Optic nerve sheath diameter in normal-tension glaucoma patients

Gregor Peter Jaggi,[1] Neil Richard Miller,[2] Josef Flammer,[3] Robert N Weinreb,[4] Luca Remonda,[5] Hanspeter Esriel Killer[1,3]

[1]Department of Ophthalmology, Kantonsspital Aarau, Switzerland
[2]Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, Maryland, USA
[3]University of Basel, Eye Institute, Switzerland
[4]Department of Ophthalmology, Hamilton Glaucoma Center, University of California, San Diego, California, USA
[5]Department of Neuroradiology, Kantonsspital Aarau, Switzerland

Correspondence to
Professor Dr.med. Hanspeter Esriel Killer, Kantonsspital Aarau, Buchserstrasse, CH-5001 Aarau, Switzerland; killer@ksa.ch

Accepted 30 January 2011
Published Online First 11 March 2011

ABSTRACT

Background To report on the optic nerve sheath diameter (ONSD) in patients with normal-tension glaucoma (NTG) compared with controls without known optic nerve (ON) or intracranial disease.

Methods In 18 patients with NTG (mean age 64.9±8.9 years; 7 women and 11 men), CT of the orbit was performed. 17 age- and gender-matched patients without ON or intracranial disease, who underwent CT of the orbits for non-ophthalmological reasons, served as controls. The widest intraorbital ONSD in axial sections was measured using a standardised technique. Study design: unmasked. Statistical analysis was performed using an independent two-tailed t Test and the non-parametric Spearman correlation test.

Results ONSD was significantly ($p<0.001$) increased in NTG patients (right side: mean 7.9±0.9 mm SD; left: 8.0±1.1 mm) compared with controls (right: 6.3±0.5 mm; left: 6.1±0.6 mm). Neither the NTG nor the control group had a significant difference in ONSD between males and females or between right and left sides.

Conclusions An increased ONSD is generally associated with increased intracranial pressure; however, ONSDs in a group of NTG patients also were significantly increased compared with controls. ON sheath compartmentation and thinning of the ON sheath are two possible explanations for an increase in the ONSD in patients with NTG.

INTRODUCTION

The pathophysiology of normal-tension glaucoma (NTG), a condition characterised by visual field loss and optic disc excavation consistent with primary open-angle glaucoma (POAG) despite apparently normal intraocular pressure (IOP), remains poorly understood. Impaired blood flow to the optic nerve (ON) and vascular dysregulation are two of the most common mechanisms that have been suggested as predisposing factors in the development of NTG.[1 2] Furthermore, there is some evidence that NTG is more common in migraineurs and that patients with NTG have a variety of serologic vascular-related abnormalities, such as elevated levels of endothelin.[1 3]

In addition to vascular risk factors, cerebrospinal fluid (CSF) pressure has been suggested as another possible contributing factor to the development of NTG. For example, Berdahl *et al* reported reduced intracranial pressure (ICP) in NTG patients.[4] This raised the possibility that axon death in patients with NTG could be due, at least in part, to an imbalance of translaminar pressure (the difference between IOP and pressure in the subarachnoid space (SAS) of the ON). In this regard, a recent study by Ren *et al* reported that translaminar pressure was significantly higher in both POAG and NTG patients, compared with controls.[5]

In the current study, we performed CT of ON sheath diameter (ONSD) in 18 patients with NTG and compared the findings with those from a control group of 17 patients without ON or intracranial disease.

METHODS

Eighteen patients (mean age 64.9±8.9 years; 7 women (62.4±8.2 years) and 11 men (66.5±9.4 years)), with bilateral NTG characterised by progressive visual field loss and optic disc appearance consistent with POAG but with IOPs always <21 mm Hg by Goldmann applanation tonometry, who were subjects included in a controlled study (Normal Tension and Chronic Open Angle Glaucoma and Cerebrospinal Fluid Composition; NIH Clinical trial—identifier: NCT00306657), underwent CT of brain and orbits combined with cisternography (in prone position, using 10 ml iopamidol) at the same time. At the beginning of cisternography, a lumbar puncture was performed that included measurement of the ICP (in order to rule out CSF pressure above 20 cm H_2O), with the patient in the lateral decubitus position. At the time of lumbar puncture, 10 ml of CSF was sampled for chemical analysis and then 10 ml iopamidol was injected intrathecally. The patient was then shifted to the prone position. None of the patients was on a medication that would influence the CSF production or resorption. A 64-detector scanner (Aquillion 64, Toshiba, Tokyo, Japan) providing 0.5 mm ×32 section collimation was used. Scanning parameters 25 cm field of view, 512×512 matrix and a soft tissue and a bone reconstruction algorithm 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 Advantage Workstation (AW) 4.1 software (General Electric, Milwaukee, Wisconsin, USA). Axial sections were used and the diameter of the portion of the ON adjacent to the globe was measured at its widest site to standardise the measurement of the ONSD (figure 1). All patients had at least six IOP measurements at different times during the day (between 08:00 and 20:00) in a seated position as well as at night (between 21:00 and 06:00) in a recumbent position (using a Perkins tonometer).

