Chapter 2
Intracranial Pressure as a Risk Factor

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Contemplations of intracranial pressure (ICP) role in glaucoma started in 1908 by Noishevsky and were confirmed later experimentally with animals [1–5]. Optic nerve head is located at the junction between the relatively high-pressure intraocular space and low-pressure subarachnoid space, therefore pressure imbalance between these two regions may be the cause of damage of retinal ganglion cells axons that cross the lamina cribrosa. As such, ICP can influence the biomechanics of the lamina cribrosa and peripapillary sclera [1–3].

Physiological values of ICP varies with body posture but is generally considered to be 5–15 mmHg in healthy supine adults, 3–7 mmHg in children and 1.5–6 mmHg in infants [6–9]. Head elevation decreases ICP by displacing cerebrospinal fluid (CSF) into the spinal canal and by improving cerebral venous drainage by opening alternative venous channels in the posterior circulation that remain closed while patients remain recumbent. Experimental studies showed that ICP in the sitting position at the level of the occipital prominence, equivalent to eye level, ranges between 0 and −10 mmHg [10]. Fleischman et al. found that ICP is stable (11.5 (2.8) mmHg) for the first 50 years of life after which there is a steady decline [11]. Pederson et al. found similar results concluding that ICP decreases by 0.69 mmHg per decade [12]. Furthermore, CSF secretion by the choroid plexuses slows with age, reducing the rate of CSF turnover and leading to accumulation of catabolites in the brain and CSF [13–15]. Interestingly, the prevalence of glaucoma increases with age [16]. Contrarily, other studies failed to find a relationship between age and ICP [17–20]. Various studies revealed that body mass index is positively associated with ICP [21–23]. A biomechanical explanation for the relationship between ICP and body mass index has been suggested for patients with idiopathic intracranial hypertension. Studies suggest that obesity, in particular central obesity, increases

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intra-abdominal pressure, which ultimately causes an increase in venous pressure and consequently ICP [24, 25].

It is established that the CSF pressure measured by lumbar puncture corresponds to ICP in the lateral decubitus position [26]. Therefore, ICP in the prone position is by classic definition CSF pressure and these terms are used interchangeably in this text, as it is carried out in clinical practice. However, it remains unclear whether CSF pressure, measured by lumbar puncture, corresponds to CSF pressure in the orbit around the optic nerve. The CSF dynamics of the retrolaminar space have unique properties since there are numerous septae present that could limit free flow of CSF [27]. In addition, unlike in other areas, the dura of optic nerve sheath contains atypical meningeal tissue with lymphoid characteristics [28]. Killer et al. found reduced CSF exchange between the basal cisterns and subarachnoid space surrounding the optic nerve in normal tension glaucoma (NTG) patients but not in control subjects. Lower ICP in NTG could explain the reduced density of the contrast-loaded CSF in the subarachnoid space of the optic nerve [29]. However, clear ICP role in glaucoma pathogenesis and especially in its progression remains unclear because the gold standard for ICP evaluation is an invasive measurement of the pressure in the CSF via lumbar puncture or via implantation a pressure sensor into a cerebral ventricle. Importantly, this invasiveness includes the potential risk for intracranial hemorrhages and infection.

Various studies revealed that ICP is lower in glaucoma [17, 30–36] (Table 2.1). Berdahl et al. in retrospective analysis of patients who had lumbar puncture revealed that ICP was 3–4 mmHg lower in primary open-angle glaucoma (POAG) [31] and

Table 2.1 Studies investigating intracranial pressure differences between glaucoma and controls

Author, year	Design	NTG		POAG		Controls	
		N	ICP	N	ICP	N	ICP
Berdahl et al. (2008) [32]	Retrospective	11	9.3 (3.2)*	57	9.6 (3.1)*	66	12.7 (3.9)
Berdahl et al. (2008) [31]	Retrospective	na	na	28	9.2 (2.9)*	49	13.0 (4.2)
Pircher et al. (2016) [41]	Retrospective	38	11.6 (3.7)	na	na	na	na
Ren et al. (2010) [30]	Prospective	11	9.5 (2.2)*	29	11.7 (2.7)*	71	12.9 (1.9)
Siaudvytyte et al. (2014) [33]	Prospective	9	7.4 (2.7)*	9	8.9 (1.9)*	9	10.5 (3.0)
Linden et al. (2017) [40]	Prospective	13	10.3 (2.7)	na	na	51	11.3 (2.2)
Jonas et al. (2013) [42]	Population-based	na	na	193 eyes	7.6 (3.8)* (OAG + ACG)	8622 eyes	10.0 (3.6)
Jonas et al. (2015) [36]	Population-based	na	na	348 eyes	7.2 (3.8)* (OAG + ACG)	6070 eyes	8.9 (3.7)

