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Primary vascular dysregulation and glaucoma

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Abstract

The pathogenesis of glaucomatous optic neuropathy is still debated. Ocular blood flow (OBF) in glaucoma patients is generally reduced, particularly in patients with progression of damage in spite of a normal IOP. However, the question of whether this OBF reduction is only secondary to the damage or whether it is a primary causal factor has remained open for a long time. In this review, we try to explain why vascular dysregulation contributes to glaucomatous damage. In people with primary vascular dysregulation, the autoregulation of ocular perfusion is disturbed. Therefore, fluctuations in intraocular pressure (IOP) or blood pressure lead to an unstable oxygen supply. This in turn increases oxidative stress, particularly in the mitochondria of the optic nerve head (ONH). The simultaneous activation of the astrocytes leads to altered gene expression, which contributes to both tissue remodeling in the ONH and the death of retinal ganglion cells. The activated astrocytes produce more metalloproteinase degrading the extracellular matrix. This results in a remodeling of the extracellular matrix, which is basic component of ONH excavation.

KEYWORDS: glaucomatous optic neuropathy, ocular blood flow, primary vascular dysregulation, Flammer syndrome.

Первичная сосудистая дисрегуляция и глаукома

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Резюме

На сегодняшний день патогенез глаукомной оптической нейропатии остается спорным вопросом. Известно, у пациентов с глаукомой, особенно с прогрессирующим поражением при нормальном уровне внутриглазного давления, также наблюдается снижение внутриглазного кровотока. Однако вопрос о том, является ли это снижение первичным или вторичным по отношению к общему повреждению тканей при глаукоме, остается открытым. В данном обзоре мы пытаемся описать роль, которую играет сосудистая дисрегуляция при глаукоме. У пациентов с первичной сосудистой дисрегуляцией происходит нарушение ауторегуляции перфузии глаза. Возникающие из-за этого перепады внутриглазного и артериального давления приводят к нестабильному поступлению кислорода в ткани. Это в свою очередь повышает оксидативный стресс, особенно в митохондриях диска зрительного нерва. Одновременная активация клеток астроглии приводит к изменениям в экспрессии генов, что вносит свой вклад как в ремоделирование тканей диска зрительного нерва, так и в гибель ганглионарных клеток сетчатки. Активированные астроциты производят больше металлопротеиназы, разрушительно действующей на внеклеточный матрикс — главный компонент экскавации диска зрительного нерва.

КЛЮЧЕВЫЕ СЛОВА: глаукомная оптическая нейропатия, внутриглазной кровоток, первичная сосудистая дисрегуляция, синдром Фламмера.

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The pathogenesis of glaucomatous damage, and in particular, the role of ocular blood flow (OBF) in it has still not been definitely explained. The discussion began, when Albrecht von Graefe described the glaucomatous excavation of the optic nerve head (ONH) in the mid-19th century. That an increased intraocular pressure (IOP) increases the risk of the initiation and progression of glaucomatous damage remains unquestioned. However, it is also unquestioned that other factors must play a role as well. The role of OBF was, and to some extent still is, very controversial. In the past, it was technically difficult to measure OBF; nowadays, however, the methodology used to accomplish this is quickly improving. We know that OBF in glaucoma patients is generally reduced, particularly in patients with progression of damage in spite of a normal IOP. However, the question of whether this OBF reduction is only secondary to the damage or whether it is a primary causal factor has remained open for a long time. In this review, we focus on the role of OBF, and particularly the role of primary vascular dysregulation (PVD) [1-3].

What is a glaucomatous damage?

Glaucomatous optic neuropathy (GON) is defined as loss of retinal ganglion cells, including their axons, combined with tissue remodeling. Together, these effects lead to a clinical picture of glaucomatous excavation. Cell loss in the retina and in the corpus geniculate nucleus is essential, but not specific for glaucoma, as such cell loss also occurs in the context of other diseases. On the other hand, tissue remodeling is specific to glaucoma. Therefore, we use the term glaucoma to describe all diseases, leading to a progressing excavation of the ONH. This means that we define glaucoma in a way that is phenomenological and independent of etiology. However, we would like to emphasize that not all authors define glaucoma in this way.

