

The optic nerve: a new window into cerebrospinal fluid composition?

H. E. Killer,^{1,2} G. P. Jaggi,² J. Flammer,¹ N. R. Miller⁴ and A. R. Huber³

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

Correspondence to: PD Dr. H.E. Killer, Kantonsspital Aarau, CH-5001 Aarau, Switzerland
E-mail: Killer@ksa.ch

Cerebrospinal fluid (CSF) pressure and composition are generally thought to be homogeneous within small limits throughout all CSF compartments. CSF sampled during lumbar puncture therefore should be representative for all CSF compartments. On the basis of clinical findings, histology and biochemical markers, we present for the first time strong evidence that the subarachnoid spaces (SAS) of the optic nerve (ON) can become separated from other CSF compartments in certain ON disorders, thus leading to an ON sheath compartment syndrome. This may result in an abnormal concentration gradient of CSF molecular markers determined in locally sampled CSF compared with CSF taken during lumbar puncture.

Keywords: beta trace protein; cerebrospinal fluid; optic nerve; subarachnoid space

Abbreviations: CSF = cerebrospinal fluid; ON = optic nerve; SAS = subarachnoid space; ONSF = optic nerve sheath fenestration; MRI = magnetic resonance imaging; PGD = prostaglandin D; NSE = neuron-specific enolase

Received November 28, 2005. Revised January 24, 2006. Accepted January 27, 2006. Advance Access publication February 27, 2006.

Introduction

Cerebrospinal fluid (CSF) is mainly produced by the choroid plexus epithelium in the ventricles, from where it flows into interconnecting chambers, namely, the cisterns and the subarachnoid spaces (SAS), including the SAS of the optic nerves (ONs) (Dichiro, 1964; Bito and Vavson, 1966; Milohart, 1972; Wood, 1982). Recent findings demonstrate that CSF dysfunction might be caused by changes of molecular flux and CSF flow rate (Reiber, 2001), which in turn could result in accumulation of toxic components. For example, abnormal flow rates are thought to be the main cause for the pathological protein concentrations seen in neurological disorders such as Alzheimer's disease (Felgenhauer, 1980; Reiber and Felgenhauer, 1987; Tumani *et al.*, 1998; Reiber, 2001). Furthermore, recent studies have allowed for description of theoretical models of CSF flux that are well supported by empirically measured protein concentrations in the CSF (Reiber, 1994, 2001). The CSF contains a variety of proteins, of which 85% are derived from the blood, for example, albumin, immunoglobulin (Ig) G, whereas approximately 15% are synthesized primarily in the brain, for example, beta-trace protein, tau protein, S100 B protein and neuron-specific enolase (NSE) (Reiber, 2001). Beta-trace protein (molecular mass 25 kDa) is the most abundant synthesized protein in the CSF. On the basis of amino acid sequencing it has been

identified as prostaglandin D (PGD) synthase and therefore has biological active properties (Hoffman *et al.*, 1993).

In contrast to all other cranial nerves, the ON (a white matter tract of the central nervous system) is covered by the meninges and surrounded by CSF throughout its entire length. A rise in intracranial pressure thus may cause impairment of axoplasmic transport leading to papilloedema (Hayreh, 1964). Because CSF is assumed to communicate freely among the different CSF compartments, it has been concluded that there also exists a homogeneous pressure and homogeneous concentration of CSF components. However, to date, no data on measurements of actual protein concentrations in the perioptic CSF space (a subarachnoid space) have been reported. Certainly, the fact that most patients with papilloedema have more or less symmetric swelling of the optic discs supports the assumption of free communication among the CSF compartments; however, cases of asymmetric and even completely unilateral papilloedema have been reported (Killer *et al.*, 1999, 2003a, b; Killer and Flammer, 2001), and a satisfactory pathophysiological explanation for these phenomena is lacking. As the pressure gradient of CSF is directed from intracranial towards the SAS of the ON, it is difficult to understand how CSF can recycle from there, as a change of direction of fluid in order to return to the site of

