be seen in a range of neurological disease, as well as normal individuals.

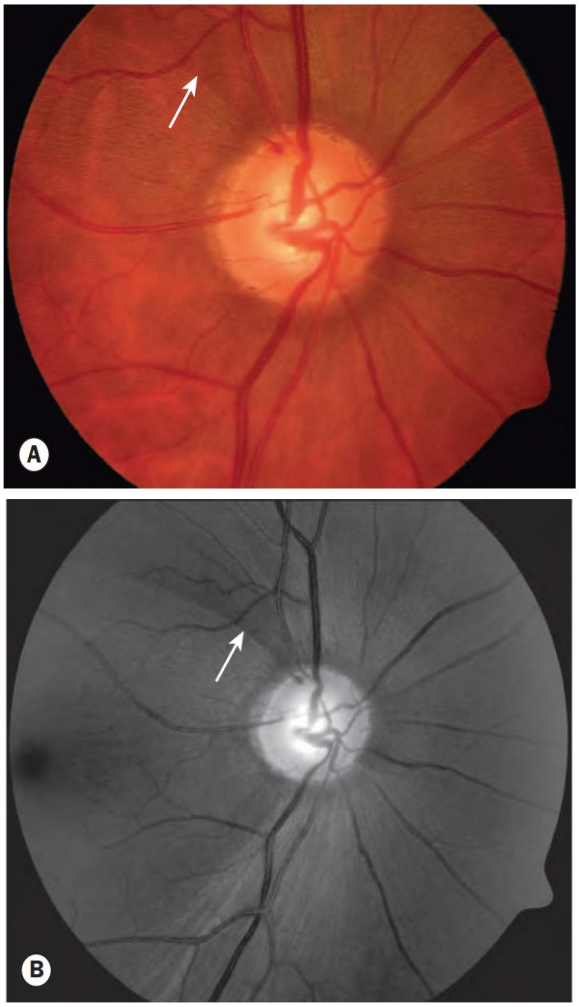

Figure 8. *Retinal nerve fibre layer defects. (A) Superotemporal wedge-shaped defect associated with a disc margin haemorrhage; (B) red-free photograph of the same eye*[3]

1.1.5.5 Imaging in glaucoma

Pachymetry

Pachymetry, the measurement of corneal thickness, in recent years has become an essential part of the assessment of glaucoma patients. Ultrasonic and optical methods are available.

Optical coherence tomography

OCT has become a routine part of the management of macular and other retinal disease; the same machine can be used for the assessment of glaucoma and has been widely adopted for this purpose (Figure 9).

• Peripapillary retinal nerve fibre layer. This involves the acquisition of a circular scan of the retina around the optic nerve head. Retinal thickness is compared with normals.

• Optic nerve head. Radial cross-sectional scans permit an objective and repeatable assessment of disc morphology, with reasonable discriminatory value.

• Ganglion cell complex (GCC) analysis involves measurement of retinal thickness at the macula in an attempt to detect early stage glaucomatous damage.

Anterior chamber depth measurement

Objective measurement of the depth of the AC is often clinically useful in glaucoma management. Indications include assessment of PAC risk, and monitoring of progression in conditions where the AC is shallowed, such as post-trabeculectomy hypotony and cilio-lenticular block. Older methods used a slit lamp with or without a special attachment, but an accurate and repeatable measurement can be obtained using ultrasonographic or optical interferometric methods.[3]

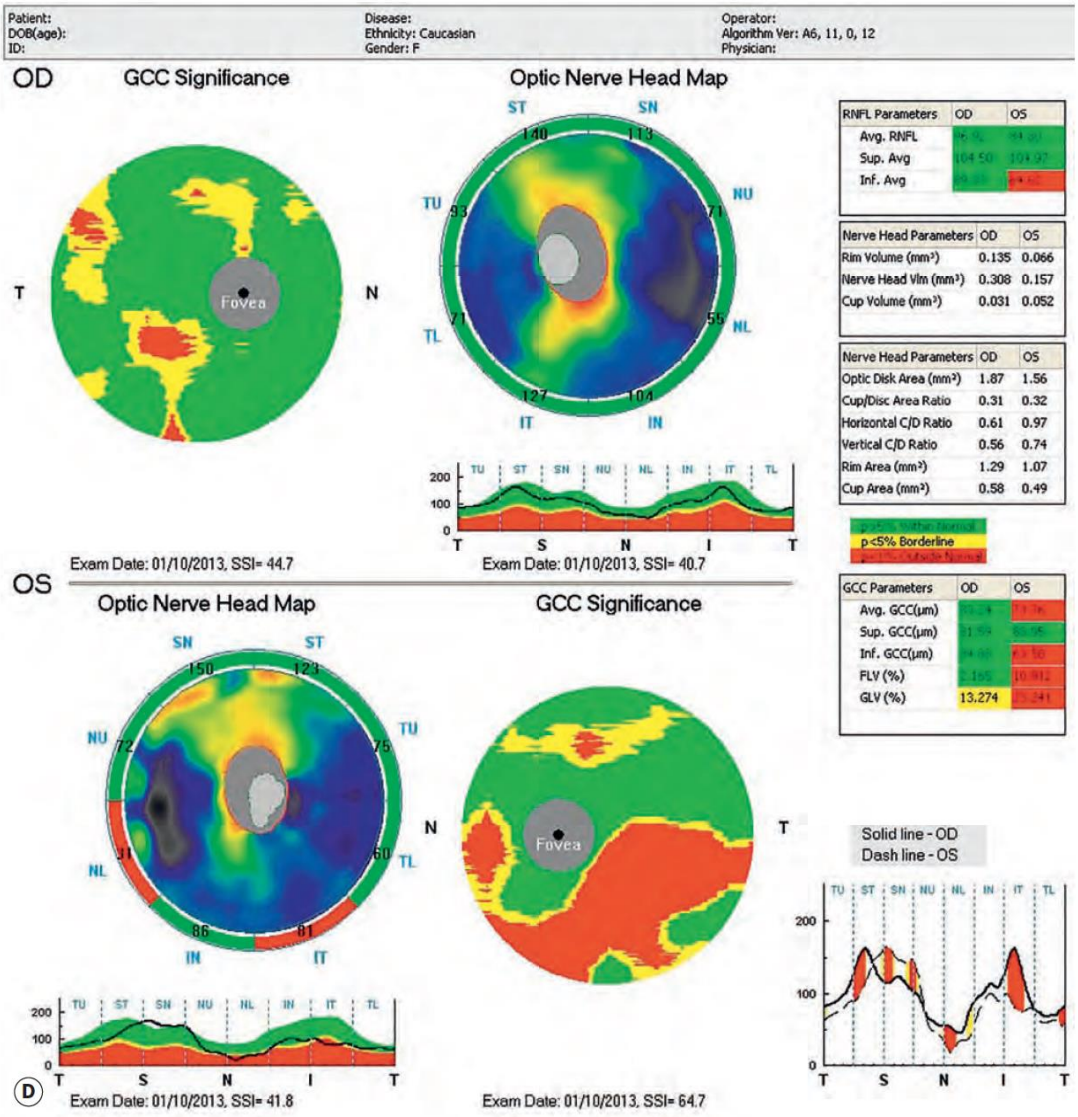

Figure 9. *Glaucoma protocol OCT showing optic nerve head, peripapillary retinal nerve fiber layer and ganglion cell complex analysis*[3]

1.1.5.6 Visual field testing

Examining visual fields is an integral part of a full ophthalmic evaluation. Several methods for assessing visual field loss are available, and the choice of which to use depends on the patient's age, health, visual acuity, ability to concentrate, and socio-economic status. Manual and/or automated visual field testing is subjective: it is totally dependent on the co-operation and responses of the patient. There are two major types of perimetry. Kinetic perimetry involves the detection of moving targets and static

perimetry involves the detection of a stationary target. Static testing in general is superior to kinetic perimetry in detecting slopes and scotomata (field defects), and tends to be more reliable and consistent, particularly for detecting glaucomatous visual field loss.

Abnormalities in the visual field are a sign of damage anywhere in the visual system from the retina through to the brain's visual cortex. Visual field defects are, therefore, not limited to glaucoma. It is very important to examine the retina and optic disc carefully to assess whether or not a visual field defect matches the appearance of the disc and retina, or fits with other clinical signs. For diagnostic purposes, it is important to test each eye separately. This is because non-congruous defects in each eye could be missed when testing both eyes together as the normal areas of field in one eye overlap the defects in the other eye.

Early glaucomatous visual field defects are subtle and easily missed. Even with modern automated and sensitive visual field analysers, glaucomatous visual field loss is not evident until at least 30% of the retinal ganglion cell axons that make up the optic nerve have been lost. Progression of visual field loss in untreated glaucoma can be quite slow, and signs of deteriorating disease can therefore be missed quite easily.[4] Nerve damage in glaucoma is believed to be inflicted at the optic nerve head, and the resultant visual field defect corresponds to the pattern of fibres in the retinal area served.

• Early changes include increased variability of responses in areas that subsequently develop defects, and slight asymmetry between the two eyes.

• Small paracentral depressions can form at a relatively early stage, often superonasally; they are probably more common in NTG.

• Nasal step represents a difference in sensitivity above and below the horizontal midline in the nasal field; the defect is bounded by the horizontal midline, corresponding to the retinal nerve fibre layer horizontal raphe.

• Temporal wedge is less common than a nasal step but has similar implications.

• Arcuate defects (Figure 10) develop as a result of coalescence of paracentral scotomas. They typically develop between 10° and 20° of

fixation as downward or upward extensions from the blind spot around fixation. With time, they tend to elongate circumferentially along the distribution of arcuate nerve fibres.

• A ring scotoma develops when superior and inferior arcuate defects become continuous, usually in advanced glaucoma (Figure 11)

• End-stage changes are characterized by a small island of central vision, typically accompanied by a temporal island.[3]

In glaucoma it is vital to repeat visual field testing to track any changes over time. Ideally, the same method of testing should be used for baseline and subsequent follow-up.

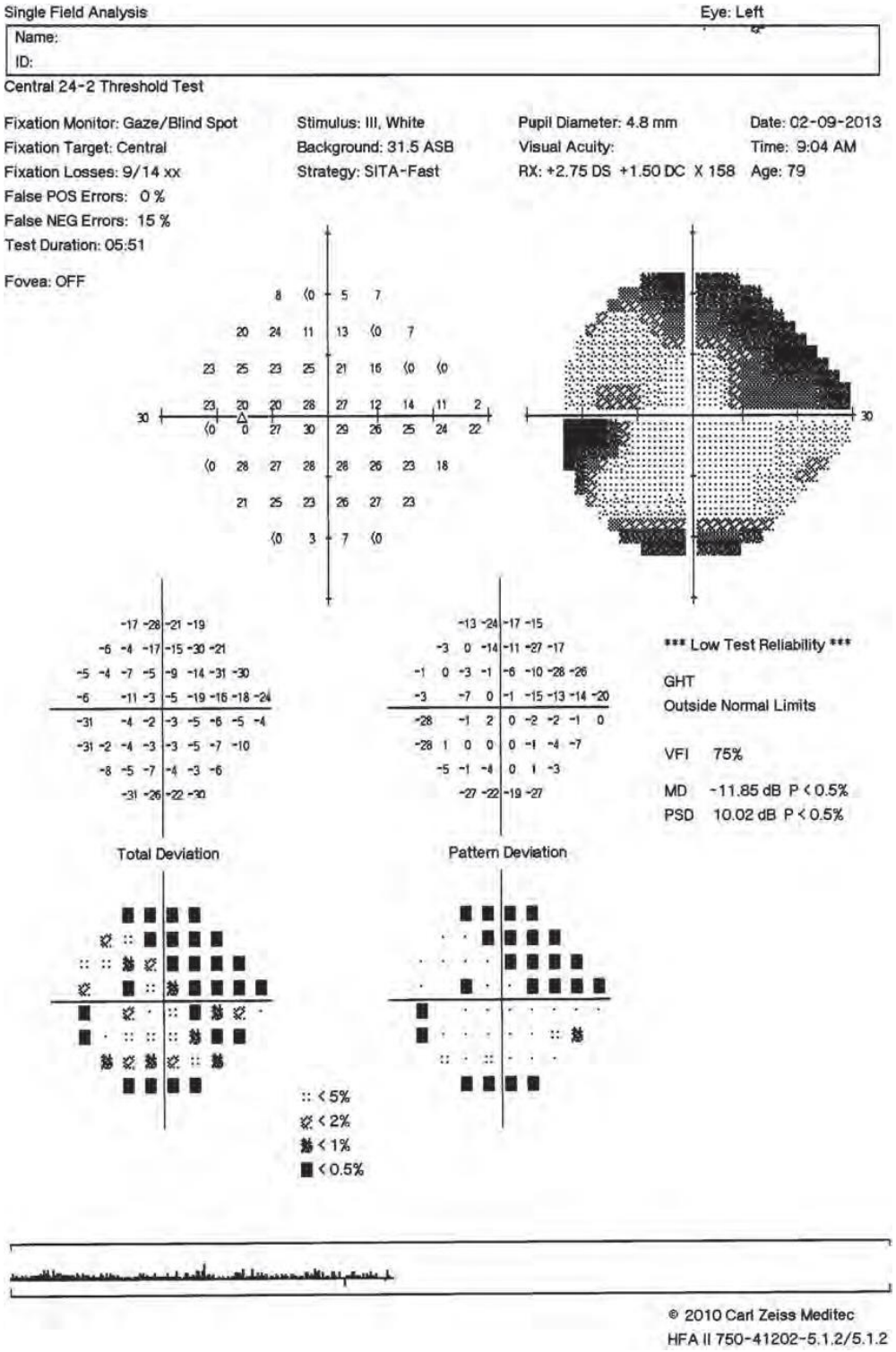

Figure 10. *Visual field showing superior arcuate scotoma and nasal step*[3]

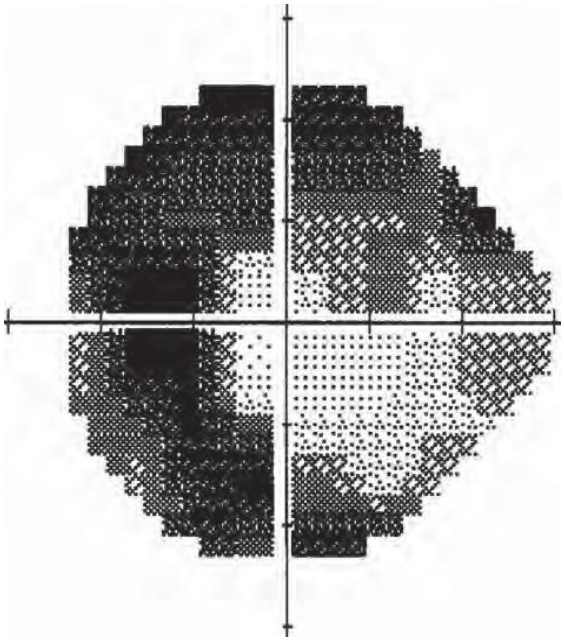

Figure 11. *Severe glaucomatous damage: grey scale display of dense superior and inferior arcuate scotomata merging into superior nasal step*[3]

1.1.6 Primary glaucoma

1.1.6.1 Primary Open-Angle Glaucoma

Although the pathogenesis of glaucoma is not fully understood, the level of intraocular pressure is related to retinal ganglion cell death. In patients with open-angle glaucoma, there is increased resistance to aqueous outflow through the trabecular meshwork. Intraocular pressure can cause mechanical stress and strain on the posterior structures of the eye, notably the lamina cribrosa and adjacent tissues. Intraocular pressure–induced stress and strain may result in compression, deformation, and remodeling of the lamina cribrosa with consequent mechanical axonal damage and disruption of axonal transport that interrupts retrograde delivery of essential trophic factors to retinal ganglion cells from their brainstem target (relay neurons of the lateral geniculate nucleus). Disrupted axonal transport occurs early in the pathogenesis of glaucoma in experimental systems.

