Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional?

H. E. Killer,[1,2] G. P. Jaggi,[2] J. Flammer,[1] N. R. Miller,[5] A. R. Huber[3] and A. Mironov[4]

[1]Eye Institute, University of Basel, [2]Department of Ophthalmology, [3]Department of Laboratory Medicine and [4]Institute of Neuroradiology, Kantonsspital Aarau, Switzerland and [5]Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, MD, USA

Correspondence to: PD Dr. H. E. Killer, Augenklinik, Kantonsspital Aarau, 5000 AaLirau, Switzerland
E-mail: Killer@ksa.ch

CSF is thought to flow continuously from the site of production in the ventricles into interconnected spaces; i.e. cisterns and subarachnoid spaces (SASs). Since the SAS of the optic nerve is defined by a cul-de-sac anatomy, it is not evident how local CSF might recycle from that region to the general SAS. The concept of free communication of CSF has recently been challenged by the description of a concentration gradient of beta-trace protein, a lipocalin-like prostaglandin D-synthase (L-PGDS), between the spinal CSF and that in the SAS of the optic nerve, indicating diminished local clearance or local overproduction of L-PGDS here. In fact, computed cisternography with a contrast agent in three patients with idiopathic intracranial hypertension and asymmetric papilloedema demonstrate a lack of contrast-loaded CSF in the SAS of the optic nerve despite it being present in the intracranial SAS, thus suggesting compartmentation of the SAS of the optic nerve. The concept of an optic nerve compartment syndrome is further supported by a concentration gradient of brain-derived L-PGDS between the spinal CSF and the CSF from the optic nerve SAS in the same patients.

Keywords: beta-trace protein; cerebrospinal fluid dynamics; computed cisternography; idiopathic intracranial hypertension; optic nerve subarachnoid space

Abbreviations: ANTG = atypical normal tension glaucoma; CLCSF = contrast-loaded cerebrospinal fluid; ICP = intracranial pressure; IIH = idiopathic intracranial hypertension; L-PGDS = lipocalin-like prostaglandin D-synthase; SAS = subarachnoid space

Received September 8, 2006. Revised October 10, 2006. Accepted October 17, 2006. Advance Access publication November 17, 2006.

Introduction

CSF is thought to be fairly homogeneous in composition and to be distributed evenly with a continuous flow through all CSF spaces, such as ventricles, cisterns and subarachnoid spaces (SAS) including the SAS of the optic nerve (Fig. 1). It is generally agreed that there is a bulk circulation from the site of origin to the site of absorption; i.e. from the ventricles to the arachnoid villi in the cranial SAS (Dichiro, 1964; Bito and Davson, 1966; Milohart, 1972; Wood, 1982). CSF circulation and direction of flow in the large CSF spaces (ventricles and spinal CSF space) have been studied with radiocisternography and other tracers. (Dichiro, 1966; Greitz *et al.*, 1992; Greitz and Hannerz, 1996). The mechanism by which CSF is propelled on its circulatory route is not fully understood but probably is influenced by the outpouring of newly produced CSF, postural effects, ventricular pulsations, the pulse pressure of the vascular choroid plexus, and a piston action of the brain (Bito and Davson, 1966; Milohart, 1972; Greitz *et al.*, 1991, 1992). CSF is renewed within 24 h, thus indicating a fast turnover. The velocity of CSF can be calculated using its total volume (Vol_{tot}) and the recycle time (R_t) as follows: velocity = Vol_{tot}/R_t. In addition to the well-established concept of CSF resorption in the arachnoid villi, *in vivo* research in animals strongly supports the concept of resorption via lymphatics (Johnston, 2000, 2003; Zakharov *et al.*, 2003). Indeed, lymphatics have been demonstrated on light and transmission electron microscopy in human tissue, and Indian ink injected into the SAS of the optic