resorption at the arachnoid villi is unlikely because of the volume gradient of CSF. A CSF outflow pathway from the SAS of the ON is therefore of physiological relevance to prevent fluid accumulation. The recent discovery of lymphatic vessels in the dura of the human ON—and their ability to drain CSF as demonstrated with a marker substance—may offer a CSF outflow route from the perioptic space (Killer *et al.*, 1999, 2003). The results of experimental studies in animals describe CSF drainage into lymphatic vessels (Boulton *et al.*, 1998; Johnston, 2000, 2003; Zakharov *et al.*, 2003). In cats CSF outflow from cisternal infusion to the distal portion of the ON has been demonstrated (Lüdemann *et al.*, 2005). In addition, the anatomy and the arrangement of trabeculae and septae in the SAS of the ON offer the possibility that a one-way valve mechanism explains local CSF entrapment as well as reduced influx of CSF into the SAS of the ON (Killer *et al.*, 1999, 2003) (Fig. 1). Unilateral and highly asymmetric dilation of the SAS of the ON can partly be explained by reduced local drainage on the side of the more pronounced papilloedema or by a bigger resistance to influx of CSF on the side of the less marked papilloedema. Owing to the small size of the SAS of the ON, local pressure measurements are difficult and to date have been performed only in cadavers (Liu and Kahn, 1993).

Material and methods

We performed ON sheath fenestration (ONSF) (Galbraith and Sullivan, 1973) in six patients after ophthalmological and neurological examination including lumbar puncture in five patients. In five patients MRI imaging of the brain and orbit was performed. One patient underwent high-resolution computed tomography. In one patient ONSF was performed on both ON. All patients were operated at the same institution (Kantonsspital Aarau) by the same surgeon (H. E. Killer). Three had unilateral optic disc swelling: one from anterior ischaemic optic neuropathy, one from ON sheath meningioma and one idiopathic optic disc swelling (presumed from a local vascular cause). The other three patients had highly asymmetric papilloedema: one from pachymeningitis, one from idiopathic intracranial hypertension and one following a cerebral haemorrhage.

Marked dilation of the perioptic CSF spaces was present on MR imaging in all three patients with papilloedema. These MRI findings were first described by Brodsky *et al.* (1998). Less-marked dilation was present in the three patients with unilateral optic disc swelling. CSF was collected in all patients from the SAS of the ON after the 'CSF gush' following the incision of the dura and from the lumbar SAS at the time of the lumbar puncture. The CSF from both compartments was examined for the content of albumin, IgG and beta-trace protein. For the determination of serum and CSF albumin, IgG and beta-trace proteins, nephelometric methods were employed using polyclonal antibodies and a nephelometer (BNII) from Dade Behring, Marburg, Germany.

Results

Beta-trace concentrations of CSF obtained from the SAS of the ON was 79.84 ± 27.14 mg/l, whereas the CSF : serum

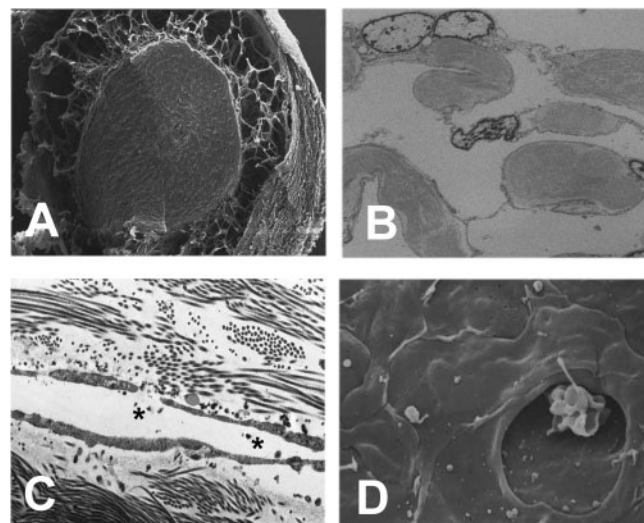


Fig. 1 Histological studies of the meninges of the human ON. (Courtesy of P. Groscurth, Department of Anatomy, University of Zürich, Switzerland). **(A)** Scanning electron microscopy of the retrobulbar portion of the SAS of the ON. Note the complex network of trabeculae bridging the SAS. **(B)** Transmission electron microscopy of arachnoid trabeculae. Note the thin layer of meningoepithelial cells surrounding each trabeculum and the cytoplasmic bridges connecting adjacent trabeculae. The anatomical arrangement of trabeculae and cytoplasmic bridges allow for local CSF entrapment in the SAS causing an ON sheath compartment syndrome. **(C)** Lymphatic capillary in the dura of the human ON sheath. Marker particles are visible in the lumen of the vessel (asterisk). **(D)** Arachnoid layer with pore for CSF outflow into the dura. Note the macrophage entering the pore.

