SURVEY OF OPHTHALMOLOGY VOLUME 52 • NUMBER 6 • NOVEMBER 2007

ELSEVIER

What Is the Present Pathogenetic Concept of Glaucomatous Optic Neuropathy?

Josef Flammer, MD, and Maneli Mozaffarieh, MD

Department of Ophthalmology, University Hospital Basel, Basel, Switzerland

Abstract. Glaucomatous optic neuropathy implies loss of neural tissue, activation of glial cells, tissue remodeling, and change of blood flow. The blood flow reduction is not only secondary but has a primary component. Activation of astrocytes leads to an altered microenvironment. An unstable ocular perfusion, either due to IOP fluctuation or a disturbed autoregulation (due to primary vascular dysregulation syndrome) leads to a mild reperfusion injury. The superoxide (O_2^-) anion produced in the mitochondria of the axons, fuses with the nitric oxide (NO) diffusing from the astrocytes, leading to the damaging peroxynitrite ($ONOO^-$). It is possible that the diffusion of endothelin and metalloproteinases to the surrounding of the optic nerve head leads to a local vasoconstriction and thereby increases the risk for venous occlusion and weakens the blood–brain barrier, which in extreme situations results in splinter hemorrhages. Activated retinal astrocytes can be visualized clinically. The involvement of primary vascular dysregulation in the pathogenesis of glaucomatous optic neuropathy may explain why women, as well as Japanese, suffer more often from normal-tension glaucoma. (**Surv Ophthalmol 52**:S162–S173, 2007.

Key words. glaucomatous optic neuropathy • ocular blood flow • oxidative stress • pathogenetic • risk factors • reperfusion damage • vascular dysregulation • oxidative stress

This review intends to summarize the present knowledge of the pathogenesis of glaucomatous damage and tries to build the different pieces of information into a concept.

Why do we need a pathogenetic concept? A pathogenetic concept links the known pheneomenology of a disease with its risk factors in order to understand how these different aspects may work together. There is a dialectic interaction between facts and concepts: On the one hand a concept has to integrate all the different facts published, and on the other hand it is the basis for the formulation of new hypothesis that in the future will be corroborated or rejected. In addition, a pathogenetic concept is also a didactic tool supporting our memory of the different aspects of a disease.

Glaucomatous Optic Neuropathy

Glaucomatous optic neuropathy (GON) comprises of the following mutually dependant basic components: loss of neural tissue, activation of glial cells, tissue remodeling, change of blood flow.

LOSS OF NEURAL TISSUE

Glaucomatous optic neuropathy implies a loss of retinal ganglion cells and their axons, but also a loss of neural cells in the lateral geniculate nucleus and to some extent even of the visual cortex.[51] It is not known whether the retinal ganglion cell loss is due to a primary insult on the cell body or on the axons. The fact that the glaucomatous damage is often bundle-shaped indicates that the primary lesion might be in the optic nerve head. In addition, the upregulation of neural thread proteins in the lymphocytes of glaucoma patients,[39] indicates that axonal lesion is primary of nature.[12] It is also possible, however, that at least at an early stage, the different compartments of the cell might be damaged independently.

Experimental studies indicate a reduction of dendritic complexity before the cells die.[123] Such

0039-6257/07/$–see front matter
doi:10.1016/j.survophthal.2007.08.012

an alteration also occurs in the central nervous system[52] and as a result of aging process.[132]

ACTIVATION OF GLIAL CELLS

Activation of glial cells is a nonspecific response to stress. This can be brought about either through mechanical or ischemic stress or any other type of injury. Such an activation implies on the one hand a change in gene expression such as the upregulation of NOS-2, COX-2, TNF-α,[49] and on the other hand, a change in morphology and to some extent also cell division and migration.

In the optic nerve head the most important glial cells are astrocytes. In experimental animals as well as in humans, astrocytes of the optic nerve head are activated in glaucoma.[59,121,128,129]

In the retina, the important glial cells are the astrocytes, lying in the inner layer of the retina and the Müller cells extending from the inner surface of the retina (inner limiting membrane) up to the photoreceptor layer. Histological and histochemical studies reveal an activation of both astrocytes and Müller cells in the retina of glaucoma patients (Fig. 1). As a consequence of activation the extentions of astrocytes in the retina are less regular and denser and thereby increase light scatter.[119] We have recently demonstrated that this can also be visualized clinically (Fig. 2).[43]

TISSUE REMODELING

A loss of neural tissue (e.g., due to a central retinal artery occlusion or anterior ischemic optic neuropathy [AION]), by itself, leads to a pale and atrophic optic nerve head (ONH) but not really to an excavation of the ONH. It is the ONH excavation, however, which is specific to glaucoma, or the other way around if the ONH is excavated, by definition, we call this corresponding disease glaucoma. Excavation implies on the one hand a loss of tissue elements such as axons, glial cells, and blood vessels,[101,122] and on the other hand a tissue remodeling leading to bowing and compression of the lamina cribrosa. Enzymes important for tissue remodeling, such as metalloproteinases (MMPs), are indeed upregulated both locally in the ONH[2] and systemically in the circulating lymphocytes.[38] Excavation is therefore not just simply the result of mechanical forces but rather the effect of an active biological process.

CHANGE OF OCULAR BLOOD FLOW

There is no doubt that ocular blood flow (OBF) is reduced in glaucomatous eyes.[26] There is, however, some debate about the cause of this reduction and whether it is causal for GON. If a tissue atrophies,

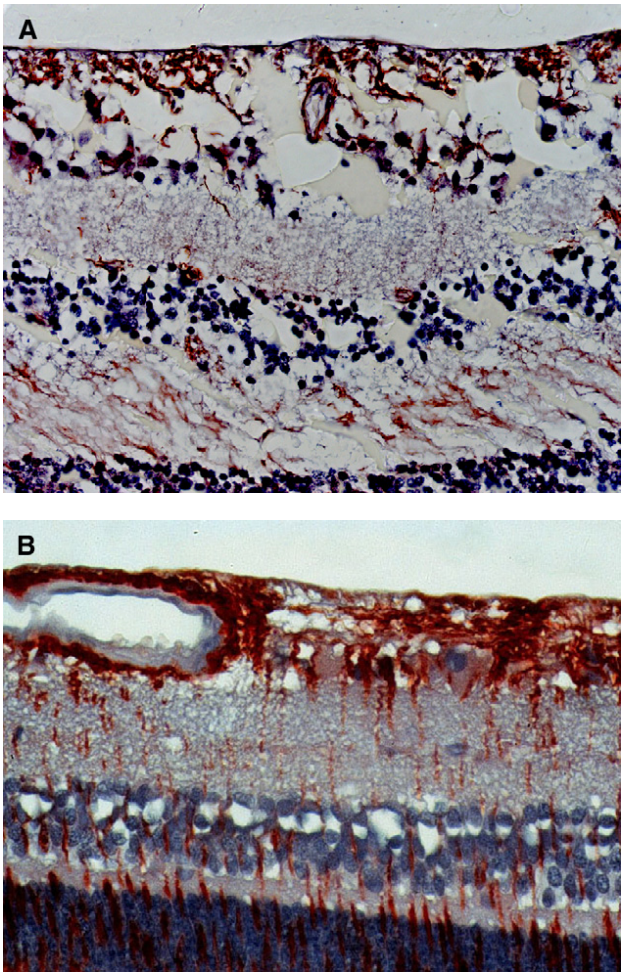

Fig. 1. Activated astrocytes and Müller cells in the retina of a healthy patient (*top*) and a glaucoma patient (*bottom*) (GFAP staining). Courtesy of Peter Meyer, MD.