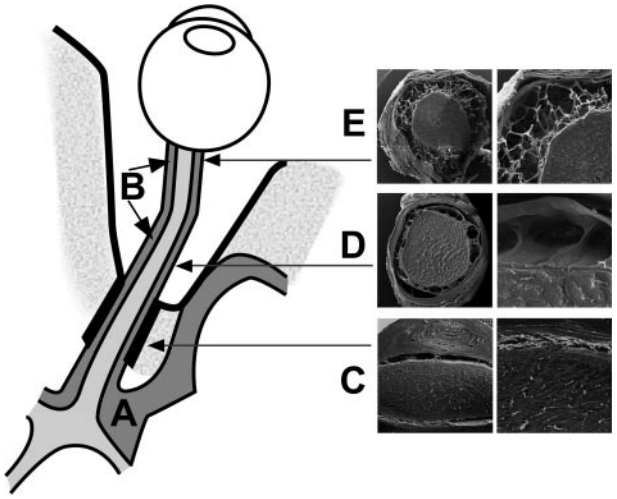

Fig. 1 Schematic representation of the CSF spaces surrounding the optic chiasm (intracranial CSF space) (**A**) and the CSF surrounding the optic nerve (orbital CSF space) (**B**). CSF flows from intracranial (**A**) into the SAS of the optic nerve (**B**). The SAS of the optic nerve is most narrow in the canalicular region (**C**). The intraorbital segment of the SAS is characterized by broad septae (**D**), whereas the retrobulbar segment is characterized by small trabeculae (**E**). Due to the CSF volume gradient the direction of flow is directed from the intracranial SAS to the orbital SAS.

nerve subsequently appears in dural lymphatics (Killer *et al.*, 1999).

The concept of a homogeneous CSF composition has been challenged based on the measurement of a marked concentration gradient of the brain-derived protein lipocalin-like prostaglandin D-synthase (L-PGDS) between the spinal CSF and that in the SAS surrounding the optic nerve in patients with idiopathic intracranial hypertension (IIH), optic nerve sheath meningioma and non-arteritic anterior ischaemic optic neuropathy (NAION) (Killer *et al.*, 2006). This concentration gradient does however not elucidate the CSF dynamics between the intracranial optic nerve SAS, nor does it explain how the CSF in the SAS of the optic nerve could recycle back to the intracranial site of resorption, apparently in violation of the laws of hydrodynamics.

Persistent papilloedema and visual loss in patients with IIH despite a functioning CSF shunt—a phenomenon that may be more common than generally appreciated—poses a conundrum that cannot be explained by the current concept of free CSF circulation throughout all CSF spaces (Guy *et al.*, 1990; Kelman *et al.*, 1991; Ramsey *et al.*, 2006). Compartmentation of the SAS of the optic nerve providing a barrier to free flow of CSF and the nerve offers a possible pathophysiological explanation for this phenomenon.

Material and methods

Three patients with IIH diagnosed by previous MR imaging of the brain and the orbits and lumbar puncture (LP) underwent complete neurological and ophthalmological examination. In all patients, bilateral asymmetric papilloedema was present on fundoscopy. All patients underwent CT-cisternography after intrathecal injection of 10 ml of contrast medium (Iopamidol, molecular weight 778 Da) by LP (Mironov *et al.*, 1993).

CT-cisternography was performed in the same room as LP and contrast application. The time interval between contrast application and CT-cisternography measured on average 2–5 min.

In order to compare the results from patients with elevated intracranial pressure (ICP) with those from patients with normal ICP, we also performed CT-cisternography in two patients who were already enrolled in another study of atypical normal tension glaucoma (ANTG).

In all patients, CT-cisternography was performed while the patients were postioned on their knees and elbows. They were then asked to turn to the left and to the right with their heads facing the floor. In order to elevate the ICP, the patients were instructed to perform a Valsalva manoeuvre. In all patients CT-cisternography was performed prior to optic nerve sheath fenestration (ONSF).

CSF was obtained during the procedure and subsequently analysed for cells, glucose, immunoglobulin G antibodies, albumin and L-PGDS. In all patients (IIH and ANTG) optic nerve sheath decompression was performed under general anaesthesia via a medial transconjunctival orbitotomy. Special care was taken not to use fluids to moisten the cornea after the orbitotomy in order not to dilute the CSF. Multiple incisions were performed in the dura of the optic nerve with a 19-gauge blade, and the trabeculae in the SAS were loosened with a tenotomy hook. After the first incision, a gush of CSF was observed, followed by further slow outflow. CSF then was sampled with a syringe using a 37-gauge needle (Killer *et al.*, 2006).

Results

No intracranial lesions were present in any of the patients on MRI; however, in the patients with IIH, orbital MRI revealed a variable degree of distension of the optic nerve sheath, most prominent in the bulbar segment adjacent to the posterior sclera (Figs 2–4). The amount of CSF surrounding the optic nerve was best seen on axial and coronal T_2-weighted sequences. Flattening of the posterior sclera with protrusion of the optic disc into the vitreous body was present in all patients with IIH to a variable degree. CT-cisternography in the IIH patients demonstrated an impaired contrast-loaded CSF (CLCSF) communication between the intracranial SAS and the SAS of the optic nerve. In two patients with IIH, CLCSF entered the SAS of the optic nerve only within the optic canal, not in the SAS of the intraorbital optic nerve, suggesting blockage of CLCSF within the canalicular portion of the optic nerve (Figs 2 and 3). In another patient with IIH, CLCSF entered the SAS of the optic nerve up to 10 mm within the orbit on the right side, whereas CLCSF on the left side entered ~5 mm (Fig. 4).

