Glaucoma Patients with Flammer Syndrome

Subjects: Ophthalmology

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Flammer syndrome (FS) describes a phenotype characterized by the presence of primary vascular dysregulation along with a number of symptoms and signs. Although most people with FS are healthy, FS favors the occurrence of certain diseases, such as normal tension glaucoma. This is because disturbed autoregulation makes the eye more sensitive to intraocular pressure (IOP) spikes or blood pressure drops. Treatment of FS is generally appropriate when patients either suffer greatly from their symptoms or if we can assume that it has contributed to a disease. In glaucoma, this may be the case if the glaucoma damage progresses despite well-controlled IOP. Both the still sparse scientific studies and our long clinical experience suggest that FS-targeted therapy not only relieves the symptoms of FS but also slows the progression of glaucoma damage in selected cases. This description is intended not only to help affected patients but to also motivate clinicians and researchers to conduct therapy studies to confirm or refute our observations.

Keywords: glaucoma ; normal tension glaucoma ; Flammer syndrome ; calcium channel blockers ; magnesium ; nutrition ; antioxidants

1. Introduction

Flammer syndrome (FS) [1][2][3][4][5] describes a phenotype characterized by the presence of primary vascular dysregulation [3][6] together with a combination of symptoms and signs that result from predisposition to generally increased sensitivity. The main focus is a modified, mostly increased response of the blood vessels to certain stimuli, such as cold or emotional stress, and the resulting phenomenon, such as cold hands. This combination of symptoms was first primarily observed in patients, especially those with normal tension glaucoma (NTG). Later, we noticed that the same combination of symptoms can also occur in healthy people but less frequently and usually less pronounced [1][3]. Therefore, we created a multiple-choice questionnaire that patients can fill out prior to consultation [5][7].

FS is not a disease but rather a predisposition that usually does not require treatment. However, treatment is recommended if diseases fostered by FS arise [7][8] or if people subjectively suffer from their symptoms. Although the syndrome is quite prevalent, there have only been a few studies dealing with the therapy. In contrast, there are many years of clinical experience. Therefore, the following recommendations are based on both studies and clinical experience. Although most people with FS are healthy and FS even seems to protect against atherosclerosis, it is a risk factor for some other diseases [8]. Here, we focus on glaucoma [3][6][7][9], specifically NTG [7].

2. Drug Treatment of Patients with FS

Glaucoma patients with FS. FS patients usually have disturbed autoregulation and are therefore more sensitive to IOP peaks and BP dips. Often, however, IOP reduction and IOP stabilization alone are not sufficient.

2.1. Drug Sensitivity

Patients with FS often tell us that they cannot tolerate certain medications very well or apparently not at all in some cases and therefore prefer herbal remedies or homeopathic therapy. Based on our experience, however, these patients can actually tolerate these drugs if we prescribe much smaller doses than normal, which can be up to 10 times lower. Interestingly, the main effect usually remains, but the side effects disappear.

The symptoms of FS decrease significantly within a few years after menopause, and NTG thus usually (but not always) stabilizes. If women take postmenopausal hormone therapy that contains estrogen, both the FS symptoms and the glaucoma can worsen again. In case of doubt, the regulation of the eye blood circulation can be measured before and after the beginning of therapy.

2.2. Pharmaceutical Improvement of Regulation of the Microcirculation

Primary vascular dysregulation [3][6], the core component of FS, has not been known for very long. It is therefore not surprising that there are only a few types of drugs available, and the number of clinical studies is limited. Unfortunately, the pharmaceutical industry has hardly addressed this issue until now.

2.2.1. Calcium Channel Blockers (CCBs)

Others feared that CCBs would lower the BP of such patients even further and that this would be dangerous, particularly for glaucoma patients. We address this risk based on the following considerations: (a) we use very low doses that hardly ever lower BP; (b) the BP lowering effect of CCB is either small or nonexistent in patients who already have low BP; (c) animal experiments have shown that nifedipine increases ocular blood flow, even when it reduces BP [10]; and (d) if the ocular perfusion would decrease, we would not observe stabilization or even improvement but rather a deterioration of the visual field.

Others have assumed that fat-soluble (centrally acting) CCBs (e.g., nimodipine) would be better than water-soluble (peripherally acting) CCBs, such as nifedipine. This applies to diseases of the brain and retina as long as the blood-brain or blood-retina barrier is intact. For glaucoma, however, we have had the opposite experience, which may be explained by the fact that there is actually no blood-brain barrier in the optic nerve head [11]. It is important to note that studies comparing different CCBs in glaucoma patients are yet to be undertaken. In very severe cases, such as acute AION in FS patients, we start with a combination of nifedipine with nimodipine and then stop the nifedipine after a few days.