Although elevated intraocular pressure is a very consistent risk factor for the presence of glaucoma, several population-based studies found

intraocular pressure was lower than 22 mm Hg in 25% to 50% of individuals with glaucoma. Despite the strong association between elevated intraocular pressure and glaucoma, substantial numbers of people with elevated intraocular pressure never develop glaucoma even during lengthy follow-up.

Genetics

POAG has been associated with at least 20 loci in the human genome. Mutations in the MYOC gene, coding for the protein myocilin that is found in the trabecular meshwork, and the OPTN gene, which codes for optineurin, are broadly accepted as causing glaucoma. A number of different mutations have been described in the MYOC gene, though the normal function of myocilin and its role in glaucoma is as yet undetermined. If a single family member develops glaucoma prior to age 35 years, the chances of a mutation in the myocilin gene may be as high as 33%. Genetic investigation of a patient and family may be considered if three or more first-degree relatives from two generations are affected, or for research purposes.

Clinical Presentation and Diagnosis

Glaucoma progresses without causing symptoms until the disease is advanced with substantial amounts of neural damage. When symptoms do occur, the disease results in vision loss with concomitant reduction in quality of life and the ability to perform daily activities, such as driving.

With retinal ganglion cell death and optic nerve fiber loss in glaucoma, characteristic changes in the appearance of the optic nerve head and retinal nerve fiber layer occur. These changes are the most important aspect of a glaucoma diagnosis and can be identified during ophthalmoscopic examination of the optic nerve head. Retinal ganglion cell loss causes progressive deterioration of visual fields, which usually begins in the midperiphery and may progress in a centripetal manner until there remains only a central or peripheral island of vision.

Because there is no single perfect reference standard for establishing the diagnosis of glaucoma, early diagnosis can be challenging. Although examination of the optic nerve head can reveal signs of neuronal loss, wide variability of its appearance in the healthy population makes identification of early damage challenging. Presence of characteristic visual field defects can confirm the diagnosis, but as many as 30% to 50% of retinal ganglion cells may be lost before defects are detectable by standard visual field testing. Longitudinal evaluation and documentation of structural damage to the optic nerve is, therefore, a critical component of the diagnosis of the disease.

Treatment

Slowing disease progression and preservation of quality of life are the main goals for glaucoma treatment. Reduction of intraocular pressure is the only proven method to treat glaucoma. Results from several multicenter clinical trials have demonstrated the benefit of lowering intraocular pressure in preventing the development and slowing the disease's progression. Target intraocular pressure levels for a particular eye are established from pretreatment pressure levels that were associated with retinal damage, the severity of damage, risk factors for progression, life expectancy, and potential for adverse effects from treatment. In general, the initial target aims for a 20% to 50% reduction in pressure; however, the target pressure needs to be continuously reassessed during patient follow-up, depending on the evolution of the disease. The target intraocular pressure should be achieved with the fewest medications and minimum adverse effects.

Several different classes of pressure-lowering medications are available. In general, prostaglandin analogues are the first-line of medical therapy. These drugs reduce intraocular pressure by reducing outflow resistance resulting in increased aqueous humor flow through the uveoscleral pathway. These drugs are administered once nightly and have few, if any, systemic adverse effects. However, they can cause local adverse effects such as conjunctival hyperemia, elongation and darkening of eyelashes, loss of orbital fat (so-called prostaglandin-associated

periorbitopathy), induced iris darkening, and periocular skin pigmentation. Other classes of topical medications are less effective in lowering intraocular pressure than prostaglandin analogues. They are used as second-line agents or when there is a contraindication or intolerance to the use of prostaglandin analogues. Some of these agents, such as β-adrenergic blockers, may have significant systemic adverse effects and are contraindicated in patients with history of chronic pulmonary obstructive disease, asthma, or bradycardia.

When medical treatment does not achieve adequate intraocular pressure reduction with acceptable adverse effects, laser or incisional surgeries are indicated. In poorly adherent patients or in those with severe disease, surgery may sometimes be offered as a first-line therapy. Laser trabeculoplasty lowers intraocular pressure by inducing biological changes in the trabecular meshwork resulting in increased aqueous outflow. The procedure has an excellent safety profile and is performed during an office visit. Although substantial intraocular pressure reductions can be achieved in the majority of patients, the effect decreases gradually over time with a failure rate of about 10% per year. Trabeculectomy is the most commonly performed incisional surgical procedure to lower intraocular pressure. It consists of excision of a small portion of the trabecular meshwork and or adjacent corneoscleral tissue to provide a drainage route for aqueous humor from within the eye to underneath the conjunctiva where it is absorbed. Devices that drain aqueous humor to an external reservoir are an alternative to trabeculectomy that are similarly effective in lowering intraocular pressure. Several alternatives to these procedures have been proposed and are being investigated. These so-called minimally invasive glaucoma surgeries potentially incur less risk of sight-threatening complications. To date, these procedures have not had the same intraocular pressure–lowering efficacy as trabeculectomy; however, they may be indicated for selected cases for which risk-benefit considerations are more favorable than those with trabeculectomy.

1.1.6.2 Primary Closed-Angle Glaucoma

The main feature distinguishing primary closed-angle glaucoma from primary open-angle glaucoma is that the angle, the site of aqueous outflow in the eye, is obstructed by apposition of the iris, resulting in an anatomically closed angle. Like open-angle glaucoma, closed-angle glaucoma is predominantly an asymptomatic disease with individuals often unaware they have the disorder until advanced visual loss has occurred. In less than a third of cases, patients may present with acute primary angle closure, a clinical condition characterized by marked conjunctival hyperemia, corneal edema, a middilated unreactive pupil, a shallow anterior chamber, and very high intraocular pressure, usually greater than 30 mm Hg. Such patients often complain of ocular pain, nausea, vomiting, and intermittent blurring of vision with haloes noticed around lights.

Primary closed-angle glaucoma is caused by disorders of the iris, the lens, and retrolenticular structures. Pupillary block is the most common mechanism of angle closure and is caused by resistance to aqueous humor flow from the posterior to anterior chambers at the pupil. Aqueous humor accumulates behind the iris increasing its convexity causing angle closure. Nonpupil block mechanisms such as a plateaulike iris configuration may be responsible for a significant proportion of angle closure in Asian patients. Closed-angle glaucoma may also be caused by dynamic physiological factors, such as an increase in iris volume with pupil dilation and choroidal effusion.

Risk Factors

Risk factors for angle closure include female sex, older age, and Asian ethnicity (e.g. Chinese). Eyes with angle closure tend to share certain biometric characteristics. The main ocular risk factor for angle closure involves having a crowded anterior segment in a small eye, with a shallow central anterior chamber depth, a thicker and more anteriorly positioned lens, and short axial length of the eye. With anterior segment optical coherence tomography, other anatomical risk factors for angle closure have

been recently identified such as smaller anterior chamber width, area and volume, thicker irides with greater iris curvature, and a greater lens vault.

Genetics

A genetic etiology for angle closure is supported by epidemiological findings: first-degree relatives of patients with it are at greater risk than the general population, the high heritability of anatomical risk factors (such as anterior chamber depth), and ethnic variations in the prevalence. Recently, a genome-wide association study involving more than 20 000 individuals from 7 countries found 3 new genetic loci for angle closure. This indicates that open-angle and closed-angle glaucoma are distinct genetic entities with different genes associated with each disease.

Clinical Presentation and Diagnosis

The distinctive clinical features of angle closure are observed in the angle of the eye by gonioscopy. Several imaging methods have been recently developed that can be used to objectively assess eyes for the presence of angle closure. Ultrasound biomicroscopy allows for the acquisition of real-time images of the angle and it is useful for identifying specific causes of angle closure. Anterior segment OCT is a noncontact imaging device that acquires high-resolution cross-sectional images of the anterior chamber.

Treatment

The management of patients with angle closure depends on the stage of disease and on correctly identifying the underlying mechanism. The first-line treatment of angle closure is laser peripheral iridotomy, a procedure in which a full thickness hole is created in the iris to eliminate pupillary block. Rare complications of iridotomy include transient increases of intraocular pressure, cornea decompensation, posterior synechiae (adhesions of iris to lens) formation, and optically induced visual disturbances. Eyes treated with iridotomy may still develop increased pressure over time; thus, it is essential to have periodic follow-up after the procedure. Studies suggest that

iridotomy is most effective in decreasing pressure in the early stages of disease, but once extensive synechial angle closure and glaucomatous optic neuropathy have developed, its effect is more subdued. If pressure remains high after iridotomy, long-term medical treatment (including topical β-blockers, α2–agonists, carbonic anhydrase inhibitors, and prostaglandin analogues) can be instituted, similar to the management of open-angle glaucoma.

As in primary open-angle glaucoma, surgical management is indicated when there is inadequate intraocular pressure lowering or is indicated for those with progression of optic nerve or visual field damage despite medical and laser treatment. Trabeculectomy, either alone or in combination with lens extraction should be considered if the pressure control remains too high despite laser and medical treatment, especially in more advanced cases of open-angle glaucoma. Lens extraction is also performed when lens-related mechanisms predominate, especially in cases in which a significant cataract impairs vision. Finally, glaucoma drainage implants may be used in patients with chronic angle closure similarly to open-angle glaucoma when trabeculectomy has failed to control pressure, or in eyes that are deemed to be at high risk of failure with trabeculectomy.[5]

1.1.6.3 Normal Tension Glaucoma

Normal tension glaucoma is a progressive optic neuropathy in which the intraocular pressure does not exceed the normal range, but optic nerve damage and visual field defects mimics primary open-angle glaucoma.

It is characterized by:

• IOP consistently equal to or less than 21 mmHg.

• Signs of optic nerve damage in a characteristic glaucomatous pattern.

• An open anterior chamber angle.

• Visual field loss as damage progresses, consistent in pattern with the nerve appearance.

• No features of secondary glaucoma or a non-glaucomatous cause for the neuropathy.

Risk factors and pathogenesis

Traditionally, the most important and only clear modifiable risk factor for glaucoma is intraocular pressure.[6] It has been established that high IOP is a part of the pathogenic process of NTG; however, the pressure theory cannot sufficiently explain how NTG causes loss of vision.[7] This is also confirmed by the incomplete efficacy of the lowering of IOP in the treatment of NTG. Therefore, new studies are addressed to finding others risk factors for NTG. Several risk factors have been shown to be related to NTG:

• Age. The mean age in years of patients with NTG reported in many studies is in the 60s.

• Sex. Some studies have suggested that there is a greater population of women with NTG than men; however, this phenomenon may be due to the longer life span of females compared to males.

• Race. The incidence of NTG in different populations is not the same. It has been reported that there is a higher incidence of NTG in Asian populations, such as Japanese, compared to European populations. As many as two-thirds of glaucoma instances in Japan may be NTG.

• Systemic diseases. Although the relationship between NTG and other diseases is not clear, some systemic diseases have been reported to concur with NTG, such as vascular disease, migraine, vasospasm, and immune-related diseases.

• Genetic factors. Many gene mutations have already been reported to be associated with NTG in demographic studies. A polymorphism of the endothelin receptor A gene has been found to be associated with NTG, which suggests the involvement of endothelin-1 (ET-1) signaling pathways in the development of NTG. Optic atrophy type 1 (OPA1) gene is reported to be related to NTG. It has been suggested that the mitochondrial OPA1 could provide defense of retinal ganglion cells from pressure-mediated retinal damage. Altered OPA1 gene expression could directly induce apoptotic cell death. Mutation in the optineurin (OPTN) gene was reported to be associated with NTG in the hereditary POAG family. The functional role of OPTN, as described in the literature, included nuclear factor kappa B

regulation, vesicular trafficking, immune response, etc. The mutated OPTN gene could induce mutation of E50K and H486R genes, resulting in death of retinal ganglion cells by weakness of antioxidation. WD repeat-containing protein 36 (WDR36) has been identified as being associated with POAG. It was reported that the mutant WDR36 could directly affect the axon growth of RGCs, leading to progressive retinal degeneration in mice. However, for many of the genes, these is still a lack of large demographic data that would support their classification as major risk factors for developing NTG. Future investigations will continue to identify more new genes, and will clarify the roles of the mutated genes and the relationship that they have with the outside environment.

• Vascular factors. Among IOP-independent, vascular factors have been most attended to. They have been classified as either systemic vascular risk factors, such as nocturnal hypotension and vasospasm, or local risk factors, such as disc hemorrhages, peripapillary atrophy, and choroidal sclerosis. The presence of decreased ocular blood flow in NTG patients and the prevalent incidence of NTG among those with vasospasm provide overwhelming evidences to indicate the significance of vascular factors in the development or progression of NTG. Vascular dysregulation increases the impact of ischemia, affecting not only retinal tissue but also the optic nerve, and contributes to the degeneration of retinal ganglion cells and their axons. Under the conditions of ischemia, many vascular-related factors have been shown to be involved in the pathogenesis of NTG, e.g. oxidative stress, ET-1, glutamine, vasogenic cytokines, etc.[8]

- Blood pressure. Among systemic risk factors, all those that cause arteriosclerosis are related with glaucoma as well: hypertension, diabetes, glucose intolerance, high body mass index (BMI), smoking etc. The relationship of ocular blood flow (OBF), blood pressure (BP), and NTG is an important topic in this area of research. High BP is a risk factor in high-tension glaucoma, as is evidenced by the positive correlation between systolic BP and IOP. On the other hand, low BP, especially the nocturnal drop of BP, has been shown to have a greater prevalence in those with NTG.[8] Choi et al. found that

marked circadian mean ocular perfusion pressure (MOPP) fluctuation was associated with nocturnal BP reduction. Circadian MOPP fluctuation seems to be related with progression of NTG. Also, the use of oral hypotensive therapy on systemic hypertension is associated with a significantly lower mean nighttime BP. In particular, diastolic BP less than 90 mmHg that resulted from antihypertensive treatment was associated with increased cupping and decreased rim area of the optic disc. In conclusion, antihypertensive medication may cause non physiologic hypotension, rendering systemic pulse pressure and MOPP fluctuation wider in subjects with autonomic dysfunction, and finally causing ischemia-reperfusion damage to the optic disc.[9]

- Vascular dysregulation. This term refers to the regulation of blood flow that is not adapted to the needs of the respective tissue. In normal healthy eyes, the retinal blood flow is autoregulated. However, the autoregulation of OBF may be disturbed in glaucomatous eyes, and the physiologic response may be different from that in normal healthy eyes. Insufficient or improper adaption of OBF, despite anatomically healthy vessels and the absence of a causative disease, is termed primary vascular dysregulation (PVD). In subjects with PVD, retinal vessels are stiffer and more irregular, and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased. The combination of PVD with a cluster of additional vascular and nonvascular signs and symptoms is called PVD syndrome or Flammer syndrome. Despite many symptoms and signs, most subjects with Flammer syndrome are healthy subjects. However, subjects with Flammer syndrome are at high risk of developing NTG. The OBF instability in these subjects with limited range of autoregulation seems to predispose the optic disc structures at risk of ischemia-reperfusion damage, finally leading to the development and progression of open-angle glaucoma.