The distinction between glaucomatous and a non-glaucomatous optic atrophy has to do with the behavior of the glia. The glia tolerates hypoxia surprisingly well as long as it is stable, that is, the oxygen supply is indeed reduced but stable. However, if the oxygen supply is unstable, free oxygen radicals are produced in the mitochondria. If their production exceeds the capacity for their elimination, oxidative stress is the result. This, along with others factors, activates glial cells, which react sensitively to oxidative stress. The activated glial cells contribute decisively to the remodeling of the extracellular matrix; in a later phase, they die, and the ONH excavates.

This is in contrast to non-glaucomatous optic atrophy, in which the loss of neural cells results in development of a glial scar and the ONH turns pale but does not excavate. It is known from animal experiments that activation of astrocytes is a prerequisite for the development of glaucomatous damage. The most important glial cells

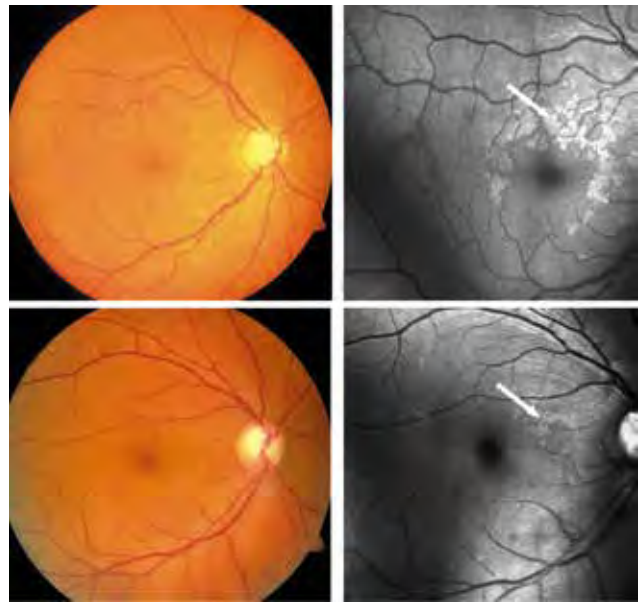

Fig. 1. While activated astrocytes are barely visible during examination with white light (left), they can be well observed (arrows) in red-free light (right). The right and left pictures show the same eyes (from [1], with permission)

in the ONH and in the superficial layer of the retina are astrocytes. When activated, not only their gene expression, but also their morphology is altered. The astrocyte processes become more irregular, thereby leading to increased light scattering. In the ONH, this results in a pale neuroretinal rim. In non-glaucomatous optic atrophy, the paleness is much more pronounced due to a glia-scar scattering the light. In the retina, the forward scatter contributes to a glare perceived by the patient and the back scatter to glinting spots seen by the ophthalmologist. The latter is best observed when examined with red-free light *(Fig. 1)*. The glinting spots occur predominantly in the early phase of glaucomatous damage (in the later phases, the astrocytes are lost), and more often in glaucoma patients with a vascular component. The altered gene expression of the astrocytes leads to the increased production of metalloproteinase and thereby to digestion of the extracellular matrix, which in turn is a prerequisite for tissue remodeling.

Activated astrocytes produce more nitric oxide. This small, short-lived molecule also diffuses into neighboring neuronal axons; there, it fuses with superoxide to form the very toxic peroxynitrite. The important role of oxidative stress raises the question of its cause, as well as its link to OBF.

Is the ocular blood flow primarily or secondarily reduced?

The vascular system of the eye has the following four parts: the anterior segment of the eye, the choroid, the retina, and the ONH. These vascular beds distinguish themselves clearly, with respect to both

the morphology and the physiology of the vessels. As already mentioned, we know today that the OBF in glaucoma patients is generally reduced in the retina, choroid and papilla, as well as in the retroocular vessels. Such a reduction can be secondary — on the one hand, a consequence of elevated IOP (above all if the autoregulation is disturbed), and on the other, resulting from glaucomatous damage, as atrophied tissues do not need the same blood supply. However, the question is whether there is an additional primary component that disturbs the OBF. An elevated IOP cannot be the only factor reducing the OBF, because 1) the OBF in normal-tension glaucoma (NTG) is even more reduced compared to the case in high-tension glaucoma, and 2) the effect of an elevated IOP is normally compensated through autoregulation. This indicates that the IOP only becomes relevant if it is either strongly elevated or if the autoregulation is disturbed. This is indeed the case in several forms of glaucoma, particularly NTG.