Under normal condition, we start with 1 mg nifedipine (i.e., 1 drop of a nifedipine solution) orally per day and then slowly increase the dose to 2, 3, or more mg depending on the patient, the BP, and the disease we are targeting. As nifedipine has a short half-life, patients dilute it in a liquid of their choice and drink it throughout the day. Because nifedipine is sensitive to light, we recommend using a light-protected bottle or keeping it in the dark (e.g., in the refrigerator or cabinet).

Fortunately, the half-life of the effect is significantly longer than the half-life of the blood level. Intake during the day instead of at night is desirable as thermographic studies have revealed that FS patients have vascular dysregulation during the day but not when they are asleep.

Many doctors hardly believe that such low doses could have an effect. Let us illustrate this by example. A researcher working for a pharmaceutical company in Basel told us about the fate of her father who lived in a developing country. He was diagnosed with NTG, and his ophthalmologist noticed a fast progression since he was on dialysis. In addition, the patient noticed a temporary deterioration in his vision after dialysis. Unfortunately, it was not possible for him to travel to us for an examination. We have observed similar events in patients on dialysis. They all had increased ET levels in the blood, which resulted in increased RVP, which contributed to progression of glaucoma damage. Assuming a similar situation, we recommended a therapy with a relatively low dose of nifedipine. A few weeks later, we received a letter from the patient informing us that his vision had improved and that his visual field deficits had decreased after the initiation of 1 and then 2 mg of nifedipine per day.

If a higher dose is necessary or desired, we replace nifedipine with amlodipine (5 mg once a day). Amlodipine has effects that are similar to nifedipine, but it has a longer half-life. However, unfortunately, it is only available in doses of 5 mg or higher.

Although FS patients usually have rather low BP, some of them develop high BP in old age. In such cases, we recommend an antihypertensive treatment containing a low dose of a CCB (e.g., a combination of an ACE inhibitor with 5 mg amlodipine).

We know that ET increases RVP [12], but not every high RVP is ET induced. Accordingly, one cannot lower every RVP with nifedipine. In addition, CCBs, and thus nifedipine, only inhibit ET-induced influx of calcium from the outside into the cell but not ET-induced release of calcium from the cell's internal storage. This means that we can reduce but not completely eliminate the effect of ET. In addition, the venous resistance that leads to the increase in RVP does not always occur at the level of the optic disc. This can also be further in the retina or deeper in the optic nerve. In such cases, CCBs that are less water soluble, such as nimodipine, help better.

CCBs have the well-known effect of lowering blood pressure and side effects such as flush or ankle edema. However, as we prescribe extremely low doses (much lower than usually prescribed by internists), we see such side effects extremely rarely. Nevertheless, to be on the safe side, we recommend 24 h blood measurement before and after starting therapy with low-dose CCB.

2.2.2. Endothelin Blockers

Endothelin blockers are particularly interesting [13]. Unfortunately, the benefit for FS subjects has not yet been investigated in detail, and they are not yet approved for this application. However, we know that RVP is mainly regulated by ET and that ET blockers reduce increased RVP [14]. Endothelin traps and the delivery of artificial transcription factors are also under investigation [15].

2.2.3. Magnesium

Magnesium (Mg) is a physiological CCB. We have shown that Mg reduces the effect of ET both in vitro and in ex vivo [16]. We have further observed a slight improvement in the visual field of glaucoma patients with FS [17]. Mg has only mild side effects, such as diarrhea, which disappears after reducing the dose. Often, it is better tolerated by taking it together with yoghurt. We normally use 10–20 mmol of Mg per day, but there are only a few studies in the available literature and the effect is relatively small. We normally start treatment with Mg, and if the effect is insufficient, we combine it with a low dose of CCB.

2.2.4. Betaxolol

Studies have demonstrated that glaucoma patients treated with betaxolol have a smaller rate of visual field deterioration than patients treated with timolol despite the fact that betaxolol reduces IOP less than timolol [18]. This can be explained by a slight calcium channel blocking effect of betaxolol. As betaxolol is beta-1 specific, it is generally tolerated by most (but not all) FS patients.

2.2.5. Triflusal

Triflusal is a compound related to aspirin. However, in contrast to aspirin, it leaves the arachidonic acid pathway intact, favors the production of nitric oxide (NO), and increases the concentration of cyclic nucleotide in endothelial cells, which results in peripheral vasodilatation [19]. We do not have much experience with it because it is not yet on the market in Switzerland.