ratio of albumin and IgG was 0.24 ± 0.17 and 0.21 ± 0.15 , respectively. Further, beta-trace concentrations and albumin and IgG ratio in CSF obtained from a spinal tap were 17.53 ± 3.06 , and 0.02 ± 0.02 and 0.01 ± 0.01 mg/l, respectively. Reference values for beta-trace protein are 15.3 mg/l (Link and Olsson, 1972; Rubenstein, 1998) (Figs 2 and 3).

Discussion

This paper describes six cases with unilateral optic disc swelling and asymmetric papilloedema with distension of the perioptic nerve sheath on orbital MRI or CT scan.

The CSF findings strongly suggest that the ON can develop into a separate CSF compartment under certain pathological conditions. In addition, despite different aetiologies of optic disc swelling, the CSF obtained from the SAS of the ON in all of these cases demonstrated markedly different biomarker concentrations compared with those in the CSF obtained from the corresponding lumbar SAS. These findings are consistent with the compartmentalization of the SAS of the ON. In addition, they suggest that additional mechanical damage (e.g. elevated local pressure) as well as biochemical injury through an accumulation of biologically active molecules may contribute to disease progression and tissue damage to

Patient	M.E.	S.A.	S.A.	K.H.	H.H.	H.U.	P.M.
Age [years]	39	23	23	61	48	52	20
Gender	f	m	m	m	m	f	f
Diagnosis	ONSM	PM	PM	IODS	SPC	AION	PC
ON Side	l	l	r	l	l	r	l
LP Pressure [cm H ₂ O]	24	50	50	none	34	20	43
Beta-Trace LP [mg/L]	18.60	18.10	18.10	none	11.80	21.00	17.60
Beta-Trace ON [mg/L]	49.90	103.00	124.00	81.10	71.10	80.90	48.90
Albumin Ratio LP (CSF/Serum)	0.01	0.03	0.03	none	0.03	0.00	0.00
Albumin Ratio ON (CSF/Serum)	0.52	0.20	0.11	0.14	0.09	0.43	0.21
IgG Ratio LP (CSF/Serum)	0.00	0.01	0.01	none	0.02	0.00	0.00
IgG Ratio ON (CSF/Serum)	0.45	0.13	none	0.12	0.05	0.32	0.17

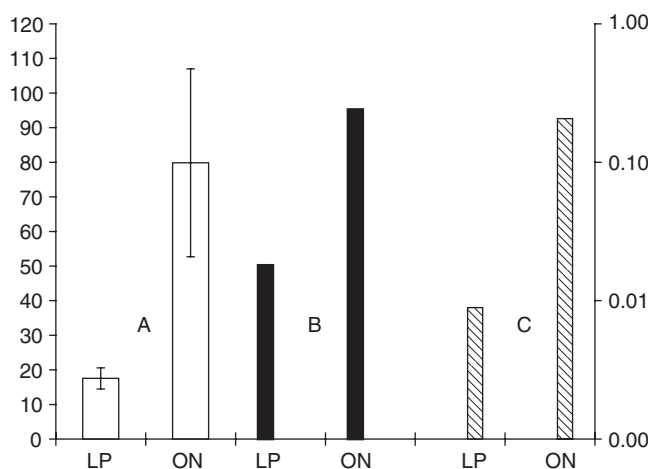


Fig. 2 Table and graph of CSF data from six patients. Table: The CSF samples are taken from seven SAS of the left (l) or/and the right (r) ON from three male (m) (mean age 44.0 ± 19.3 years) and three female (f) (mean age 37.0 ± 16.0 years) patients after informed consent. Clinical diagnosis: pseudotumour cerebri (PC) and secondary pseudotumour cerebri (SPC), anterior ischaemic optic neuropathy (AION), pachymeningitis (PM), idiopathic optic disc swelling (IODS) and ON sheath meningioma (ONSM). Lumbar puncture (LP) was performed in five patients and markers determined as described. Graph: Beta trace (A; light bars) in (mg/l) \pm SD, CSF/serum ratio of albumin (B, dark bars), and of IgG (C, hatched bars) of mean \pm SD and logarithmic from six patients obtained by spinal tap (LP) and puncture of the SAS of the ON.