Primary vascular dysregulation: The disturbance of autoregulation

Unfortunately, autoregulation is not consistently defined in the literature. We define it here as the ability of an organ or part of an organ to maintain the blood flow, independent of perfusion pressure. Naturally, this ability has limits. Major drops or rises of perfusion pressure exceed the capacity of autoregulation.

The following facts support the argument that there is a primary vascular component:

- The blood flow disturbances in glaucoma are not limited to the eye, but also occur in other organs, for example, in the extremities. In the fingertips of patients, especially those with NTG (see chapter "Diagnosis of Flammer syndrome"), the blood flow is reduced and the reaction to cold provocation is increased *(Fig. 2)*;
- The reduction of OBF mostly precedes glaucomatous optic neuropathy;
- OBF reduction predicts future progression of the damage; and
- Autoregulation is disturbed in glaucoma patients, progressing despite normal or normalized IOP. The disturbed autoregulation in these patients also explains the correlation between the OBF and the peripheral blood flow in such cases.

Risk factors for the progression of glaucomatous optic neuropathy

It is not easy to allocate risk to specific factors, as these potential factors interact. We would like explain this by taking IOP and blood flow as an example. Elevated IOP or low blood pressure are not damaging as long as a good regulation of OBF can compensate for these factors. However, if the autoregulation is disturbed, every fluctuation of IOP or blood pressure is immediately translated to OBF fluctuation. In such a condition, either the IOP (or blood pressure) or the disturbed autoregulation can be seen as the factor causing the damage. Thus, even more important than the individual factors are the interactions between them.

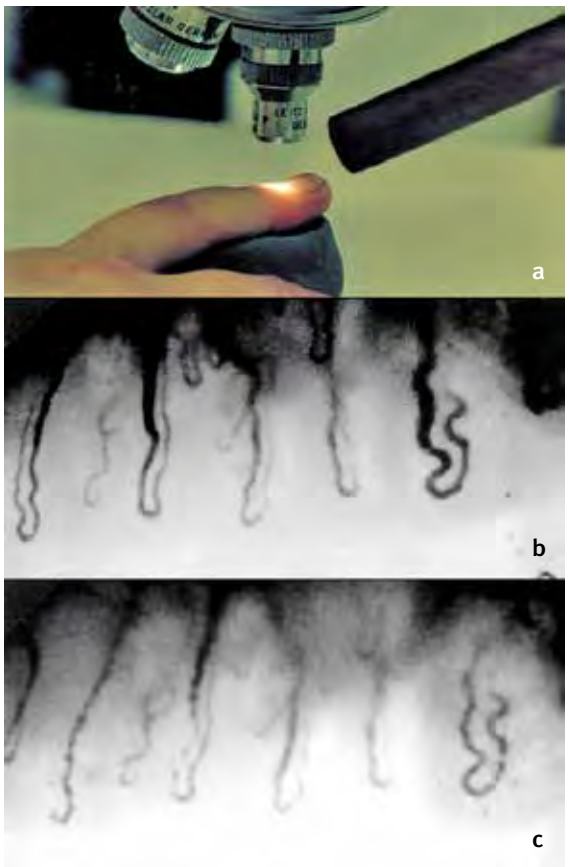

Fig. 2. Nailfold capillaroscopy with a cold provocation test. a) The nailfold capillaries are observed through a microscope, while cold air is supplied by a pipe; b) video image of normal blood flow in the capillaries; c) blood flow cessation after cold provocation (from [1], with permission)

An unstable oxygen supply due to a fluctuating blood flow leads to oxidative stress