2.2.6. Propranolol

Propranolol is a beta-blocker as well as a weak CCB. Taking very low doses (5–10 mg per day) for days or weeks help some FS patients when emotional stress is unavoidable and causes symptoms.

2.2.7. Carbonic Anhydrase Inhibitors (CAI)

Acetazolamide is used to reduce both IOP and intracranial pressure. It also dilatates eye and brain vessels [20] and is therefore also used to study the cerebral perfusion reserve. Many decades ago, we and others found that acetazolamide can improve the visual fields in certain glaucoma patients [21]. Later, we realized that these patients had FS. With acetazolamide, we can determine whether some of the visual field defects are still reversible. Acetazolamide is rarely used as a long-term therapy because of its side effects.

CAIs used locally, such as dorzolamides, have fewer systematic side effects and also improve blood flow, albeit to a lesser extent than acetazolamides [22]. Therefore, they are ideal for glaucoma patients with FS despite their limited ability to lower IOP.

2.2.8. NO Donators

NO donators are theoretically interesting for treatment of FS. Unfortunately, very little research has been done on the use of such drugs in FS patients. Nevertheless, it has already been shown that nitrates can lower RVP (ARVO Annual Meeting Abstract, 2017).

Calcium-L-methylfolate (the biologically active form of folic acid) not only reduces homocysteine but also increases NO production via activation of the NO synthetase, thereby improving vasodilatation. Vitamin supplementation containing L-methylfolate (Ocufolin® forte) has shown promise. It improves diabetic and hypertensive retinopathy [23], conjunctival microcirculation [24], and retinal blood flow in diabetes patients [25]. Ocufolin® forte has been studied little in glaucoma so far. However, we already know that it reduces elevated retinal venous pressure (in preparation).

2.2.9. Antioxidants

We have already emphasized the importance of oxidative stress and antioxidant nutrition in the nutritional recommendations section. Although oxidative stress can occur systemically, local stress in certain organs and cells is

even more important. Even within a cell, oxidative stress is often very localized (e.g., in mitochondria). Therefore, we cannot simply reduce all oxidative stress with any antioxidant. For example, in patients with glaucoma, stress occurs mainly (but not only) in the mitochondria of the axons in the optic nerve head. A balanced varied antioxidative diet contains molecules that reach these sites. The situation is different with antioxidative supplementation or therapy. Here, one must be purposefully selective. Ginkgo biloba, for example, has proven to reach the mitochondria of axons and exert their effect there. Other molecules are also promising and are currently being investigated (e.g., vitamin supplementation containing calcium-L-methylfolate). Doses of any antioxidants that are too high should imperatively be avoided because all antioxidants become prooxidants if the concentration in the body is too high.

2.3. Pharmaceutical Treatment of Systemic Hypotension

Arterial hypertension (high BP) is a frequent and well-known risk factor for many diseases. Correspondingly, there are also many treatment options. Less well known, however, is the fact that arterial hypotension (low BP), one of the leading FS symptoms [26][27], can also be a risk factor. Many studies have shown that low BP, increased BP fluctuations, nocturnal dips of BP, and orthostatic hypotension increase the risk of occurrence and progression of glaucomatous damage [28]. We are therefore often asked by patients what they can do to increase BP.

We always start with simple interventions, such as increasing salt (sodium chloride) intake mostly in the evening and physical activity. To better control the intake of additional salt, the pharmacist can prepare salt tablets. If the salt is poorly tolerated, it can be taken together with tomato juice.

FS patients should avoid certain drugs as much as possible. Many medications, especially sleeping pills and sedatives, have a side effect of lowering BP. The advantages and disadvantages of such treatments must therefore be weighed against each other.

In the case of orthostatic hypotension, we recommend that patients get up slowly in the morning. We recommend support stockings for people who are in a profession that requires them to stand (or sit) for a long time.

If all this is not sufficient, pharmacological therapy may be considered in rare cases. Although vasoconstrictive drugs are relatively often prescribed for this purpose, they reduce blood flow to the eyes despite an increase in BP and are therefore counterproductive in such cases.

We have had good experiences with a very low dose of fludrocortisone (2 × 0.1 mg per week) [29]. Fludrocortisone is a mineralocorticoid and not a glucocorticoid and therefore has fewer side effects than glucocorticoids.

The good news is that BP does not necessarily need to be totally normalized. In patients with severe hypotension, even a slight increase in BP leads to significantly better vascular regulation.

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