In one patient from the ANTG study group, CLCSF reached the mid-orbital portion of the optic nerve on both sides. A discrete CLCSF signal could be demonstrated only on the nasal side of the bulbar region of the right optic nerve, whereas no CLCSF reached the bulbar segment of

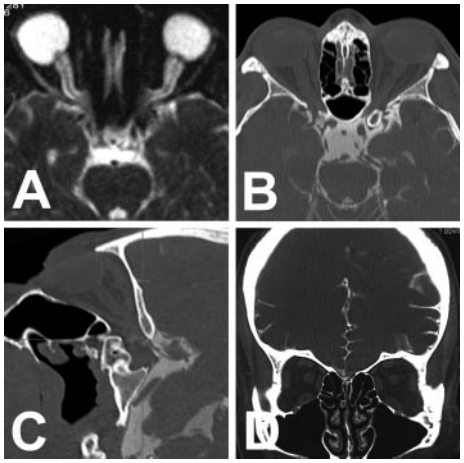

Fig. 2 (**A**) T_2 sequence of MRI demonstrates fluid congestion in the SAS of both optic nerves. Note flattening of the posterior sclera and papilloedema in both eyes. (**B** and **C**) CT-cisternography, axial/sagittal view: Distinct CLCSF in all intracranial CSF spaces. Note, full filling in the chiasmal cistern. (**D**) Coronary CT-cisternography does not show CLCSF in the SAS of both SAS of the optic nerve. The CT-cisternography shows an extension of the optic nerve shape with stasis of contrast agent loaded CSF at the level of the distal optic nerve sheath immediately before the optic canal.

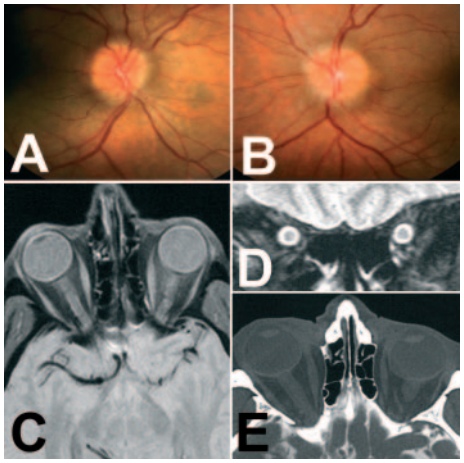

Fig. 3 (**A** and **B**) Asymmetric papilloedema, more pronounced in the left eye. (Note obscuration of the vessels on the nasal disc). (**C**) Axial MRI T_1 sequence, displaying congested optic nerve sheath on both sides and flattening of the posterior sclera. (**D**) Coronal orbital MRI, T_2 sequence demonstrating fluid accumulation and dilatation of both SAS of the optic nerves. (**E**) CT cistography. CLCSF in the intracranial CSF spaces. No CLCSF in both SAS of the optic nerves.

the left optic nerve (Fig. 5). In another ANTG patient, the CLCSF demonstrated a modest signal on the right with a patchy distribution and no CLCSF on the left (Fig. 5). In contrast to the patients with elevated ICP, an inversion of the L-PGDS ratio (L-PGDS optic nerve/L-PGDS LP) was measured (Table 1).

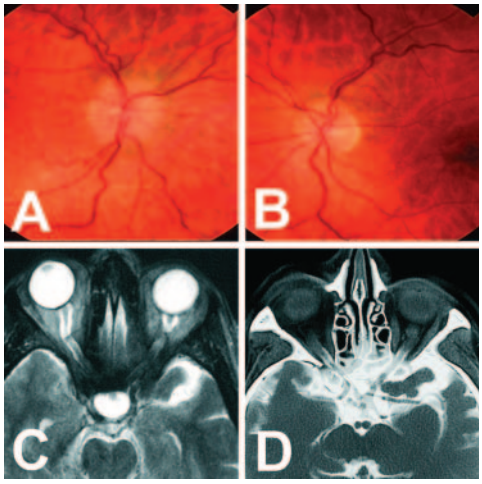

Fig. 4 (**A** and **B**) Asymmetric papilloedema, more pronounced in the right eye. (**C**) The T_2-weighted MRI image shows marked dilatation of both subarachnoid spaces of both optic nerve sheaths. (**D**) CT-cisternography demonstrates a stop of CLCSF in the posterior region of the intraorbital optic nerve on the right and the left. Note, no CLCSF in both bulbar regions of the optic nerves.

