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Treatment of patients with Flammer Syndrome (FS)

Experiences of Josef Flammer,
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Flammer syndrome (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, or if people subjectively suffer from their symptoms. Recommendations concerning lifestyle management, nutrition, and drug therapy that have proven helpful in our clinical practice are discussed here.

1. What should patients with FS avoid?

Patients with FS generally observe themselves well, and they know what is good and what is not good for them. Nevertheless, they are usually grateful and relieved when their doctor discusses these important aspects with them.

Cold exposure:

Cold hands and/or feet are a leading symptom of FS. That's why people with FS generally prefer to avoid the cold, and they often notice that they can fall asleep sooner if they warm up their feet or wear socks to bed. Others report symptoms like chest pain, when they drink cold liquids. While this is usually harmless, cold can also be dangerous in rare cases:

We were treating a FS patient with normal tension glaucoma (NTG) who noticed a sudden increase in her visual field defect while skiing in very cold weather. The perimetry on the very next day revealed a new large absolute scotoma.

Two female NTG patients independently of each other fell unconscious after jumping into the cold waters of the North Sea. Both ladies had to be rescued by their partners, and this happened twice to one of them. A young doctor with pronounced FS suffered a heart attack when he jumped into a cold swimming pool.

These clinical observations have also been confirmed by many experimental studies. At the same summit in Rigi Kaltbad, Katarzyna Konieczka presented a study, which had revealed that the visual fields of glaucoma patients with FS temporarily worsened when they put one hand in cold water, while the visual fields of patients without FS remained stable.

Psychological stress:

Everybody experiences emotional stress from time to time, which can trigger a variety of different physical symptoms. In people with FS, these symptoms are mostly vascular. For instance, they notice cold hands or white and red spots on their face or neck.

Using thermographic images, we have observed that in people with FS, during emotional stress, some areas of their face cool down while other areas warm up at the same time.

A very successful young musician suffered from an NTG. During capillary microscopy of the nail fold, the cold provocation caused a blood flow standstill of 60 seconds. When she later told of a problem with her husband, the blood flow stopped for 130 seconds.

These symptoms and signs are harmless. If, however such phenomena occur in other organs such as the eye, it can potentially cause damage:

One NTG patient with FS was stable for years, but within a 3-month period, her visual field deteriorated very much. Only when we asked her specifically did she describe the heavy burden she felt from her daughter's divorce.

Three bankers with FS who had developed an anterior ischemic optic neuropathy (AION) came to our office. Two of them got sick during the great financial crisis of 2008 and the third individual came later, but also when he lost money in the stock market.

Another young patient with FS had an argument with her superior. She developed an AION in her left eye on the same day and was treated in an emergency center with corticosteroids. They were ineffective, and she became blind in her affected left eye. Three months later, under similar conditions, she noticed visual disturbances in her right eye, and she visited our clinic. We diagnosed a fresh AION in her right eye and immediately initiated a full FS therapy (see below). Her visual field, visual acuity, and optic nerve-head recovered. Today, many years later, this right eye is still healthy.

A man with FS in his mid-50s lost his job. On his way home, he caused a car accident. He was sent to a hospital with minor injuries. When he arrived, he noticed that he could not see anything in one eye. An AION was diagnosed, but unfortunately, he was not transferred to us until a few days later. He remained blind in this eye.

An older teacher at a high school who had already lost one eye to an AION some years earlier had an argument with the parents of one of his pupils. That same evening, he developed an AION in his remaining good eye. Fortunately, we had the opportunity to start treatment the same evening and his eye largely recovered. Today, many years later, the man is retired and is subjectively not disturbed by his visual field deficits and can read well with this eye. His FS symptoms have decreased.

A monk with FS was treated for an AION. A few weeks later, similar symptoms appeared in his other eye, and he finally came to us. We found a massive increase in retinal venous pressure (RVP), a phenomenon we occasionally observe in FS patients. After we decreased the RVP (see below), the first eye improved slightly, and the second eye improved significantly.

Another man with FS and an advanced NTG felt under significant pressure to perform in his job as a goldsmith. He took early retirement and his FS symptoms subsided for the most part, and the glaucoma stabilized.