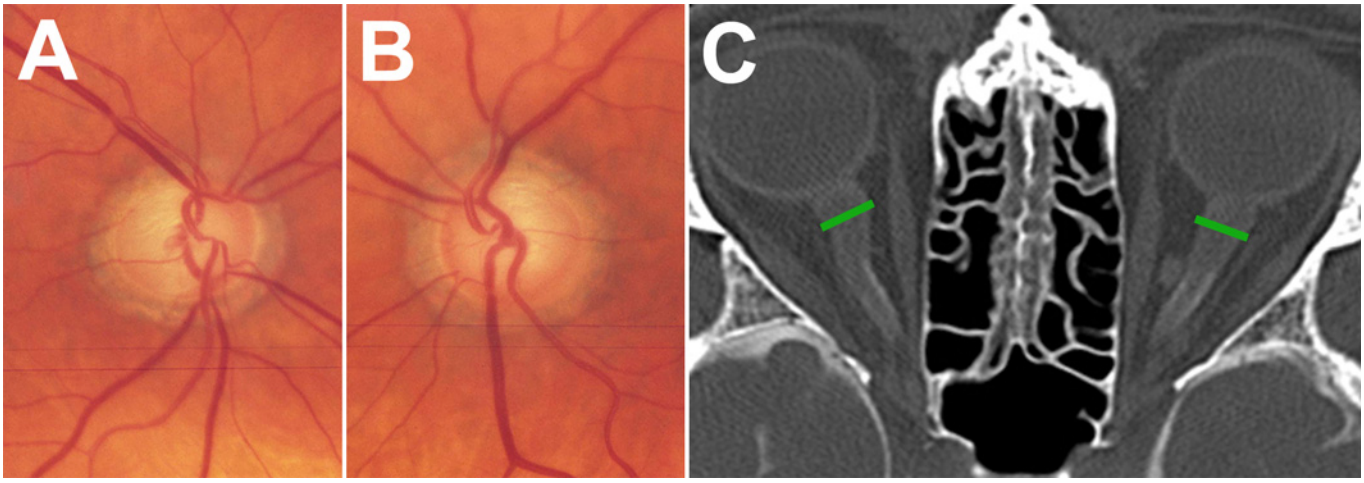

Figure 1 Optic disc of the right eye (A) and left eye (B) and CT cisternography (C) of patient number six, demonstrating impaired influx of contrast-loaded cerebrospinal fluid (CSF) into the anterior portion of the intraorbital subarachnoid space (SAS) of both optic nerves (ON). Note distention of both ON sheaths, most pronounced in the retrobulbar region. Widest optic nerve sheath diameter (ONSD): right 8.07 mm and left 8.17 mm (green bars).

Seventeen age- and gender-matched individuals (mean age 66.2±15.1 years; 4 women (61.3±22.5 years) and 13 men (67.7±12.9 years)) without known intracranial or ON disease, who underwent CT scanning for maxillary and ethmoid sinus disease, served as controls, and they were recruited in a retrospective manner. Measurements of ONSD were obtained as described above (table 1).

For analysis of ONSD in NTG patients and controls, the independent two-tailed t test was used. For analysis of correlations between ONSD and age, the non-parametric Spearman rank order correlation Coefficient was used (SPSS 14.0; SPSS Inc).