blood vessels degenerate secondarily.[29] Secondary reduction of ocular blood flow can also be observed in glaucoma. In addition, blood flow is reduced if reduction of perfusion pressure (PP) exceeds the capacity of autoregulation. If autoregulation is disturbed already a mild reduction of PP reduces OBF. Interestingly, however, there is a component of OBF reduction that is independent of the damage (often precedes the damage),[87] and independent of IOP (it is even more pronounced in normal-tension glaucoma [NTG] than high-tension glaucoma [HTG]),[63] and that is not confined to the eye (it can even be observed in the nailfold capillaries).[31] In other words, OBF change can have a structural component, a component related to low PP, and additionally, a primary, quite generalized component. Several independent studies demonstrated that OBF reduction allows a prediction of future progression of damage[30,75,105] and is therefore of major clinical relevance. In addition, signs of ischemia, such as the upregulation of the hypoxia

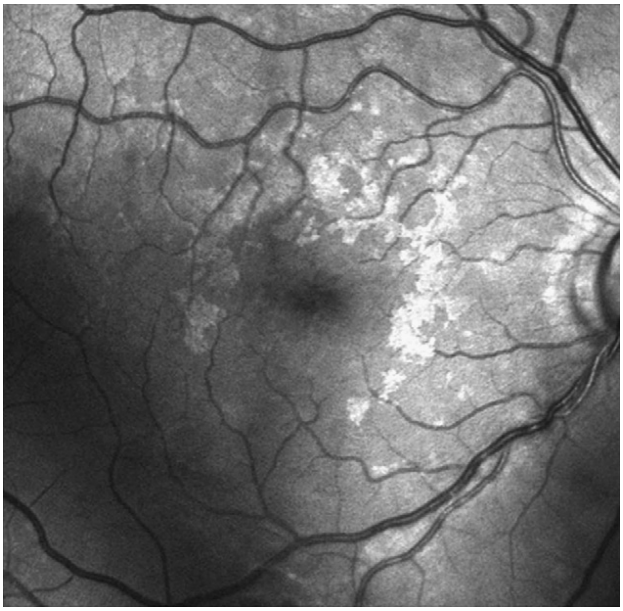

Fig. 2. Activated astrocytes lead to increased light-scattering as demonstrated in a red-free fundus-photo (see Grieshaber et al[43]).

inducible factor 1-α, can be observed in the retina and the ONH of glaucoma patients.[116] In summary, OBF in glaucoma is reduced, leading to subtle ischemic signs. The reduction of OBF is, on the one hand, secondary of nature, either due to low PP or due to structural damage, and on the other hand, primary of nature. This primary component will be discussed.

Risk Factors for Glaucoma

Factors associated with an increase of IOP are not the same as factors associated with the development of GON. Furthermore, factors related to either IOP increase or to damage may not automatically be causal.

RISK FACTORS FOR IOP INCREASE

All factors known to be risk factors for arteriosclerosis are also risk factors for an increase in IOP (age, smoking, dislipidemia, diabetes mellitus, systemic hypertension, male sex, obesity, etc).[26] The association between IOP increase and these factors is relatively weak but nevertheless significant.[89,131] Furthemore, treatment of these risk factors (such as physical exercise, weight loss, and treatment of dislipidemia)[70] reduces IOP slightly. It is still a debate why these risk factors are associated with an increase in IOP. On the one hand, ischemia can damage the outflow system, in particular the trabecular meshwork (TM), and thereby increase IOP.[84] On the other hand, changes brought about at the molecular level in the TM of glaucoma patients have similarities to changes in the vessel walls of artherosclerotic patients, for example, the expression of ELAM-1.[120] This signifies that the two pathologies (of the TM and of the arterial wall) may have common causes and similar pathomechanisms.

RISK FACTORS FOR GON

The best known risk factor for GON is an increase in IOP. But by far not all subjects with an increase in IOP will acquire damage, and a significant number of glaucoma patients never have an increase in IOP. The correlation between IOP level and progression is very weak.[124] Interestingly, some patients acquire damage before they suffer from an increase in IOP.[107] IOP-decreasing therapy, on the average, improves the prognosis in all types of glaucoma patients. The benefit of IOP-lowering treatment, however, is different in the different groups. It is excellent in patients with angle-closure glaucoma,[17] it is good in primary open-angle glaucoma (POAG),[70] and relatively modest in NTG patients.[4]

Furthermore, there is overwhelming evidence that systemic arterial hypotension is a relevant risk factor for GON.[60,61] This has been described for decades.[11,13,16,28,117] Like an elevated IOP, a low blood pressure does not lead to GON in all subjects. This can be explained by a more or less potent OBF autoregulation (see subsequent discussion).

When considering risk factors we have to keep in mind with which kind of patient we are dealing. NTG patients who acquired the damage despite a normal IOP obviously have a very different risk profile than the so-called "ocular hypertensives," who, when entering a study, have not yet acquired damage despite a high IOP. Risk factors for NTG are female sex,[91] race (it occurs more often in Japan than in European or American countries),[111] primary vascular dysregulation (PVD),[24] and low blood pressure.[60,61] Whether corneal thickness plays a role is at the moment open to debate.[103,125] Risk factors for conversion from OHT to POAG are, besides an increased IOP, a thin cornea,[9] age, and a pre-existing alteration of the ONH or visual field; diabetes, on the other hand, seems to be a significant protective factor.[40]

Ocular Blood Flow and Glaucomatous Optic Neuropathy

Whether OBF plays a role in the pathogenesis of GON has often been discussed in the past. For decades the literature remained controversial.

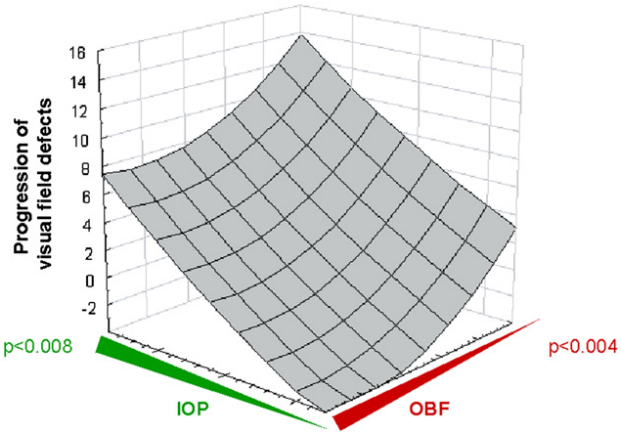

Fig. 3. The higher the intraocular pressure, the higher the chance of progression. Likewise, the lower the ocular blood flow, the higher the chance of progression. (Satilmis M et al.[105])

IS OBF LINKED TO GON?

We already mentioned that in glaucoma patients, on the average, OBF is reduced in all parts of the eye, including the iris, retina, choroid, ONH, and retroocular vessels.[26] It is also clear from several studies that OBF has a predictive value (Fig. 3). But does a reduced OBF indeed lead to GON? Reduction of OBF in experimental animals, for example by a local application of endothelin, leads to an atrophic optic nerve head but only mild excavation. OBF is also reduced in conditions other than glaucoma. In multiple sclerosis, for example, the high level of circulating endothelin[57] leads to a marked reduction of OBF.[94] These patients, however, either have a normal or pale optic nerve head but do not excavate more often than healthy controls. Even patients with a carotid artery occlusion do not develop NTG significantly more often than healthy controls.[98]

We are therefore faced with the seemingly contradictory situation that, whereas in glaucoma blood flow is reduced and this reduction has a relative strong predictive power, the OBF reduction (as shown in experimental studies and in other clinical conditions), although leading to some atrophy, does not lead to glaucomatous damage. To explain this paradox we formulated the working hypothesis that the link between glaucoma and OBF is not so much the blood flow reduction but rather the instability of OBF leading to a repeated mild reperfusion injury (RI).[19]

THE INSTABILITY OF OBF

Before we discuss why an unstable oxygen supply may contribute to the development of GON, we shall discuss the clinical conditions leading to an unstable OBF. OBF is unstable if either IOP fluctuates at such a high level or blood pressure fluctuates at such a low level that it exceeds the capacity of a normal autoregulation. The same OBF instability occurs if IOP fluctuates in a normal or mildly increased range or if blood pressure fluctuates in a normal or mildly decreased range(if autoregulation is disturbed). Indeed, IOP fluctuation, blood pressure dips, and disturbed autoregulation have all clearly been linked to progression of damage.

