Unexpected Effect of Calcium Channel Blockers on the Optic Nerve Compartment Syndrome

Unerwarteter Effekt von Kalziumantagonisten auf Optikus-Kompartiment-Syndrom

Authors K. Konieczka[1], M. G. Todorova[1], R. I. Bojinova[2], T. Binggeli[1], T. N. Chackathayil[1], J. Flammer[1]

Affiliations
[1] University of Basel, Department of Ophthalmology, Basel, Switzerland (Chairman ad interim: Prof. S. Orguel)
[2] McGill University Department of Medicine, Montreal, Canada (Chair: Dr. James Martin)

Key words
- optic nerve compartment syndrome (ONCS)
- Flammer syndrome (FS)
- primary vascular dysregulation (PVD)
- primary open angle glaucoma (POAG)
- calcium channel blockers
- endothelin-1

Schlüsselwörter
- Optikus-Kompartiment-Syndrom (ONCS)
- Flammer-Syndrom (FS)
- primäre vaskuläre Dysregulation (PVD)
- primäres Offenwinkelglaukom (POAG)
- Kalziumantagonisten
- Endothelin-1

Bibliography
DOI http://dx.doi.org/10.1055/s-0042-102619
Klin Monatsbl Augenheilkd 2016; 233: 387–390 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0023-2165

Correspondence
Katarzyna Konieczka, MD
University of Basel
Department of Ophthalmology
Mittlere Strasse 91
4031 Basel
Switzerland
Tel.: + 41/61/2 65 88 03
Fax: + 41/61/2 65 86 52
Katarzyna.Konieczka@usb.ch

Abstract

Background: The optic nerve compartment syndrome is a pathological condition in which cerebrospinal fluid of the subarachnoid space surrounding the optic nerve is partly or totally segregated from the cerebrospinal fluid of the intracranial subarachnoid space, leading – inter alia – to an increase in the diameter of the optic nerve sheath. The pathogenesis of this condition remains unclear. We have observed clinically that optic nerve compartment syndrome often occurs in normal tension glaucoma patients with Flammer syndrome. To treat Flammer syndrome, some glaucoma patients received a low dose of a calcium channel blocker and we analysed whether this treatment also had an effect on the optic nerve compartment syndrome.

Patients and Methods: We retrospectively analysed the data of 10 eyes of seven patients suffering from a combination of primary open angle glaucoma, optic nerve compartment syndrome, and Flammer syndrome. We included subjects who had eye socket echography before and after a few months of therapy with a calcium channel blocker.

Therapy and Results: All patients received a low dose of a calcium channel blocker (nifedipine or amlodipine) to treat Flammer syndrome. As expected, the symptoms of Flammer syndrome were mitigated. To our surprise, the optic nerve compartment syndrome also improved in eight of the 10 eyes (80%), but remained unchanged in the remainder.

Conclusions: To some extent, the optic nerve compartment syndrome is related to the combination of primary open angle glaucoma and Flammer syndrome. On the basis of our results, we hypothesise that treatment of Flammer syndrome may also improve the optic nerve compartment syndrome.

Zusammenfassung

Hintergrund: Das Optikus-Kompartiment-Syndrom ist eine Erkrankung, bei der die freie Kommunikation des Liquors cerebrospinalis des Nervus opticus mit dem Liquor des Zentralnervensystems ganz oder teilweise unterbrochen ist. Dies führt u.a. zur Ausdehnung der Optikus-Scheide. Die Pathogenese dieser Erkrankung ist noch unklar. Klinische Erfahrung lässt vermuten, dass Optikus-Kompartiment-Syndrom bei den Patienten gehäuft vorkommt, die gleichzeitig an Normaldruckglaukom und Flammer-Syndrom leiden. Weil solche Patienten wegen ihrem Flammer-Syndrom mit einem niedrig dosierten Kalziumantagonisten behandelt wurden, analysierten wir retrospektiv, ob diese Behandlung auch auf das Optikus-Kompartiment-Syndrom einen Einfluss hatte.

Patienten und Methoden: Wir haben retrospektiv die Daten von 10 Augen von 7 Patienten mit der Kombination von primärem Offenwinkelglaukom, Optikus-Kompartiment-Syndrom und Flammer-Syndrom analysiert. Eingeschlossen wurden Patienten, bei denen eine echografische Untersuchung der Orbita vor und nach einer Therapie mit einem Kalziumantagonisten durchgeführt wurde. Die Therapie dauerte jeweils einige Monate.

Therapie und Ergebnisse: Wegen dem Flammer-Syndrom hatten die Patienten eine Therapie mit einem niedrig dosiertem Kalziumantagonisten (Nifedipin oder Amlodipin). Unter dieser Therapie haben sich erwartungsgemäss die Symptome und Zeichen vom Flammer-Syndrom verbessert. Überraschenderweise hat sich in diesem Zeitraum auch Optikus-Kompartiment-Syndrom in 8 von 10 Augen (80%) verbessert, in 2 von 10 Augen blieb es hingegen unverändert.