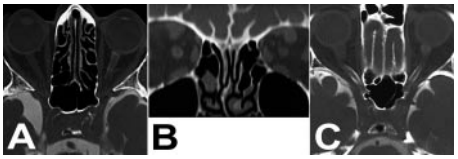

Fig. 5 Two patients with ANTG. (**A**) Axial CT-cisternography demonstrating normal intracranial CLCSF signal. The right SAS of the optic nerve demonstrates a modest patchy filling signal of CLCSF while the left SAS is devoid of CLCSF. (**B**) CT-cisternography coronary view (same patient as **A**). Compared with the intracranial signal, the SAS of the right optic nerve shows only a modest signal of CLCSF while there is no CLCSF signal in the SAS of the left optic nerve. (**C**) Axial CT-cisternography. CLCSF reaches into the mid-orbital portion of both optic nerve.

Discussion

In contrast to all other cranial nerves, the optic nerve is—to start with—by histological definition not really a nerve, but a white-matter tract of the CNS that extends into the orbit where it is surrounded by CSF throughout its entire length. As a consequence of this unique anatomy, the optic nerve can become involved in CNS disorders characterized by elevated ICP; e.g. IIH, intracranial masses, and inflammatory and infectious disease. The cul-de-sac structure of the covering of the optic nerve is the anatomical hallmark of the optic nerve and may be the crucial issue in understanding the CSF dynamics between the intracranial SAS and the SAS of the optic nerve. Free bidirectional communication between these areas has previously been taken for granted; however, this concept has recently been challenged by the description of a marked concentration gradient of L-PGDS (beta-trace protein) between the spinal CSF and the CSF in the SAS of the optic nerve that was measured in patients

Table 1 Clinical characteristics of the patients studied

Patient	C.M.	T.Z.	M.F.	H.E.	N.E.
Age (years)	56	49	30	75	64
Gender	F	F	F	F	M
Diagnosis	IIH	IIH	IIH	ANTG	ANTG
Side	R	L	L	R	R
BMI (kg/m^2)	31	34	35	22	25
LP pressure (cm H_2O)	30	31	30	18	16
L-PGDS LP (mg/l)	32.20	18.00	17.00	73.20	34.10
L-PGDS ON (mg/l)	70.80	132.00	47.80	27.00	30.60
L-PGDS ratio ON/LP (%)	220	733	281	37	90

M = male, F = female, L = left, R = right. ANTG = atypical normal tension glaucoma; BMI = body mass index; IIH = idiopathic intracranial hypertension (pseudotumour cerebri); LP = lumbar puncture; L-PGDS = lipocalin-like prostaglandin D-synthase (beta-trace); ON = optic nerve.

with IIH, NAION, and optic nerve sheath meningioma (Killer *et al.*, 2006). Whether or not this concentration gradient of L-PGDS is due to a local surplus production of CSF or a lack of clearance from the SAS of the optic nerve is not yet understood. Although orbital MR imaging in patients with IIH demonstrates changes consistent with CSF congestion and bulging of the meningeal sheath, it does not provide either qualitative or quantitative information regarding the biochemical composition of the local CSF, nor does the appearance of CSF in the SAS of the optic nerve differ from that of the intracranial CSF. Furthermore, there is no hydrodynamic theory that would explain how the cranial CSF that enters the SAS of the optic nerve could change its direction of flow against the volume gradient that directs it from the site of production and higher volume (intracranially) towards the SAS of the optic nerve. Two possible outflow routes from the SAS of the optic nerve have been suggested. Outflow from the SAS of the distal portion of the optic nerve into the orbit was demonstrated in animal studies via leakage of contrast agent and radioisotopes (Weed, 1914; Field and Brierly, 1949; McComb *et al.*, 1982; Shen *et al.*, 1985; Fogt *et al.*, 2004; Lüdemann *et al.*, 2005). Drainage via lymphatics is a new powerful concept that has demonstrated a great capacity for CSF outflow from the CNS (Johnston, 2000, 2003). Lymphatics in the dura of the human optic nerve may also offer an outflow pathway (Gausas *et al.*, 1999; Killer *et al.*, 1999).

The possibility of impaired exchange between the intracranial CSF and that in the SAS of optic nerve has only recently become of interest because of reports about persistent papilloedema and visual loss in patients with IIH despite a functioning lumboperitoneal shunt (Kelman *et al.*, 1991).