A 14-year-old girl with FS was under tremendous stress because she couldn't fulfill her own expectations. She developed an AION, and unfortunately, we did not see her until 2 weeks after the event. She remained blind in one eye, but her other eye remained healthy for years by employing mild prophylactic therapy.

A young man with FS was responsible for the maintenance and repair of postbuses. One day, chips were introduced to acknowledge workers' individual achievements. This put him under massive psychological and emotional pressure, and he developed a central serous chorioretinopathy. An indocyanine green angiography revealed a distinct venous dysregulation in the choroid of the affected eye, and to a lesser extent, also in the unaffected eye, a phenomenon discovered by Christian Prünte and presented also at this first Ocular Blood Flow Summit 2019. The patient completely recovered after he changed jobs.

Even more frequently than AION we saw retinal vein occlusions after stress in otherwise completely healthy people with FS, including doctors in our hospital and professors from our university. A young sportswoman developed very high RVP up to a venous stasis retinopathy after breaking up with her boyfriend, though she recovered slowly once treatment was administered (see below).

Of course, stress simply cannot be avoided. However, it is possible to arrange private and professional life in a way such that stress becomes less pronounced. There are also strategies, such as autogenic training and yoga, that can help a person deal with unavoidable stress. Sometimes professional support is needed, and if potentially dangerous vascular reactions persist, prophylactic drug therapy may make sense (see below).

Extreme physical activity:

Exercise is healthy for everybody, including people with FS, as long as it's not too extreme. Since we have observed that people with outdoor job suffer much less frequently from both FS symptoms and FS associated diseases than people with indoor jobs, we recommend exercising and / or playing sports outdoors as often as possible. We have also observed that exposure to daylight reduces FS symptoms. With this in mind, we recommend exercising or playing sports outside during the day instead of inside or at night.

Occasionally, we have observed patients exercising or playing sports for long periods, and some almost become addicted to it. Many FS patients jog or cycle very intensively. Reducing these extreme activities usually improves vascular regulation.

A young man with FS and advanced NTG rode his bike for several hours every day in a mountain area because he felt he needed it. While monitoring his blood pressure (BP) over a 24-hour period, his systolic BP dropped to 65 mm Hg at night, and sometimes it dropped

even lower. We recommended that he shorten his trips to about one hour a day. Fortunately, his nighttime BP dropped less and his glaucoma stabilized.

Patients with FS are also more sensitive to vibrations:
A young woman with FS noticed a slight earthquake, while other people in her environment did not notice it. Vibrations of the hands can lead to vasoconstrictions, and such individuals should not work with compressors. They are also more sensitive to mechanical traction:
It is very common for FS patients to require more treatment and recovery time after whiplash injury.

Rapid increase in altitude:

The response to lower oxygen concentrations present at higher elevations is in FS subjects stronger than in individuals without FS and in addition, they take longer to adapt:

A young lady with FS treated for a venous stasis retinopathy fell unconscious on a hot air balloon ride over the Alps. She regained consciousness immediately after the balloon dropped to a lower elevation.

A young FS man took a cable car from 1,500 to 3,200 m above sea level. He was unconscious when he arrived, so he was immediately taken back to the valley by gondola where he quickly recovered.

In a flight simulator study, we found that young healthy FS subjects were less able to tolerate the reduced atmospheric pressure, and for some of them it was so bad that they had to abort the study, while subjects without FS tolerated it very well.

2. Nutritional recommendations for patients with FS

While most dietary advice is rightly aimed at reducing body weight, people with FS should make sure that their body mass index (BMI) does not fall too low. The lower a person's BMI, the more intense the FS symptoms are. A **normal body weight** should be aimed. After fasting, the symptoms increase significantly, and we therefore advise against fasting by people with FS.

Glaucoma patients with FS, have increased oxidative stress, particularly in the mitochondria of neural axons. The food should therefore contain as many **natural antioxidants** as possible. We refer here to the Basler recommendations for the nutrition of glaucoma patients with FS and to a video on oxidative stress that can be also found on this FS website.