- Ocular blood flow. OBF depends on perfusion pressure (PP) and local resistances. The perfusion pressure is determined by the difference between blood pressure and IOP (assuming it equals the venous pressure). OBF is reduced in glaucomatous patients. There are evidences that a low or fluctuating PP is a risk factor for glaucoma, both for increases or fluctuations in IOP, in patients with vascular dysregulation. In general, all vascular risk factors determine ischemia and increase the possibility of ischemia-reperfusion damage, as a consequence of flow variations.
- Arterial stiffness. This is a loss of arterial elasticity, one of the major signs of vascular aging. Increased arterial stiffness has been recognized as an independent risk factor for cardiovascular diseases. Some researchers have investigated the association between arterial stiffness and glaucoma. However, the role of arterial stiffness in the pathogenesis of glaucoma is still controversial.

• Mechanical risk factors. These include increased IOP, thinner lamina cribrosa (LC), larger LC displacement, anatomical variations of LC, or translaminar pressure dynamics (IOP and ICP). Many recent studies have demonstrated a correlation between ICP and glaucomatous damage, as confirmed by this study as well.

Considering all the main risk factors mentioned, a pathogenic mechanism has been proposed. Both the mechanical stress and the ischemia-reperfusion damage are able to determine the activation of astrocytes, by activating the epidermal growth factor receptor (EGFR) and releasing endothelin. This determines a positive feedback on the release of mediators like endothelin and NO, damaging to axonal cells.[10] Apoptosis is the major pathway of retinal ganglion cell death in glaucoma. Apoptosis could be promoted both by a direct damage, vascular or oxidative, or indirect damage, mediated by the activation of astrocytes and gliosis.[8]

Clinical features

From a clinical point of view, normal tension glaucoma is asymptomatic, especially at the initial stage. The optic nerve damage can result in permanent vision loss that is so gradual that a patient may not be aware of it.

Diagnosis

History and examination are essentially the same as for POAG but specific points warrant attention.

• History

- Migraine and Raynaud phenomenon.
- Episodes of shock.
- Head or eye injury.
- Headache and other neurological symptoms (intracranial lesion).
- Medication, e.g. systemic steroids, beta-blockers.

• IOP is usually in the high teens, but may rarely be in the low teens. In asymmetrical disease the more damaged disc typically corresponds to the eye with the higher IOP.

• Optic nerve head

- The optic nerve head may be larger on average in NTG than in POAG.
- The pattern of cupping is similar, but acquired optic disc pits and focal nerve fibre layer defects may be more common.
- Peripapillary atrophic changes may be more prevalent.
- Disc haemorrhages (Figure 12) may be more frequent than in POAG, and are associated with a greater likelihood of progression.
- Pallor disproportionate to cupping should prompt a suspicion of an alternative diagnosis.

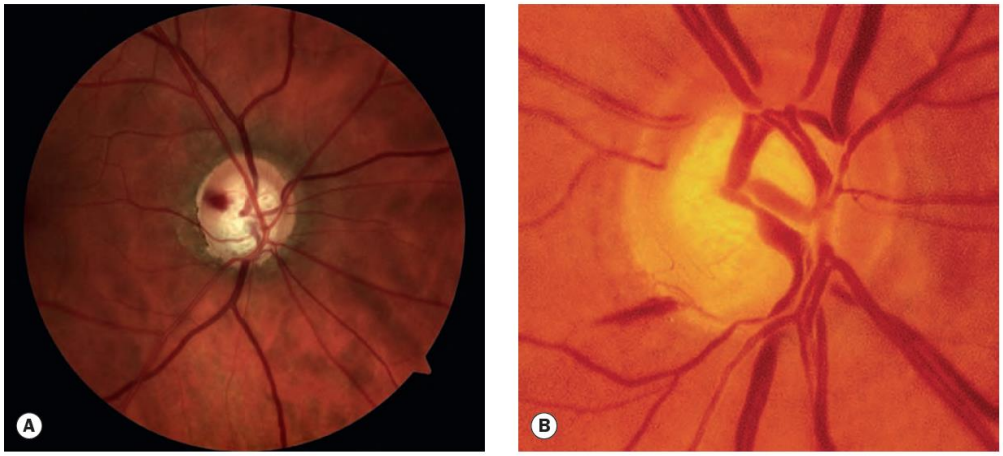

Figure 12. *(A) and (B) Disc haemorrages*[3]

• Visual field defects are essentially the same as in POAG although there is some evidence that they tend to be closer to fixation, deeper, steeper and more localized. In probably more than half of patients, field changes are non-progressive over a period of 5 years or more without treatment. However, perhaps because of delayed diagnosis, patients tend to present with more advanced damage than in POAG. A high level of suspicion for a deficit pattern suggesting a lesion posterior to the optic nerve is important.

• Other investigations are as for POAG although in selected patients the following can be considered.

- Assessment of systemic vascular risk factors.
- Blood pressure measurement can be used to calculate ocular perfusion pressure; 24-hour ambulatory monitoring will exclude nocturnal systemic hypotension in selected patients.
- Blood tests for other causes of non-glaucomatous optic neuropathy such as vitamin B12, red cell folate, full blood count, erythrocyte sedimentation rate/C-reactive protein, treponemal serology including Lyme disease, serum angiotensin-converting enzyme level, plasma protein electrophoresis and autoantibody screen.
- Cranial MRI.
- Ocular blood flow assessment (e.g. laser flowmetry) may have useful clinical potential.

Differential diagnosis

• Angle closure should always be ruled out by meticulous dark-room gonioscopy.

• Low central corneal thickness leading to underestimation of IOP; suspicion has also been raised that a thin posterior ocular wall may increase mechanical stress in the region of the lamina cribrosa. Prior refractive surgery and corneal ectasia also lead to falsely low IOP readings, sometimes dramatically so.

• POAG presenting with apparently normal IOP because of wide diurnal fluctuation. Plotting a diurnal IOP curve over an 8-hour period (phasing) during office hours may detect daytime elevation, but detection of nocturnal IOP spikes requires substantial resource commitment.

• Previous episodes of raised IOP may have occurred as a result of ocular trauma, uveitis or local or systemic steroid therapy. Masking by systemic treatment such as an oral betablocker, commenced after glaucomatous damage has already been sustained.

• Spontaneously resolved pigmentary glaucoma. The typical examination features of pigmentary glaucoma tend to become less evident with increasing age. The IOP in some cases of POAG may also spontaneously normalize over time.

• Progressive retinal nerve fibre defects not due to glaucoma such as may occur in myopic degeneration and optic disc drusen.

• Congenital disc anomalies simulating glaucomatous cupping, such as disc pits and colobomas.

• Neurological lesions causing optic nerve or chiasmal compression can produce visual field defects that may be misinterpreted as glaucomatous, and neuroimaging should be performed if there is any suspicion; some practitioners routinely perform a cranial MRI in all cases of NTG.

• Previous anterior ischaemic optic neuropathy (AION) may give rise to a disc appearance and visual field defect consistent with glaucoma. Non-arteritic AION often occurs in a ‘crowded’ disc, and the fellow eye should be examined for this; prior retinal vascular occlusion should also be considered.

• Previous acute optic nerve insult such as hypovolaemic or septicaemic shock, or head injury.

• Miscellaneous optic neuropathies including inflammatory, infiltrative and drug-induced pathology will often be clinically obvious, but can occasionally masquerade as NTG.[3]

An important step in diagnosis is to rule out chronic anemia, cardiopathies, acute blood loss, episodes of systemic hypotension, decreased cerebral blood flow, blood dysplasias, neurosyphilis, etc, from the medical history.[8]

Treatment

Further lowering of IOP is effective in reducing progression in many or most patients. However, as a large proportion of untreated patients will not deteriorate (approximately 50% at 5 years), in many cases progression should be demonstrated before commencing treatment. Exceptions include advanced glaucomatous damage, particularly if threatening central vision, and young age. Regular assessment including perimetry should be performed at 4–6 monthly intervals initially.

• Medical treatment. The alpha-2 agonist brimonidine may have a neuroprotective effect on the retina and optic nerve in addition to its IOP-lowering effect and may be superior to beta-blockers. Carbonic anhydrase inhibitors, particularly dorzolamide, may improve ocular perfusion. Prostaglandin derivatives tend to have a greater ocular hypotensive effect, which may be an over-riding consideration. Topical beta-blockers can have a dramatic effect on BP in a minority, and may contribute to nocturnal dips, though selective blockade (e.g. betaxolol) may actually have a beneficial effect on optic nerve perfusion.

• Laser trabeculoplasty, particularly SLT, is a reasonable option to achieve IOP targets.

• Surgery may be considered if progression occurs despite IOP in the low teens; antimetabolite enhancement of trabeculectomy is likely to be indicated in order to achieve a satisfactorily low pressure.

• Control of systemic vascular disease such as diabetes, hypertension and hyperlipidaemia may be important, in order theoretically to optimize optic nerve perfusion.

• Systemic calcium-channel blockers to address vasospasm have been advocated by some authorities. Antihypotensive measures. If significant nocturnal dips in BP are detected, it may be necessary to reduce antihypertensive medication, especially if taken at bedtime. Non-selective topical beta-blockers in particular may cause a profound drop in systemic blood pressure in some individuals. Selected patients might be encouraged to increase their salted food intake, in consultation with the patient's cardiovascular physician.

• Neuroprotective agents of proven benefit are not yet available; memantine is used to retard neuronal death in some CNS disorders, and its use has been adopted in glaucoma by some practitioners. Ginkgo biloba or an antiplatelet agent may confer some benefit in selected cases.

1.2 Trans-laminar hypothesis

Since the lamina cribrosa of the optic nerve head forms the border between the intraocular space (with a higher pressure) and the retrobulbar space (with a lower pressure), a pressure gradient exists across the lamina cribrosa. This gradient can be expressed as the difference between intraocular pressure and the pressure in the retrobulbar cerebrospinal fluid and optic nerve tissue space (Figure 13). This trans-lamina cribrosa pressure gradient (ΔP) is important for ocular diseases in which the pressure on one or on both sides of the lamina cribrosa is either abnormally high and/or abnormally low. An abnormal pressure gradient influences the physiology and pathophysiology of the optic nerve head, including the orthograde and retrograde axoplasmic flow. In that context, it should be kept in mind that the term "intraocular pressure (or IOP)" is a misnomer. What we call "IOP" is just the transcorneal pressure difference. The true pressure in an eye with an IOP of 20mm Hg is 780mm Hg (760 mm Hg (atmospheric pressure) plus 20 mmHg). For the optic nerve, however, it is not the transcorneal pressure difference which counts, but the trans-lamina cribrosa pressure difference and the trans-lamina cribrosa pressure gradient.[11]

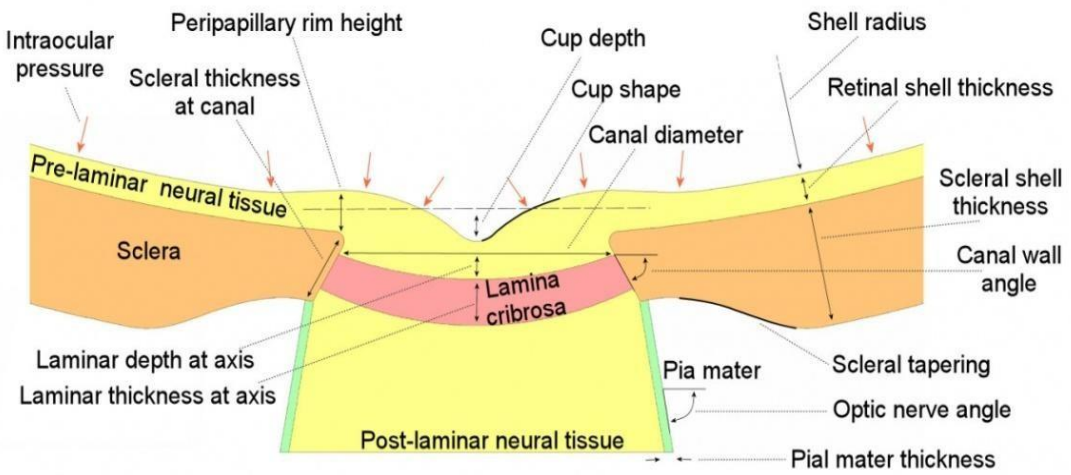

Figure 13. *A schematic representation of the posterior segment of the eye*

1.2.1 The lamina cribrosa and the trans-laminar pressure gradient

Lamina cribrosa (LC) is the extension of the peripapillar margin of the sclera. It consists of collagen fibers and its thickness is 500 µm. The microstructure of the lamina cribrosa is characterized by 500-600 pores, through which pass the fibers of the optic nerve, the central retinal artery and vein. It forms the anatomical floor of the optic nerve head and separates two pressurized compartments, ocular and cranial. These pores are of differing diameter and depth depending on location within the disc-like structure. The pores in the superior and inferior portions of the lamina cribrosa are larger and contain a greater number of nerve fibres (Figure 14). The optic nerve is nourished by capillaries within the lamina cribrosa, which is supplied by the short posterior ciliary arteries. The superior and inferior portions are also where damage from glaucoma first occurs. Since less connective tissue exists between these pores to provide structural and nutritional support, the fibres may be more susceptible to mechanical or vascular changes from an increased pressure gradient.[12]

