A study of the response of pleurocephalic oedema of the optic disc (papilloedema due to idiopathic intracranial hypertension) to treatment

Thesis
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List of abbreviations

AION	anterior ischaemic optic neuropathy
BCVA	best corrected visual acuity
BID	Bis en die (four times a day)
CE	Common era
CRA	central retinal artery
CRV	central retinal vein
CSF	cerebrospinal fluid
CSLO	confocal scanning laser ophthalmoscopy
CT	computerized tomography
Db	decibel
EBS	enlarged blind spot
GC	ganglion cell
GCC	ganglion cell complex
GCL	ganglion cell layer
HRT	Heidelberg Retinal Tomograph
ICP	Intracranial pressure
IIH	idiopathic intracranial hypertension
IIHTT	idiopathic intracranial hypertension treatment trial
IOP	intraocular pressure
IPL	inner plexiform layer
LP	lumbar puncture.
LPS	lumboperitoneal shunt
MD	mean deviation
Mg	milligram
µm	micrometer
mm	millimeter
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
NFL	nerve fiber layer
NORDIC	Neuro-Ophthalmology Research Disease Investigator Consortium
	optical coherence tomography
OCT	optic disc
OD	Ocular Hypertension Treatment study
OHTT	optic nerve head
ONH	optic nerve sheath decompression
ONSD	Optic Neuritis Treatment Trial

ONTT	peripapillary retinal nerve fiber layer
PRNFL	pattern standard deviation.
PSD	per os
p.o.	Quaque en die (Once a day)
QID	Pearson's correlation coefficient
r	retinal ganglion cell
RGC	retinal nerve fiber layer
RNFL	retinal pigment epithelium
RPE	standard deviation
SD	spectral domain optical coherence tomography
SD-OCT	Swedish Interactive Threshold Algorithm
SITA	Scanning LASER ophthalmoscopy
SLO	time domain optical coherence tomography
TR-OCT	total retinal
TR	visual acuity
VA	ventriculoperitoneal
VP	

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Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is characterized by elevated intracranial pressure (ICP) with no apparent cause ***(Waisbourd et al., 2011).***

This condition occurs most commonly in overweight women during childbearing age. It has also been associated with other factors, such as a certain medications, anemia, and untreated obstructive sleep apnea ***(Kesler et al., 2004).***

Visual disturbances mainly transient visual obscurations, photophobia and diplopia are usually met with. Papilloedema, the ophthalmologic hallmark of IIH, is usually symmetrical between both eyes and it is rarely absent ***(Waisbourd et al., 2011).***

The disease course is often lengthy, and therapy must be guided by clinical signs, the extent of papilloedema, and the CSF opening pressure ***(Salgarello et al., 2001).***

During the past few decades several approaches have been used to analyze the papilloedema due to intracranial hypertension either functionally or morphologically. In particular, the relations between functional and morphological variables of the optic nerve have been investigated ***(Salgarello et al., 1996).***

The prominent role of automated perimetry in detecting the earliest functional losses and following up the progression of dysfunction has been stressed by different studies. Qualitative correlation between high-grade papilloedema and perimetric loss has been found by some investigators, it has been suggested that the severity of visual field loss in individual patients cannot be predicted from the severity of papilloedema ***(Chan et al., 2009).***

Optical coherence tomography is a potential tool to quantify the changes in the degree of papilloedema and to monitor the efficacy of the treatment interventions ***(Jones et al., 2001).***

It measures retinal thickness, peripapillary retinal nerve fiber layer thickness (PRNFL), and quantify optic nerve head (ONH) morphology (e.g. disc size and cup-disc ratio). Its findings are reasonably reproducible on successive measurements ***(Rebolleda and Munoz-Negrete, 2009).***

Aim of the study

To observe and describe the response of pleurocephalic oedema of the optic disc to different modalities of treatment both functionally and morphologically.