With regard to OBF, there is an apparent paradox that on one hand, certain dysfunction of OBF contributes to the damage, but on the other, atherosclerosis — while being a risk factor for IOP elevation — does not essentially contribute to GON per se. This can be explained in that it is not so much the reduction of OBF itself that is a risk factor for GON, but rather the fluctuation of blood flow. OBF fluctuation in turn leads to an unstable oxygen supply and thereby to oxidative stress (particularly in the mitochondria). Oxidative stress not only damages the axons, but also activates astrocytes; the astrocytes then increase the secretion of many molecules, including metalloproteinases, which contribute to tissue remodeling. *Figure 3* shows the typical appearance of an ONH, in which vascular factors

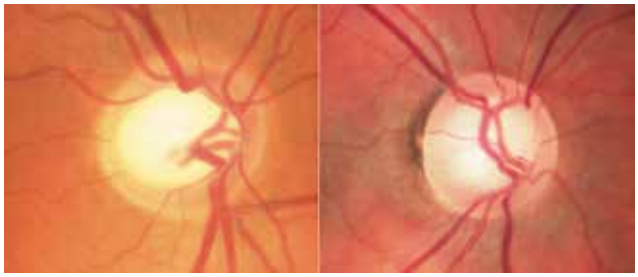

Fig. 3. Typical IOP-related glaucomatous optic neuropathy with vessels shifted to the nasal side of the cup (left). In contrast, typical vascular-related glaucomatous optic neuropathy with clearly weaker nasal displacement of vessels (right)

have crucially contributed to GON. If an excavation is predominantly IOP-dependent, the blood vessels are nasally displaced. However, if the excavation is rather due to OBF fluctuation, the retinal vessels are only slightly nasally displaced.

Primary vascular dysregulation is the most frequent cause of autoregulation disturbance in glaucoma, particularly in NTG. While there are obviously many different risk factors for GON, in this article, we focus on the role of the PVD.

Vascular dysregulations: Primary and secondary types

To adapt to the ever-changing needs of blood supply, the width of the blood vessel must be permanently regulated. Many factors are involved in this regulation, particularly the vascular endothelial cells.

Blood flow disturbances are seen in sick vessels (e.g., in atherosclerosis or inflammation), but also in anatomically healthy vessels. If, despite the normal morphology of the blood vessels, their regulation cannot adapt to the needs of the tissue, this is called a functional vascular dysregulation. This can imply an inadequate constriction (vasospasm) or an insufficient dilation of an artery, arteriole, or capillary in spite of the body's requirements. Often, a relative constriction is combined with a simultaneous inadequate dilation in another area of the vascular bed, especially the veins. Both phenomena have in common a circulation that does not suit the momentary requirement. Such vascular dysregulations are often combined with other vascular dysfunctions (e.g., barrier dysfunction [3]), as well as non-vascular symptoms and signs, as described further below.

We distinguish primary vascular dysregulation from secondary vascular dysregulation (SVD). SVD is the result of disease in a remote organ. For example, blood flow in the ONH can be dysregulated due to autoimmune arthritis. In contrast, the PVD is a (probably inborn) predisposition of anatomically healthy vessels to react differently to stimuli.

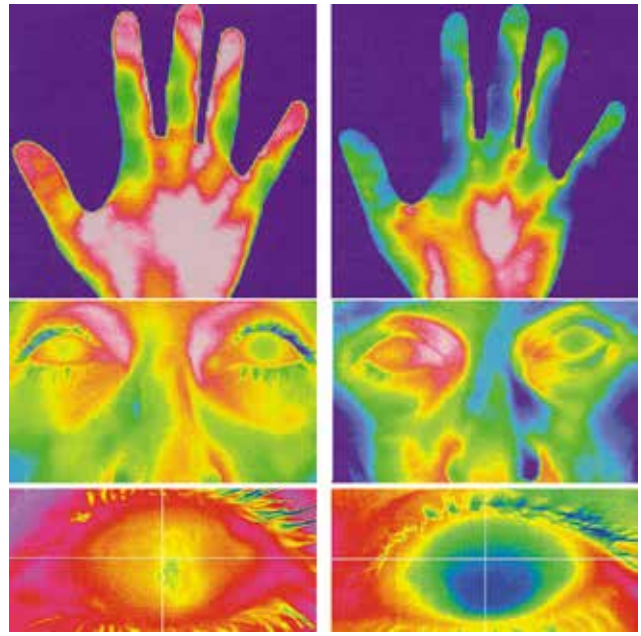

Fig. 4. Thermography of the hand, face, and eye of a person without (left) and a person with Flammer syndrome (right) recorded at room temperature (from [1], with permission). The results are shown in false color. In people with Flammer syndrome (right), the surface is colder, that is, we see a shift of color from red to blue