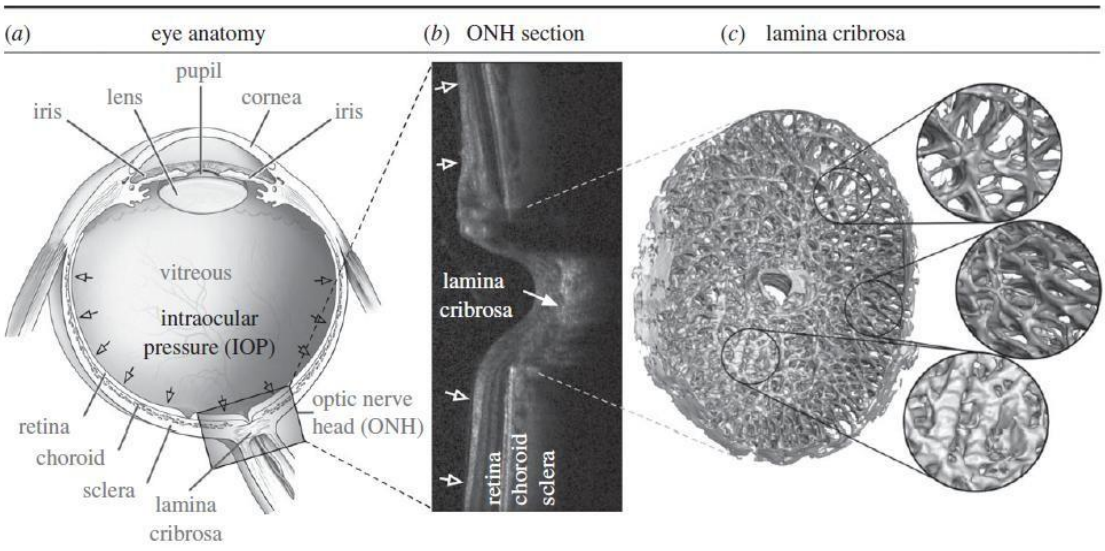

Figure 14. *(a) Eye anatomy, (b) OCT section of the optic nerve head, (c) Digital reconstruction of the anatomy of the lamina cribrosa, showing trabeculae and pores*[13]

Regarding the anatomy of this area, the lamina cribrosa forms a barrier between the anterior intraocular compartment and the posterior retrolaminar compartment that contains the subarachnoid space (SAS) surrounding the optic nerve as it attaches to the eye globe. The SAS of the optic nerve contains cerebrospinal fluid (CSF) continuous with that of the SAS surrounding the brain and spinal cord. The LC thereby functions to stabilize the intraocular contents (preventing their leakage and maintaining turgor) while supporting and allowing the transmission of the retinal ganglion cell axons and central retinal artery and vein between the compartments through its many pores. Its anterior surface is exposed to the IOP, while the posterior surface faces the retrolaminar compartment pressure (of which CSF is a major contributor).

In normal conditions, IOP is 10-20 mmHg and intracranial pressure (ICP) is 5-15 mmHg. Simultaneous measurement of the IOP and ICP in healthy adults has shown that the optic nerve is exposed in the supine position to a posteriorly directed IOP - ICP difference (ΔP) of about 6.7 mmHg, whereas in the sitting position, the ICP is lower than in the supine position, resulting in ΔPs as high as 15 mmHg.[14]

Alterations in the pressures of either compartment have been observed to result in mechanical deformation of this barrier in the form of bowing, which corresponds to the direction of the pressure gradient across the LC. The gradient across the thickness of the LC is also dependent on the thickness of the LC, with thinner LC associated with larger ΔP values and more severe glaucomatous damage.[15]

1.2.2 Trans-laminar hypothesis in the pathogenesis of normal tension glaucoma

According to the anatomy and physiology of the LC system, it is clear that changes in the trans-laminar gradient can alter position and functioning of the lamina cribrosa. It has been demostrated that IOP and ICP influence the morphologic characteristics of the optic disc and the position

of the lamina cribrosa.[16] An example of this is papilledema, a bilateral swelling of the head of the optic nerve, caused by increased ICP. Higher ICP leads to an inversion of the trans-laminar gradient and a protrusion of the lamina cribrosa and optic disc (Figure 15C). Vice versa, a lower ICP or a higher IOP can increase the trans-laminar gradient and displace the lamina cribrosa and optic disc posteriorly (Figure 15B). This mechanical deformation adversely affects the traversing retinal ganglion cells (RGC), and central retinal vessels with resultant shearing and deformation forces causing neuronal dysfunction, ischemia and damage. The bowing of the LC may stress the blood vessels that perforate it to supply RGC axons, with resultant ischaemia and neuronal loss evident at the optic nerve head. This deformation of the lamina and the resulting change in the structure of the pores that transmit the RGC axons may also result in disruption of axoplasmic flow by direct mechanical deformation, thereby representing another method of ΔP-induced cell dysfunction.[15]

So, the lamina cribrosa's ability to maintain shape is important in protecting the structures that pass through it: the retinal ganglion cell axons, the central retinal artery and the central retinal vein. The ability of the lamina cribrosa to withstand the pressure gradient without deforming is dependent on its thickness, the rigidity of the extracellular matrix and the peripheral scleral tension.[12] Jonas et al. showed that the lamina cribrosa is thinner (201 m vs. 457 m) and posteriorly bowed in glaucomatous human eyes, suggesting that pressure related damage to the optic nerve is caused by a pressure gradient and not by exposure to high absolute pressure.[16] The hypothesis of the pathogenic role of trans-laminar gradient in determining glaucomatous damage is confirmed by several studies. Ren et al. demonstrated, in a prospective study, that in the open-angle glaucoma with normal IOP the ICP is low, and the trans-laminar gradient is high.[17] Wang et al., in their methanalis suggest that trans-laminar gradient can play a more important role in pathogenesis of POAG than that play by isolated IOP and ICP.[18] A corean study tried to assess the association between trans-laminar gradient and prevalence of NTG on patients participating to the Korean National Health and Nutrition Examination Survey. The study showed that

the trans-laminar gradient is significantly associated with NTG in high-teen patients (those with IOP between 15 and 21 mmHg).[19] Furthermore, another study demonstrates how a higher trans-laminar gradient is associated with neuroretinal rim loss and visual field defects in glaucomatous patients.[20]

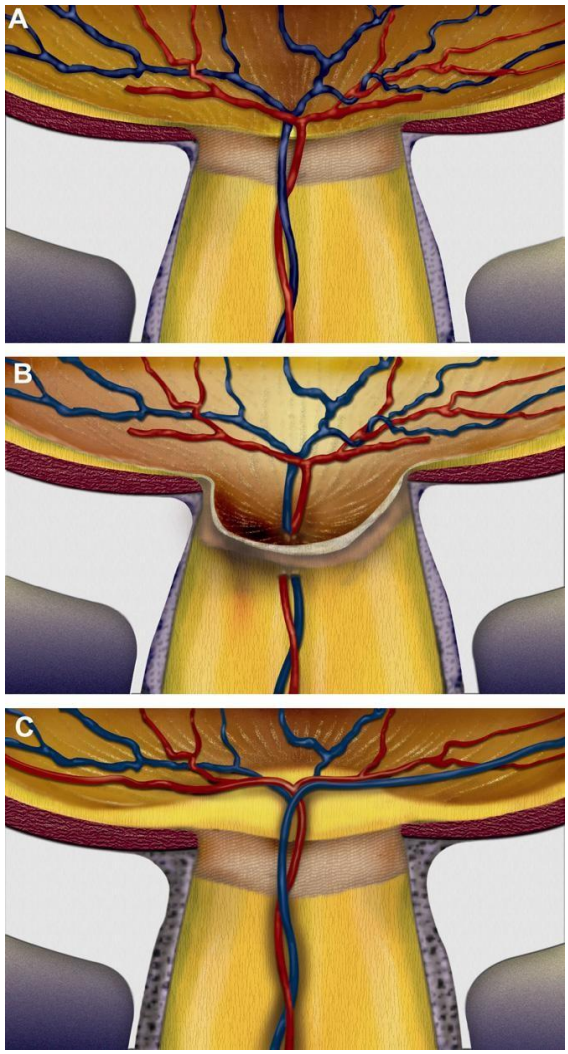

Figure 15. *Graphic representation of optic nerve head and relationship between IOP and ICP. (A) Normal configuration of lamina cribrosa and optic nerve. (B) Glaucoma: both high IOP and low ICP determine a high trans laminar gradient, directed posteriorly, with optic nerve excavation. (C) Papilledema: both low IOP and high ICP determine a trans laminar gradient anteriorly directed, with swelling of optic nerve*[21]

1.2.3 Intracranial pressure

The trans-laminar gradient (ΔP) is determined by the difference between IOP and ICP. Since IOP is, by definition, normal in patients with normal tension glaucoma, it is clear that any alteration of the gradient is determined by a reduction of ICP.

Over 30 years ago, Volkov pointed out that a low cerebrospinal fluid pressure (CSFP) could pathogenetically be associated with glaucomatous optic neuropathy. The same idea had earlier been expressed by Szymansky and Wladyczko. Yablonski, Ritch and Pokorny postulated that an abnormally low cerebrospinal fluid pressure around the optic nerve may be the reason for a barotraumatically induced optic nerve damage in normal-tension glaucoma.[22]

These hypotheses have been confirmed by several studies that measured ICP in glaucomatous patients. Berdahl et al. demonstrated that the ICP is significantly lower (of 33%) in patients with POAG.[16] Two recent case reports confirm how a lowering of ICP, in these cases induced by a shunt, can determine a glaucomatous damage. Yusuf et al. illustrated the case of a 27 year old man with a premature onset of NTG after he had undergone 8 CSF shunt revision procedures over a 25-year period, secondary to recurrent low CSFP, following surgical excision of a pinealoblastoma, aged 2.[23] Chen et al. reported a case of worsening NTG immediately following ventriculoperitoneal (VP) shunt placement to lower cerebrospinal fluid pressure.[24]

Therefore, intracranial hypotension, by increasing the trans-laminar gradient, determines an optic nerve damage, with the mechanisms described above. Given that this damage occurs progressively, an important aspect to take into consideration is the time of exposure of the optic nerve to this altered gradient. It can be assumed that determinants of glaucomatous neuropathy are not only ICP values, but also the time of exposure to that value. Therefore, the optic neuropathy would result from the duration of the period of hyper or hypotension.

1.2.3.1 Cerebrospinal fluid dynamics

Intracranial pressure is mainly determined by pressure of cerebrospinal fluid. CSF is produced at a rate of 0.2 - 0.7 ml per minute or 600-700 ml per day. The total volume of CSF in the adult ranges from 140 to 270 ml.

The majority of CSF is produced from within the two lateral ventricles. From here, CSF passes through the interventricular foramina to the third ventricle, then the cerebral aqueduct to the fourth ventricle. From the fourth ventricle, the fluid passes into the subarachnoid space through four openings – the central canal of the spinal cord, the median aperture, and the two lateral apertures. CSF is present within the subarachnoid space, which covers the brain, spinal cord, and stretches below the end of the spinal cord to the sacrum. There is a connection from the subarachnoid space to the bony labyrinth of the inner ear making the cerebrospinal fluid continuous with the perilymph in 93% of people. CSF moves in a single outward direction from the ventricles, but multidirectionally in the subarachnoid space. Fluid movement is pulsatile, matching the pressure waves generated in blood vessels by the beating of the heart. Some authors dispute this, posing that there is no unidirectional CSF circulation, but cardiac cycle-dependent bi-directional systolic-diastolic to-and-fro cranio-spinal CSF movements.

CSF is derived from blood plasma and is largely similar to it, except that CSF is nearly protein-free compared with plasma and has some different electrolyte levels. Most (about two-thirds to 80%) of CSF is produced by the choroid plexus. The choroid plexus is a network of blood vessels present within sections of the four ventricles of the brain. It is present throughout the ventricular system except for the cerebral aqueduct, frontal horn of the lateral ventricle, and occipital horn of the lateral ventricle. CSF is also produced by the single layer of column-shaped ependymal cells which line the ventricles; by the lining surrounding the subarachnoid space; and a small amount directly from the tiny spaces surrounding blood vessels around the brain. CSF is produced by the choroid plexus in two steps. Firstly, a filtered form of plasma moves

from fenestrated capillaries in the choroid plexus into an interstitial space, with movement guided by a difference in pressure between the blood in the capillaries and the interstitial fluid. This fluid then needs to pass through the epithelium cells lining the choroid plexus into the ventricles, an active process requiring the transport of sodium, potassium and chloride that draws water into CSF by creating osmotic pressure. Unlike blood passing from the capillaries into the choroid plexus, the epithelial cells lining the choroid plexus contain tight junctions between cells, which act to prevent most substances flowing freely into CSF.

CSF returns to the vascular system by entering the dural venous sinuses via arachnoid granulations. These are outpouchings of the arachnoid mater into the venous sinuses around the brain, with valves to ensure one-way drainage. This occurs because of a pressure difference between the arachnoid mater and venous sinuses. CSF has also been seen to drain into lymphatic vessels, particularly those surrounding the nose via drainage along the olfactory nerve through the cribriform plate. The pathway and extent are currently not known, but may involve CSF flow along some cranial nerves and be more prominent in the neonate. CSF turns over at a rate of three to four times a day. CSF has also been seen to be reabsorbed through the sheathes of cranial and spinal nerve sheathes, and through the ependyma.

The composition and rate of CSF generation are influenced by hormones and the content and pressure of blood and CSF. For example, when CSF pressure is higher, there is less of a pressure difference between the capillary blood in choroid plexuses and CSF, decreasing the rate at which fluids move into the choroid plexus and CSF generation. The autonomic nervous system influences choroid plexus CSF secretion, with activation of the sympathetic nervous system increasing secretion and the parasympathetic nervous system decreasing it. Changes in the pH of the blood can affect the activity of carbonic anhydrase, and some drugs (such as frusemide, acting on the Na-K-Cl cotransporter) have the potential to impact membrane channels.[25]

CSF serves several purposes, but its main functions are:

• Protection: CSF protects the brain tissue from injury when jolted or hit, by providing a fluid buffer that acts as a shock absorber from some forms of mechanical injury.

• Homeostasis: CSF allows for regulation of the distribution of substances between cells of the brain, and neuroendocrine factors, to which slight changes can cause problems or damage to the nervous system. Also, CSF allows for the removal of waste products from the brain. Metabolic waste products diffuse rapidly into CSF and are removed into the bloodstream as CSF is absorbed.

An alteration of the cerebrospinal fluid dynamic at every level – production, circulation or reabsorption – could determine an alteration of ICP. This can be influenced from other factors as well. Berdahl in a study pointed out that various systemic parameters may affect CSF pressure. CSF pressure increases with increased body mass index (BMI) and decreases with age. Blood pressure has been reported to influence CSF pressure in some studies but not others. Women appear to have a slightly lower CSF pressure than men and CSF pressure shows diurnal fluctuation, as do blood pressure and intraocular pressure. Additionally, postural changes likely alter CSF pressure near the optic nerve. Finally, many factors that may affect CSF pressure, such as medications, genetics, race, and others, have yet to be studied conclusively.[4]

1.2.3.2 Measurement of intracranial pressure

Considering the probable pathogenetic role of ICP in glaucoma, it would be crucial to have a fast, accurate and minimally invasive way of measuring ICP in the subarachnoid space that surrounds the optic nerve. Unfortunately, this is not possible yet.