Asymmetric and unilateral papilloedema is another conundrum that requires a better understanding of CSF dynamics. Although papilloedema in patients with IIH tends to be symmetric, asymmetric disc swelling and even IIH without papilloedema have been described (Marcelis and Silberstein, 1991; Strominger *et al.*, 1992; Huna-Baron *et al.*, 2001). Considering the current understanding of CSF communication, patients with IIH without papilloedema are even more intriguing than asymmetric and unilateral papilloedema (Lipton and Michelson, 1972; Seggia and De Menezes, 1993). Although papilloedema is defined as disc swelling due to elevated ICP (Hayreh, 1968), typical radiological and fundoscopical features have been reported in patients without elevated ICP that presented with swollen discs resembling papilloedema due to retrobulbar neuritis and arachnoid cysts (Gass *et al.*, 1996; Brodsky and Vaphiades, 1998; Killer and Flammer, 2001; Killer *et al.*, 2003*b*; Hickman *et al.*, 2005). Partial or total compartmentation of the SAS of the optic nerve would offer a pathophysiological explanation for such cases; however, other than biological evidence (L-PGDS concentration ratio), there have been no data to support the concept of an optic nerve compartment syndrome.

One might expect studies of CSF dynamics *in vivo* to provide information about the location of impeded CSF flow and probably about mechanisms resulting in impaired flow. However, although radionuclide cisternography is often used to provide information regarding CSF flow, the SAS of the optic nerve is too small for this technique to render reliable information about the CSF in this area. It is for this reason that we have used CT-cisternography with contrast. This technique has been used in the past for the diagnosis of CSF leaks in patients with fractures of the skull base (Mironov *et al.*, 1993). The molecular size of the contrast agent (Iopamidol; 778 Da) allows easy access to the SAS of the optic nerve (molecular weight of L-PGDS 28 000 Da).

In the present study, CT-cisternography with contrast demonstrated blockage (stasis) and impaired influx of CLCSF in patients with IIH as well as to some extent in the ANTG study group patients. The information from this technique, combined with the finding of L-PGDS concentration gradients, provides strong evidence for optic nerve sheath compartmentation in patients with IIH.

If a total block of the CSF occurs in some situations, it is feasible to assume that a partial block may occur in other conditions. An interesting candidate is ANTG. In glaucomatous optic neuropathy the astrocytes are activated. This leads to an upregulation of factors such as matrix

metallo-proteinases, tumour necrosis factor α or endothelin. While on one hand, these factors may lead to arachnoiditis and thereby slow down CSF renewal, an increased concentration of these factors in the CSF on the other hand may contribute to the optic nerve damage. Endothelin, for example, is known to be increased in glaucoma patients—both locally and systemically. It not only reduces blood flow in the microcirculation but also interferes with the axoplasmatic transport (Hernandez, 2000). Ongoing studies will clarify whether such physiological molecules reach local concentrations that may be toxic to the optic nerve.

The development of compartmentation may depend on several pathophysiological mechanisms. The smallest diameter of the SAS of the optic nerve is within the optic canal. Although the osseous component of the canalicular portion of the optic nerve could theoretically play a role in the development of compartmentation, most patients with fibrous dysplasia retain normal vision in spite of narrowing of the optic canal (Lee *et al.*, 2002). It seems therefore more likely that the site of the pathophysiology is within the dura mater and the arachnoid and its adherent structures, including the trabeculae and septae (Killer *et al.*, 1999, 2003*a*; Sens *et al.*, 2003). Inflammatory changes in the SAS of the optic nerve leading to distension of the sheath and subsequent disc swelling has been suggested in patients with anterior optic neuritis (Killer *et al.*, 2003*b*; Hickman *et al.*, 2005). Anatomical studies of the SAS in post-mortem specimens from patients without neurological disease demonstrate polymorphonuclear leucocytes attached to the arachnoid layer (Killer *et al.*, 2003*a*). In addition, studies in rats demonstrate large numbers of MHC type II cells on the arachnoid in the SAS (Braun *et al.*, 1993). Leucocytes, macrophages, lymphoblasts and monocytes were detected following injection with bacillus Calmette-Guerin (Merchant and Low, 1977). It seems therefore feasible that even mild inflammatory stimuli may produce arachnoiditis and trabeculitis with secondary fibrosis, eventually leading to an optic nerve sheath compartment syndrome. The same process may occur in patients with subarachnoid haemorrhage (Julow *et al.*, 1979). Inflammatory processes might also contribute to the closing of the arachnoid apertures that drain CSF into the meningeal lymphatics thus adding to the CSF compartmentation.

