Cerebrospinal fluid exchange in the optic nerve in normal-tension glaucoma

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ABSTRACT

Aim To report on the cerebrospinal fluid (CSF) exchange between the intracranial spaces (ie, basal cisterns) and the subarachnoid space (SAS) of the optic nerve (ON) in subjects with normal-tension glaucoma (NTG) compared with control subjects without NTG or other forms of glaucoma.

Methods CT cisternography of the brain and orbits was performed in 18 patients with NTG (7 women, 11 men; mean age 64.9±8.9 years) and in four patients without glaucoma or intracranial disease (4 women; mean age 62.8±18.4 years). The density of contrast-loaded cerebrospinal fluid (CLCSF) in the intracranial spaces and in the SAS surrounding the ONs was measured in Hounsfield units.

Study design Unmasked, prospective series. Statistical analysis was performed using an independent two-tailed t test and the non-parametric Spearman correlation test.

Results The density of CLCSF in the SAS surrounding the ONs was significantly reduced compared with its density in the intracranial CSF spaces and in the SAS of ONs measured in the control group (p=0.006). There were no significant differences between men and women within the NTG group (p>0.35).

Conclusions The finding of a difference in the concentration gradients between the CLCSF within the intracranial spaces and the SAS of the ONs in this group of NTG patients compared with control subjects supports the hypothesis of a disturbed CSF exchange between the CSF in the intracranial spaces and the CSF in the SAS surrounding the ONs. The disturbance of CSF dynamics in this specific CSF pathway can be explained by ON compartmentation. The clinical importance of this finding warrants further investigation.

INTRODUCTION

The pathophysiology of normal-tension glaucoma (NTG), a condition characterised by visual field loss and optic disc excavation identical to primary open-angle glaucoma (POAG) despite apparently normal intraocular pressure (IOP), remains poorly understood. Impaired blood flow to the optic nerve (ON) head and vascular dysregulation are thought to be two of the predisposing factors.1 2 Furthermore, there is some evidence that NTG patients have a variety of serological vascular-related abnormalities such as elevated levels of endothelin, a potent vasoconstrictor.3 In addition to vascular risk factors, it has been suggested that cerebrospinal fluid (CSF) pressure is a contributing factor to the development of NTG. For example, two recent studies reported lower intracranial pressure (ICP) in NTG patients than in POAG patients.4 5 This finding raised the possibility that axon death in patients with NTG could be due, at least in part, to an imbalance of transmalar pressure, that is, the difference between IOP and pressure in the subarachnoid space (SAS) of the ON. Ren et al reported that the transmalar pressure gradient was significantly higher in both POAG and NTG patients compared with controls.5 In addition, Watanabe et al showed a correlation between ICP and increased ON sheath diameter.6 Using CT scanning, we have found that patients with NTG have increased ON sheath diameters similar to those of patients with increased ICP.7 In the present study, we performed CT cisternography measurements of the contrast density in the SAS of the ONs and compared them with the contrast density of CSF in the basal cisterns of patients with NTG and in subjects without any ON or intracranial disease. Cisternography is a neuroradiological technique used to detect CSF leaks after suspected disruption of the dura mater and can be used to demonstrate CSF flow.8
resorption of CSF. A 64-detector scanner (Aquillion 64, Toshiba, Tokyo, Japan) providing 0.5 mm×32 section collimation was used. Scanning parameters were a 25 cm field of view with a 512×512 matrix, and soft tissue and bone reconstruction algorithms were employed. The field of view included the foramen magnum and the nose. Multiplanar reconstruction images were obtained in the axial, coronal and sagittal planes with a 1 mm slice thickness. CT images were analysed on a workstation using the AW (Advantage Workstation) 4.1 software (General Electric, Milwaukee, Wisconsin, USA). Contrast density was measured in Hounsfield units (HU). Measurements were performed intracranially in the basal cisterns (ie, suprasellar and preopticine cisterns) as well as in the SAS surrounding the orbital portion of the ON (figures 1 and 2). To find the site with the highest contrast density, the cursor was moved over the area of interest until the highest HU number was determined. In all patients, the highest measurement in HU from the same location was used to standardise the procedure.

Four subjects (mean age 62.8±18.4 years; all women) without known intracranial disease or any form of glaucoma including NTG who also underwent CT cisternography as part of another study served as controls. Measurements of contrast-loaded cerebrospinal fluid (CLCSF) density intracranially and in the SAS surrounding the ONs were obtained in these subjects as described above.

