Diseases associated with Flammer Syndrome: An Update

Katarzyna Konieczka*, Josef Flammer¹ and Carl Erb²

¹Department of Ophthalmology, University of Basel, Switzerland
²Eye Clinic Wittenbergplatz, Germany

*Corresponding author: Katarzyna Konieczka, Department of Ophthalmology, University of Basel, Mittlere Strasse 91 CH-4056 Basel, Switzerland

Abstract

Flammer syndrome describes the predisposition for an altered reaction of the blood vessels to stimuli such as coldness, emotional stress, and / or hypoxia - together with a group of additional signs and symptoms. The essential component of Flammer syndrome is primary dysregulation of blood vessels. While most people with Flammer syndrome are healthy, they have an increased risk of certain ocular diseases, such as: glaucomatous optic neuropathy, Leber's hereditary optic neuropathy, optic nerve compartment syndrome, retinitis pigmentosa, retinal arterial and vein occlusions, central serous chorioretinopathy, visual snow, as well as certain systemic diseases, such as multiple sclerosis, breast cancer and metastatic disease, or altitude sickness. The relationship between Flammer syndrome and diseases like anorexia nervosa, sudden hearing loss, thyroid dysfunctions or pancreatic cancer are currently under investigations. This review is an update to our previous review on the same subject.

Keywords: Flammer syndrome, Primary Vascular Dysregulation, Glaucomatous Optic Neuropathy, Leber’s Hereditary Optic Neuropathy, Optic Nerve Compartment Syndrome, Retinitis Pigmentosa, Retinal Arterial and Vein Occlusions, Central Serous Chorioretinopathy, Visual Snow, Multiple Sclerosis, Breast Cancer and Metastatic Disease, Altitude Sickness, Anorexia Nervosa, Sudden Hearing Loss, Thyroid Dysfunctions, Pancreatic Cancer

Introduction

Although some diseases have only one cause, most diseases are caused by the interaction of many factors. It is common for environmental factors to interact with genetic factors. The Flammer syndrome is the phenotype of a genetic predisposition to react differently to stimuli. This predisposition protects affected people from certain diseases but makes them more susceptible to other diseases. This review is an update on our previous review on diseases potentially related to Flammer syndrome [1].

Flammer Syndrome

Flammer syndrome [FS] describes the predisposition for an altered reaction of the blood vessels to stimuli such as coldness, emotional stress, and / or hypoxia - together with a group of additional signs and symptoms [2-5]. The essential component of FS is primary dysregulation of blood vessels [3]. The term "Flammer syndrome" [2] was introduced in the scientific literature only recently [2,6,7], but many aspects of FS were described in older publications under the terms "vasospastic syndrome" [8] or "primary vascular dysregulation" [3]. The history of the discovery of the FS and its introduction into the scientific literature have been described in a recent review [9]. Most people with FS are healthy. Those affected often have symptoms, but because they are unaware of the syndrome, they do not realize that these symptoms are interconnected. Moreover, most people with FS have had symptoms since their youth, and they have a mother or a father who also displayed them. Therefor they consider them as normal. People with FS have also often learned to alleviate the symptoms, for example by wearing bed socks at night. Clinical observations suggest that FS...
may even have protective effects resulting in a good life expectancy, because they have less often classical cardiovascular risk factors - such as high blood pressure, dyslipidemia or overweight. People with FS also seem to be protected against metabolic syndrome [10], probably due to increased adiponectin levels [11]. Of course, arterial hypertension, hypercholesterolemia or even obesity can also occur in FS people, especially when they get older, but simply much less often than in other people. The same therefore also applies to classical cardiovascular diseases. However, people with FS are at certain risk for other diseases. These include some eye diseases, but also multiple sclerosis, altitude sickness and certain cancers. While many relationships have not yet been clarified and are currently being studied in a variety of research projects, we summarize here the already known facts.