Anatomy of the retinal nerve fiber layer and optic nerve head

The retinal nerve fiber layer

The normal human optic nerve is made up of 1.0-1.2 million axons of retinal ganglion cells (GCs), which converge at the optic disc (OD). These fibers make up the retinal nerve fiber layer (NFL) and lie in the inner retina, just below the internal limiting membrane ***(Sigelman and Ozanics, 1982).***

The NFL contains the axons of the GCs (the so-called 'centripetal' or 'afferent' fibers), glial cells, a rich capillary bed and centrifugal (or efferent) fibers ***(Bron et al., 1997).***

The centripetal fibers (the axons of the GCs):

The axons of the GCs are arranged in arcades delineated by the processes of Muller and other glial cells. Individual afferent fibers measure from 0.6µm to 2.0µm in diameter. They contain prominent microtubules, mitochondria and smooth endoplasmic reticulum. They have a bidirectional axoplasmic flow that occurs at two rates: at the slow rate (0. 5-5 mm/day) which carries high molecular-weight proteins that are utilized for axonal growth, maintenance and repair; the fast rate (10- 2000 mm/day) caters to molecules that are involved in synaptic function. The axons remain unmyelinated until they reach the lamina cribrosa of the optic nerve (ON) ***(Sigelman and Ozanics, 1982).***

The NFL is thickest at the nasal edge of the OD, where it measures 20-30µm. The thickness decreases from the OD to the ora serrata, where the ganglion cell layer (GCL) and the NFL blend to form a single layer. The papillomacular bundle represents the thinnest portion of the NFL around the optic disc; it is the last portion of the OD to be affected in papilloedema ***(Bron et al., 1997).***

Because axons are so numerous close to the optic nerve head (ONH) they become heaped up, especially on the nasal side, which causes an elevation (the papilla) to be formed towards the vitreal surface. Thus, the nasal aspect of the OD is the most

susceptible to changes of papilloedema because of its greater collection of nerve bundles and blood vessels ***(Bron et al., 1997).***

The centrifugal fibers:

Centrifugal fibers that originate from the central nervous system terminate in the inner plexiform layer (IPL) or in the innermost part of the inner nuclear layer. Usually they associate with amacrine cells or capillary walls, where they exert vasomotor effects ***(Bron et al., 1997).***

Topographic organization of the nerve fibers in the retina and the optic disc head:

The axons of the ganglion cells take a radial course parallel to the inner limiting membrane and converge on the optic nerve, except for those axons that arise from ganglion cells immediately temporal to the optic disc, which are the first to develop and form the center of the optic nerve. These fibers are distinguished as the papillomacular bundle. The axons originating from ganglion cells temporal to the fovea take an increasingly arcuate course to bypass this region .The superior and inferior fibers are separated at their origin by a horizontal arbitary raphe that extends from the fovea to the extreme temporal periphery of the retina. Figure (1) shows the course of the axons of the ganglion cells in the NFL of the retina ***(Sigelman and Ozanics, 1982).***

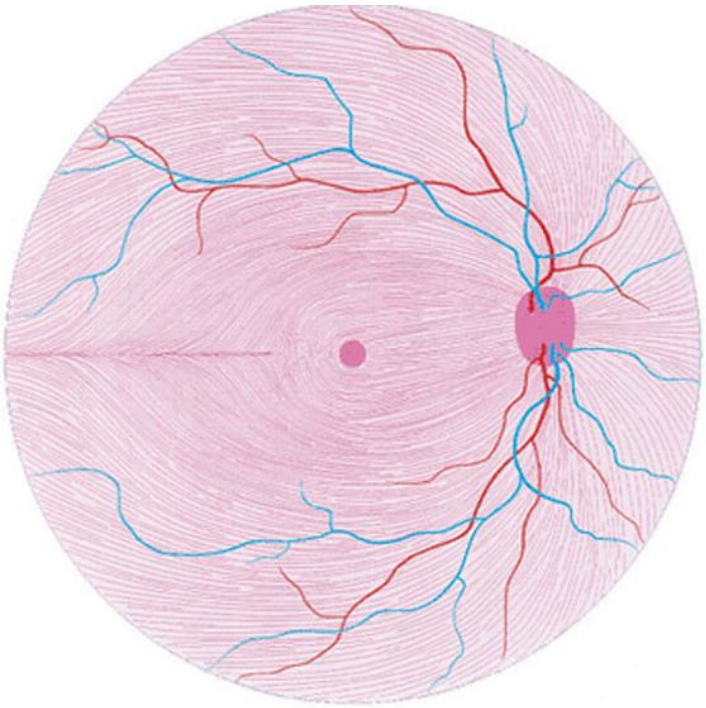

Fig. (1) Schematic representation of the course of ganglion cell axons in the retina. The retinotopic origin of these nerve fibers is respected throughout the visual pathway (Harrington and Drake, 1990).