Schlussfolgerungen: Patienten mit einem primären Offenwinkelglaukom und Flammer-Syndrom zeigen gehäuft ein Optikus-Kompartiment-Syn-

drom. Basierend auf den hier beschriebenen Beobachtungen, formulieren wir die Hypothese, dass die Behandlung des Flammer-Syndroms auch eine günstige Wirkung auf das Optikus-Kompartiment-Syndrom hat.

Abbreviations

CCB:	calcium channel blocker
FS:	Flammer syndrome
NTG:	normal tension glaucoma
ONCS:	optic nerve compartment syndrome
ONH:	optic nerve head
POAG:	primary open angle glaucoma
PVD:	primary vascular dysregulation
VF:	visual field

Background

The optic nerve is a white matter tract of the brain within its own subarachnoid space; it is enveloped by the dura mater, the arachnoid, and the pia mater. The subarachnoid space is filled with circulating cerebrospinal fluid that in healthy subjects freely communicates with the chiasmal cistern of the brain. Optic nerve compartment syndrome (ONCS) [1] is a pathological condition in which cerebrospinal fluid is partly or totally segregated between the subarachnoid space surrounding the optic nerve and the intracranial subarachnoid space, leading to extension of the optic nerve sheath diameter and an altered chemical composition of the cerebrospinal fluid. Optic nerve compartmentalization has been demonstrated in patients with papilledema, anterior and posterior ischemic optic neuropathy, and normal tension glaucoma [1,2]. However, the pathogenesis of ONCS remains unclear.

Clinical observations suggest that ONCS often occurs in patients with primary vascular dysregulation (PVD) [3,4], which is the major vascular component of Flammer syndrome (FS) [5]. FS is a risk factor for certain diseases such as glaucoma, particularly for normal tension glaucoma [6]. In this paper, we describe a group of patients suffering from a combination of a) glaucoma, b) ONCS, and c) FS. As treatment for FS, these patients received a low dose of a calcium channel blocker (CCB) [3,7] and we analyzed whether this CCB therapy also influenced ONCS.

Patients and Methods

Included in this retrospective study were 10 eyes of seven patients assessed at the Department of Ophthalmology at the University of Basel. All of our patients had a combination of a) primary open angle glaucoma (POAG), b) ONCS, and c) FS. All patients included underwent a set of examinations.

The presence or absence of ONCS was established based on eye socket echography. We measured the optic nerve width in primary gaze and compared it with the width in the following three additional positions: 30° abduction, total abduction and 30° adduction. A reduction in optic nerve width of 10% or more (in relation to the primary gaze) was considered as a positive sign for ONCS. If the test was positive in 1 of the 3 eye positions, the ONCS was defined as "slight" (+). If the test was positive in 2 of the 3 eye positions – the ONCS was defined as "moderate" (++), and if in 3 of the 3 eye positions – as an "explicit" (+++). Negative tests in all three eye positions were interpreted as absence of the ONCS (−). Echography before and after CCB treatment was performed by an experienced ophthalmologist. FS was diagnosed if both patient's history for FS was positive and the responses of retinal vessels to flicker light in Dynamic Vessel Analysis were pathological [5]. We asked the patients for typical FS symptoms and signs such as cold hands/or feet, low blood pressure, low body weight, reduced feeling of thirst, prolonged sleep onset time, increased smell and pain sensation, migraines, tinnitus, reversible skin blotches, etc.

All patients had visual field (VF) defects due to glaucoma (corresponding to the ONH excavation) and additional VF defects either due to FS or ONCS or both. The relevant parameters are summarized in **Table 1**. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Therapy and Results

Patients were treated with a combination of a CCB (nifedipine or amlodipine) 2–5 mg/a day and magnesium 10–20 mmol/a day. One of the patients was treated only with magnesium (a physiological CCB). All other therapies remained unchanged during the observation period. The follow-up echography was done between two and 24 months after introducing therapy.

As expected, the symptoms of FS improved under treatment with a low dose CCB. Interestingly, ONCS also markedly improved in eight of the 10 eyes (80%), whereas it remained unchanged in two of the 10 eyes (20%) (**Table 2**). The VFs also improved more or less (not shown here). Whether this VF improvement was due to the mitigation of the FS symptoms and signs or due to the improvement of the ONCS cannot be differentiated.

Discussion

In patients presenting with the combination of POAG, ONCS, and FS, we observed that ONCS often improved under therapy with a low dose of a CCB.