Ocular Signs of FS

Josef Flammer - the clinician and scientist who discovered the FS - is an ophthalmologist; therefore, the connections between FS and ocular diseases have been the most heavily studied. The term “Flammer syndrome” was finally introduced in the literature by Katarzyna Konieczka [2,6,7], also an ophthalmologist. Thus, we will discuss the ocular effects of FS first. The symptoms and signs of FS occur in affected people even when they are healthy, but they occur more frequently and more severely when the FS individuals have diseases associated with FS. This also applies to ocular signs. In the eyes of individuals with FS, the following signs are often observed: Reduced autoregulation of ocular blood flow [12], with the consequence that the blood supply to the eye is largely determined by the perfusion pressure. This in turn explains why in these people the blood supply to the eye correlates with the blood flow in the fingers [13]. Further signs are stiffening of retinal vessels [14] and increased spatial vascular irregularity [15]. The reaction of retinal vessels to flickering light is diminished in individuals with FS [16]. This is an indirect sign of a kind of endotheliopathy [17].

Another ocular sign of FS are optic disc hemorrhages, which occur often in FS patients with glaucoma, but sometimes also in individuals with FS without glaucoma [18]. The retinal venous pressure can be higher than the intraocular pressure in various diseases, such as glaucoma, especially if these patients have FS [19]. The glial cells, particularly the astrocytes in the retina are more frequently and more strongly activated in glaucoma patients with FS than without FS [20]. Individuals with FS sometimes feel pain, particularly behind the upper eyelid [21] due to relative hypoxia in the ciliary muscle. Relatively rare, but very disturbing for the patients, are scintillations – described in the literature as visual snow – which are perceived with open and closed eyes. While our clinical observations are impressive, the exact relationship between FS and visual snow has yet to be demonstrated in future studies.

Ocular Diseases Related to FS

Here we discuss diseases with more or less known causes, which nevertheless occur more frequently in people with FS. We must therefore assume that FS can play a role in the occurrence or course of these diseases [1]. This concerns the following diseases: glaucomatous optic neuropathy, Leber’s hereditary optic neuropathy, optic nerve compartment syndrome, retinitis pigmentosa, vascular occlusions, central serous chorioretinopathy, and visual snow [1].

**Glaucomatous optic neuropathy [GON]** is characterized by an excavation of the optic nerve head [ONH], as well as a loss of nerve fibers, with corresponding visual field deficits. There are many known risk factors for GON; the best known is elevated intraocular pressure, which in turn has many different causes. Other factors that influence the occurrence or course of GON include vascular factors, especially primary vascular dysregulation [3], the essential component of FS. This is especially true for normal tension glaucoma [22]. Here we already understand the connections quite well. A component of primary vascular dysregulation is an impaired regulation of ocular perfusion. As a result, fluctuations of intraocular pressure or blood pressure lead to unstable oxygen supply to the eye. This in turn boosts oxidative stress - particularly in the mitochondria of the ONH - and activates astrocytes. All this ultimately leads to cell death and ONH excavation. Individuals with FS also have on average lower ocular perfusion due to increased retinal venous pressure [19], increased vascular resistance, and decreased blood pressure [23]. This pathogenetic concept of GON development has been described in previous reviews [24,25], as well as the relationship between glaucoma and FS [22,26-29].

**Leber’s hereditary optic neuropathy [LHON]** is a rare inherited disease resulting from mutations in maternal mitochondrial DNA [mtDNA]. LHON leads to acute or subacute visual loss beginning in one eye, with the fellow eye becoming similarly affected within weeks. In the late stage, the ONH is pale, with shallow excavation. This has triggered discussions about whether there is a link between LHON and normal-tension glaucoma [30]. Mitochondrial dysfunction is a major component in both. Based on our clinical observations, most patients with LHON also have FS [3,31]. It is conceivable that the oxidative stress induced by unstable oxygen supply escalates the risk of a mtDNA mutation to manifest clinically [31].

**Optic nerve compartment syndrome [ONCS]** [32,33] is a pathological condition in which the cerebrospinal fluid [CSF] in the subarachnoid space surrounding the optic nerve is partially or totally segregated from the CSF in the intracranial subarachnoid space, increasing the local CSF - pressure and thereby distending the optic nerve sheath. The pathogenesis of this condition remains unclear. Clinical observations reveal that most patients with both glaucoma and ONCS, also suffer from FS [3], [33,34]. We assume that the locally increased oxidative stress leads to swelling of the arachnoid trabeculae, septa, and pillars in the subarachnoidal space of the optic nerve. In addition, a locally elevated endothelin level constricts the lymph vessels and reduces the outflow of the cerebrospinal fluid. This explains the positive effect of calcium channel blockers [34].
There is also a connection between retinitis pigmentosa (RP) and FS [35-37]. RP comprises a heterogeneous group of hereditary diseases that lead to a loss of retinal cell function. Primarily the photoreceptors of the peripheral retina are affected, later the whole retina, including the macula, may be affected. That RP has a genetic cause is indisputable [38], but that doesn't rule out the possibility that other factors influence the manifestation and progression of the disease [35]. One of the potential factors is reduced ocular blood flow [39-41]. Reduced ocular blood flow in RP is partly but not entirely explained by tissue atrophy. The assumption of an additional reduction of blood flow is supported by observations that the ocular blood flow is reduced already in early stages and is not confined to the eye [39,42]. We described the hypothesis that FS is one of the major causes for such a primary component of blood flow reduction in RP [35]. Thereby oxidative stress, induced by unstable blood flow in FS subjects, may play an important role [43].