Primary vascular dysregulation (PVD)

People with PVD react differently (often more intensely) to various stimuli like cold and emotional or mechanical stress. The consequence is a reversible reduced — or sometimes elevated — blood circulation in the corresponding organs or parts of them. In the past, the term "vasospastic syndrome" was used to describe an undesirable reduction in blood flow due to multifocal vasoconstriction. However, the term PVD syndrome comprises many additional symptoms and signs that may be unrelated to blood flow. Since this includes not only vascular aspects, the term PVD syndrome was not satisfactory, and a better one was required. As Josef Flammer was the first to comprehensively describe this syndrome [1-3], we introduced the term Flammer syndrome [4, 5].

Symptoms and signs of Flammer syndrome

People with Flammer syndrome *(Table 1)* exhibit numerous symptoms and signs which are indeed not specific, but which occur considerably more frequently than they do in other people. The syndrome can be more or less pronounced.

The most remarkable symptom is cold hands *(Fig. 4)* and/or feet. The extremities can already be cold under normal environmental temperatures, but will become especially so when provoked by cold or vibration, or if the subject is under emotional stress.

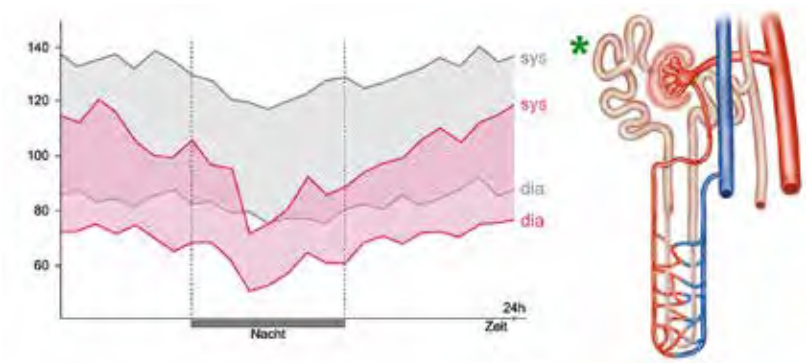

Fig. 5. Example of a 24-hour blood pressure profile of a person without (grey) and of a person with Flammer syndrome (red). The arterial hypotension is particularly caused by a reduction of sodium reabsorption in the proximal tubules (asterisk) of the kidneys (from [1], with permission)

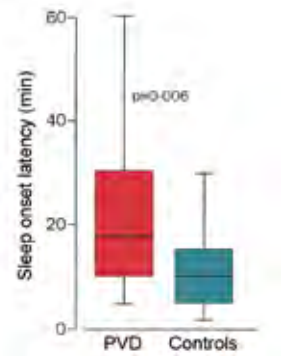

Fig. 6. Sleep onset latency in people with (left) and without Flammer syndrome (right). The results are shown with a box plots. PVD = primary vascular dysregulation (n=32), controls (n=31) (modified after Pache M., Kräuchi K., Cajochen C., Wirz-Justice A., Dubler B., Flammer J., Kaiser H.J. (2001) Cold feet and prolonged sleep-onset latency in vasospastic syndrome. The Lancet, with permission)