Incidentally, it has been known for decades that IOP fluctuation is a stronger risk factor than a stable increase in IOP, both for the progression of scotomas,[88] as well as for the diffuse reduction of differential light sensitivity in OHT patients.[22] This has been confirmed in recent studies.[6] Likewise, blood pressure fluctuation (for example nocturnal dips) is a more relevant risk factor than a stable low blood pressure.[41] Again, in terms of circulation, the effect of IOP fluctuating on a high level in subjects with a normal autoregulation is similar to the effect of IOP fluctuating in the normal range in a patient with disturbed autoregulation. Indeed, it has been demonstrated in several studies that the majority of patients that progress despite a normal or normalized IOP have an autoregulation that is, on the average, weaker than in normals or in glaucoma patients stabilized after IOP reduction.[35]

The main cause for the disturbed autoregulation of OBF is the PVD syndrome.[34] We will discuss this syndrome in this context briefly, but a detailed description is given by Grieshaber et al in this issue.[45]

THE REGULATION OF OBF

Blood flow in our body is highly regulated in order to adapt to the local needs. The overall perfusion is determined by the cardiac output. The distribution of this cardiac output to the different organs and parts of the organs is regulated by the relative resistance to flow—in other words, by the regulation of the size of the vessels. The size of the vessels, in turn, is regulated by many different systems like autonomic innervation, circulating hormones, and vasoactive factors released by endothelial cells.

Different vascular beds in the eye are regulated differently. The retinal vessels behave similarly to brain vessels with the exception that they do not have any automonic innervation.[78] The size of the retinal vessels is regulated by the endothelial cells compensating, for example, the variation in perfusion pressure (autoregulation), and by the neural retinal tissue providing adaption to retinal activity

(the so-called neural vascular coupling). In contrast, choroidal vessels are regulated by a dense autonomic innervation.[3,73] Besides providing oxygen to the deeper layers of the retina, one of the additional tasks of choroidal blood flow regulation is to keep temperature in the back of the eye constant.

The circulation in the ONH is somewhat similar to the circulation in the retina with some anatomical and physiological particularities: whereas the arterial supply is provided through the ciliary circulation, the venous drainage occurs through the retinal veins. The prelaminar area has only a few arterioles and venules, but instead many long capillaries. The size of the vessels in the ONH, and to some extent also, the vessels around the ONH, are highly influenced by circulating hormones diffusing from the fenestrated choriocapillaries into the ONH and its surroundings.[108,109]

Considering this very extended and sophisticated regulation, it is not surprising that under certain conditions this regulation may be disturbed. To describe this situation we introduced the term *vascular dysregulation*.[24] As mentioned before, blood flow is regulated to adapt to the blood supply according to the local needs. These needs include oxygen supply, detoxification of waste products, but also adaptation of temperature and volume, and so forth. Circulatory problems occur if the vessels themselves are diseased, for example, by inflammation, artherosclerosis, or thrombosis. But even anatomically healthy vessels cause problems if given incorrect information (e.g., from endothelial cells). This is known as vascular dysregulation.

THE VASCULAR DYSREGULATION SYNDROME

We differentiate between a primary vascular dysregulation (PVD) and a secondary vascular dysregulation (SVD).[27] Whereas PVD is an inborn predisposition to respond differently to various stimuli, an SVD is a local or systemic dysregulation as a consequence of an underlying disease. A number of diseases, including autoimmune diseases such as multiple sclerosis[57,94] or rheumatoid arthritis,[96] lead to a marked increase of circulating endothelin. Increased levels of endothelin, in turn, reduce OBF, but do not interfere with autoregulation. Therefore, SVD reduces baseline OBF without having a major impact on autoregulation.[34] In contrast, PVD, although only mildly influencing baseline OBF, has a major impact on autoregulation. Therefore fluctuating perfusion pressure leads to a fluctuation of OBF in patients with PVD but less so in patients with SVD. This explains why PVD is a major risk factor for GON whereas SVD remains a minor risk factor.[27]

PVD has an inherited component. Subjects often indicate that their parents, in particular their mothers, also suffered from cold hands and other symptoms. It typically manifests itself first during puberty and declines with age. In females the symptoms often mitigate after menopause but can increase again when patients are treated with estrogen-replacement therapy.[21]

There is no gold standard for the diagnosis of PVD although cold provocation in nailfold capillaromicroscopy is the most often used diagnostic test.[104] There are, however, many clinical signs that points towards PVD: these subjects often have cold extremities like cold hands or feet,[54] they tend to have normal or low body mass index,[33] the feeling of thirst is often reduced (they drink because they know they have to drink and not so much because they are thirsty),[114] they tend to have low blood pressure especially when they are young,[92] and they more often suffer from migraines than non-PVD subjects[32] (although PVD and migraine are two distinct entities). PVD subjects have often an altered drug sensitivity due to differential expression of ABC transporter proteins.[127] The sensitivity for certain groups of drugs such as calcium channel blockers and systemic beta-blockers is increased. This means that they require lower doses of these drugs to achieve the same effects and to avoid side effects. Sensitivity is normal or rather decreased for certain other drugs such as painkillers. PVD patients have a good sense of smell. They have, on average, a longer sleep-onset time, especially when they are cold.[95] They often have a meticulous personality and are successful in their professions.[21]

In terms of circulation, they respond more strongly with vasoconstriction to mechanical stress (e.g., whiplash trauma), psychological stress, or cold.[27] Unlike others, in PVD patients OBF is correlated with peripheral circulation, for example, in the fingers.[56] In terms of retinal circulation, PVD subjects respond less to flickering light (neurovascular coupling),[48] they have increased spatial irregularities,[67] and they have fast pulse waves, indicating higher stiffness.[47] Especially relevant in this context is the fact that in healthy PVD patients autoregulation is disturbed,[34] as is the case in glaucoma patients progressing despite a normalized IOP.[35]

We like to emphasize that most people with PVD are healthy. They do, however, have a higher chance for certain diseases. This includes the risk of AION,[62] vein occlusions,[77] central serous chorioretinopathy,[100] Susac syndrome,[25] and glaucoma.[23,31]

Why does PVD occur more often in women than men? The fact that the symptom manifests in puberty and decreases with age indicates that hormones, in particular estrogens, play a role. This

explains why the syndrome can aggravate when estrogen is substituted after menopause.[21] Men with PVD tend to more often suffer from serous chorioretinopathy. Most probably testosterone plays a role for this manifestation.[44]

THE LINK BETWEEN PVD AND OTHER RISK FACTORS FOR GON

Considering PVD as a risk factor for GON explains why women suffer more often from NTG than men[91] (women are more likely to be disposed to PVD); why migraine is a risk factor for GON[97] (patients suffering from PVD also suffer more often from migraines[32]); why Japanese or Koreans more often suffer from NTG,[111] (Japanese and Koreans suffer significantly more often from PVD[7,79]).