Our study using CT-cisternography provides a pathophysiological explanation—optic nerve compartment syndrome—for persistent papilloedema and progressive visual loss in patients with apparently functioning CSF shunts as well as the occurrence of unilateral or asymmetric papilloedema. At the same time, our findings raise questions concerning the biological effects of accumulated CSF and its components on the optic nerve following the development of this syndrome. A possible toxic effect of reduced CSF clearance on brain tissue has recently been postulated (Rubenstein, 1998; Silverberg *et al.*, 2003). As the biochemical effects of L-PGDS are several, including neuroprotection of astrocytes on one hand and apoptotic activity and modulation of inflammatory processes on the other, it is to be expected that high concentrations of this agent will have a significant effect on the optic nerve (Logdberg and Wester, 2000; Govoni *et al.*, 2001; Ragolia *et al.*, 2001, 2003; Taniike *et al.*, 2002; Kagitani-Shimono *et al.*, 2006). The immediate retrobulbar portion of the nerve—from where CSF was sampled during sheath decompression—may be particularly vulnerable to these toxic effects. Histochemical and immunocytochemical studies have demonstrated a striking inverse relationship between myelination and mitochondrial distribution with the highest concentration of unprotected mitochondria in the bulbar region of the optic nerve (Bristow *et al.*, 2002). Damage to the mitochondria in this region—and to the pial vasculature—may contribute to the loss of visual function in IIH as well as other types of optic nerve disease. The crucial role of mitochondria for an intact optic nerve becomes evident from patients with Leber's optic neuropathy (Biousse and Newman, 2001).

In conclusion, understanding unilateral and asymmetric papilloedema in patients with elevated ICP is not possible without focusing on the SAS of the optic nerve. Damage in this setting can only be understood in the context of the close relationship of the optic nerve with the surrounding CSF and its proximity to the axons, mitochondria and the pia septal blood supply. We believe that the best explanation for both (unilateral and asymmetric papilloedema in patients with elevated ICP) is that the CSF in the SAS of the optic nerve may become sequestered, thus producing a compartment syndrome. The lack of CLCSF in the SAS of the optic nerve found in this study combined with the marked concentration gradient of a mainly brain-derived component—L-PGDS—between the spinal CSF and the SAS of the involved optic nerve strongly supports this concept of an optic nerve sheath compartment containing highly biological active molecules.

Based on the concentration gradient of L-PGDS and the corresponding CT-cisternography studies there is strong evidence for compartmentation of the SAS of the optic nerve. As there are at present no data on the normal population, the link between compartmentation and disease of the optic nerve is therefore based on the analogy of disturbed CSF dynamics and disease of the CNS (Rubenstein, 1998; Silverberg *et al.*, 2003).

Acknowledgements

We thank T. Vogel (chief laboratory assistant) for reliable assistance and E. Taub, MD for helpful comments on the manuscript. Thanks also to P. Groscurth, MD (Institute of Anatomy, University of Zürich, Switzerland) for the scanning electron microscopic images, and to O. Rüst (Institute of Neuroradiology, Kantonsspital Aarau, Switzerland) for good collaboration.

Competing Interests Statement: The authors declare that they have no competing financial interests.

References

Biousse V, Newman NJ. Neuro-ophthalmology of mitochondrial diseases. Semin Neurol 2001; 21: 275–91.

Bito LZ, Davson H. Local variations in cerebrospinal fluid composition and tis relationship to the composition of the extracellular fluid of the cortex. Exp Neurol 1966; 14: 264–80.

Braun JS, Kaissling B, Le Hir M, Zenker W. Cellular components of the immune barrier in the spinal meninges and dorsal root ganglia of the normal rat: immunohistochemical (MHC class II) and electron-microscopic observations. Cell Tissue Res 1993; 273: 209–17.

Bristow EA, Griffiths PG, Andrews RM, Johnson MA, Turnbull DM. The distribution of mitochondrial activity in relation to optic nerve structure. Arch Ophthalmol 2002; 120: 791–6.

Brodsky M, Vaphiades M. Magnetic resonance imaging in pseudotumor cerebri. Ophthalmology 1998; 105: 1686–93.

Di Chiro G. Movement of the cerebrospinal fluid in human beings. Nature 1964; 204: 290–1.

Di Chiro G. Observations on the circulation of the cerebrospinal fluid. Acta Radiol Diagn 1966; 5: 988–1002.