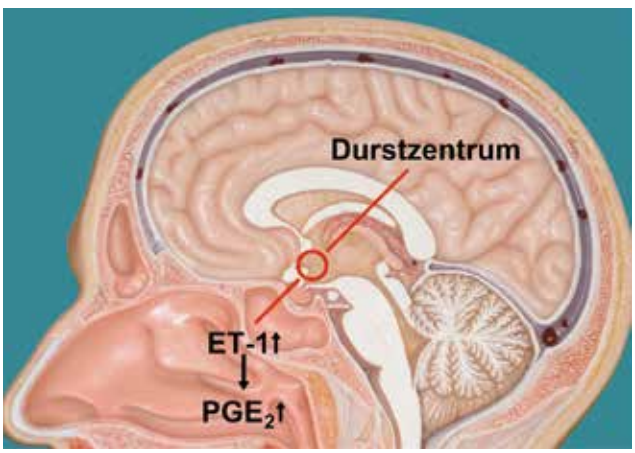

Fig. 7. The feeling of thirst in the people with Flammer syndrome is reduced due to activation of the endothelin-1/prostaglandin-E2-axis. This suppresses the thirst center in the brain

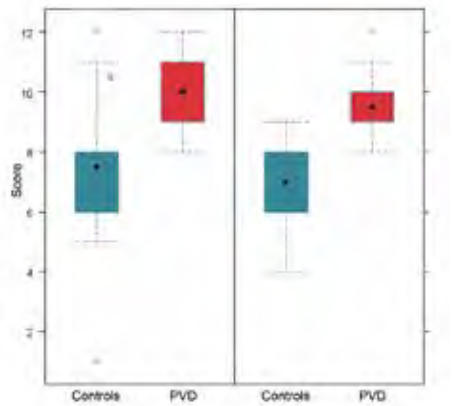

Fig. 8. In subjects with Flammer syndrome, odor sensation is increased (modified after Mozaffarieh M., Hauenstein D., Schoetzau A., Konieczka K., Flammer J. (2010) Smell perception in normal tension glaucoma patients. Mol Vis, with permission)

Table 1

Symptoms and signs of Flammer syndrome

Often (but not obligatory) symptoms and signs

- Cold hands and/or feet
- Low blood pressure
- Low body mass index
- Reduced feeling of thirst
- Long sleep onset time
- Increased sensitivity: increased odor sensation, increased pain sensation, increased response to certain drugs (e.g., calcium channel blockers, beta blockers)
- Migraine
- Tinnitus
- Reversible patches of white and red discoloration of the skin

"Gold standard" for diagnosis:

Blood flow cessation in the capillaries of the finger nailfold after standardized cold provocation › 11 seconds

The blood pressure is mostly low *(Fig. 5)*, particularly when sleeping or when changing from supine to upright position (orthostatic hypotension). Blood pressure in these subjects often normalizes in the course of life, and is sometimes even high in old age. The systemic hypotension in these subjects is among other things a result of increased loss of sodium due to reduced reabsorption of sodium in the proximal tubules of the kidneys; this results from the activation of the endothelin-1/prostaglandin-E2-axis.

The sleep onset time is prolonged *(Fig. 6)*. The reason for this is that initiation of sleep in humans (and partly also in animals) is strictly coupled to a certain feet temperature. As people with Flammer syndrome often have colder feet, they also need longer to warm them up to the critical temperature. Moreover, their circadian rhythm is often delayed by approximately one hour. This means that in the evening, these people fall asleep later, also waking up later in the morning.

The feeling of thirst is reduced in people with Flammer syndrome. This is also the consequence of activation of the endothelin-1/prostaglandin-E2-axis *(Fig. 7)*.

It is therefore not specific, as it can also be observed in other conditions with increased plasma levels of endothelin, such as in patients with multiple sclerosis. Sensitivity in general is increased, including sensitivity to smells *(Fig. 8)* or to certain drugs. Some classes of drugs (e.g., calcium channel blockers or systemic beta blockers) are badly tolerated at normal doses, but well-tolerated at very low doses. The major cause for this lies in the altered expression of ABC-transport proteins, which also transport drugs through the cell membranes. Likewise, sensitivity to pain is increased due to the effect of endothelin on the peripheral pain threshold.

Vasoconstrictions — as a reaction to cold or psychological stress — also often appear in the eye. Usually, this is relatively harmless, but in rare cases, it even leads to retinal artery or vein occlusions. If the vasoconstriction occurs in the ear, the subjects suffer from tinnitus, hearing impairment, or even sudden hearing loss. In the heart, it manifests mainly in the form of silent ischemia.