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 and control groups did not differ significantly in either age or gender (p>0.283) (figure 2). In the 18 NTG patients, right ONSDs ranged from 5.3 to 9.2 mm (mean value 7.92±0.91 mm SD). ONSDs in female subjects (n=7) ranged from 5.3 to 8.6 mm (7.5±1.10), whereas in males (n=11), it ranged from 7.2 to 9.2 mm (8.2±0.65). Left ONSDs in NTG patients ranged from 6.1 to 10.3 mm (8.0±1.06): 6.2 to 9.1 mm (7.7 ±1.02) in females and 6.1 to 10.3 (8.1±1.09) in males. In the 17 control subjects, right ONSDs ranged from 5.3 to 7.1 mm (6.3±0.49): 5.9 to 7.0 mm (6.5±0.45) in females (n=4) and 5.3 to 7.1 mm (6.3±0.51) in males (n=13). Left ONSDs in the control subjects ranged from 5.0 to 6.9 mm (6.1±0.62): 5.3 to 6.4 mm (6.0±0.49) in females and 5.0 to 7.0 mm (6.2±0.66) in males (table 1 and figure 3). In all NTG patients, the pressure (ICP) measured during lumbar puncture was less than 20 cm H_2O.

Overall, the maximal intraorbital ONSD measured by CT differed significantly between the NTG patients and the control subjects (t test: p<0.001 for both right and left ONSDs). The difference in ONSDs in the subgroup of right ONs in female NTG patients (n=7) compared with right ONs in female controls (n=4) did not quite reach statistical significance (p=0.073); however, all other subgroup analyses comparing ONSDs of NTG patients and controls showed p values ranging from <0.001 to 0.029 (figure 2).

Table 1 Optic nerve sheath diameter (ONSD) (mm) of normal-tension glaucoma (NTG) patients and controls, separated for right (OD) and left (OS) side. Age for male (m) and female (f) in years. Lumbar CSF pressure (p CSF) (cm H_2O) measured at the time of cisternography (CT of the orbit)

ONSD in NTG					
Patients and Controls			ONSD (mm)		p CSF (cm H_2O)
Nr.	Age m	Age f	ONSD OD	ONSD OS	
Patients:					
1		76	7.41	7.03	14
2	64		8.79	7.96	<20
3		64	8.62	9.11	<20
4	52		8.22	7.93	14
5	63		8.34	7.33	10
6	81		8.07	8.17	<20
7	54		9.23	8.17	10
8		65	7.40	8.55	14
9	72		7.33	8.09	<20
10	60		8.34	8.53	19
11		56	8.30	8.40	<20
12	74		8.61	9.43	<20
13	73		8.81	10.32	<20
14	76		7.56	6.10	8
15	62		7.16	7.43	14
16		60	8.04	7.09	12
17		66	7.09	6.20	19
18		50	5.30	7.70	12
Controls					
1Co	69		7.09	6.93	no data
2Co		77	6.99	6.16	no data
3Co		68	6.59	5.98	no data
4Co	64		6.52	6.67	no data
5Co	74		6.92	6.68	no data
6Co	60		6.45	6.43	no data
7Co	68		6.31	6.67	no data
8Co	78		5.34	5.07	no data
9Co	89		6.26	5.04	no data
10Co	65		6.06	5.39	no data
11Co	76		5.43	5.53	no data
12Co		28	5.90	5.29	no data
13Co	36		6.26	6.48	no data
14Co		72	6.48	6.43	no data
15Co	60		6.71	6.30	no data
16Co	61		6.22	6.70	no data
17Co	80		5.99	6.20	no data

ONSD in NTG

ONSD		n	Mean [mm]	±SD	t-Test results (p) Co OD: Co OD f	Co OD m	Co OS: Co OS f	Co OS m	NTG OD: NTG OD f	NTG OD m	NTG OS: NTG OS f	NTG OS m
Co OD			6.3	0.5			0.281		***< 0.001***		*< 0.001*	
	Co OD f	4	6.5	0.5		0.449	0.165	0.293	**0.073**	*< 0.001*	*0.023*	*0.001*
	Co OD m	13	6.3	0.5			0.320	0.630	*0.029*	***< 0.001***	*0.008*	*< 0.001*
Co OS			6.1	0.6					*< 0.001*		***< 0.001***	
	Co OS f	4	6.0	0.5				0.542	*0.013*	*< 0.001*	***0.004***	*< 0.001*
	Co OS m	13	6.2	0.7					*0.020*	*< 0.001*	*0.005*	***< 0.001***
NTG OD			7.9	0.9							0.877	
	NTG OD f	7	7.5	1.1						0.127	0.637	0.221
	NTG OD m	11	8.2	0.7							0.280	0.816
NTG OS			8.0	1.1								
	NTG OS f	7	7.7	1.0								0.437
	NTG OS m	11	8.1	1.1								