The observation that PVD is also a main cause for splinter hemorrhages[46] at the border of the ONH explains why ONH hemorrhages occur more often in NTG than in HTG patients,[66] and more often in women than in men. The role of PVD also explains why certain patients with a low blood pressure acquire damage whereas others do not.[20] If systemic hypotension is due to a failure of the autonomic nervous system (for example in patients with Shy-Drager syndrome or in patients with diabetic polyneuropathy), the autoregulation is still functioning and therefore compensates for low perfusion pressure. If, however, low BP is due to PVD, the same subjects also suffer from a disturbed autoregulation rendering them sensitive to a drop in perfusion pressure. The main cause of low blood pressure in PVD subjects is an increased loss of salt in the proximal tubuli of the kidney due to a mild stimulation of the endothelin B-receptors.[90]

Considering PVD as a risk factor for GON, we can also explain why glaucoma patients (in particular, NTG patients) suffer more often from silent myocardial ischemia than healthy controls.[118] PVD is, namely, also a cause for silent myocardial ischemia.

In summary, the hypothesis of PVD being a risk factor for GON explains why and how a number of other risk factors play a role.

REPERFUSION DAMAGE

A marked reduction of blood supply to an organ leads to an infarction. This can also occur in the eye (including the ONH), as in any other organ. This can be due to an inflammation of blood vessels, or due to artherosclerosis. If blood flow reduction is less extensive and reversible a so-called reperfusion injury (RI) occurs. RI refers to damage to tissues caused when blood supply returns to the tissue after a period of ischemia. The absence of oxygen and nutrients from tissue creates a condition in which the restoration of circulation results in inflammation and oxidative damage rather than restoration of normal function. In a major RI (as it can occur, for example, in organ transplantation), a major inflammatory response and tissue damage occurs. White blood cells carried to the area by the newly returning blood release numerous inflammatory factors including interleukins or free radicals in response to tissue damage. The restored blood flow re-introducing oxygen thereby damages proteins, lipids, and the plasma membrane. The damage to the cells, in turn, causes the release of more free radicals. In prolonged ischemia hypoxanthin is formed as a result of the breakdown of ATP and the enzyme xanthine dehydrogenase is converted to xanthine oxidase. This also results in molecular oxygen being converted to the highly reactive superoxide and hydroxyl radicals.[53,64]

Unlike these major events, the RI in glaucoma patients and especially in the ONH is very mild but occurs repeatedly.[19] In addition, the CNS lacks xanthine oxidase. The major source of the oxidative stress in reperfusion, therefore, stems from the mitochondondria, which are very crowded in the ONH due to high energy consumption in these nerve fibers lacking myelin sheaths.[5] The assumption of RI being involved in the pathogenesis also explains why sleep apnea,[81] or reversible shock-like states,[15] can lead to GON.

In summary, the instability of OBF leads to a mild, but repeated, RI increasing the oxidative stress, particularly in the ONH with consequences described subsequently.

THE ROLE OF OXIDATIVE STRESS

The production of reactive oxygen species (ROS) higher than the capacity to cope with them leads to a so-called oxidative stress. Oxidative stress is involved in both inflammatory and degenerative diseases including glaucoma. The corresponding knowledge,[115] as well as the potential therapeutic consequences,[83] have recently been reviewed. We therefore focus on the question whether the effect of oxidative stress can be demonstrated and measured in glaucoma patients.

We cannot separate the physiology or the pathophysiology of an organ such as the eye from the rest of the body.[93] Glaucoma therefore can be considered as a sick eye in a more or less sick body. It is therefore feasible to also observe changes in the blood of glaucoma patients[37,130] that might ultimately be used as biomarkers.[36]

LYMPHOCYTES AS BIOMARKERS

To test our hypothesis of an oxidative stress due to RI we analyzed the gene expression of lymphocytes of glaucoma patients.

Why lymphocytes?

It has been shown that lymphocytes change gene expression in brain injury,[12] or in neurodegenerative diseases such as Alzheimer disease.[69] In addition, astrocytes of glaucoma patients express MHC-II complexes, indicating that there might be some communication between astrocytes and the immune system.[128] In addition, during reperfusion the communication between lymphocytes and the corresponding endothelial cells is intensified.[58]

As a proof of principle we analyzed the expression of the neural thread protein (NTP) genes. The NTP is produced during embryology to guide the growth of axons. It is therefore only minimally expressed in adults. If however, in experimental animals axons in the CNS are cut, the lymphocytes produce NTP. Interestingly, this is also the case in glaucoma patients.[39] Based on this observation we used lymphocytes to test whether the pattern of changes of gene expression confirms the assumption of an oxidative stress. If oxidative stress does occur (due to RI) we would expect increased number of DNA breaks, an upregulation of ET-1, an upregulation of MMP-9, and increased activity of proteosomes. This is indeed the case.

DNA breaks can be measured with comet assay analysis. This analysis revealed an increase in DNA breaks in glaucoma patients.[80]

The oxidative stress also leads to an unspecific increase in ET-1. Indeed several (but not all)[68] studies have demonstrated an increase in ET, especially in patients that progress despite normalized IOP.[18]

MMP-2 and MMP-9 are upregulated in the ONH of glaucoma patients.[2] We have demonstrated an upregulation of MMP-9 even in circulating lymphocytes.[38] The upregulation of MMP-9 not only fits the hypothesis of RI, but is also explains important parts of the pathogenetic process.

In oxidative stress all kinds of macromolecules are attacked, including proteins. Unlike damaged DNA, damaged proteins cannot be repaired. Nature has developed sophisticated methods to eliminate damaged intracellular proteins. These proteins are first marked by ubiquitin and then pulled electrostatically into the proteosomes where they are cut in pieces, which are then recycled. The activity of the proteosomes gives an indirect measure of proteins damaged. Indeed, the expression of 20S proteosome alpha subunit is upregulated in glaucoma,[126] further supporting the hypothesis of an oxidative stress.

In summary, the changes observed in lymphocytes of glaucoma patients clearly support the hypothesis of an increased oxidative stress most likely due to a mild repeated RI.

THE ROLE OF METALLOPROTEINASES

Metalloproteinases (MMPs) are enzymes that digest extracellular matrix. Because they contain a metal atom (mostly zinc) in their active center, they are called MMPs. Extracellular matrix is subjected to a permanent turn-over. Such a turnover is markedly increased during embryology but also in many physiological and pathophysiological conditions. MMP-2 and MMP-9 are upregulated in the astrocytes of the ONH of glaucoma patients and, as described previously, MMP-9 is produced by lymphocytes of glaucoma patients. MMPs, in particular MMP-9, are involved in many processes relevant for glaucoma.

MMP-9 is a prerequisite for apoptosis of retinal ganglion cells.[50] In MMP-9 knock-out mice,[10] as well as in animals in which MMP-9 is pharmacologically inhibited, the retinal ganglion cells do not die by apoptosis.[74] Furthermore, MMP-9 is involved in tissue remodeling of the ONH and thereby contributes to the change of the shape of the lamina cribrosa.[65] MMP-9 is also involved in the breakdown of the blood–brain barrier of the ONH that in extreme cases may lead to splinter hemorrhages.[46]

As described previously, the cause of MMP-9 upregulation most probably is the oxidative stress due to RI. The fact that MMP-9 is also increased in patients with sleep apnea,[113] which may also be a risk factor for GON, supports this hypothesis. Interestingly, MMP-9 is also increased in patients with floppy eyelid syndrome, which, in turn, can be a consequence of sleep apnea.[76,106] Floppy eyelid syndrome has been described as a risk factor for NTG and occurs more often in patients with sleep apnea.[1] Efficient treatment of sleep apnea reduces MMP-9 and leads to some reversibility of floppy eyelid syndrome.