Also potentially related to FS are vascular occlusions. The major causes of arterial occlusions such as the retinal arterial occlusions are thrombi or emboli due to atherosclerosis. Nevertheless, such occlusions can sometimes occur in young patients in the absence of classical vascular risk factors. In our experience, such vascular occlusions can occur in people with FS, especially under psychological stress or strong cold exposure. These occlusions can affect the ONH [44] and, less often, the choroid [45], the cilioretinal vessels [46], and the retina [3]. A relationship between Susac syndrome and FS has also been reported [47]. In addition, retinal and ONH infarctions have also been described as a perioperative complication in FS patients [48,49].

Retinal vein occlusions were previously believed to be always a consequence of thrombosis. Josef Flammer’s research group hypothesized that occlusion may also be a consequence of a local constriction of a retinal vein [50,51]. There are several causes for such a venous constriction, but FS is obviously a predisposing condition [50]. Whereas a mild local venous constriction increases retinal venous pressure, a more pronounced constriction can result in a retinal vein occlusion [51,52]. These venous constrictions are induced by vasoconstrictive molecules, particularly endothelin-1. Endothelin is a very strong vasoconstrictor that can diffuse to the veins from neighboring sick arteries or from circulating blood via fenestrated choriocapillaries into the ONH. Under hypoxic conditions, endothelin is also produced in the surrounding tissue. This explains why not only arteriosclerosis, high blood pressure, and increased intraocular pressure but also FS increase the risk for vein occlusions.

Central serous chorioretinopathy (CSCR) is a disease characterized by a serous detachment of the retina in the acute phase. The detachment is the consequence of one or more defects of the outer blood-retina barrier, i.e. the pigment epithelium. Fluid from the choroid thus passes under the retina. The defects usually disappear spontaneously, in certain cases the disease can become chronic. The pathogenesis is still largely unclear. A number of risk factors have been identified, for example male gender, corticosteroids usage, psychologic stress, pregnancy, some endocrine disorders, etc. We postulated that FS might be a risk factor for CSCR [1,3]. Many of our CSCR patients also had signs and symptoms of FS. A report years ago pointed out that the disease is accompanied by a local vascular dysfunction of the choroid, particularly dilated veins [53]. It has also been reported that the disease occurs more frequently in type - A personalities and manifests itself particularly often in patients who are under psychological stress. We know that typical reaction to stress in individuals with FS is transient vasodilatation and/or vasodilatations. In the acute phase, endothelin is significantly elevated in the blood. A postulated local increase of the endothelin concentration can explain the venous stasis in the choroid, as well as the local opening of the external blood-retina barrier [54].

Patients with "visual snow" report continuous tiny dots in the entire visual field similar to the noise of an analogue television. It is a unique visual disturbance clinically distinct from migraine aura, although these patients often also suffer from migraine at the same time [55]. Based on our clinical experience, many patients suffering from visual snow have pronounced symptoms and signs of FS. The causality of this association needs however to be clarified.

Systemic Signs and Symptoms of FS

FS signs and symptoms occur mainly when related diseases occur; but they can also be present in completely healthy people with FS. For this reason, we will first discuss FS symptoms independent from diseases. The two most prominent symptoms of FS are cold hands and/or feet [8] and low blood pressure [56]. In addition, persons with FS often are very slim [57]. Typically, they take a long time to fall asleep and exhibit a phase delay in the circadian rhythm. The sensation of thirst is reduced, probably caused by slightly elevated levels of endothelin-1 in circulating blood [58]. This suppresses the thirst center in the brain via PG-E2. Individuals with FS are generally more sensitive; they have increased sensitivity to certain drugs [for example to calcium channel blockers or beta-blockers], increased pain sensation, increased smell sensation, and increased sensitivity to high altitude. Individuals with FS have more frequent headaches and migraines. Persons with FS often suffer from tinnitus and have a tendency toward perfectionism. They also have prolonged blood flow cessation in the nailfold capillaries after cold provocation. People with FS have an autonomic imbalance with sympathetic predominance [59]. Nevertheless, the causal relationship with the vascular dysregulation is unclear, because non-autonomic innervated retinal vessels are also involved in FS [3]. Individuals with FS have altered gene expression [60] and increased systemic oxidative stress [61]. More details can be found in our previous publications [2,3].