Age		n	Mean [y]	±SD	Co: Co f	Co m	NTG: NTG f	NTG m
Co		*17*	66.2	15.1			0.763	
	Co f	4	61.3	22.5		0.617	0.925	0.680
	Co m	13	67.7	12.9			0.283	0.789
NTG		*18*	64.9	8.9				
	NTG f	7	62.4	8.2				0.354
	NTG m	11	66.5	9.4				

Spearman's correlation test:			
OD	ONSD vs Age	p= 0.618	rho= 0.087
OS	ONSD vs Age	p= 0.137	rho= 0.256

Figure 2 Results of statistical analysis of optic nerve sheath diameter (ONSD) and age in normal-tension glaucoma (NTG) patients compared with controls (Co), separated for right (OD) and left (OS) side, as well as for female (f) and male (m). T test values of subgroups with special interest concerning the hypothesis in this study, which are reported in the results section, are shown in bold type. Italic type indicates significance.

There was no significant difference in ONSDs between female and male NTG patients, neither for the right side (p=0.13) nor for the left side (p=0.44), or between female and male control subjects (right side p=0.45; left side p=0.54). There was also no statistically significant difference between right and left ONSDs in either the NTG patient group (female p=0.64; male p=0.82) or the control group (female p=0.17; male p=0.63) (figure 2). There was no significant correlation between age and ONSDs for the right (Spearman's correlation; ρ=0.087, p=0.618) or left (ρ=0.256, p=0.137) sides (figure 4).

DISCUSSION

In this study, measurements of the maximum ONSD using thin-section axial CT scans revealed that the ONSDs in patients with NTG were significantly larger than those in control subjects without ON or intracranial disease. Although the ONSDs in control subjects in this study were somewhat larger than the ONSDs described for normal subjects in a previous study using ultrasonography performed by Lam *et al*,[6] our study nevertheless demonstrates clear-cut ONSD enlargement in patients diagnosed with NTG, a feature previously recognised only in patients with increased ICP associated with papilloedema and in patients with certain rare disorders of the ON sheath.[7–10]

We believe there are three potential explanations for our findings. First, the enlarged ONSDs in patients with NTG may be due to higher tissue elasticity in such patients. The dura of the ON sheath has a thickness of 0.35–0.5 mm, with its thickest part close to the sclera.[11 12] Ultrasound measurements of ON sheath thickness during changes in CSF pressure show large variations among individuals, possibly related to interindividual sheath elasticity.[13] But why should sheath elasticity differ between normal subjects and patients with NTG? One possible explanation could be a difference in tissue composition mediated by metalloproteinases. These highly interactive and complex inflammatory mediators are thought to play a role in corneal thinning,[14] which in different concentrations could also affect the ON sheath elasticity. Indeed, metalloproteinase expression has been found to be elevated in the white blood cells of NTG patients.[15]

Watanabe *et al* described a correlation between ONSD and ICP based on measurements performed using MRI.[16] Using the

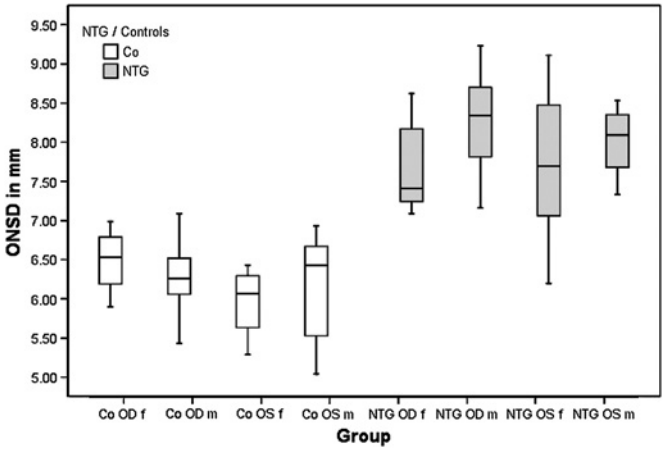

Figure 3 Box plot of optic nerve sheath diameter (ONSD) (mm) in controls (Co) and normal-tension glaucoma (NTG) patients, separated for female (f) and male (m) as well as for right (OD) and left (OS) sides. NTG patients total n=18 (female 7 and male 11) and controls total n=17 (female 4 and male 13).