Invasive measurements of pressure are the standard method for direct ICP monitoring and several different invasive methods exist. ICP measurement can be undertaken at various intracranial anatomical locations determined by different techniques: intraventricular, epidural, subdural, subarachnoidal, and intraparenchymal. Furthermore, under certain

circumstances ICP may be assessed by lumbar puncture for patients with communicating CSF pathways. The standard technique is an invasive procedure that involves catheter insertion into the intracranial compartment, usually through a small hole drilled in the skull. A pressure probe/sensor is then advanced through the brain tissue into the ventricular space, or the brain parenchyma, epidural space (between skull and dura), or subdural space (between brain and dura).

Quincke (1891) introduced the lumbar puncture (LP) technique as an option to investigate the intrathecal environment. It involves the percutaneous introduction of a needle into the lumbar spinal CSF space and the measurement of a column of water, which reflects intraspinal pressure. Lang et al. believed that LP could accurately estimate ICP when CSF circulates freely and when the fluid column is appropriately positioned with respect to the brain. As mentioned above, under certain circumstances ICP may be assessed by lumbar puncture for patients with communicating CSF pathways. Lumbar puncture is not strictly an ICP measurement, but a neuraxis CSF pressure (CSFP) measurement. Mertz et al. found that there is a good correlation between the brain sensor's CSFP and lumbar pressure.[21]

The main problem is not only the correspondence between CSF pressure at lumbar and intracranial level, but also between lumbar pressure and the pressure around the optic nerve. Indeed, CSF occupies a fluid-filled compartment that changes position within space and is subject to gravity. Therefore, the pressure exerted by CSF varies with position of the area in question relative to the vertical position of the whole compartment. In a sitting position, the CSF-containing lumbar subarachnoid space has a pressure of 0 mmHg at the level of the occiput of the skull, a height similar to the globe. Thus, the pressure around the optic nerve is likely less than that measured with lumbar puncture performed in a lateral decubitus position. Furthermore, recent investigations into CSF within the subarachnoid space surrounding the optic nerve suggest that there are variations in CSF flow surrounding the globe. The subarachnoid space encircling the optic nerve can be divided into three sections by the architecture of the trabeculae, septa and pillars that exist within the space. This divisive architecture could

account for changes in CSF flow and even cause a ‘compartment syndrome’ in the subarachnoid space. This could result in variation in CSFP at the lamina cribrosa and thus possibly alter the trans-laminar gradient.[10]

To estimate CSFP, Lee et al. used a formula published previously by Xie et al. in a pilot study. They formed an algorithm for determining CSFP based on three parameters: diastolic blood pressure, BMI, and age.

Estimated CSFP [mmHg] = 0.44 × BMI [kg/m^2] + 0.16 × diastolic blood pressure [mmHg]—0.18 × age [years]—1.91

They applied the formula to groups of subjects by comparing the estimated CSFP with the direct CSFP measurements. Using the calculated CSFP, the trans-laminar gradient was calculated as IOP -CSFP.[16]

1.2.4 Biochemical hypothesis

The biochemical hypothesis of the pathogenesis of NTG is also related to CSF dynamics, but not strictly to ICP. According to this hypothesis, the glaucomatous damage would be correlated to the alterations of CSF circulation that happen with ageing. CSF production and turnover have been shown to be decreased in aging and in pathologic conditions, such as Alzheimer disease and normal pressure hydrocephalus. CSF circulatory failure, ultimately resulting in reduced neurotoxin clearance along the optic nerves, could be an alternative explanation as to why glaucoma develops in patients with low intracranial pressure. This theory explains the lower ICP evidenced in glaucomatous patients as a consequence of reduced production of CSF.[22]

1.3 Hydrocephalus

Hydrocephalus is an active distension of the ventricular system of the brain resulting from inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation.

1.3.1 Classification

Hydrocephalus can be classified as follows, depending on various factors.

- Congenital / Acquired

• Onset

- Fetal / neonatal / pediatric / adult onset
- Acute / subacute / chronic onset

• Etiology

- Primary / secondary / idiopathic

• Associated diseases

- Disgenetic / post-hemorrhagic / post-meningitic / post-traumatic
- Cerebral tumor associated / spinal tumor associated / cerebral abscess associated etc.

• Physiopathology

- Ipersecretive / obstructive / resorptive
- Communicant / non communicant

• Cerebrospinal fluid circulation

- Obstructive / non obstructive
- External / internal / interstitial

• Dynamics

- High pressure / normal pressure

1.3.2 Normal pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is an accumulation of cerebrospinal fluid that causes the ventricles in the brain to become enlarged, sometimes with little or no increase in intracranial pressure. In most cases of NPH, the cause of blockage to the CSF absorptive pathways is unclear. The name for this condition, "normal pressure hydrocephalus", originates from Dr. Salomon Hakim's 1964 paper describing certain cases of hydrocephalus in which a triad of neurologic symptoms occurred in the presence of "normal" CSF pressure, gait disturbances, dementia, and impaired bladder control. These findings were observed before continuous pressure-recording techniques were available. The phrase "normal pressure" is misleading as many patients experience fluctuations in CSF pressure that range from high to low and are variable within those parameters. However, "normal pressure hydrocephalus" continues to be the common name for the condition.

NPH can be idiopathic (iNPH) or secondary to subarachnoid hemorrhage, meningitis, encephalitis, cerebral trauma, cerebral tumor, cerebral irradiation. All these processes determine a cicatricial obstruction to the cerebrospinal fluid circulation.

1.3.2.1 Epidemiology

According to a recent epidemiological study,[26] the prevalence of normal pressure hydrocephalus is 0,2 % in patients aged 70-79 years and 5.9% in those aged 80 years and older, with no difference between men and women. The incidence of iNPH is between 2 and 6% among people affected by any dementia condition; it is considered an infrequent disease, but its occurrence is probably underestimated because of diagnostic challenges.[27]

1.3.2.2 Etiology

Many theories have been advanced to explain the mechanisms underlying the development of the NPH syndrome. However, the basic pathophysiological processes still remain unclear. Clearly, NPH may be a

form of CSF circulation disorder, but progressive ventriculomegaly may not be the only active process in this condition. The inability to clear potentially toxic metabolites, such as amyloid-b peptides and tau protein, could result in increased concentrations in brain fluid, leading to neuronal damage or dysfunction. The presence of B waves, abnormal CSF pressure spikes, may result in intermittently raised intracranial pressures, particularly during rapid eye movement (REM) sleep. The presence of these waves and the change in properties of aging brain parenchyma may make the older age group susceptible to progressive ventricular enlargement. The major theory streams proposed for the pathogenesis of NPH can be divided into structural, cerebral blood flow, and CSF flow subgroups.

Structural hypothesis

• *Tissue Distortion and Biomechanics*

Hakim and other authors have hypothesized that the starting point in the pathophysiology of NPH is tissue distortion secondary to raised intraventricular pressure. Initially, the pressure is highest in the periventricular area; the farther away from the ventricles the pressure is measured, the less elevation is evident. The raised pressure is thought to distort the periventricular tissue, including the parenchyma and vessels, either by compression or by stretching. There is loss of tissue elasticity and/or atrophy caused by the pressure forces acting on the brain parenchyma as well as ischemia from damage to blood vessels. This results in a state of normal CSF pressures that result in a reversal of the gradient of pressure and stress at the brain periphery or cerebral mantle.

• *Interstitial Fluid Pressure Increase*

It is thought that loss of elasticity in the brain parenchyma results in a pressure gradient between the ventricles and periventricular tissues. Indeed, there may also be a pressure gradient between convexity subarachnoid spaces and the brain parenchyma; the pulse waveform in CSF recordings appears to be slightly greater (although not always) than in parenchyma, but a pressure gradient between convexity and subarachnoid

spaces has never been documented. Animal studies have demonstrated that disruption of the periventricular matrix integrity could result in pressure gradients favoring progressive ventriculomegaly. Both situations may result in the movement of CSF into the parenchyma in the form of interstitial edema. The stagnation of excess fluid in the interstitial space disrupts the balance between hydrostatic pressures (driving fluid out of capillaries) and osmotic pressures (driving fluid into capillaries). There may be reversal of interstitial fluid flow, resulting in swelling of the extracellular space, in turn resulting in failure of drainage of vasoactive metabolites that may reduce local cerebrovascular reactivity. The accumulation of toxic metabolites in the interstitial fluid may also disrupt cell and blood vessel walls, resulting in further leakage of fluid into the interstitial space.

Cerebral Blood Flow hypothesis

• *Watershed Ischemia*

There is evidence that the cerebral vasculature may be compromised in NPH. Positron emission tomography (PET), xenon-enhanced CT, and SPECT studies all indicate widespread cortical and subcortical hypometabolism and impaired global cerebral blood flow (CBF). This may result in dysfunctional regional cerebral autoregulation, and watershed ischemia may occur in the corona radiata between territories supplied by perforators from the middle cerebral artery and medullary branches from the pial arteries. There has, however, been a frustrating lack of congruence within the group of studies examining CBF in NPH. The main problems are the diversity of different techniques employed for the measurement of CBF. There are no gold standard tests for the assessment of CBF as a diagnostic or prognostic tool. Most studies have included both idiopathic and secondary forms of NPH. Only a few studies have attempted to combine CBF measurement with structural imaging co-registration to achieve a good anatomical basis for comparisons of CBF data.

• *Vascular Disease*

The coincidental presence of deep white matter hyperintensities on imaging in some patients with NPH has also provoked debate about the possibility of cerebral small vessel disease and vascular encephalopathy. It is thought that ventricular expansion may distort the connections and/or blood vessels between the basal ganglia and frontal cortex. This distortion may disrupt white matter tracts involved in frontal executive function, gait, and micturition, producing the symptoms of gait apraxia and urinary incontinence. The stretching of blood vessels may also produce multiple areas of deep lacunar infarction. This may result in ischemia of the white matter areas supplied by these blood vessels. The parenchymal architecture may also be affected by the presence of these lacunar infarctions, leading to a loss of elasticity. Such a progression may allow progressive ventricular expansion in the context of normal intracranial pressures, which is a particular phenomenon noted in NPH. It is thought that despite normal baseline pressures, abnormal CSF pressure spikes called B waves exert intermittent high pressure on the periventricular tissue, especially during REM sleep. Overlapping vascular diseases with CSF disorder has been studied during infusion studies using transcranial Doppler ultrasonography. Those patients with increased resistance to CSF outflow (Rcsf) had more frequently normal autoregulation of CBF and those with normal Rcsf (normal CSF circulation) had more frequently disturbed autoregulation—probably due to vascular disease.

CSF Flow hypothesis

• *CSF Hydrodynamics*

Normal pressure hydrocephalus is thought to be a form of CSF circulation disorder, involving an imbalance between CSF production, circulation, and reabsorption. The resulting excess accumulation of CSF is thought to result in ventriculomegaly. In NPH, however, unlike other forms of hydrocephalus, the CSF pressure is not abnormally raised, which implies that such a simplistic hydrodynamic theory would be insufficient to explain the pathophysiology of this condition. Historically, increased resistance to

CSF outflow measured during an infusion test been implicated as a factor responsible for development of hydrocephalus, although this has been challenged in recent studies.

It has been suggested that abnormalities of the brain parenchyma that naturally occur in the aging brain (loss of elasticity of the neuropil, extracellular matrix, and parenchyma) also contribute to the development of NPH. These abnormalities are thought to make the cerebral mantle more susceptible to B waves, which slowly increase ventricular size by exerting intermittent high pressures on the brain parenchyma, resulting in ischemic damage. These pressures are thought to behave in a "water hammer" fashion. Therefore, in addition to disturbances within the CSF circulation, there may also be an imbalance between the forces driving progressive ventriculomegaly and the architectural forces within the brain parenchyma that should naturally oppose this. An additional force driving ventricular enlargement may be increased amplitude of the ICP pulse waveform, but this hypothesis is not supported by any observable correlation between ventricular dilation and magnitude of such amplitude measured during infusion studies or overnight monitoring of ICP.

There is physiological evidence to suggest that such an imbalance exists. Czosnyka et al. examined the question of age dependence of CSF pressure-volume compensation by performing CSF infusion studies in a group of patients with symptomatic hydrocephalus and normal ICP. They demonstrated Rcsf increased in a nonlinear fashion with advancing age and was associated with a decrease in the CSF production rate, which also occurred with increasing age. Both the pulse amplitude of the ICP waveform and the slope of the amplitude-ICP regression line increased significantly with advancing age. There was a nonlinear increase in the elastance coefficient with age, and this was thought to represent progressive brain parenchymal stiffness.

• *Failure of Drainage of Vasoactive Metabolites*

Abnormalities in CSF production and turnover may also lead to inefficient or failed clearance of toxic molecules. Silverberg and colleagues

proposed that an inability to clear potentially toxic metabolic products, such as amyloid-b peptides and tau protein, could lead to an increase in their concentration in brain interstitial fluid, creating a potentially hostile milieu for neuronal function and survival. It is further proposed that the two changes noted in aging, reduced CSF production and increased Rcsf, may be implicated in the pathophysiology of Alzheimer's disease and NPH. A predominance of reduced CSF production and turnover may manifest as Alzheimer's disease. Conversely, NPH may result from a predominant increase in Rcsf. There may be a disease spectrum that includes a subset of patients who either have both conditions or have risks of developing both even if one process is predominant.

This implies that CSF diversion (i.e. the placement of a shunt) may be helpful in other conditions within the dementia spectrum. Indeed, it may be more accurate to describe a disease component remediable to shunting that occurs predominantly in classical NPH but may also be present in a subset of patients with an overlap of conditions. Silverberg et al. then published the results of a prospective, randomized, double-blinded, placebo-controlled trial evaluating the safety and effectiveness of a surgically implanted shunt in patients with probable Alzheimer's disease. The trial involved 215 patients. Participants received either a low-flow ventriculoperitoneal (VP) shunt or a sham (occluded) shunt for 9 months. The results of the study did not demonstrate any benefit for low-flow CSF shunting in patients with mild to severe Alzheimer's disease. It is unclear whether increased clearance of toxic macromolecules through CSF diversion was insufficient to improve the condition or inadequate clearance was achieved due to established deposition of macromolecules into fibrillary tangles. Indeed, it may be that a sufficient level of CSF circulatory disorder is required to benefit from shunting, although the threshold of Rcsf that is associated with improvement from shunting still continues to provoke debate.[28]

Unifying theories

Many hypotheses have been advanced in order to explain normal tension hydrocephalus. One was made by Bateman in a spectrum hypothesis incorporating Alzheimer's disease, vascular dementia and normal pressure hydrocephalus. All three forms of dementia share the same risk factors, which for the most part are vascular risk factors. Bateman proposes that there is an underlying vascular pathophysiology behind these conditions, which is related to the strength of the pulse waves induced in the craniospinal cavity by the arterial vascular tree. It is proposed the manifestation of the dementia in any one patient is dependent on the way that the pulsations interact with the brain and its venous and perivascular drainage. This interaction is predominately dependent on the compliance of the craniospinal cavity and the chronicity of the increased pulse wave stress.[29]

Another hypothesis was advanced by Bradley et al., whose purpose was to determine if NPH could result from decreased resorption of cerebrospinal fluid by the arachnoidal villi, leading to benign external hydrocephalus in infancy, followed by deep white matter ischemia in late adulthood (the more hydrophilic environment increasing resistance to CSF flow through the extracellular space of the brain). According to Bradley, idiopathic NPH is proposed to be a “two hit” disease: “benign external hydrocephalus” in infancy followed by deep white matter ischemia in late adulthood.[30] Thus, this theory implies that NPH patients have had enlarged ventricles since infancy. A study confirmed an increase in intracranial volume in a group of patients with NPH, but not in every patient. So, this theory is not applicable to every case of idiopathic normal pressure hydrocephalus.