blood vessels, axons and neurons (Link and Olsson, 1972; Logdberg and Wester, 2000; Urade and Hayaishi, 2000; Reiber, 2001; Fujitani *et al.*, 2002; Taniike *et al.*, 2002; Ragolia *et al.*, 2003; Zakharov *et al.*, 2003).

Although elevated concentrations of IgG and albumin, seen in patients with blood-brain barrier dysfunction, might have been caused by the surgical procedure, the increased concentration of CSF beta-trace protein in the SAS of the ON can only be due to abnormal local synthesis or pathological flow dynamics (reduced beta-trace clearing) in the occluded compartment. Whether or not this markedly increased concentration of beta-trace further aggravates compartmentalization is not known at this time. Ours is the first report to provide information concerning the biochemical constituents of the CSF in the SAS of the ON and the difference between the concentrations of these constituents in the periopic SAS versus the lumbar SAS.

Furthermore, the results provide strong evidence for compartmentalization of the SAS of the ON, thus leading under certain circumstances to the development of an

ON sheath compartment syndrome. Several studies have demonstrated apoptosis-inducing properties of beta-trace in neuronal tissues (Link and Olsson, 1972; Logdberg and Wester, 2000; Urade and Hayaishi, 2000; Fujitani *et al.*, 2002; Taniike *et al.*, 2002; Ragolia *et al.*, 2003). Given the biological potential of some molecules in the CSF, it could be postulated that the accumulation of these biologically active molecules (e.g. beta-trace) in blocked compartments of the CSF space would cause significant, possibly devastating, damage to the tissues in the vicinity of the affected area. A relationship between an impaired CSF circulatory system, impaired clearance of noxious substances in the CSF and dementias of the aged has recently been proposed (Rubenstein, 1998; Silverberg *et al.*, 2003). Following this line of thought, our findings may prove helpful to shed a new light onto the pathophysiology of progressive anterior and posterior ischaemic optic neuropathy or more common ON disorders, such as chronic open-angle and normal-tension glaucoma, which in many cases show progressive visual field loss despite well-regulated intraocular pressure,

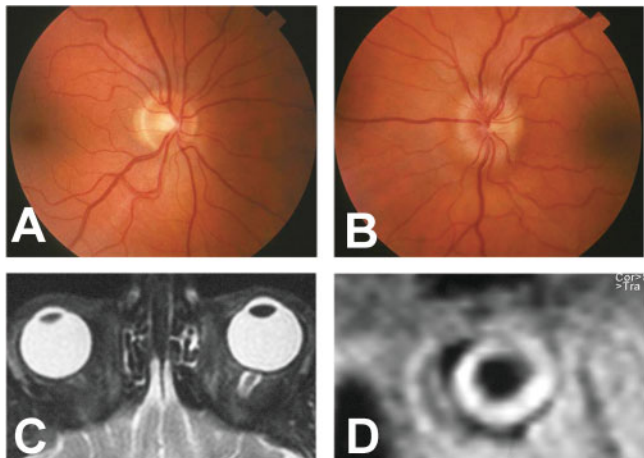


Fig. 3 Fundus photography and MRI studies of a patient with unilateral papilloedema (due to nerve sheath meningioma). (A) Unremarkable optic disc on the right. (B) Unilateral optic disc swelling due to left ON sheath meningioma. (C) Distended perioptic nerve sheath on the left with accumulation of CSF (white on T2-weighted magnetic resonance image, axial view). These radiological features meet the criteria for papilloedema as described previously by Brodsky and Vaphiades (1998). (D) Coronal view of the left orbit. Note marked distension of the SAS and accumulation of CSF.

suggesting additional pathophysiological components (Gliklich *et al.*, 1989).

Acknowledgement

We would like to thank Ronald M. Burde—former head of Department of Ophthalmology, Albert Einstein College of Medicine, New York—for continued inspiration and friendship.

Conflict of interest statement. None declared.

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