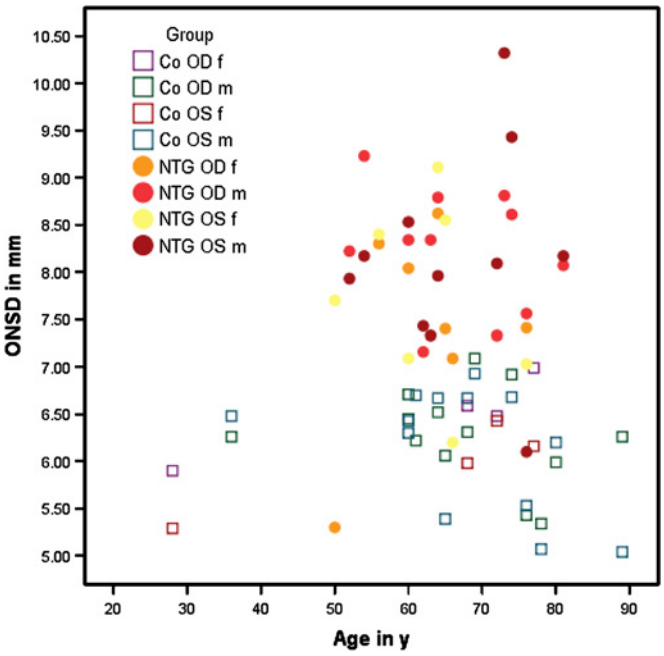

Figure 4 Scatter plot showing cases of normal-tension glaucoma patients (NTG) and controls (Co), separated for female (f), male (m) and right (OD), left (OS) side of optic nerve sheath diameter (ONSD) (mm) correlated with age (y). Spearman non-parametric correlation test showed no significance for right ($p=0.618$; $\rho=0.087$) or left ($p=0.137$; $\rho=0.256$) side.

sigmoid curve described by Watanabe *et al*, our patients would be expected to have increased ICP on lumbar puncture as well. This, however, was not the case, as in all NTG patients, the CSF pressure during lumbar puncture was less than 20 cm H_2O. Obviously, it would be best to measure directly the perioptic pressure in NTG patients and in normal subjects; however, such measurements are technically difficult and carry substantial risks to vision.

As the enlargement of the ONSD is a classical feature of papilloedema and therefore associated with elevated ICP, the normal or rather low ICP in our patients, as described previously in patients with NTG,[4 5] is only in conflict with our ONSD measurement when we believe in a freely communicating CSF pathway. This belief however has been challenged by the finding of a vast concentration gradient of contrast-loaded CSF between the basal cisterns and the perioptic space. Indeed, using contrast-loaded cisternography, our group has demonstrated disturbances in CSF flow dynamics in a small sample of NTG patients.[17] The anatomy of the SAS is of a dynamic character and can be modified by compartmentation of the SAS, as recently demonstrated in an animal model that showed impressive swelling of the meningothelial cells, thus leading to a change in the architecture of the CSF flow-modifying structures, such as the trabeculae and septae, thereby narrowing the small SAS even more.[18 19] Although our study seems to be conflicting with the ONSD finding in patients with elevated ICP, compartmentation of the SAS maintained by a valve-like process during Valsalva manoeuvre could still explain the findings.

In addition to the elevated pressure in the SAS of the ON and thinning of the ON sheath, a third mechanism needs to be considered. The ON is located in the intraconal portion of the orbit that is confined by the extraocular muscles. Given this location, the intraconal pressure might influence the ONSD. Patients with thyroid disease are at risk for ON compression and the diameter of the ON sheath in this population might give a hint concerning the validity of this hypothesis.