An increase in **omega-3 fatty acids**, especially in the form of sea food can be helpful. It reduces FS symptoms by upregulating the uncoupling proteins, thereby increasing ATP-independent heat production.

Although the **magnesium** (**Mg**) plasma concentration in FS patients is usually normal, the diet should contain sufficient Mg. The Mg-supplement is discussed below.

FS patients often have very low BP. While it is generally rightly recommended to reduce salt intake, particularly for patients with arterial hypertension, FS patients with severe arterial hypotension should consume **enough salt**, especially in the evening, to avoid major drops in BP during sleep.

People with FS also have a reduced feeling of thirst, which often leaves them dehydrated. Therefore, it is important that they make sure that they **drink enough** fluids, even in the evening before going to sleep.

3. Drug treatment of patients with FS

Of course, we only treat if necessary and this is especially true for drug therapy. As ophthalmologists, we treat FS patients with eye diseases such as glaucoma, particular NTG, retinal vein occlusions despite the lack of classical risk factors, and central serous chorioretinopathy. However, it is important to emphasize that it does not only affect the eye. Many of our patients or their relatives have also experienced non-ocular FS associated diseases such as acute hearing loss, heart attacks despite lacking classical risk factors, or certain autoimmune diseases etc. The therapy that we employ is administered in a holistic manner, and we do not treat just one organ such as the eye.

Drug sensitivity

Patients with FS often tell us that they cannot tolerate certain medications very well or sometimes apparently not at all and therefor prefer herbal remedies or homeopathic therapy. Based on our experience however can these patients 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.

We draw the attention of patients with FS to the fact that their children are also more likely to have FS. The 18-year-old son of one of our NTG patients with FS was hospitalized at an internal medicine clinic due to general infection. During the stay, his BP dropped so low that he had to be given adrenaline intravenously. The resulting vasoconstrictive reaction was so violent that he lost fingers, toes, and the tip of his nose.

We recommend that FS patients start a drug treatment at a very low dose whenever possible, and then increase it slowly until they see the desired effect or side effects occur. We recommend that a person with FS should be particularly cautious with all vasoconstrictive medications. Often, neither the doctors nor the patients notice that many different medications (e.g. some psychotropic drugs) have a vasoconstrictive side effect.

Special care should be taken when planning operations including the carefully consideration of anesthesia. See more information on our webpage on *Flammer Syndrome / Literature / perioperative visual loss*.

We investigated the effect of glaucoma drugs on corneal temperature. After one drop of brimonidine (but not placebo) the temperature of the cornea dropped for approximately 90

minutes due to the vasoconstrictive effect of brimonidine. Interestingly, this effect was significantly stronger in patients with FS than in patients without FS. Our glaucoma patients with FS generally did not tolerate brimonidine very well compared to patients without FS.

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

Pharmaceutical improvement of regulation of the microcirculation

Primary vascular dysregulation 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 not yet addressed this issue. Nevertheless, we are already able to effectively help these patients. We have had our best experience with calcium channel blockers and magnesium.

Calcium channel blockers (CCBs)

In ex vivo studies, we have demonstrated that in ocular circulation, CCBs significantly reduce the effect of Endothelin-1 (ET). In FS patients, we found a slight increase in plasma levels of ET. But even more important was our observation that the lower the BP, the greater the ET sensitivity in these patients.

Even before we knew this rational justification for CCB treatment, we already had clinical experience with it. The positive visual field response to CCBs in certain patients was one of the cornerstones of discovering primary vascular dysregulation and FS. We've conducted various visual field studies, and over time, we noticed that it was always the same patients who showed a visual field response, whether it was an improvement of caroboanhydrase inhibitors, CCBs, CO2 respiration, or a worsening of cold provocation. And the visual field response occurred in the same patients who also showed a prolonged arrest in blood circulation of the nail fold after cold provocation and shortening of this arrest after CCBs.