In conclusion, theories regarding normal pressure hydrocephalus’ pathogenesis are still debated. Probably, these theories are not mutually exclusive, and could all contribute to development and evolution of this pathologic condition. Further studies are mandatories, due to the fact that normal pressure hydrocephalus has a great responsivity to treatment.

1.3.2.3 Clinical manifestations

NPH exhibits a classic triad of clinical findings, known as the Hakim's triad, which consists of gait deviation, dementia, and urinary incontinence. The symptoms are all caused by compression of periventricular structures by the enlarged ventricles. The triad of Hakim syndrome is present in approximately 50% of cases, however, only one or a combination of two symptoms should be considered for investigation and diagnosis.[31] Gait deviations are present in nearly all patients and usually is the first symptom. Demencia and urinary incontinence often appear later in the illness.[27] The onset of iNPH symptoms is insidious and should have been evident for at least 6 months.[32] Some patients and families are not aware of symptoms until a precipitating event occurs (e.g., a fall or a change in symptoms after a surgical procedure).

Gait

In idiopathic normal pressure hydrocephalus, a higher-level gait disorder is seen with disturbed postural and locomotor reflexes in the absence of primary sensorimotor deficits. Findings include difficulty with transitional movements (sitting to standing or standing to sitting); gait initiation failure; poor foot clearance with shuffling, tripping, falling, or festination; multistep turns with instability; and retropulsion or anteropulsion of stance. The use of a standardized gait evaluation (e.g., the Tinetti score, Boon Scale, or the timed up-and-go test) can be helpful. Spasticity, hyperreflexia, and other upper motor neuron findings are not typical. Symptoms of iNPH are symmetric; therefore, lateralizing findings should increase suspicion of other disorders.

Dementia

The dementia of iNPH includes apathy or amotivation, daytime sleepiness, psychomotor slowing, and other features of frontal-subcortical dysfunction. Functional losses with dementia in iNPH overlap with those of other dementias, including difficulty managing finances, taking medications properly, driving, and keeping track of appointments. Impaired expressive

or receptive language, impaired naming, agnosia, poor immediate recall that does not benefit from cueing, hallucinations, and failure to recognize close family or friends should raise concern for other causes of dementia. Delirium implies the presence of a concomitant disorder or medication side effect.

Urinary incontinence

The bladder dysfunction of iNPH is usually urinary urgency with difficulty inhibiting bladder emptying. In the early stages, patients may experience urgency without incontinence or with loss of a few drops of urine before reaching the toilet. Nighttime urinary frequency is common. Patients are usually aware of their need to urinate and are concerned about their accidents. Incontinence without awareness of urinary urge or that one's clothes are wet is not characteristic of iNPH.[32]

1.3.2.4 Diagnosis

For a correct diagnosis of NPH the starting point is a comprehensive history and neurologic examination, review of neuroimaging, and evaluation of the differential diagnosis. The clinical presentation alone is usually not sufficient to diagnose iNPH, as each of the primary iNPH symptoms can have multiple potential etiologies, and enlarged ventricles can be seen with either hydrocephalus or brain atrophy. However, key neurologic features should always be taken into consideration. The neurologic history should include known risk factors for communicating hydrocephalus, including meningitis, encephalitis, traumatic brain injury (including concussion), subarachnoid hemorrhage, and brain radiation. Enlarged head circumference is also a risk factor that may indicate a congenital component to the disorder.

Neuroimaging plays an important role in NPH diagnosis. Either computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain is necessary—yet, alone, never sufficient—to establish the diagnosis of NPH. MRI is considered superior to CT in terms of providing more information on diagnostic relevance and avoiding exposure to ionizing

radiation. High-speed and high-resolution MRI techniques can better identify aqueductal stenosis, and MRI phase-contrast techniques show the hyperdynamic aqueductal CSF flow that has been associated with shunt-responsive iNPH.

It is important to underline that the terms hydrocephalus and ventriculomegaly are not synonymous. Although all patients with iNPH should have enlarged ventricles, not all elderly patients with enlarged ventricles have iNPH. In neurodegenerative disorders, cerebral atrophy results in ventriculomegaly (so-called hydrocephalus ex vacuo). Neuroimaging can be used to raise or lower suspicion of iNPH; however, it can rarely exclude it entirely.

The distinction between normal and enlarged ventricular size for age is difficult to ascertain; however, for screening purposes, the Evans ratio (the ratio of the widest diameter of the frontal horns to the widest diameter of the brain on the same axial slice) suffices (Figure 16). The International and Japanese guidelines use a threshold of ≥ 0.3, but research on normal elderly subjects suggests a threshold of ≥ 0.33.[32]

Imaging characteristics of hydrocephalus are: enlargement of the anterior or posterior recesses of the third ventricle, downward convexity of the floor of the third ventricle, effacement of the arachnoid spaces of the convexity (including the sylvian cisterns), commensurate dilatation of the temporal horn with the lateral ventricles and rounding, and atrial dilatation. Also, the concentric enlargement of the frontal horns produces an appearance of "Mickey Mouse Face" on axial scans (Figure 17).

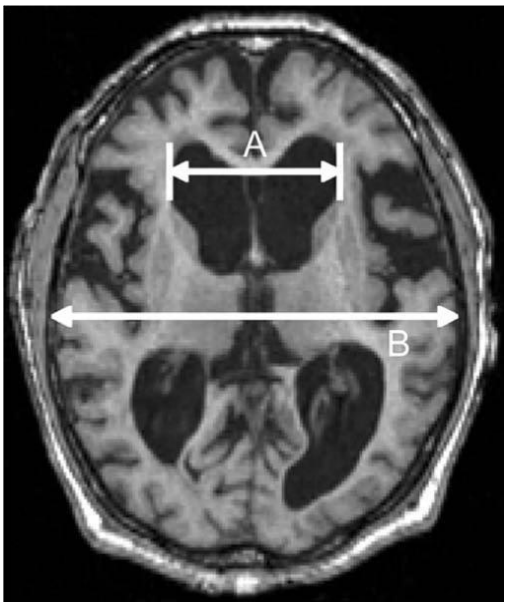

Figure 16. *Head MRI. Evans ratio is calculated as the ratio of the widest diameter of the frontal horns (A) to the widest diameter of the brain (B) on the same axial slice*[33]

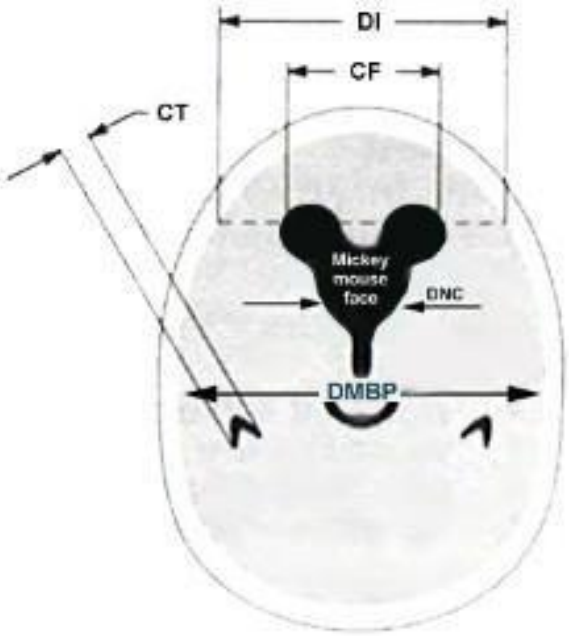

Figure 17. *Mickey Mouse Face (DI = intraparietal diameter, CF = frontal horn, CT = temporal horn, DMBP = biparietal mean diameter, DNC = caudate nuclei distance)*

In conclusion, there is no standardized way to diagnose iNPH, and various assessments have been applied. It is difficult to compare severity of symptoms, as there is no consensus on the diagnostic protocol. Some common elements in today's diagnostics include:[34]

- one/two or more of the classic triad symptoms
- normal intracranial pressure
- enlarged ventricles on CT/ MRI
- cereprospinal fluid (CSF) stasis/increased resistance to outflow
- improvement of symptoms after CSF removal (tap test)
- some also included a lack of secondary causes in the diagnostic criteria

Other elements to take into consideration are: age over 60 years old, language deficit due to executive or motivational disfunction (not aphasia), Parkinson-like symptoms like tremor and bradykinesia, psychiatric symptoms such as depression or bipolar disorder.

Differential diagnosis

Many elderly people suffer from combined motor and cognitive dysfunction (and sometimes from incontinence as well). Moreover, three-quarters of patients with (i)NPH simultaneously have vascular or Alzheimer's dementia. Thus, the differential diagnosis of NPH can be quite difficult. Findings that make the diagnosis of NPH less likely include the following:

- Intracranial pressure above 25 cm H_2O (this rules out iNPH, by definition)
- Age under 40 (iNPH unlikely)
- Asymmetrical or transient symptoms
- Cortical deficits, e.g., aphasia, apraxia, or paresis
- Progressive dementia without gait disturbance (even if the ventricles are enlarged)
- Lack of progression of symptoms (a controversial point, as authors differ on the period of time in which symptoms should be seen to progress).

The differential diagnosis of gait disturbances includes peripheral neuropathy, spinal canal stenosis, disorders of the inner ear, chronic alcoholism, and deficiencies of vitamin B6 and B12. The differential diagnosis of urinary disturbances includes urinary tract infections, bladder or prostate cancer, benign prostatic hyperplasia. The differential diagnosis of cognitive deficits includes various types of dementing disease: Alzheimer's disease, Lewy-body dementia, Parkinson's disease and vascular parkinsonism etc. The tests ordered to evaluate the differential diagnosis include the so-called "dementia bloodwork" (complete blood count, biochemical profile, B_{12}, folate, thyroid-stimulating hormone, and when indicated, rapid plasma reagin, Lyme, vitamin D); neuropsychological testing; MRI of the cervical, thoracic, or lumbar spine; EMG/nerve conduction velocity; and urology consultation.[32]

1.3.2.5 Treatment

The gold standard treatment of NPH is shunt surgery. In most cases, the shunt is performed by connecting a small tube from the brain ventricles to the peritoneal cavity, a ventriculo-peritoneal (VP) shunt. This allows excess fluid in the ventricles to be drained. The goal of treating with a shunt is to improve the patient's symptoms while avoiding complications. Therefore, before the surgery, patients must be tested to assess the prognosis of the treatment.

Prognostic tests

• *Intracranial pressure monitoring*

Intracranial pressure monitoring is useful to select patients that can most probably benefit from a ventriculo-peritoneal shunt. An ICP-sensitive transducer is used to monitor prolonged ICP and amplitude changes. B-waves represent oscillations of ICP and are often recorded. Eide & Sorteberg reported that when using ICP monitoring as a diagnostic tool for identification of iNPH patients, improvement after surgery can be expected in 90% of subjects.[34]

• *Tests of CFS drainage*

The International and Japanese guidelines recommend tests of CSF drainage (lumbar puncture or CSF drainage via spinal catheter); however, the International guidelines also recommend infusion testing. The rationale for testing a patient's response to CSF drainage is that doing so emulates the physiologic effect of a shunt. If iNPH is present, a response to CSF removal should be seen and shunt surgery should help. However, if iNPH is absent or contributes only minimally, no response to CSF removal is seen and shunt surgery is unlikely to help.[32]

• *Lumbar infusion test*

CSF infusion test is usually done by inserting a cannula into the dural sac in the lower lumbar region. CSF pressure is recorded before and after infusion of Ringer solution or artificial CSF. Infusion test via an external ventricular catheter is also possible. Resistance to outflow (R_{out}) is calculated on the basis of the infusion test. Although R_{out} increases with age, a R_{out} > 10 mmHg/ml/min. is often considered elevated. In patients with INPH, R_{out} is found to decrease with the time of duration of symptoms, observed when symptoms exceed 2.5 years. It is therefore suggested that R_{out} should be adjusted in patients whose anamnesis exceeds 2-3 years.

Surgery, rehabilitation or conservative treatment

The treatment of iNPH based on the evidence can be categorized into three pillars: conservative treatment, ventriculo-peritoneal shunt and endoscopic third ventriculostomy (ETV). The conservative option has fallen into disuse after various studies showing good results after surgical intervention. Thus, it is widely accepted that surgical treatment of patients with NPH is mandatory because surgery has been associated with a positive impact on the course of the disease, which affects the quality of life of patients and caregivers. Rehabilitation strategies should always be included in the treatment of INPH. However, it is considered a supplementary treatment option.

VP shunt is by far the most common method used to treat iNPH worldwide (Figure 18). Since iNPH is understood as a communicating hydrocephalus, ETV has been somewhat discouraged as treatment. Although the most common shunt today is VP shunt, different types of shunt may be used: ventriculoatrial shunt, ventriculopleural shunt and lomboperitoneal shunt.