The independent two-tailed t test and the non-parametric Spearman rank order correlation coefficient (SPSS 14.0; SPSS Inc) were used for statistical analysis. This study was designed and performed according to the tenets of the Declaration of Helsinki and was approved by the local ethics committee.

RESULTS

The subjects in the NTG group did not differ significantly in age compared with the four female control subjects with respect to either women (p=0.98) or men (p=0.58). In addition, there was no significant difference in age between women and men with NTG (p=0.35). There was no significant difference in ICP between subjects in the NTG group (mean 13.3±5.5 cm H2O) and the control subjects (mean 13.0±5.7 cm H2O) (p=0.96) or between women and men with NTG (p=0.43) (table 1).

CT cisternography

In the eight eyes from the four control subjects, the densities of contrast medium by CT cisternography in the SAS surrounding the ON ranged from 185 to 1005 HU (mean density 529±285.8 HU) and the densities in the basal cisterns ranged from 347 to 828 HU (mean density 531±208.3 HU) (table 1). In the 36 eyes with NTG, densities of contrast medium in the SAS of the ONs ranged from 28 to 378 HU (mean density 144±88.4 HU) and differed significantly from the densities in the control eyes (p=0.006), whereas contrast densities in the basal cisterns of the NTG patients ranged from 332 to 913 HU (mean density 566±166.5 HU) and did not differ significantly from the controls (p=0.67) (table 1, figure 3).

The difference between the measured contrast density in the SAS surrounding the ON (ON-SAS) and the intracranial SAS (IC-SAS) in the basal cisterns was calculated for each case separately. The results revealed a large and highly significant
Table 1  Cerebrospinal fluid dynamics in normal-tension glaucoma patients and controls

<table>
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<tr>
<th>No.</th>
<th>Age m</th>
<th>Age f</th>
<th>Contrast density (HU)</th>
<th>p CSF (LP) (cm H2O)</th>
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<td></td>
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<td>ON-SAS-R</td>
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Values for densities of contrast loaded cerebrospinal fluid (CSF) in hours units (HU), measured intracranial in the basal cistern (IC-SAS) and the subarachnoid space (SAS) of the optic nerve (ON) for the right (ON-SAS-R) and the left (ON-SAS-L) ON, as well as CSF pressure (p CSF) in cm H2O (<20 = less than 20 cm H2O) measured during lumbar puncture (LP), in 18 normal tension glaucoma (NTG) patients (7 females (f) and 11 male (m)) and controls (Co).

Figure 3  Box-plot of contrast density measurements in Hounsfield units in the basal cistern (IC-SAS) as well as in the subarachnoid space (SAS) of the right (ON-SAS-R) and the left (ON-SAS-L) optic nerve (ON) in four controls (Co), all of whom were women, and 18 normal-tension glaucoma (NTG) patients, showing median and quartiles as well as standard deviation and outlier case (corresponding to case numbers in table 1).

DISCUSSION

This study of 18 patients with bilateral NTG demonstrates a significantly higher intracranial density of CLCSF in the intracranial spaces (basal cisterns) compared with the density of CLCSF in the SAS surrounding the ON (figure 3). This difference was not present in the small control group without NTG. This finding can be explained by a reduced CSF exchange between the basal cisterns and the SAS surrounding the ON, leading to reduced CSF turnover in the SAS of the ON.

The velocity of CSF flow depends largely on the CSF pressure difference that follows changes of CSF volume due to newly produced CSF. A lower CSF pressure difference will therefore result in a lower CSF velocity (ie, slower propulsion). Several studies in glaucoma patients report a lower lumbar pressure in patients with NTG than in patients with POAG, whereas a recent study reported a higher lumbar pressure in 17 patients with ocular hypertension compared with control subjects.

Lower ICP indeed could explain the reduced density of the CLCSF in the SAS of the ONs as demonstrated by cisternography; however, this explanation is inconsistent with our previous finding of increased ON sheath diameters measured in patients with NTG that demonstrate similar diameters as seen in patients with papilloedema.7 10 Based on a concept of continuous CSF pressure and velocity, these findings seem contradictory, as distension of the ON sheath is a typical feature of elevated ICP, not lower ICP.11 This apparent inconsistency can, however, be explained if the concept of continuous CSF flow and pressure is incorrect.12–14

CSF flow is directed from the intracranial spaces (ventricles, basal cisterns) through the optic canals to the SAS of the ONs. Unlike the intracranial CSF spaces, which are basically open spaces, the SAS surrounding the ON contains numerous trabeculae and septae that reduce both CSF volume and CSF flow. In addition, the SAS of the ON (including the trabeculae and septae) is lined with meningotheelial cells (MECs).15 These cells, which have a major role in the metabolic status of the CSF and are more abundant in patients with POAG than in normal subjects.16 In addition, an in vitro study from our laboratory demonstrated MEC proliferation of up to 20% when MECs were submitted to extrinsic increased pressure.17 Furthermore, in a sheep model, these cells were noted to enlarge when flow through the SAS of the ON was restricted with gentle ligation of the ON.18 It thus may be postulated that an increase in both the number and volume of MECs results in narrowing of the SAS surrounding the ONs thus increasing the resistance to the flow of CSF from the basal cisterns.