There are several limitations to our study. First, the number of patients in both the NTG and the control groups is small. Second, the controls were recruited in a retrospective manner. Although the control subjects were not known to have either ON or intracranial disease, none had undergone a complete ophthalmological assessment. Given the low incidence of NTG, the chance that there is more than one patient in the control group with NTG is virtually minimal. It would also be interesting to perform a large prospective study of ONSD, which included patients with clear-cut POAG having both normal and elevated IOP. Nevertheless, our findings indicate that regardless of the mechanism, patients with NTG have an abnormality of their ON sheaths that may be the cause or the effect of their condition.

Acknowledgements The authors would like to thank Andreas Schoetzau, University of Basel, for helpful support in statistics.

Competing interests None.

Ethics approval This study was conducted with the approval of the Kantonale Ethikkommission Aargau—this study is part of the 'Normal Tension and Chronic Open Angle Glaucoma and Cerebrospinal Fluid Composition'.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Drance SM,** Sweeney VP, Morgan RW, *et al*. Studies of factors involved in the production of low tension glaucoma. *Arch Ophthalmol* 1973;**89**:457—65.
2. **Flammer J,** Orgül S, Costa VP, *et al*. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002;**21**:359—93.
3. **Emre M,** Orgül S, Haufschild T, *et al*. Increased plasma endothelin-1 levels in patients with progressive open angle glaucoma. *Br J Ophthalmol* 2005;**89**:60—3.
4. **Berdahl JP,** Fautsch MP, Stinnett SS, *et al*. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. *Invest Ophthalmol Vis Sci* 2008;**49**:5412—18.
5. **Ren R,** Jonas JB, Tian G, *et al*. Cerebrospinal fluid pressure in glaucoma: a prospective study. *Ophthalmology* 2010;**117**:259—66.
6. **Lam BL,** Glasier CM, Feuer WJ. Subarachnoid fluid of the optic nerve in normal adults. *Ophthalmology* 1997;**104**:1629—33.
7. **Jinkins JR.** Optic hydrops: isolated nerve sheath dilation demonstrated by CT. *AJNR Am J Neuroradiol* 1987;**8**:867—70.
8. **Sutherland AI,** Morris DS, Owen CG, *et al*. Optic nerve sheath diameter, intracranial pressure and acute mountain sickness on Mount Everest: a longitudinal cohort study. *Br J Sports Med* 2008;**42**:183—8.
9. **Soldatos T,** Chatzimichail K, Papathanasiou M, *et al*. Optic nerve sonography: a new window for the non-invasive evaluation of intracranial pressure in brain injury. *Emerg Med J* 2009;**26**:630—4.
10. **Kimberly HH,** Noble VE. Using MRI of the optic nerve sheath to detect elevated intracranial pressure. *Crit Care* 2008;**12**:181.
11. **Andres KH.** On the fine structure of the arachnoidea and dura mater of mammals (In German). *Z Zellforsch Mikrosk Anat* 1967;**79**:272—95.
12. **Anderson DR.** Fine structure and function of ocular tissues. The optic nerve. *Int Ophthalmol Clin* 1973;**13**:229—42.
13. **Hansen HC,** Helmke K. Validation of the optic nerve sheath response to changing cerebrospinal fluid pressure: ultrasound findings during intrathecal infusion tests. *J Neurosurg* 1997;**87**:34—40.
14. **Balasubramanian SA,** Pye DC, Willcox MD. Are proteinases the reason for keratoconus? *Curr Eye Res* 2010;**35**:185—91.
15. **Golubnitschaja O,** Yeghiazaryan K, Liu R, *et al*. Increased expression of matrix metalloproteinases in mononuclear blood cells of normal-tension glaucoma patients. *J Glaucoma* 2004;**13**:66—72.
16. **Watanabe A,** Kinouchi H, Horikoshi T, *et al*. Effect of intracranial pressure on the diameter of the optic nerve sheath. *J Neurosurg* 2008;**109**:255—8.
17. **Killer HE,** Jaggi GP, Flammer J, *et al*. Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional? *Brain* 2007;**130**:514—20.
18. **Jaggi GP,** Harlev M, Ziegler U, *et al*. Cerebrospinal fluid segregation optic neuropathy: an experimental model and a hypothesis. *Br J Ophthalmol* 2010;**94**:1088—93.
19. **Brodsky MC,** Vaphiades M. Magnetic resonance imaging in pseudotumor cerebri. *Ophthalmology* 1998;**105**:1686—93.