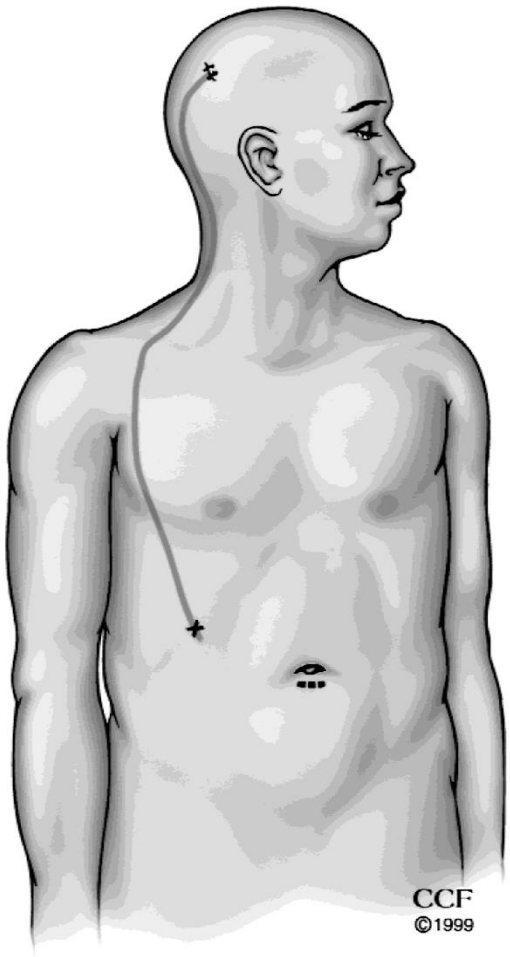

Figure 18. *Typical subcutaneous position of ventriculoperitoneal shunt.*

Many studies have demonstrated a short-term improvement after VP shunt, from 60 to 90%.[35] Meier et al. reported a post-operative success of 80%, while after 3 years it decreased at 67%,[36] as reported in a study by Pujari et al. as well.[37] On the other hand, other studies reported a permanent clinical improvement, even after many years from the shunt placement.[38]

Favorable indicators of postoperative improvement include: early onset of gait disorders and onset of symptoms for less than six months. Adverse indicators include: the absence of changes in gait or its emergence after the onset of the disease, early onset dementia, mild to severe dementia, dementia for more than two years, diffuse brain atrophy and severe impairment of the white matter.[31]

Ventriculoperitoneal shunt complications

VP shunt complication rates have been estimated atapproximately 35%, also due to the intrinsic fragility of the nervous system of the elderly. Among the potential complications are intracranial and abdominal ones:[25]

- Subdural hematoma or hygroma
- Intraparenchymal hemorrhage or intraventricular hemorrhage
- Epilepsy
- Shunt infections
- Overshunting
- Peritonitis
- Hydrocele
- Catheter migration into the scrotum or with perforation of other bowels
- Bowel obstruction
- Shunt obstruction or disconnection

Shunt Devices for the treatment of hydrocephalus

The choice of the appropriate valve is crucial for the outcome of the VP shunt. The shunt valve intrinsically functions as a kind of resistance mechanism within the shunt system, which serves to control intracranial pressure in patients with hydrocephalus. The main characteristics of each valve are shown as follows:

I. First generation valves: the fixed differential pressure (DP) valve
II. Second generation valves: the DP valve with antisiphon mechanism; programmable (adjustable) DP valves

III. Third generation valves: programmable (adjustable) DP valves with antisiphon mechanisms
IV. Fourth generation valves: the programmable (adjustable) antisiphon valve

With programmable valves the pressure setting can be easily regulated, and a second surgical operation is avoided as the valve's operating characteristics may be changed non-invasively. The antisiphon consists in a mobile membrane that moves and narrows the lumen of the shunt in response to a negative pressure in the system. This mechanism helps avoiding overshunting and improves the outcome for the patients. In fact, in a shunted patient the main complication to avoid is overshunting, an excessive drainage of CSF. This determines low pressure symptoms (mostly headache) and can lead to subdural hematomas. Overshunting can be prevented by an adequate choice of the type of valve and an accurate pressure setting. Indeed, the most important factor in shunt management is control of ICP, not shunt flow. After 20-30 minutes in a standing position, during which the ICP continues to decrease, the patient can experience overshunting symptoms. In shunted patients in standing position, pressures can be described by the following equation:

Perfusion Pressure (PP) = Hydrostatic Pressure (HP) + Intracranial Pressure (ICP) – Intraabdominal Pressure (IAP)

When the perfusion pressure becomes equal to valve pressure, the condition is considered stable. Intracranial pressure tends to decrease until the perfusion pressure becomes equal to valve pressure. Because PP and valve pressure are balanced, shunt flow in the stable condition is minimal, similar to titration at approximately 0.6 ml/min. When setting the programmable DP valve, one DP value must be selected which is suitable for either the upright position or the recumbent position. The DP suitable for the upright position may cause underdrainage during sleep, and DP for the recumbent position may cause overdrainage in the upright position. Various approaches for determining the initial pressure of programmable DP valves have been reported. Reinprecht et al. and Bergsneider et al. recommended setting the opening pressure at the highest setting initially, followed by

decreases depending on the patient's clinical condition. This method is usually best for reducing overdrainage complications, however, hospitalization time may be prolonged, and symptoms remain unchanged until a suitable setting is achieved.[39] [40] Zemack et al. proposed setting the initial pressure based on the patient's age, duration of the underlying disease, ventricular size, and results of the lumbar infusion test. This method is not strictly quantitative and is too complicated and invasive for clinical use.

In conclusion, the valve setting has to take into consideration the patient and the type of valve implanted. The programmable DP valve is recommended as a first line shunt valve, not only because of its superior efficacy but also from a medico-economic standpoint. Also, the most important goal in shunt management is to control ICP, not to control shunt flow.[41]

2. PURPOSE OF THE STUDY

The purpose of this study was to investigate the correlation of changes in the pressure gradient between intraocular and intracranial compartments at the lamina cribrosa level with normal tension glaucoma. If trans-lamina cribrosa gradient changes have a role in the pathogenesis of normal tension glaucoma, shunt surgery might induce or accelerate glaucomatous damage in patients affected by normal pressure hydrocephalus. Therefore, shunt-treated NPH may be an appropriate model for testing the hypothesis that intracranial hypertension is protective, while hypotension is a risk factor for NTG over time. We estimated the prevalence of optic nerve damage in patients with NPH who had received ventriculoperitoneal shunt placement and we calculated the extent of the optic nerve exposure to pressure gradient changes in relation to NTG occurrence.

3. MATERIALS AND METHODS

3.1 Research design

This retro-prospective study was conducted at the Clinica Neurochirurgica and Clinica Oculistica of AOU Careggi. The analysis was carried out in a sequential manner in order to stop enrollment when an NTG prevalence significantly higher than that of the Italian population was reached. Given that the prevalence of NTG is 1.1% in Italians over 70 years of age,[1] the required sample size for having 80% statistical power to detect a (alpha =0.05) 3-fold significant increase was 260. With the aim of selecting patients, we reviewed from our files the records of all NPH patients who had undergone VP shunt placement according to previously reported protocols.[42]

3.2 Studied population

Neurosurgical exclusion criteria were:

• cognitive status insufficient to grant informed consent (Mini mental state examination[43] score ≤ 18)

• less than 6 months' follow up

• pre or post shunt pathologies associated with ICP changes (e.g. endocranical tumors, hemorrhages with mass effect) or with disturbance of CSF dynamics (e.g. subarachnoid hemorrhage and infections)

• surgical complications

• shunt malfunction

• shunt closure

• programmable valve opening pressure adjustment to a value higher than that set a surgery.

NPH had been diagnosed on the basis of ventriculomegaly (Evans ratio>0.30) and of at least two of the triad disturbances associated with the condition. Patients had been selected for surgery on the basis of definite improvement after prolonged external lumbar drainage. Candidates were randomly scheduled for a single-session visit where written consent was acquired. The patients' age at this visit and at NPH onset, date of surgery, type of valve, opening pressure valve setting (as ICP proxy) at surgery and at any adjustment, and the time interval between adjustments were recorded. Moreover, Hakim's triad[44] was assessed using the same preshunt criteria. In comparison with preshunt status, a patient was considered improved when he or she gained at least 2 points by the union of the urinary and gait scales or when the patient gained 1 point on either the urinary or the gait scales and at least 3 points on the Mini-Mental State Examination test.

Ophthalmic anamnesis was obtained to exclude patients with preshunt glaucoma. Ophthalmic exclusion criteria were:

• pre-existing glaucoma

• pre-shunt or intervening diseases affecting the optic nerve, compromising clinical or instrumental inspection (ocular trauma, retinal detachment, uveitis, optic nerve inflammation, advanced cataract, corneal opacity).

Enrolled patients received visual acuity and IOP measurement (Goldman applanation tonometry), biomicroscopy evaluation of the anterior segment, and fundus examination (after dilation with 1% tropicamide drops). Corneal central thickness (CCT) was evaluated in both eyes by specular microscpy (CSO Perseus, Italy). Optical coherence tomography (DRI OCT Triton plus, Topcon Medical System Inc., Oakland, NJ, USA) of the optic nerve head was performed in each patient's eyes to asses disc retinal nerve fiber layer and optic nerve head morphology. A visual field test (Humphrey Field Analyzer, Zeiss, Germany) was done (in a subsequent session) in those patients in whom one or more of the following findings were monolaterally or bilaterally found:

• increased excavation, bayonet vessels, lamina cribrosa exposure, presence of splinter hemorrhages, thinning of the neural rim and pallor of the optic nerve head at inspection;
• disc retinal fiber layer < 75μm in at least one quadrant, associated with an optic nerve head vertical cup disc ratio > 0.50 at optical coherence tomography.

Monolateral or bilateral findings of focal, generalized or mixed defects revealed by the visual field test were assessed by evaluating the mean deviation and pattern standard deviation. The cellular ganglion layer and macular retinal nerve fiber layer were evaluated as well.

Patients were considered to have NGT if they had an IOP < 21mmHg, corneal central thickness ≥ 520 μm, vertical cup disc ratio >0.50, disc retinal nerve fiber layer < 75μm in at least one quadrant, macular retinal nerve fiber layer <35 μm, visual field mean deviation <2 dB and pattern standard deviation >2dB.

4. RESULTS

A total of 320 NPH patients underwent VP shunt placement between 2006 and 2016 and met the criteria for an enrollment in the study. 25 patients were evaluated. Two of these 25 patients did not undergo ophthalmic appraisal because of noncompliance. One patient had primary open-angle glaucoma (both eyes > 28 mmHg, average corneal central thickness 530 μm) and was excluded from the study. Out of the remaining 22 patients, 9 had NTG, resulting in a prevalence of 40.9% (95% CI 20.7%-63.6%).

We expect that about 1 in 90 people over age 75 has NTG.[1] Therefore, let we test the null hypothesis that this sample comes from a population where the NTG rate is 1/90. The probability of obtaining 9 or more NTG patients, given by the sampling distribution of the binomial, is $p= 1.13 \times 10^{-12}$. Therefore, we decided to suspend further enrollment for the aims of the present study.

Table 1 shows the characteristics of the 22 (12 males and 10 females) shunted NPH patients, whose 44 eyes were all amenable to analysis. In the NTG group, the median age was 78.1 years (range 72.8-87.2); the median IOP was 16.0 mmHg (range 12-20); the median corneal thickness was 540.5μm (range 516-621); the median disc retinal nerve fiber layer was 95μm (range 77-115), the median vertical cup disc ratio was 0.71 (range 0.54- 0.79); the median rim area was 1.09 mm^2 (range 0.39-1.59); the median cup disc area ratio was 0.58 (range 0.29-0.75). In the group of non-NTG patients, the median age was 75.3 (range 68.3- 86.2); the median IOP was 16.0 mmHg (range 12-20); the median corneal thickness was 535 μm (range 521-619); the median disc retinal nerve fiber layer was 93μm (range 83-110), the median vertical cup disc ratio was 0.53 (range 0.22-0.65); the

median rim area was 2.49 mm^2 (range 1.63-3.03); the median cup disc area ratio was 0.28 (range 0.07-0.38).

Not significant differences in the following characteristics emerged between NTG and non–NTG patients: sex p= 0.64; age at visit p=0.25; IOP p= 0.36; corneal central thickness p= 0.06; disc retinal nerve fiber layer p=0.30. These were found between the two groups when measuring the following parameters: horizontal cup disc ratio p= 3.8×10^{-6}; vertical cup disc ratio p=6.7×10^{-7}; rim area p= 1.2×10^{8}; cup disc area ratio p= $6,2 \times 10^{-8}$. Visual field defects associated with macular retinal nerve fiber layer and cellular ganglion layer alterations confirmed the NTG diagnosis (Figure 19).

Characteristic	NTG Group	No NTG Group	p Value*
Sex, % male	55.6	53.8	0.64 °
Age in yrs	78.1 (72.8-87.2)	75.3 (68.3-86.2)	0.25
Average IOP in mmHg	16.0 (12-20)	16.0 (12.0-20.0)	0.36
Average CCT in µm	540.5 (516-621)	535 (521-619)	0.06
Average disc RNFL in µm	95 (77-115)	93 (83-110)	0.30
Average vertical cup disc ratio	0.71 (0.54- 0.79)	0.53 (0.22-0.65)	<0.001
Average rim area in mm^2	1.09 (0.39-1.59)	2.49 (1.63-3.03)	<0.001
Average cup disc area ratio	0.58 (0.29-0.75)	0.28 (0.07-0.38)	<0.001

Table 1. *Demographic and ophthalmic characteristics of 9 patients (18 eyes) who developed NTG and 13 patients (26 eyes) who did not develop NTG after placement of VP shunt to treat NPH*

**Based on Mann-Whitney U-test unless otherwise indicated*

° Fisher exact test

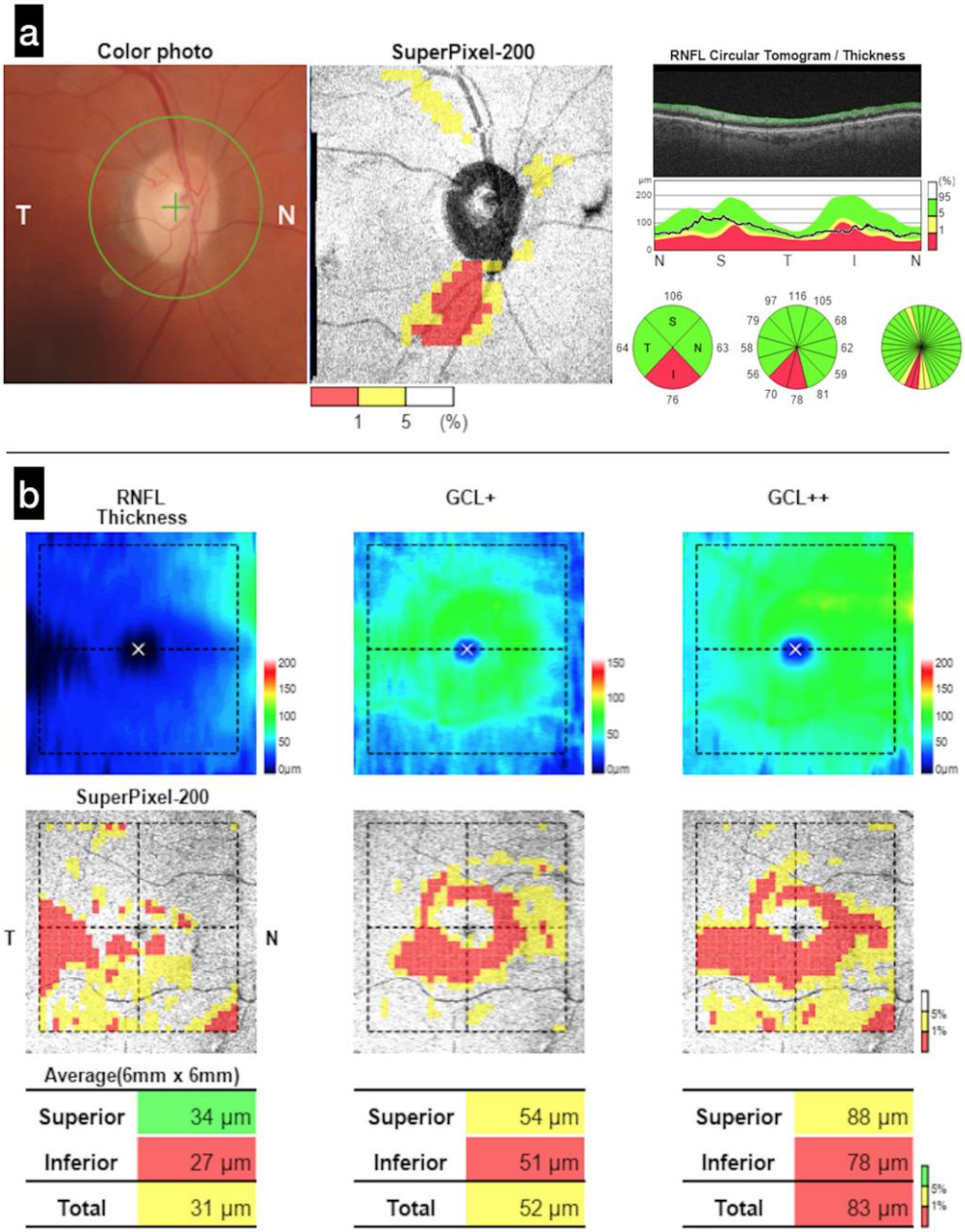

Figure 19. *Optical coherence tomography (DRI OCT Triton plus, Topcon Medical System Inc., Oakland, NJ, USA) analysis of the optic nerve head and macular region showing: a) in the peripapillar area a thickness reduction of nerve fiber layer in the inferior quadrant; b) in the macular region a thinning of perifoveal ganglion cells layer and nerve fiber layer*