Unfortunately, we could not analyze a potential effect of CCBs on ONCS in patients without FS for the following reason: ONCS is currently not an indication for treatment with a CCB and therefore we have very limited clinical experience with treatment of the ONCS in patients without FS. The effect of CCBs on optic nerve width in healthy controls is also not yet known.

The causal relationship between ONCS and glaucoma and between ONCS and FS is not yet clear. We made the clinical observation that patients suffering from both glaucoma and FS, particularly often suffer from ONCS. Now we made the additional observation that treatment of FS may also have a beneficial effect on ONCS. An example of the improvement of the VFs is presented in **Fig. 1**, and an improvement of the ONCS in presented in **Fig. 2**.

At the moment, we can only speculate as to why CCBs might have a beneficial effect on ONCS. The dura of the human optic nerve contains lymphatic vessels [8]. They are assumed to be possible

Patient Nr	Age	Gender	Eye	ONCS	Glaucoma	Other ocular diagnoses
1	41	M	RE	+	POAG	Myopia magna
			LE	++	POAG	Myopia magna
2	63	F	RE	–	NTG	
			LE	+++	NTG	
3	49	M	RE	++	POAG	Status post retinal detachment after cataract extraction, myopia
			LE	+++	POAG	Myopia
4	70	M	RE	+	POAG	
			LE	–	POAG	
5	77	F	RE	+	POAG	Pseudophakia
			LE	–	POAG	Pseudophakia
6	51	M	RE	+	POAG	Myopia
			LE	–	POAG	Myopia
7	68	F	RE	++	POAG	Pseudophakia
			LI	+	POAG	Pseudophakia

Table 1 Ocular and systemic parameters of the patients.

ONCS = optic nerve compartment syndrome, POAG = primary open angle glaucoma, NTG = normal tension glaucoma, RE = right eye, LE = left eye; -= no ONCS, + = slight ONCS, ++ = moderate ONCS, +++ = explicit ONCS

Patient Nr	Eye	ONCS before therapy	ONCS after therapy	Therapy of PVD/FS
1	RE	+	–	amlodine, magnesium
	LE	++	–	amlodine, magnesium
2	LE	+++	–	nifedipine, magnesium
3	RE	++	++	nifedipine, magnesium
	LE	+++	–	nifedipine, magnesium
4	RE	+	–	nifedipine, magnesium
5	RE	+	–	nifedipine, magnesium
6	RE	+	–	magnesium
7	RE	++	+	nifedipine, magnesium
	LE	+	+	nifedipine, magnesium

Table 2 Semi-quantification of the optic nerve compartment syndrome (ONCS) based on the outcomes of eye socket echography before and after treatment with a calcium channel blocker.

Measurements of the optic nerve width were performed in four eye positions: in primary gaze, 30° abduction, total abduction and 30° adduction. A reduction in optic nerve width of 10% or more in relation to the primary gaze was considered positive for presence of ONCS. If the test was positive in 1 of the 3 positions, the ONCS was defined as "slight" (+). If the test was positive in 2 of the 3 positions – the ONCS was defined as "moderate" (++). If the test was positive in 3 of the 3 positions – the ONCS was defined as "explicit" (+++). The negative tests in all 3 positions indicated absence of the ONCS (–).

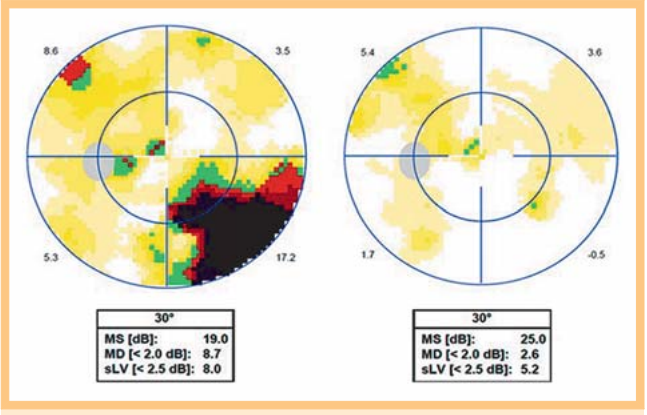

Fig. 1 Example of a visual fields (Octopus, program G2) before (left) and after (right) treatment with a calcium channel blocker.

outflow pathways for cerebrospinal fluid from the subarachnoid space of the optic nerve [9,10]. In *ex vivo* studies, endothelin-1 increased lymphatic vasomotion and caused vasospasm [11]. Nifedipine inhibits contractile activity in human lymphatic vessels [12]. Because CCBs are known to reduce the effect of endothelin-1, we hypothesize that CCBs reduce the contractile activity of the lymphatic capillaries in the dura of the optic nerve and thereby improve the outflow of the cerebrospinal fluid from the subarachnoid space surrounding the optic nerve. This could at least partly explain the improvement of ONCS.