MMPs potentially also influence corneal thickness. Thin cornea seems to be a risk factor for GON.[8] Interestingly, it has been reported that glaucoma patients with thin cornea have significantly more vascular risk factors than patients with a thick cornea.[14]

The Pathogenetic Concept of GON

Among others, there are two major pathogenetic components: damage to the axons and the activation of the astrocytes (Fig. 4).

Mechanical stress (e.g., by an increase in IOP) activates astrocytes by stimulating the epidermal growth factor receptor (EGFR).[71] Astrocytes, however, are also activated by endothelin, which is upregulated as a consequence of cell stress—for example, by RI.

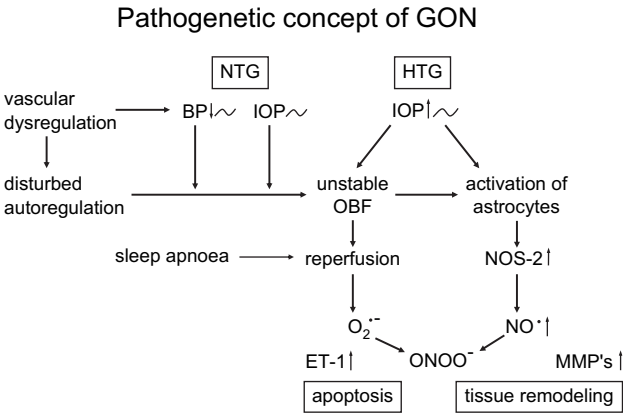

Fig. 4. Simplified pathogenetic concept of glaucomatous optic neuropathy. Unstable ocular perfusion leads to a reperfusion damage in the axons. In parallel the glial cells are activated leading to an altered micro-environment.

The major insult to the axons is brought about by RI, which is the consequence of an unstable oxygen supply (due to unstable ocular perfusion). The ocular perfusion is unstable if either the IOP fluctuates at a high level (HTG) or even due to IOP fluctuating in the normal range in cases with a disturbed autoregulation. The main cause for a disturbed autoregulation is a systemic PVD. Blood pressure fluctuation can also lead to unstable ocular perfusion, especially when combined with disturbed autoregulation. This is the case when low blood pressure is due to PVD.

The activation of the astrocytes alters the local microenvironment in the ONH and its surroundings. This also includes a high level of endothelin, which not only can further reduce circulation but also interferes with axonal transport.[112] The upregulation of NOS-2 leads to an increase in NO concentration. NO is a small free radical that can

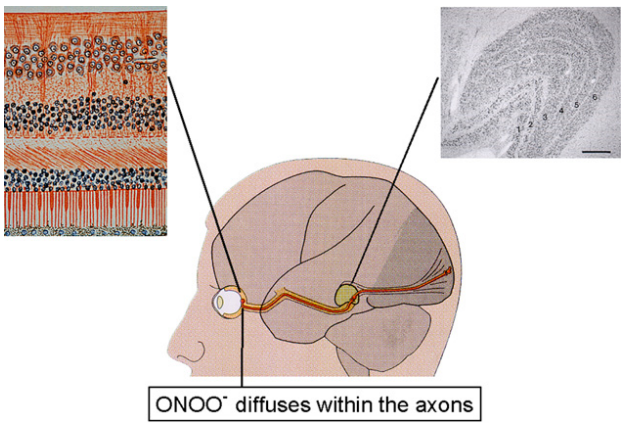

Fig. 5. The simultaneous increase of NO and O_2^- leads to the formation of peroxynitrite.[85] This may diffuse both into the retina and into the lateral geniculate nucleus.

easily diffuse to neighboring cells. Nevertheless due to the very short half-life the effect is limited to neighboring cells. NO itself is not damaging. If, however, NO also reaches the axons where there is a high concentration of superoxide radicals (O_2^-) as a result of RI, it leads to the formation of peroxynitirte ($ONOO^-$).[55,86] Both superoxide and peroxynitrite are trapped within the axons, and they can, however, diffuse along the axons both towards the retina and towards the lateral gniculate nucleus inducing apoptosis of neural cells (Fig. 5). The nitrosylation of SH-groups, even in the lateral geniculate nucleus indicates, that indeed, peroxynitrite plays a role.[72]

In parallel to the loss of retinal ganglion cells and their axons, tissue remodeling takes place, which is not only a consequence of mechanical forces, but also of an active biological process including the effect of MMPs.

The diffusion of endothelin and MMP-9 (which both occur in increased concentration in the circulating blood), diffuses from the choroid into the surrounding of the ONH leading to both vasoconstriction[102] and weakening of the blood–brain barrier, which in extreme situations even leads to small splinter hemorrhages.[46] A peripapillary atrophy facilitates the diffusion of ET and MMP, explaining the correlation with the frequency of hemorrhages.[110]

Mechanical stress,[133] but even more the RI,[99] leads to activation of astrocytes and Müller cells also in the retina, a phenomenon that can be seen clinically.[43]

Risk factors such as PVD are often present decades before GON develops. How can this be explained? An unstable OBF leads to an increased production of ROS. Young people, however, can cope with this well. If ROS production exceeds this capacity, however, oxidative stress damages different molecules. As long as nature is capable of repairing damaged molecules (e.g., DNA) or eliminating damaged molecules (proteins via proteosomes) no major structural damage occurs. But if oxidative stress exceeds the capacity of repair mechanisms, structural damage sums up and leads, finally, to a clinically relevant damage that we call a disease, such as glaucoma.

Understanding these different pathophysiological components may lead to new additional therapeutical options, which are discussed by Mozaffarieh et al in this issue.[82]

Method of Literature Search

A systematic search of the Medline database using the PubMed Web site for the years 1966 through

January 2007 was conducted using the following key words: *POAG, pathogenesis, glaucoma, vasospasm, vascular dysregulation, autoregulation, ischemia, endothelin, glaucomatous optic neuropathy, glial cells, tissue remodeling, ocular blood flow, risk factors, trabecular meshwork, primary vascular dysregulation, nitric oxide synthase, secondary vascular dysregulation, reperfusion damage, oxidative stress, free radicals, migraines, perfusion pressure, metalloproteinase.* All articles read were in English and German, and when articles in other languages were of relevance, their abstracts in English were read. The Old Medline was searched for articles published between 1953 and 1965 using the same keywords.