A recent study of 10 patients with normal-pressure hydrocephalus described a close relationship between the lumbar pressure and the intraparenchymal pressure of the brain; however, the findings were not compared with those from a group of age- and gender-matched normal subjects. In addition, the parenchymal pressure rather than the ventricular pressure was measured, and because of the different compliances of the brain parenchyma and the ventricular wall, a linear relationship may not be present. Indeed, the authors themselves noted that their assumption that lumbar pressure equals ICP is only correct if the CSF flow throughout these regions is continuous—an assumption for which there are no data.19 In fact, a recent study on patients with papilloedema would seem to contradict this assumption.
Even if lumbar pressure were to equal ventricular pressure, the question still remains whether or not this relationship can be extrapolated to the SAS surrounding the ON. There are several sound reasons to doubt such a relationship. First, the volumes of the ventricles and the SAS surrounding the ON are very different. Second, the anatomy within the SAS surrounding the ON is sufficiently different from the anatomy within the ventricles to allow a simple extrapolation of pressure from one region to the other. The fact that CLCSF density in the SAS surrounding the ON is reduced in our patients with NTG together with the dilation of the retrobulbar portion of the ON as we have reported previously, suggests that this region can develop into a compartment with a different CSF composition, different CSF dynamics and probably a different pressure in patients with NTG compared with otherwise normal individuals, much as is the case in patients with papilloedema.

Finally, patients with papilloedema demonstrate an increased concentration of lipocalin-like prostaglandin D synthase (L-PGDS) in the SAS surrounding the ON compared with its concentration in the spinal CSF. L-PGDS plays a significant role in the metabolism and health of the central nervous system. Indeed, elevated concentrations of L-PGDS demonstrate damage to astrocytes as well as diminished ATP production in an in vitro model. Given the large molecular weight of this protein (26 kD), it is feasible that the presence of such a large molecule in such a small peri optic space prevents the influx of smaller molecules, such as iopamidol (778 D). The presence of a large and potentially harmful molecule as L-PGDS could at least partly explain the absence of CLCSF in the peri optic space in our patients (figure 4).

We acknowledge that the results of this study do not explain the entire complex pathophysiology of NTG, but none of the present hypotheses on the pathophysiology of NTG does so. In fact, it may very well be that NTG is not a separate entity from open-angle glaucoma at all. Nevertheless, based on the present study, which demonstrates impaired circulation of CSF in a probably compartmented SAS of the ON in patients with NTG, we believe it important to consider the possibility of a detrimental effect of CSF stasis on axons and glial cells of the ON similar to that which may occur in patients with normal-pressure hydrocephalus. The high re-cycling rate as well as the impressive protoem of CSF indicates its importance for the biochemical milieu of neurons, glial cells and axons as well as its role as a transport system for clearing the CSF of toxic metabolites and other substances that may damage the various components of the ON (eg, stasis of CSF is thought to be associated with dementia). An obvious weakness of this study is the paucity of normal controls. Because cisternography is an invasive procedure and because its use for experimental purposes in control subjects is extremely limited for safety reasons, it is difficult to recruit normal subjects. In addition, as the control subjects had an unexplained ON disease that probably might be explained on the basis of a vascular aetiology, it is conceivable that the results are not truly those of normal individuals. In contrast to our small control group the NTG patients represent a population with ‘chronic and progressive’ ON disease and the change in CSF exchange might therefore reflect the impact of chronicity. Although we do not have the proper controls (normal subjects), we have the laws of physics, such as the second law of thermodynamics. And these laws tell us that the CLCSF should distribute homogeneously in an open system. Further studies should be performed to confirm or exclude the role of CSF composition and flow in the ONs of patients with NTG.

Competing interests None.

Ethics approval This study was conducted with the approval of the ethical committee of the hospital and the local government—Kantonales Ethikkommittee Aargau.

Contributors All authors contributed equally to this paper.

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