Flammer syndrome occurs more often in women than in men, academics rather than blue-collar workers, slim rather than obese subjects, and Asians rather than in Caucasians. It is more frequent in reliable people, as well as people suffering from migraine (including retinal migraine). In some people with this syndrome, illustrative but completely harmless patches of white and red discoloration are seen in the face or in the neck when they are under stress. All of these symptoms usually decrease with age. People with Flammer syndrome mostly have few symptoms as long as they are not exposed to trigger factors like cold, emotional and mechanical stress, drugs, migraine attacks, hunger, and so on.

Ocular blood flow in Flammer syndrome correlates with nailfold blood flow

In the absence of trigger factors, the OBF is generally normal or only slightly reduced. In healthy people, a rise in IOP or dip in blood pressure is balanced through the autoregulation of the OBF. In Flammer syndrome, this autoregulation is reduced or even absent. Hence, fluctuations of perfusion pressure lead to an unstable blood flow, and therefore to a fluctuating oxygen supply, with the abovementioned consequences. Interesting and clinically useful for us is the observation that the OBF in people with Flammer syndrome — but not in others — is correlated to the peripheral blood flow (e.g., in the nailfold; *Fig. 2*). In the absence of autoregulation, systemic factors dominate, and this explains the correlation.

Hemorrhages in the optic nerve head and the nailfolds are related

Although optic disc hemorrhages are not specific for glaucoma, they are related to the future progression of damage. Like Flammer syndrome, they occur more often in NTG than in high-tension glaucoma and in women than in men. Interestingly, the occurrences of hemorrhages in the ONH and in the nailfolds are statistically related. This suggests a systemic cause. While such hemorrhages in glaucoma were already described more than 100 years ago, their pathogenesis is still unclear. We assume that these hemorrhages are not a result of a rupture, but rather of a barrier dysfunction of blood vessels [3].

Involvement of the Flammer syndrome in normal-tension glaucoma

Although Flammer syndrome can contribute to the development, manifestation, or progression of different systemic and ocular diseases, such as retinal artery and vein occlusions, anterior ischemic optic neuropathy, Susac syndrome, optic nerve compartment syndrome, central serous chorioretinopathy, Leber hereditary optic neuropathy, or retinitis pigmentosa (see [3]), it has been described mainly in the context of glaucoma, especially NTG. The link between Flammer syndrome and glaucomatous damage is locally elevated oxidative stress, especially in the mitochondria of the ONH. As long as the antioxidant mechanisms are not overly challenged, people with Flammer syndrome stay healthy. However, if the balance is shifted, the oxidative stress leads to tissue damage. Up to a certain level, this damage can still be repaired, but if the repair system is also overstrained, damage slowly accumulates, appearing clinically as GON.

Diagnosis of Flammer syndrome: The role of the patient's history

In clinical practice, one can diagnose Flammer syndrome with a focused patient history and clinical examination with fairly good accuracy. If required, a suspected case can then be confirmed through additional elaborate examinations. Among these examinations are the following: capillary microscopy with cold provocation, dynamic retinal vessel analysis with flicker light stimulation, quantification of gene expression in the lymphocytes, and endothelin-1 level in the blood.

The blood flow cessation in the capillaries of the finger nailfold after cold provocation is often considered the "gold standard" for diagnosis. This examination is carried out with the help of capillary microscopy *(Fig. 2)*. If a patient shows a blood flow cessation of more than 11 seconds in the capillaries after standardized cold provocation, this is a clear indication of a vascular dysregulation.

Likewise, a reduced neurovascular coupling is typical; this can be observed with a dynamic retinal vessel analyzer (DVA). Stimulation of the retina with flickering light leads to a dilation of the retinal vessels (both arteries and veins) within seconds. This response is reduced *(Fig. 9)* or even absent in Flammer syndrome.