Based on our clinical experience, ONCS in early stages often responds to CCBs. In more advanced stages however, ONCS responds better to steroids than to CCBs, and in late stages the only effective treatment may be an optic nerve sheath fenestration.

Some questions still remain, namely: what is the exact relationship among glaucoma, FS and ONCS, and if CCBs have indeed an effect on ONCS, what is the mechanism?

Conclusion

We observed a certain relationship between POAG, FS and ONCS, and hypothesize that treatment of FS may also have a beneficial effect on ONCS. The outcome of this retrospective analysis needs to be confirmed in prospective studies.

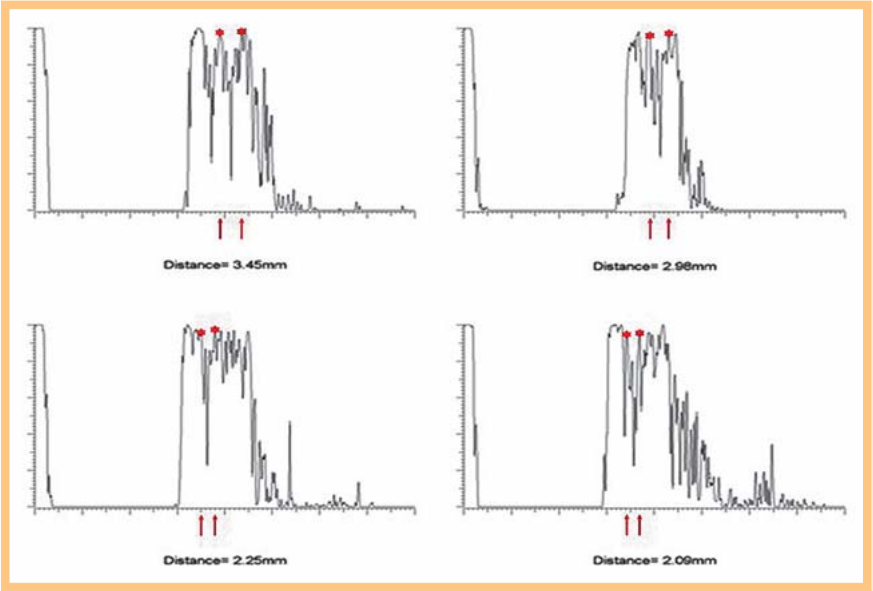

Fig. 2 Examples of ultrasound examination of an eye before and after treatment with a calcium channel blocker. The optic nerve width is marked in red. Top = outcome before treatment, bottom = outcome after treatment, left = primary gaze, right = 30° abduction.

Conflict of Interest

The authors declare having no conflicts of interest.

References

1 *Killer HE.* Compartment syndromes of the optic nerve and open-angle glaucoma. J Glaucoma 2013; 22: S19–S20
2 *Killer HE, Jaggi GP, Flammer J et al.* Is open-angle glaucoma caused by impaired cerebrospinal fluid circulation: around the optic nerve? Clin Experiment Ophthalmol 2008; 36: 308–311
3 *Flammer J, Konieczka K, Flammer AJ.* The primary vascular dysregulation syndrome: implications for eye diseases. EPMA J 2013; 4: 14
4 *Flammer J, Konieczka K, Bruno RM et al.* The eye and the heart. Eur Heart J 2013; 34: 1270–1278
5 *Konieczka K, Ritch R, Traverso CE et al.* Flammer syndrome. EPMA J 2014; 5: 11
6 *Konieczka K, Frankl S, Todorova MG et al.* Unstable oxygen supply and glaucoma. Klin Monbl Augenheilkd 2014; 231: 121–126
7 *Mozaffarieh M, Flammer J.* New insights in the pathogenesis and treatment of normal tension glaucoma. Curr Opin Pharmacol 2013; 13: 43–49
8 *Killer HE, Laeng HR, Groscurth P.* Lymphatic capillaries in the meninges of the human optic nerve. J Neuroophthalmol 1999; 19: 222–228
9 *Killer HE, Jaggi GP, Miller NR et al.* Does immunohistochemistry allow easy detection of lymphatics in the optic nerve sheath? J Histochem Cytochem 2008; 56: 1087–1092
10 *Killer HE.* Production and circulation of cerebrospinal fluid with respect to the subarachnoid space of the optic nerve. J Glaucoma 2013; 22: S8–S10
11 *Zhao J, van Helden DF.* ET-1-associated vasomotion and vasospasm in lymphatic vessels of the guinea-pig mesentery. Br J Pharmacol 2003; 140: 1399–1413
12 *Telinius N, Mohanakumar S, Majgaard J et al.* Human lymphatic vessel contractile activity is inhibited in vitro but not in vivo by the calcium channel blocker nifedipine. J Physiol 2014; 592: 4697–4714