The retinotopic organization of the nerve axons is rigidly preserved at the nerve fiber layer, just anterior to the GCL, as they reach the periphery of the nerve head. Although the configuration of nerve fibers within the retina has long been understood, the correct orientation of retinal nerve fibers in the ONH has been the subject of considerable debate. Prior to 1930, the common view was the nerve fibers from the peripheral retina entered the central portion of the ONH. It has since been established that the reverse is true as shown in figure (2). In the peripapillary retina, newly arising axons pass through the NFL to reach its internal surface. Axons arising here cross those of peripheral origin and pass at the vitreal surface of the NFL to the center of the nerve head ***(Tuulonen et al., 1993).***

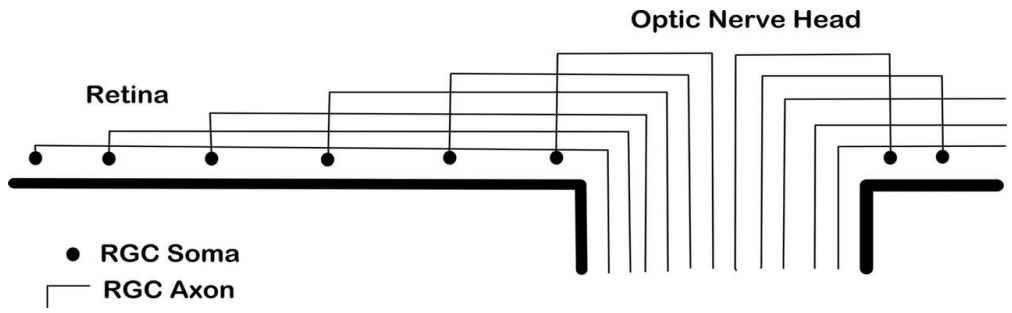

Fig. (2) The speculative lamination of axons within the retina (Carreras et al., 2014).
RGC: retinal ganglion cell.

The intraocular optic nerve head (Optic papilla, Optic disc):

The intraocular portion of the optic nerve extends from its anterior surface in contact with the vitreous to a plane which is level with that of the posterior scleral surface (about 1 mm). The choroid ends abruptly here, as do all elements of the retina except its axons. These bend at a right-angle into the nerve head and pass posteriorly through the scleral canal. The nerve head exhibits three zones as shown in figure (3) but the immediately retrolaminar nerve is usually described with it as follows:

1. the superficial NFL, a prelaminar zone anterior to the level of Bruch's membrane (pars retinalis);

2. the prelaminar zone level with the choroid (pars choroidalis);

3. the lamina cribrosa (pars scleralis);

4. the retrolaminar portion Immediately behind the lamina.

The Superficial NFL:

This is covered by the inner limiting membrane of Elschnig, which is composed of astrocytes and is in continuity with the inner limiting membrane of the retina. Glial cells and interaxonal processes are relatively sparse here but increase progressively towards the retrolaminar nerve. Astrocytes make up approximately 10% of the volume of the nerve head ***(Bron et al., 1997).***

The prelaminar zone:

The prelaminar region contains bundles of axons lying within astrocytic channels. The astrocytic processes are largely circumferential. This loose glial tissue does not bind the axon bundles together as do the Muller cells of the retina and therefore fibers here are more easily separated. This may explain why the disc swells so easily in papilloedema while the adjacent retina does not. The trabeculae between the axon bundles carry capillaries, most of which are surrounded by a narrow perivascular connective tissue space. A limiting membrane formed from glial footplates surrounds this region ***(Bron et al., 1997).***

The presence of glial cells in this (as in other parts of the optic nerve) accords with its development. The optic peduncle is predominantly neuroglial before optic nerve fibers grow into it. Moreover, when the hyaloid artery (which arises from the arteria centralis) degenerates, the neuroglial cells surrounding its origin persist anteriorly as an astrocytic lamella, the central tissue meniscus of Kuhnt. This is in continuity with the inner limiting membrane at the surface of the disc and with glial tissue surrounding the adventitia of the central vessels (the intercalary tissue of Elschnig) ***(Bron et al., 1997).***

At the periphery of the prelaminar part of the optic nerve, the axons are separated from the connective tissue of the scleral canal and/or choroid by a cuff of astrocytes of varying thickness, termed the border tissue of Jacoby. It then extends forwards to intervene between prelaminar axons and the termination of the posterior retinal layers, as the intermediary tissue of Kuhnt ***(Bron et al., 1997).***

The rim of sclera at the scleral foramen is termed the border tissue of Elschnig. It is sometimes prolonged forwards, especially on the temporal side, to intervene between the peripapillary choroid and the glial, border tissue of Jacoby. It is composed of dense collagenous tissue with many glial and elastic fibers and some pigment ***(Bron et al., 1997).***