ACG angle-closure glaucoma, *ICP* intracranial pressure, *N* number of subjects, *na* not available, *NTG* normal-tension glaucoma, *OAG* open-angle glaucoma, *POAG* primary open-angle glaucoma
*Significance level $P<0.05$ (between glaucoma and controls)

NTG, compared with healthy subjects and patients with ocular hypertension (OHT) [32]. Patients with NTG had even lower ICP compared to POAG patients [32]. Ren et al. in a prospective study found similar results to those in the retrospective studies, with the control group having the highest ICP. They also noted that NTG patients had lower ICP compared to either POAG [30]. These findings suggest a role of ICP in the developing of NTG. Other authors also found lower ICP in glaucoma [33, 35, 36]. Interestingly, 3–4 mmHg difference in ICP is similar to the difference in intraocular pressure (IOP) between POAG and control subjects in large well-known population studies [37, 38]. Furthermore, IOP difference of 4 mmHg is more associated with progression of glaucoma [39]. Recent study by Linden et al. concluded that there was no evidence of reduced ICP in NTG patients as compared to healthy controls, either in supine or in upright position [40]. Similarly, Pircher et al. were not able to confirm a reduced ICP in NTG. Because no control group was investigated, they compared the results with those of previous studies [41].

Berdahl et al. found that OHT patients had 2 mmHg higher ICP compared to healthy subjects [32]. Similarly, Ren et al. found 4 mmHg difference in ICP between OHT and control subjects [17]. These findings suggest that high ICP may prevent the progression of OHT to POAG.

The Central India Eye and Medical Study reported that higher estimated CSF pressure was significantly associated with a lower prevalence of glaucoma (both open-angle glaucoma (OAG) and angle-closure glaucoma (ACG)). If the total glaucoma group was divided into OAG and ACG, the absolute value of the standardized coefficient beta was higher for OAG than for ACG. If the OAG groups was further subdivided into normal-IOP OAG and high-IOP OAG groups, the associations between higher estimated CSF pressure and lower glaucoma prevalence was better for the normal-IOP OAG group [35]. Li et al. in a population-based study of Bai Chinese living in rural China, did not find any significant association or trend between the baseline estimated CSF pressure and the incidence of POAG, after a mean follow-up of 5 years [43].

Gallina et al. demonstrated that patients whose ICP has been lowered as treatment for normal pressure hydrocephalus are almost 40 times more likely to suffer from NTG than elderly Italian patients without hydrocephalus. Crucial risk factor for development of NTG in patients with shunt-treated normal pressure hydrocephalus was the duration of optic nerve exposure to the lowering of ICP [44]. Yang et al. showed that experimental and chronic reduction of CSF pressure in monkeys was associated with progressive reduction in retinal nerve fiber layer thickness, neuroretinal rim area or volume and increase in cup-to-disc area ratio in some monkeys [45]. Berdahl et al. in multivariate analysis showed that larger cup-to-disc ratio was associated with lower CSF pressure [31]. In later study they were not able to find correlation between cup-to-disc ratio and ICP, IOP or translaminar pressure difference (TPD). The lack of correlation may be the result of using IOP to categorize patients into POAG, NTG, OHT or controls [32]. Siaudvytyte et al. found a positive correlation between ICP and neuroretinal rim area in NTG [34]. Ren et al. in a prospective study found association between ICP and amount of glaucomatous optic nerve damage (neuroretinal rim area and mean visual field

defect) in POAG and OHT subjects [18]. In another study Ren et al. also found relationship between ICP and glaucomatous visual field defect [30]. Contrary, Pircher et al. did not reveal significant relationship between visual field defect and ICP in NTG patients [41]. Other authors also did not find correlation between visual field status and ICP [31, 40].

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