References

1. Abdal H, Pizzimenti JJ, Purvis CC: The eye in sleep apnea syndrome. Sleep Med 7:107–15, 2006
2. Agapova OA, Ricard CS, Salvador-Silva M, et al: Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human optic nerve head astrocytes. Glia 33:205–16, 2001
3. Albrecht MC, Kaufman PL, Lutjen-Drecoll E, et al: Choroidal innervation and optic neuropathy in macacque monkeys with laser- or anterior chamber perfusion-induced short-term elevation of intraocular pressure. Exp Eye Res 82:1060–7, 2006
4. Anderson DR, Drance SM, Schulzer M, et al: Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. Am J Ophthalmol 136:820–9, 2003
5. Andrews RM, Griffiths PG, Johnson MA, et al: Histochemical localisation of mitochondrial enzyme activity in human optic nerve and retina. Br J Ophthalmol 83:231–5, 1999
6. Asrani S, Zeimer R, Wilensky J, et al: Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma 9:134–42, 2000
7. Beltrame JF, Sasayama S, Maseri A: Racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients. J Am Coll Cardiol 33: 1442–52, 1999
8. Brandt JD: Corneal thickness in glaucoma screening, diagnosis, and management. Curr Opin Ophthalmol 15: 85–9, 2004
9. Brandt JD, Beiser JA, Gordon MO, et al: Central corneal thickness and measured IOP response to topical ocular hypotensive medication in the Ocular Hypertension Treatment Study. Am J Ophthalmol 138:717–22, 2004
10. Chintala SK, Zhang X, Austin JS, et al: Deficiency in matrix metalloproteinase gelatinase B (MMP-9) protects against retinal ganglion cell death after optic nerve ligation. J Biol Chem 277:47461–8, 2002
11. Collignon N, Dewe W, Guillaume S, et al: Ambulatory blood pressure monitoring in glaucoma patients. The nocturnal systolic dip and its relationship with disease progression. Int Ophthalmol 22:19–25, 1998
12. de la Monte SM, Garner W, Wands JR: Neuronal thread protein gene modulation with cerebral infarction. J Cereb Blood Flow Metab 17:623–35, 1997
13. Demailly P, Cambien F, Plouin PF, et al: Do patients with low tension glaucoma have particular cardiovascular characteristics? Ophthalmologica 188:65–75, 1984
14. Doyle A, Bensaid A, Lachkar Y: Central corneal thickness and vascular risk factors in normal tension glaucoma. Acta Ophthalmol Scand 83:191–5, 2005
15. Drance SM: The visual field of low tension glaucoma and shock-induced optic neuropathy. Arch Ophthalmol 95: 1359–61, 1977
16. Drance SM, Morgan RW, Sweeney VP: Shock-induced optic neuropathy: a cause of nonprogressive glaucoma. N Engl J Med 288:392–5, 1973
17. Duan XM, Zou YH, Liu XL, et al: [Visual fields changes in chronic angle closure glaucoma patients after their intraocular pressures were well controlled]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 26:410–4, 2004
18. Emre M, Orgül S, Haufschild T, et al: Increased plasma endothelin-1 levels in patients with progressive open angle glaucoma. Br J Ophthalmol 89:60–3, 2005
19. Flammer J: [Glaucomatous optic neuropathy: a reperfusion injury]. Klin Monatsbl Augenheilkd 218:290–1, 2001
20. Flammer J: The vascular concept of glaucoma. Surv Ophthalmol 38(Suppl):S3–6, 1994
21. Flammer J: Glaucoma: a guide for patients. Seattle, WA, Bern, Hofgrefe and Huber Publishers, 2006
22. Flammer J, Eppler E, Niesel P: [Quantitative perimetry in the glaucoma patient without local visual field defects]. Graefes Arch Clin Exp Ophthalmol 219:92–4, 1982
23. Flammer J, Guthauser U, Mahler F: Do ocular vasospasms help cause normal tension glaucoma? Doc Ophthalmol Proc Series 49:397–9, 1987
24. Flammer J, Haefliger IO, Orgül S, et al: Vascular dysregulation: a principal risk factor for glaucomatous damage? J Glaucoma 8:212–9, 1999
25. Flammer J, Kaiser H, Haufschild T: Susac syndrome: a vasospastic disorder? Eur J Ophthalmol 11:175–9, 2001
26. Flammer J, Orgül S, Costa VP, et al: The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 21:359–93, 2002
27. Flammer J, Pache M, Resink T: Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. Prog Retin Eye Res 20:319–49, 2001
28. Freyler H, Novack GD, Menapace R, et al: [Comparison of the effectiveness and safety of levobunolol and timolol in ocular hypertension and chronic open-angle glaucoma]. Klin Monatsbl Augenheilkd 193:257–60, 1988
29. Fujino H, Kohzuki H, Takeda I, et al: Regression of capillary network in atrophied soleus muscle induced by hindlimb unweighting. J Appl Physiol 98:1407–13, 2005
30. Galassi F, Sodi A, Ucci F, et al: Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. Arch Ophthalmol 121:1711–5, 2003
31. Gasser P, Flammer J: Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. Am J Ophthalmol 111:585–8, 1991
32. Gasser P, Meienberg O: Finger microcirculation in classical migraine. A video-microscopic study of nailfold capillaries. Eur Neurol 31:168–71, 1991
33. Gasser P, Stümpfig D, Schötzau A, et al: Body mass index in glaucoma. J Glaucoma 8:8–11, 1999
34. Gherghel D, Orgül S, Dubler B, et al: Is vascular regulation in the central retinal artery altered in persons with vasospasm? Arch Ophthalmol 117:1359–62, 1999
35. Gherghel D, Orgül S, Gugleta K, et al: Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with glaucoma with progressive damage. Am J Ophthalmol 130:597–605, 2000
36. Golubnitschaja O, Flammer J, et al: What are the biomarkers for glaucoma? Surv Ophthalmol 52(Suppl 2). S155–S161, 2007
37. Golubnitschaja O, Wunderlich K, Decker C, et al: Molecular imaging of perfusion disturbances in glaucoma. Amino Acids 23:293–9, 2002
38. Golubnitschaja O, Yeghiazaryan K, Liu R, et al: Increased expression of matrix metalloproteinases in mononuclear blood cells of normal-tension glaucoma patients. J Glaucoma 13:66–72, 2004
39. Golubnitschaja-Labudova O, Liu R, Decker C, et al: Altered gene expression in lymphocytes of patients with normal-tension glaucoma. Curr Eye Res 21:867–76, 2000