Field EJ, Brierly JB. The retro-orbital tissues as a site of outflow of cerebrospinal fluid. Proc R Soc Med 1949; 42: 447–50.

Fogt F, Zimmerman RL, Daly T, Gausas RE. Observation of lymphatic vessels in orbital fat of patients with inflammatory conditions: a form fruste of lymphangiogenesis? Int J Mol Med 2004; 13: 681–3.

Gass A, Barker GJ, Riordan-Eva P, MacManus D, Sanders M, Tofts PS, et al. MRI of the optic nerve in benign intracranial hypertension. Neuroradiology 1996; 38: 769–73.

Gausas RE, Gonnering RS, Lemke BN, Dortzbach RK, Sherman DD. Identification of human orbital lymphatics. Ophthal Plast Reconstr Surg 1999; 15: 252–9.

Govoni S, Masoero E, Favalli L, Rozza A, Scelsi R, Viappiani S, et al. The cycloxygenase-2 inhibitor SC58236 is neuroprotective in an in vivo model of focal ischemia in the rat. Neurosci Lett 2001; 303: 91–4.

Greitz D, Hannerz J. A proposed model of cerebrospinal fluid circulation: observations with radionuclide cisternography. Am J Neuroradiol 1996; 17: 431–8.

Greitz D, Nordell B, Ericsson A, Stahlberg F, Thomsen C. Notes on the driving forces of the CSF circulation with special emphasis on the piston action of the brain. Neuroradiology 1991; 33 (Suppl): 178–81.

Greitz D, Wirestam R, Franck A, Nordell B, Thomsen C, Stahlberg F. Pulsatile brain movement and associated hydrodynamics studied by magnetic resonance phase imaging. The Monro-Kellie doctrine revisited. Neuroradiology 1992; 34: 370–80.

Guy J, Johnston PK, Corbett JJ, Day AL, Glaser JS. Treatment of visual loss in pseudotumor cerebri associated with uremia. Neurology 1990; 40: 28–32.

Hayreh SS. Pathogenesis of oedema of the optic disc. Doc Ophthalmol 1968; 24: 289–411.

Hernandez MR. The optic nerve head in glaucoma: role of astrocytes in tissue remodelling. Prog Retin Eye Res 2000; 19: 297–321.

Hickman SJ, Miszkiel KA, Plant GT, Miller DH. The optic nerve sheath on MRI in acute optic neuritis. Neuroradiology 2005; 47: 51–5.

Huna-Baron R, Landau K, Rosenberg M, Warren FA, Kupersmith MJ. Unilateral swollen disc due to increased intracranial pressure. Neurology 2001; 56: 1588–90.

Johnston M. Relationship between cerebrospinal fluid and extracranial lymph. Lymphology 2000; 33: 1–3.

Johnston M. The importance of lymphatics in cerebrospinal fluid transport. Lymphat Res Biol 2003; 1: 41–4.

Julow J, Ishii M, Iwabuchi T. Scanning electron microscopy of the subarachnoid macrophages after subarachnoid haemorrhage, and their possible role in the formation of subarachnoid fibrosis. Acta Neurochir 1979; 50: 273–80.

Kagitani-Shimono K, Mohri I, Oda H, Ozono K, Suzuki K, Urade Y, et al. Lipocalin-type prostaglandin D synthase (beta-trace) is upregulated in the alphaB-crystallin-positive oligodendrocytes and astrocytes in the chronic multiple sclerosis. Neuropathol Appl Neurobiol 2006; 32: 64–73.

Kelman SE, Sergott RC, Cioffi GA, Savino PJ, Bosley TM, Elman MJ. Modified optic nerve decompression in patients with functioning lumboperitoneal shunts and progressive visual loss. Ophthalmology 1991; 98: 1449–53.

Killer HE, Flammer J. Unilateral papilledema caused by a fronto-temporoparietal arachnoid cyst. Am J Ophthalmol 2001; 132: 589–91.

Killer HE, Laeng HR, Groscurth P. Lymphatic capillaries in the meninges of the human optic nerve. J Neuroophthalmol 1999; 19: 222–8.

Killer HE, Laeng HR, Flammer J, Groscurth P. Architecture of arachnoid trabeculae, pillars, and septa in the subarachnoid space of the human optic nerve: anatomy and clinical considerations. Br J Ophthalmol 2003a; 87: 777–81.

Killer HE, Mironov A, Flammer J. Optic neuritis with marked distension of the optic nerve sheath due to local fluid congestion. Br J Ophthamol 2003b; 87: 249.