Controversial discussions regarding the benefits associated with CCBs began to surface, particularly for glaucoma patients. We had to clear up a lot of misunderstandings. First of all, we cannot simply expect a positive outcome in all patients, but only if primary vascular dysregulation or FS is actually present.
There were also fears of a "steel effect", this means that the vessels in healthy areas would be dilated and that as a result even less blood would flow in the diseased areas. However, this is unlikely as such a steel effect would hardly explain visual field improvements, and it became evident that CCBs dilate pathologically contracted blood vessels more than healthy ones.
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 to nonexistent in patients who already have low BP, (c)

animal experiments have shown that nifedipine increases ocular blood flow, even when it reduces BP, and d) our most important parameter in glaucoma is the visual field.

Others have assumed that fat-soluble (centrally acting) CCBs (e.g. nimodipine) would be better than water-soluble (peripherally acting) CCBs like 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've had the opposite experience, which may be explained by the fact that there is actually no blood-brain barrier in the optic nerve head (see book Flammer et. al..: Basic science of ophthalmology 2013). It is important to note that studies comparing different CCBs in glaucoma patients have 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. Since nifedipine has a short half-life, the 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 keep 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. The intake during the day and not 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 is 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. 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 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, though it has a longer half-life. But unfortunately, it is only available in a dose of 5 mg or higher.

Sometimes FS patients get arterial hypertension when they get older. In such cases we recommend an antihypertensive treatment containing a low dose a CCB (e.g. a combination of an ACE-inhibitor with 5 mg amlodipine).

We know that ET increases RVP, but not every high RVP is ET induced. Accordingly, one cannot lower every RVP with nifedipine. In addition, CCBs and thus also nifedipine only inhibit the ET induced influx of calcium from the outside into the cell, but not the 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.

Endothelin blockers:

Endothelin blockers are particularly interesting, but 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 ET blockers reduce increased RVP.
Endothelin traps and the delivery of artificial transcription factors are also under investigation.

Magnesium:

Magnesium (Mg) is a physiological CCB. We have shown that Mg reduces the effect of ET both in vitro and in ex vivo. We have further observed a slight improvement in the visual field of glaucoma patients with FS. 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, 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 a CCB.

Betaxolol:

Studies have demonstrated that glaucoma patients treated with betaxolol had a smaller rate of visual field deterioration than patients treated with timolol despite the fact that betaxolol reduces IOP less than timolol. 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.

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. We don't have much experience with it because it is not yet on the market in Switzerland.

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.

Carbonic anhydrase inhibitors (CAI):

Acetazolamide is used to reduce both IOP and intracranial pressure. It also dilatates eye and brain vessels, and it 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. 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. Therefore, they are ideal for glaucoma patients with FS despite their limited ability to lower IOP.

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.

Calcium-L-Methylfolate (the active form of folic acid) has also shown promise, as it not only reduces homocysteine but also increases NO production via activation of the NO-synthetase, thereby improving vasodilatation. While beneficial effects have been demonstrated (e.g., in diabetic patients), it has not been studied so far in patients with FS.

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., 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.

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) 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. 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 or **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 have to stay in their profession for a long time.

If all this is not sufficient, pharmacological therapy may be considered from time to time. 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 x 0.1 mg per week). 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.

4. What does this all mean in practice?

We already mentioned that not all people with FS need treatment. The good news is that very different FS-related phenomena usually respond to treatment in parallel. We found that FS patients often display the following disease signs at the same time: NTG, disturbed autoregulation of ocular blood flow, increased retinal venous pressure, and optic nerve compartment syndrome. In most cases, treatment with a low dose of nifedipine (mostly combined with magnesium) simultaneously improved the regulation of retinal vessels, reduced RVP, and reduced optic nerve compartment syndrome**.**

How do we ensure that a chosen therapy works? In the end, the main criterion is organ and system function (e.g. the visual field in glaucoma). However, in most cases, we would like to see the effect more quickly. There are subjective criteria. If, for example, a patient notices that his hands have become warmer, then we are very likely on the right track.

But there are also helpful objective parameters: A reduction of the RVP or an improved reaction of the retinal vessels to flickering light or a shortening of the flow standstill after cold provocation in capillary microscopy shows us that the treatment has a positive effect.

Note*: Here we describe the experiences we have gained with our own patients. We do not know how far they can be extrapolated to other patient groups. Therefore, we cannot assume any medical or legal responsibility for the care of other patients.*