40. Gordon MO, Beiser JA, Brandt JD, et al: The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 120:714–20, discussion 829–30, 2002
41. Graham SL, Drance SM, Wijsman K, et al: Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. Ophthalmology 102:61–9, 1995
42. Grieshaber MC, Flammer J: Blood flow in glaucoma. Curr Opin Ophthalmol 16:79–83, 2005
43. Grieshaber MC, Orgul S, Schoetzau A, et al: Relationship between retinal glial cell activation in glaucoma and vascular dysregulation. J Glaucoma 16: 215–9, 2007
44. Grieshaber MC, Staub JJ, Flammer J: The potential role of testosterone in central serous chorioretinopathy. Br J Ophthalmol 91:118–9, 2007
45. Grieshaber MC, Sunaric G, Flammer J: What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol 52(Suppl 2). xxx–xxx, 2007
46. Grieshaber MC, Terhorst T, Flammer J: The pathogenesis of optic disc splinter haemorrhages: a new hypothesis. Acta Ophthalmol Scand 84:62–8, 2006
47. Gugleta K, Kochkorov A, Katamay R, et al: On pulse-wave propagation in the ocular circulation. Invest Ophthalmol Vis Sci 47:4019–25, 2006
48. Gugleta K, Zawinka C, Rickenbacher I, et al: Analysis of retinal vasodilation after flicker light stimulation in relation to vasospastic propensity. Invest Ophthalmol Vis Sci 47:4034–41, 2006
49. Guo G, Bhat NR: Hypoxia/reoxygenation differentially modulates NF-kappaB activation and iNOS expression in astrocytes and microglia. Antioxid Redox Signal 8:911–8, 2006
50. Guo L, Moss SE, Alexander RA, et al: Retinal ganglion cell apoptosis in glaucoma is related to intraocular pressure and IOP-induced effects on extracellular matrix. Invest Ophthalmol Vis Sci 46:175–82, 2005
51. Gupta N, Ang LC, Noël de Tilly L, et al: Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. Br J Ophthalmol 90: 674–8, 2006
52. Gupta N, Ly T, Zhang Q, et al: Chronic ocular hypertension induces dendrite pathology in the lateral geniculate nucleus of the brain. Exp Eye Res 84:176–84, 2007
53. Gute DC, Ishida T, Yarimizu K, et al: Inflammatory responses to ischemia and reperfusion in skeletal muscle. Mol Cell Biochem 179:169–87, 1998
54. Guthauser U, Flammer J, Mahler F: The relationship between digital and ocular vasospasm. Graefes Arch Clin Exp Ophthalmol 226:224–6, 1988
55. Haefliger IO, Dettmann E, Liu R, et al: Potential role of nitric oxide and endothelin in the pathogenesis of glaucoma. Surv Ophthalmol 43(Suppl 1):S51–8, 1999
56. Hafez AS, Bizzarro R, Descovich D, et al: Correlation between finger blood flow and changes in optic nerve head blood flow following therapeutic intraocular pressure reduction. J Glaucoma 14:448–54, 2005
57. Haufschild T, Shaw SG, Kesselring J, et al: Increased endothelin-1 plasma levels in patients with multiple sclerosis. J Neuroophthalmol 21:37–8, 2001
58. He P, Zhang H, Zhu L, et al: Leukocyte-platelet aggregate adhesion and vascular permeability in intact microvessels: role of activated endothelial cells. Am J Physiol Heart Circ Physiol 291:H591–9, 2006
59. Hernandez MR, Agapova OA, Yang P, et al: Differential gene expression in astrocytes from human normal and glaucomatous optic nerve head analyzed by cDNA microarray. Glia 38:45–64, 2002
60. Kaiser HJ, Flammer J: Systemic Hypotension: a risk factor for glaucomatous damage? Ophthalmologica 203:15–8, 1991
61. Kaiser HJ, Flammer J, Graf T, et al: Systemic blood pressure in glaucoma patients. Graefes Arch Clin Exp Ophthalmol 231:677–80, 1993
62. Kaiser HJ, Flammer J, Messerli J, et al: Vasospasm-a risk factor for nonarteric anterior ischaemic optic neuropathy? Neuro Ophthalmol 16:5–10, 1996
63. Kaiser HJ, Schoetzau A, Stümpfig D, et al: Blood-flow velocities of the extraocular vessels in patients with high-tension and normal-tension primary open-angle glaucoma. Am J Ophthalmol 123:320–7, 1997
64. Karageuzyan KG: Oxidative stress in the molecular mechanism of pathogenesis at different diseased states of organism in clinics and experiment. Curr Drug Targets Inflamm Allergy 4:85–98, 2005
65. Kirwan RP, Crean JK, Fenerty CH, et al: Effect of cyclical mechanical stretch and exogenous transforming growth factor-beta1 on matrix metalloproteinase-2 activity in lamina cribrosa cells from the human optic nerve head. J Glaucoma 13:327–34, 2004
66. Kitazawa Y, Shirato S, Yamamoto T: Optic disc hemorrhage in low-tension glaucoma. Ophthalmology 93:853–7, 1986
67. Kochkorov A, Gugleta K, Zawinka C, et al: Short-term retinal vessel diameter variability in relation to the history of cold extremities. Invest Ophthalmol Vis Sci 47:4026–33, 2006
68. Kunimatsu S, Mayama C, Tomidokoro A, et al: Plasma endothelin-1 level in Japanese normal tension glaucoma patients. Curr Eye Res 31:727–31, 2006
69. Kvetnoy M, Hernandez-Yago J, Kvetnaia V, et al: Tau-protein expression in human blood lymphocytes: a promising marker and suitable sample for life-time diagnosis of Alzheimer's disease. Neuro Endocrinol Lett 21:313–8, 2000
70. Lichter PR, Musch DC, Gillespie BW, et al: Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 108:1943–53, 2001
71. Liu B, Chen H, Johns TG, et al: Epidermal growth factor receptor activation: an upstream signal for transition of quiescent astrocytes into reactive astrocytes after neural injury. J Neurosci 26:7532–40, 2006
72. Luthra A, Gupta N, Kaufman PL, et al: Oxidative injury by peroxynitrite in neural and vascular tissue of the lateral geniculate nucleus in experimental glaucoma. Exp Eye Res 80:43–9, 2005
73. Lütjen-Drecoll E: Choroidal innervation in primate eyes. Exp Eye Res 82:357–61, 2006
74. Manabe S, Gu Z, Lipton SA: Activation of matrix metalloproteinase-9 via neuronal nitric oxide synthase contributes to NMDA-induced retinal ganglion cell death. Invest Ophthalmol Vis Sci 46:4747–53, 2005
75. Martínez A, Sánchez M: Predictive value of colour Doppler imaging in a prospective study of visual field progression in primary open-angle glaucoma. Acta Ophthalmol Scand 83: 716–22, 2005
76. McNab AA: Floppy eyelid syndrome and obstructive sleep apnea. Ophthal Plast Reconstr Surg 13:98–114, 1997
77. Messerli J, Flammer J: [Central vein thrombosis in younger patients]. Klin Monatsbl Augenheilkd 208:303–5, 1996
78. Metea MR, Newman EA: Signaling within the neurovascular unit in the retina. Exp Physiol 92:635–40, 2007
79. Mocco J, Ransom ER, Komotar RJ, et al: Racial differences in cerebral vasospasm: a systematic review of the literature. Neurosurgery 58:305–14, 2006
80. Moenkemann H, Flammer J, Wunderlich K, et al: Increased DNA breaks and up-regulation of both G(1) and G(2) checkpoint genes p21(WAF1/CIP1) and 14-3-3 sigma in circulating leukocytes of glaucoma patients and vasospastic individuals. Amino Acids 28:199–205, 2005
81. Mojon DS, Hess CW, Goldblum D, et al: High prevalence of glaucoma in patients with sleep apnea syndrome. Ophthalmology 106:1009–12, 1999
82. Mozaffarieh M, Flammer J: Is there more to glaucoma treatment than lowering IOP? Surv Ophthalmol 52(Suppl 2): S174–9, 2007
83. Mozaffarieh M, Grieshaber MC, Orgul S, et al: The potential value of natural antioxidative treatment in glaucoma. Submitted.