Killer HE, Jaggi GP, Flammer J, Miller NR, Huber A. The optic nerve: a new window into cerebrospinal fluid composition? Brain 2006; 129: 1027–30.

Lee JS, FitzGibbon E, Butman JA, Dufresne CR, Kushner H, Wientroub S, et al. Normal vision despite narrowing of the optic canal in fibrous dysplasia. N Engl J Med 2002; 347: 1670–6.

Lipton HL, Michelson PE. Pseudotumor cerebri syndrome without papilledema. JAMA 1972; 220: 1591–2.

Logdberg L, Wester L. Immunocalins: a lipocalin subfamily that modulates immune and inflammatory responses. Biochim Biophys Acta 2000; 1482: 284–97.

Lüdemann W, Berens von Rautenfeld D, Samii M, Brinker T. Ultrastrucutre of the cerebrospinal fluid outflow along the optic nerve into the lymphatic system. Childs Nerv Syst 2005; 21: 96–103.

Marcelis J, Silberstein SD. Idiopathic intracranial hypertension without papilledema. Arch Neurol 1991; 48: 392–9.

McComb JB, Hyman S, Weiss MH. Lymphatic drainage of cerebrospinal fluid in the cat. In: Shapiro IN, Marmarou A, Portnoy J, editors. Hydrocephalus. New York: Raven Press; 1982. p. 83–98.

Merchant RE, Low FN. Scanning electron microscopy of the subarachnoid space in the dog. V. Macrophages challenged by bacillus Calmette-Guerin. J Comp Neurol 1977; 172: 381–407.

Milohart TH. Hydrocephalus and the cerebrospinal fluid. Baltimore: Williams and Wilkins; 1972.

Mironov A, Probst C, Podvinec M. Die diagnostische Bedeutung der CT-Zisternographie bei posttraumatischer Liqourrhö. Klin Neuroradiol 1993; 3: 16–9 [article in German].

Ragolia L, Palaia T, Frese L, Fishbane S, Maesaka JK. Prostaglandin D2 synthase induces apoptosis in PC12 neuronal cells. Neuroreport 2001; 12: 2623–8.

Ragolia L, Palaia T, Paric E, Maesaka JK. Elevated L-PGDS activity contributes to PMA induced apoptosis concomitant with downregulation of PI3-K. Am J Physiol Cell Physiol 2003; 284: C119–26.

Ramsey CN III, Proctor BL, Baker RS, Pittman T. Prevention of visual loss caused by shunt failure: a potential role for optic nerve sheath fenestration. Report of three cases. J Neurosurg 2006; 104 (Suppl 2): 149–51.

Rubenstein E. Relationship of senescence of cerebrospinal fluid circulatory system to dementias of the aged. Lancet 1998; 351: 283–5.

Seggia JC, De Menezes ML. Pseudotumor cerebri without optic papilledema. Arq Neuropsiquiatr 1993; 51: 511–8 [Article in spanish].

Sens FM, Killer HE, Meyer P. Gradient-index (GRIN) endoscopic examinations from the inner structures of the optic nerve meninges. Klin Monatsbl Augenheilkd 2003; 220: 83–5 [Article in German].

Shen JY, Kelly DE, Hyman S, McComb JG. Intraorbital cerebrospinal fluid outflow and the posterior uveal compartment of the hamster eye. Cell Tissue Res 1985; 240: 77–87.

Silverberg GD, Mayo M, Saul T, Rubenstein E, McGuire D. Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis. Lancet Neurol 2003; 2: 506–11.

Strominger MB, Weiss GB, Mehler MF. Asymptomatic unilateral papilledema in pseudotumor cerebri. J Clin Neuroophthalmol 1992; 12: 238–41.

Taniike M, Mohri I, Eguchi N, Beuckmann CT, Suzuki K, Urade Y. Perineuronal oligodendrocytes protect against neuronal apoptosis through the production of

lipocalin-type prostaglandin D synthase in a genetic demyelinating model. J Neurosci 2002; 22: 4885–96.

Weed LH. Studies on cerebro-spinal fluid. The pathways of escape from the subarachnoid spaces with particular reference to the arachnoid villi. J Med Res 1914; 31: 51–91.

Wood JH. Neurobiology of cerebrospinal fluid, 2nd edn. New York: Plenum Press; 1982.

Zakharov A, Papaiconomou C, Djenic J, Midha R, Johnston M. Lymphatic cerebrospinal fluid absorption pathways in neonatal sheep revealed by subarachnoid injection of microfil. Neuropathol Appl Neurobiol 2003; 29: 563–73.