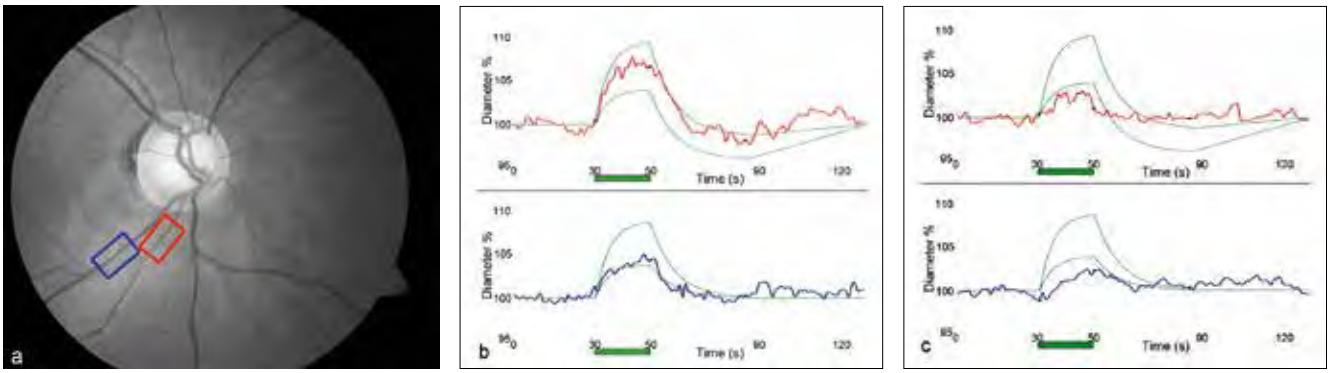

Fig. 9. Responses of retinal blood vessels to the flickering light measured with dynamic retinal vessel analyser (DVA) (a). Normal responses in healthy subjects (b) and reduced responses in glaucoma patients (c). Red: arteries; blue: veins; green: area of normal reaction (from [3], with permission)

Also helpful is 24-hour blood pressure monitoring. Of particular interest are systemic hypotension, blood pressure dips, and increased fluctuations.

Principally in all these examinations, similar results can be found in both non-glaucomatous people with Flammer syndrome and in glaucoma patients progressing despite a normal or normalized IOP. Interestingly, even the alteration of gene expression in the lymphocytes of both these groups is the same or very similar. All of this proves that there must be a relationship between Flammer syndrome and glaucoma.

Therapy in Flammer syndrome cases: The role of magnesium

Flammer syndrome is generally harmless and therefore requires no treatment. However, if people suffer strongly from their symptoms, or if a related disease such as NTG develops, treatment should be considered. The intensity of the treatment depends on the clinical picture. Unfortunately, up to the present, little research has been done on therapy for this condition.

We primarily treat patients with magnesium, a physiological calcium channel blocker. This reduces the vasoconstrictive effect of endothelin-1 and improves the regulation of OBF. Indeed, a relatively high dose of 10–20 mmol/day is needed, which fortunately has almost no side effects.

If this is not sufficient, we combine magnesium with a very low dose of calcium channel blocker, preferably nifedipine or amlodipine. Controlled studies have shown that calcium channel blockers can even improve but particularly stabilize the visual fields of NTG patients. A low dose is important for the following reasons: 1- low doses already have a good effect on the regulation of vessels; 2) these patients have elevated drug sensitivity; and 3) in most cases, we do not want to further decrease blood pressure. Nevertheless, blood pressure should be controlled after the initiation of the treatment. In patients with elevated blood pressure, the dose of the calcium channel blocker can either be increased or the low-dose calcium channel blocker can be combined with an ACE inhibitor.

To protect the mitochondria from oxidative stress we recommend ginkgo biloba (120 mg of extract per day). We further recommend antioxidative nutrition, such as green and black tea, coffee, red wine, blue fruits and berries, tomatoes, fish [6], and so on. Cocoa (dark chocolate) improves the function of the endothelium, and thus vascular regulation. Omega-3 fatty acids (preferably in the form of fish) also improve vascular regulation.

If the blood pressure is too low, we suggest an increase in salt intake. In extreme cases, we prescribe a low doses of fludrocortisone (0.1 mg 2x per week). Such a mineralocorticoid has fewer side effects than glucocorticoids.

In addition, carbonic anhydrase inhibitors (also locally applied) also improve the OBF. The beta blocker betaxolol has a calcium channel blocking side effect, and is therefore suitable in people with Flammer syndrome.

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