84. Nakabayashi M: Review of the ischemia hypothesis for ocular hypertension other than congenital glaucoma and closed-angle glaucoma. Ophthalmologica 218:344–9, 2004
85. Neufeld AH, Hernandez MR, Gonzalez M: Nitric oxide synthase in the human glaucomatous optic nerve head. Arch Ophthalmol 115:497–503, 1997
86. Neufeld AH, Liu B: Glaucomatous optic neuropathy: when glia misbehave. Neuroscientist 9:485–95, 2003
87. Nicolela MT, Drance SM, Rankin SJ, et al: Color Doppler imaging in patients with asymmetric glaucoma and unilateral visual field loss. Am J Ophthalmol 121:502–10, 1996
88. Niesel P, Flammer J: Correlations between intraocular pressure, visual field and visual acuity, based on 11 years of observations of treated chronic glaucomas. Int Ophthalmol 3:31–5, 1980
89. Oh SW, Lee S, Park C, et al: Elevated intraocular pressure is associated with insulin resistance and metabolic syndrome. Diabetes Metab Res Rev 21:434–40, 2005
90. Ohuchi T, Yanagisawa M, Gariepy CE: Renal tubular effects of endothelin-B receptor signaling: its role in cardiovascular homeostasis and extracellular volume regulation. Curr Opin Nephrol Hypertens 9:435–9, 2000
91. Orgul S, Flammer J, Gasser P, et al: Female preponderance in normal tension glaucoma. Ann Ophthalmol 27:355–9, 1995
92. Orgül S, Kaiser HJ, Flammer J, et al: Systemic blood pressure and capillary blood-cell velocity in glaucoma patients: a preliminary study. Eur J Ophthalmol 5:88–91, 1995
93. Pache M, Flammer J: A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma. Surv Ophthalmol 51:179–212, 2006
94. Pache M, Kaiser HJ, Akhalbedashvili N, et al: Extraocular blood flow and endothelin-1 plasma levels in patients with multiple sclerosis. Eur Neurol 49:164–8, 2003
95. Pache M, Kräuchi K, Cajochen C, et al: Cold feet and prolonged sleep-onset latency in vasospastic syndrome. Lancet 358:125–6, 2001
96. Pache M, Schwarz HA, Kaiser HJ, et al: Elevated plasma endothelin-1 levels and vascular dysregulation in patients with rheumatoid arthritis. Med Sci Monit 8:CR616–9, 2002
97. Phelps CD, Corbett JJ: Migraine and low-tension glaucoma. A case-control study. Invest Ophthalmol Vis Sci 26:1105–8, 1985
98. Pillunat LE, Stodtmeister R: Inzidenz des niederdruckglaukoms bei haemodynamisch relevanter karotisstenose. Spektrum Augenheilkd 2:24–7, 1987
99. Prasanna G, Krishnamoorthy R, Clark AF, et al: Human optic nerve head astrocytes as a target for endothelin-1. Invest Ophthalmol Vis Sci 43:2704–13, 2002
100. Prünte C, Flammer J: Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 121:26–34, 1996
101. Quigley HA, Green WR: The histology of human glaucoma cupping and optic nerve damage: clinicopathologic correlation in 21 eyes. Ophthalmology 86:1803–30, 1979
102. Rader J, Feuer WJ, Anderson DR: Peripapillary vasoconstriction in the glaucomas and the anterior ischemic optic neuropathies. Am J Ophthalmol 117:72–80, 1994
103. Rogers DL, Cantor RN, Catoira Y, et al: Central corneal thickness and visual field loss in fellow eyes of patients with open-angle glaucoma. Am J Ophthalmol 143:159–61, 2007
104. Saner H, Würbel H, Mahler F, et al: Microvasculatory evaluation of vasospastic syndromes. Adv Exp Med Biol 220:215–8, 1987
105. Satilmis M, Orgül S, Doubler B, et al: Rate of progression of glaucoma correlates with retrobulbar circulation and intraocular pressure. Am J Ophthalmol 135:664–9, 2003
106. Schlötzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, et al: The Pathogenesis of floppy eyelid syndrome: involvement of matrix metalloproteinases in elastic fiber degradation. Ophthalmology 112:694–704, 2005
107. Schwartz B, Tomita G, Takamoto T: Glaucoma-like discs with subsequent increased ocular pressures. Ophthalmology 98:41–9, 1991
108. Sossi N, Anderson DR: Blockage of axonal transport in optic nerve induced by elevation of intraocular pressure. Effect of arterial hypertension induced by angiotensin I. Arch Ophthalmol 101:94–7, 1983
109. Sossi N, Anderson DR: Effect of elevated intraocular pressure on blood flow. Occurrence in cat optic nerve head studied with iodoantipyrine I 125. Arch Ophthalmol 101:98–101, 1983
110. Sugiyama K, Tomita G, Kitazawa Y, et al: The associations of optic disc hemorrhage with retinal nerve fiber layer defect and peripapillary atrophy in normal-tension glaucoma. Ophthalmology 104:1926–33, 1997
111. Suzuki Y, Iwase A, Araie M, et al: Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. Ophthalmology 113:1613–7, 2006
112. Taniguchi T, Shimazawa M, Sasaoka M, et al: Endothelin-1 impairs retrograde axonal transport and leads to axonal injury in rat optic nerve. Curr Neurovasc Res 3:81–8, 2006
113. Tazaki T, Minoguchi K, Yokoe T, et al: Increased levels and activity of matrix metalloproteinase-9 in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 170:1354–9, 2004
114. Teuchner B, Orgül S, Ulmer H, et al: Reduced thirst in patients with a vasospastic syndrome. Acta Ophthalmol Scand 82:738–40, 2004
115. Tezel G: Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res 25:490–513, 2006
116. Tezel G, Wax MB: Hypoxia-inducible factor 1alpha in the glaucomatous retina and optic nerve head. Arch Ophthalmol 122:1348–56, 2004
117. von Worch A, Kaestner R: Das glaukom ohne hochdruck. Folia Ophthalmol 10:221–4, 1985
118. Waldmann E, Gasser P, Dubler B, et al: Silent myocardial ischemia in glaucoma and cataract patients. Graefes Arch Clin Exp Ophthalmol 234:595–8, 1996
119. Wang L, Cioffi GA, Cull G, et al: Immunohistologic evidence for retinal glial cell changes in human glaucoma. Invest Ophthalmol Vis Sci 43:1088–94, 2002
120. Wang N, Chintala SK, Fini ME, et al: Activation of a tissue-specific stress response in the aqueous outflow pathway of the eye defines the glaucoma disease phenotype. Nat Med 7:304–9, 2001
121. Wax MB, Tezel G: Neurobiology of glaucomatous optic neuropathy: diverse cellular events in neurodegeneration and neuroprotection. Mol Neurobiol 26:45–55, 2002
122. Wax MB, Tezel G, Edward PD: Clinical and ocular histopathological findings in a patient with normal-pressure glaucoma. Arch Ophthalmol 116:993–1001, 1998
123. Weber AJ, Kaufman PL, Hubbard WC: Morphology of single ganglion cells in the glaucomatous primate retina. Invest Ophthalmol Vis Sci 39:2304–20, 1998
124. Weber J, Koll W, Krieglstein GK: Intraocular pressure and visual field decay in chronic glaucoma. Ger J Ophthalmol 2:165–9, 1993
125. Wu LL, Suzuki Y, Ideta R, et al: Central corneal thickness of normal tension glaucoma patients in Japan. Jpn J Ophthalmol 44:643–7, 2000
126. Wunderlich K, Golubnitschaja O, Pache M, et al: Increased plasma levels of 20S proteasome alpha-subunit in glaucoma patients: an observational pilot study. Mol Vis 8:431–5, 2002
127. Wunderlich K, Zimmerman C, Gutmann H, et al: Vasospastic persons exhibit differential expression of ABC-transport proteins. Mol Vis 9:756–61, 2003
128. Yang J, Yang P, Tezel G, et al: Induction of HLA-DR expression in human lamina cribrosa astrocytes by cytokines and simulated ischemia. Invest Ophthalmol Vis Sci 42:365–71, 2001
129. Yang P, Agapova O, Parker A, et al: DNA microarray analysis of gene expression in human optic nerve head astrocytes in response to hydrostatic pressure. Physiol Genomics 17:157–69, 2004

130. Yeghiazaryan K, Flammer J, Wunderlich K, et al: An enhanced expression of ABC 1 transporter in circulating leukocytes as a potential molecular marker for the diagnostics of glaucoma. Amino Acids 28:207–11, 2005
131. Yoshida M, Ishikawa M, Kokaze A, et al: Association of lifestyle with intraocular pressure in middle-aged and older Japanese residents. Jpn J Ophthalmol 47:191–8, 2003
132. Zhang C, Hua T, Zhu Z, et al: Age-related changes of structures in cerebellar cortex of cat. J Biosci 31:55–60, 2006
133. Zhang X, Neufeld AH: Activation of the epidermal growth factor receptor in optic nerve astrocytes leads to early and transient induction of cyclooxygenase-2. Invest Ophthalmol Vis Sci 46:2035–41, 2005

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Reprint address: Josef Flammer, MD, University Eye Clinic Basel, Mittlere Str. 91, P.O. Box, CH-4031 Basel, Switzerland.