General Diseases Related to FS

Multiple sclerosis (MS) is a demyelinating degenerative disease of the central nervous system of unknown etiology. Patients with MS suffer significantly more frequent from signs and symptoms of
FS than controls [3,62], but we still do not know why. There are two options: MS may cause FS symptoms, or people with FS may have a higher risk of developing MS. It is quite interesting that patients with MS often indicate they had symptoms of FS before they developed MS. J. Flammer et al. hypothesized that the clinically undetected microinfarctions may trigger an autoimmune disease [3]. The increased oxidative stress in FS subjects may further contribute to the pathogenesis of MS. In a later stage of the disease, the inflammation induces a secondary vascular dysregulation, which further contributes to the chronic progression of MS [63].

**Cancer and metastatic disease:** The development of cancer is complex and the cause multifactorial. At present we know little about the connections between FS and the occurrence and course of cancer. Associations between cancer and FS have already been published [64,65] and discussed. Intermittent hypoxia and oxidative stress due to FS may contribute to breast cancer and its progression into metastatic disease [66]. In some other tumors, such as pancreatic cancer, we have a clinical suspicion of a connection with FS.

**Altitude sickness** is a general term encompassing a spectrum of disorders that occur at higher altitudes. The primary cause of altitude sickness is the low oxygen level at higher altitudes that leads to tissue hypoxia and thereby to an increase in hypoxia-inducible factor 1-alpha. This leads to increased expression of several hormones, such as endothelin-1 and erythropoietin. Individuals with FS have both higher plasma levels of endothelin and higher sensitivity to endothelin [67]. Altitude sickness is therefore more pronounced in FS people [3,68,69].

**Diseases Under Investigation**

Clinical evidence points out that signs and symptoms of FS often occur in patients with *anorexia nervosa*. This relationship is presently under investigation. Interestingly, fasting intensifies FS symptoms. This is consistent with the observation that fasting reduces the responses of retinal arteries and veins to flickering light [70]. Clinical observations have also revealed a link between FS and *Tinnitus, sudden hearing loss*, and even Ménière’s disease. These relationships are also currently under investigation. Patients with both normal tension glaucoma and FS often have

**Thyroid dysfunctions.** Other patients have antibodies against the thyroid despite normal gland function. Patients with FS also suffer relatively frequently from Hashimoto thyroiditis. Again, subclinical microinfarctions may triggering autoimmunity. The relationship between FS and some heart diseases - such as

**Prinzmetal angina** - is likely, but has, to the best of our knowledge, not yet been investigated. However, the fact that persons with FS often suffer from silent myocardial ischemia has already been reported [3].

A *whiplash trauma* is the result of the sudden deceleration or acceleration of the thorax independent of head movement. Such injuries usually occur as a result of a rear-end collision. Symptoms caused by the injury are grouped together as “whiplash associated disorders” and encompass neck pain, headaches, dizziness, and sleep disturbances. In our clinical observations, patients with whiplash trauma have more and longer lasting symptoms when they also suffer from FS. We have a clinical suspicion that there is an association between

*Pancreatic cancer* and FS. To prove this scientifically, however, we need further data. This relationship is currently being investigated.

**Conclusion**

Although FS appears to even protect against certain diseases - such as metabolic syndrome and cardiovascular events – there are many indications that it increases the risk for other diseases, such as eye diseases or multiple sclerosis. We have made the clinical observation that FS treatment significantly slows down or even completely stops the progression of visual field damage in patients with glaucoma, particularly normal tension glaucoma. It is however not yet known whether treatment of FS also slows progression of other related diseases.

**Disclosures/Conflict of interest**

The authors declare that there is no conflict of interest.

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Katarzyna Konieczka. Biomed J Sci & Tech Res

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