Table 2 displays data on the neurosurgical assessment of patients with NPH undergoing VP shunt treatment in the NTG and no-NTG groups, respectively. In the NTG group (5 males and 4 females), the median age of NPH onset was 71.6 years (range 65.5-77.4 years); the median age at shunt placement was 72,5 years (range 66.0 -78.3 years); the median age at single study visit was 78.1 years (range 72.8-87.2 years). VP shunt placement involved implantation of a medium pressure (8.1 mmHg) fixed valve in 3 cases and an adjustable valve in 6 cases (set at 8.1 mmHg in 5 patients and at 6.6 mmHg in 1 patient). The initial valve setting remained unchanged in 5 of 9 patients, while the others underwent one or more downward adjustments. Compared with their neurological status at shunt placement, 6 patients were improved at the visit, while 3 were not. In the no-NTG group the estimated median age of NPH onset was 69.6 years (range 61.8-82.5 years); the median age at shunt placement was 73.7 years (range 62.8-84.5 years); the median age at visit was 75.3 years (range 68.3-86.2 years). Shunt placement involved implantation of a medium pressure (8.1 mmHg) fixed valve in 4 cases and an adjustable valve in 9 cases (set at 8.1 mmHg in 8 patients and at 8.8 mmHg in 1 patient). The initial valve setting remained unchanged in 10 of 13 patients, while the other 3 patients underwent one or more downward adjustments. Compared with their neurological status at shunt placement, 9 patients were improved at the visit, while 4 were not. Homogeneity test showed: age at NPH onset p= 0.28; age at shunt p= 0.39; age at visit p=0.25; valve type p=0.63; initial valve setting p= 0.46; number of valve adjustments p=0.32; valve setting at visit p=0.06; clinical improvement p=0.63.

Characteristic	NTG Group	No-NTG Group
Age at NPH onset (years)	71.6 (65.5-77.4)	69.6 (61.8-82.5)
Age at VP shunt (years)	72.5 (66.0-78.3)	73.7 (62.8-84.5)
Age at visit (years)	78.1 (72.8-87.2)	75.3 (68.3-86.2)
Initial pressure of valve setting (mm H_2O)	110	110
Valve setting at visit (mm H_2O)	90	110
Valve type **fixed** **adjustable**	 3 6	 4 9
Clinical improvement **yes** **no**	 6 3	 9 4
Protection period: symptom onset - diversion (months)	12	18
Exposure period: diversion - visit (months)	76	20

Table 2. *Neurosurgical assessment of patients with NPH undergoing VP shunt treatment in the NTG (9 patients) and no-NTG (13 patients) groups*

To test if ΔP, i.e., the difference between IOP and ICP (valve opening pressure value at visit), decrease/increase over time is a protective or risk factor for NTG, we calculated the following parameters from the primary data. The median duration of the "protection period", i.e. the time span between NPH onset and shunt dates, was 12 months (range 3-36 months) in the NTG group and 18 months (range 12-96 months) in the no-NTG group (p=0.033). The median duration of the "exposure period", i.e. the time span between the shunt placement and visit dates, was 76 months (range 13-122 months) in the NTG group and 20 months (range 6-102 months) in the no-NTG group (p=0.102). The median ΔICP - the difference between an arbitrarily chosen pre-shunt ICP value of 9.1 mm Hg and the opening pressure setting at visit - was 1.0 mm Hg (range 1.0–5.4 mm Hg) in the NTG group and 1.0 mm Hg (range 1–3.9 mm Hg) in the no-NTG group (p = 0.159). The median value of ΔICP × duration of exposure in months was 76.0 mm Hg × months (range 17.8–362.4) and 24.1 mm Hg × months (range 5.9–102.0) in the NTG and no-NTG groups, respectively (p = 0.048). For cases in which 1 or more adjustments took place, ΔICP and duration of exposure were split into defined intervals and their products were summed. Moreover, we adjusted median age for protection period and exposure period as follows: adjusted age = age at visit + [(exposure period/protection period)-1]. The median adjusted age was 85.1 years (range 73.4-94.1 years) in the NTG group and 78.8 years (range 67.9-86.0 years) in the no-NTG group (p=0.001).

5. DISCUSSION

With this study we observed that patients whose ICP has been lowered as treatment for NPH are almost 40 times more likely to suffer from NTG than elderly Italian patients without hydrocephalus.[1] We believe that our study indicates that the occurrence of NTG may in fact be related to the lowering of ICP, thus supporting the hypothesis that an imbalance between IOP and ICP in favor of the intraocular compartment is critical in the development of optic nerve damage.

Precise ΔP values are difficult to estimate. While IOP measurement is straightforward, obtaining reliable ICP values requires craniotomy and placement of an intracranial sensor, which is an invasive and risky procedure.[45] Lumbar puncture, besides its inherent invasiveness, provides ICP values which are flawed, since the ICP around optic nerve may substantially differ from the lumbar puncture opening pressure.[15] Several non-invasive ICP measurement approaches, including tympanic membrane displacement, ophthalmo-dinamometry, and measurement of optic nerve sheath diameter, as well as mathematical formulas are considered fairly inaccurate,[46] even though a promising trans-cranial Doppler ultrasonography method is being explored.[47] Due to these difficulties in obtaining reliable ICP values, in our study a group of patients with a controlled and lowered ICP was selected, giving us the maximum reachable ICP, thanks to the therapeutic insertion of an endoventricular catheter connected to a pressure valve. In a model where only downward ICP adjustments are considered, this approximation did not affect our discussion and allowed us to analyze whether and how ΔP changes related to CSF diversion operate in determining glaucomatous damage.

It should be noted that patients who experienced any pathological condition possibly inducing changes in ICP, as well as those patients who

underwent upward valve adjustments, were excluded from the study. This allowed us to attribute the occurrence or the nonoccurrence of optic nerve damage only to the shunt-related lowering of ICP. We determined that this damage was also seen as an increase in the cup disc area ratio and a reduction in the disc rim area. Our results are in line with those of Siaudvytyte et al.,[47] who found that the neuroretinal rim area is directly proportional to ICP in patients with NTG.

More importantly, we observed that a crucial risk factor is the duration of optic nerve exposure to the ICP lowering. The amount of time between shunt placement and observation, i.e., the exposure period, was 76 months in the NTG group versus 20 months in the no-NTG group. Also, the median exposure to definite ICP decreases was 76.0 mm Hg × months in the NTG group versus 24.1 mm Hg × months in the no-NTG group ($p < 0.05$).

Moreover, from our data it appears that the relationship between ICP and time also works protectively, where the interval between NPH onset and shunt placement represents a phase of relatively higher ICP. We showed that the median duration of the "protective" phase was significantly longer ($p < 0.05$) in the no-NTG group than in the NTG group (18 vs 12 months, respectively). It should be noted that these data are biased by the uncertainty regarding the time of onset of NPH, which depends upon patient report. On the whole, our results highlight time as a key element in determining optic nerve damage and should encourage further studies to search for a $\Delta P \times$ time threshold value.

Age remains the major risk factor for NTG,[3] and interestingly, the results of our study show that median age, when corrected by protection and exposure periods, was 85.1 in the NTG group versus 78.8 years in the no-NTG group ($p < 0.001$). In this context, the case reported by Chen et al.,[24] who described the occurrence and disappearance of optic disc hemorrhages following down- and upregulation, respectively, of valve opening pressure in a 93-year-old shunt-treated NPH patient with a history of well-controlled NTG, may be instructive. In a context of advanced age, a "fragile" optic nerve may be vulnerable to only modest amounts of ΔP changes. Hence, any

search for a ΔP × time threshold value should take the subject's age into account.

This paper argues for close cooperation between the ophthalmologist and neurosurgeon. A preliminary ophthalmic evaluation of an NPH patient should assess possible concomitance with glaucoma. IOP values also need to be measured. If IOP is in the normal range and signs of optic nerve damage are not detected, a candidate for CSF diversion procedures should be informed of a real, although still unquantifiable, risk of incurring glaucomatous damage. Identification of baseline ΔP values could drive the fine tuning of valve adjustments for optimal NPH control while minimizing the risk of NTG.

We anticipate that NPH patients with higher pre-shunt ICP are more likely to benefit from modest downward adjustments without incurring glaucomatous damage. These same patients have more room for improvement of possible postoperative optic nerve damage through careful upward adjustments below the threshold of recurrence of NPH signs.

Lifetime evaluations of optic nerve status should be scheduled for shunt-treated patients. Since the time span when optic nerve damage may ensue after the shunt is unknown, it is not possible to define the timing of the ophthalmic follow-up to intercept visual impairment as early as possible. Considering that the shortest interval between shunt placement and NTG detection was 13 months in our limited experience, it is reasonable to check the optic nerve within a year of the previous evaluation. Periodic ophthalmic follow-up should be continued life-long. In fact, 2 of the 11 shunted patients that underwent the latest ophthalmological follow-up resulted positive for NTG, even after more than 10 years from the VP shunt placement.

IOP values should be known before any downward valve adjustment is made in an effort to improve NPH. Since this procedure implies a ΔP increase, patients with higher IOP should be more closely checked because of their higher NTG risk. If NTG was detected preoperatively, NPH patients undergoing CSF diversion procedures should be warned that their glaucoma can significantly and suddenly worsen, particularly in the presence of a

relatively low ICP. In principle, these considerations also would hold true when high-pressure glaucoma is encountered.

Another issue raised by our study concerns the management of NPH patients who have been treated with CSF shunting in the past. Since a high NTG rate is expected, we believe that all such patients should receive neuro-ophthalmic follow-up as described above.

When treating a patient with glaucomatous damage associated with normal IOP, the ophthalmologist could take advantage of ICP value knowledge to modulate IOP lowering by medical or even surgical treatments. Moreover, possible comorbidities resulting in decreased ICP should be investigated in patients with glaucomatous damage, particularly if they are young. Conversely, possible optic nerve damage should be suspected in patients with conditions responsible for a decrease in ICP, such as a CSF leakage.

6. CONCLUSIONS

Glaucoma, one of the major causes of blindness worldwide, is a chronic neurodegenerative disease of the optic nerve, which consists of progressive loss of the retinal ganglion cell fibers and visual field defects. High intraocular pressure has long been considered the most important risk factor for the onset and progression of glaucoma. Ever since, it was defined as a clinical entity (in the second half of the 19th century) and until a decade ago, treatment for glaucoma has focused on lowering intraocular pressure to stop progression. Yet, glaucomatous optic nerve damage progresses even when intraocular pressure is under control and, in normal tension glaucoma, optic disc changes and visual field defects appear while intraocular pressure is considered normal. Extensive investigations into the pathophysiology of glaucoma now reveal the role of multiple factors in the development of retinal ganglion cell death. A better understanding of the pathophysiological mechanisms involved in the onset and progression of glaucomatous optic neuropathy is crucial in the development of better therapeutic options.

The trans-lamina cribrosa pressure gradient has been extensively reported in literature as a possible pathogenic mechanism of glaucoma. Lamina cribrosa is the extension of the peripapillar margin of the sclera and is characterized by hundreds of pores, through which pass the fibers of the optic nerve, the central retinal artery and vein. It forms the anatomical floor of the optic nerve head and separates two pressurized compartments, ocular and cranial. In normal conditions, intraocular pressure is 10-20 mmHg and intracranial pressure is 5-15 mmHg. Therefore, the optic nerve is exposed to a posteriorly directed trans-laminar gradient of about 5 mmHg. Alterations of this gradient induce a mechanical deformation of the lamina cribrosa, that causes damages to the ganglionic cells, the central retinal artery and vein, with neuronal dysfunction and ischemia. According to the trans-lamina

cribrosa gradient hypothesis, increases of this gradient, due to either high intraocular pressure or low intracranial pressure, could be responsible for optic nerve damage, as supported by measurements in patients with hypertensive glaucoma and normal tension glaucoma. This hypothesis has been confirmed by several studies that detected lower intracranial pressure values in patients with normal tension glaucoma, compared to the general population.

The purpose of this study was to investigate the high incidence rate of normal tension glaucoma in patients with shunt-treated normal pressure hydrocephalus. Due to the difficulty in obtaining reliable intra cranial pressure values, in our study a group of patients with a controlled and lowered ICP was selected, giving us the maximum reachable ICP, thanks to the therapeutic insertion of an endoventricular catheter connected to a pressure valve.

The results of the study reported a prevalence of normal tension glaucoma in shunt-treated patients of 40% (versus 0,4-0,9% in the general population, same age). These data were considered statistically significant and allowed to confirm low intracranial pressure a risk factor for normal tension glaucoma. Practical implications of such results are evident: a close monitoring of ophthalmic parameters will be necessary in shunt-treated patients.

The small number of patients involved in the study and other characteristics of the studied diseases – such as the difficulty in obtaining a reliable ICP value and the progressive nature of glaucomatous damage – did not allow us to obtain significant results on every parameter. Further investigations will be important not only to confirm the validity of the trans–lamina cribrosa gradient hypothesis in a wider spectrum of diseases, but also to allow for intervention where possible.

In conclusion, our study adds a new result strengthening the trans-laminar hypothesis in the pathogenesis of normal tension glaucoma. This result provides several clinical implications for the management and prevention of high impact illnesses, such as glaucoma and hydrocephalus. As both of these diseases are typical comorbidities of the elderly, it will

become more and more common that ophthalmologists and neurosurgeons have to take care of the same patient, paying particular attention to those with intracranial pressure alterations.

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