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Review Article

Dietary Support for People with the Flammer-Syndrome

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Abstract

Blood flow - including ocular blood flow (OBF) - is important for transportation (e.g. O2), thermoregulation, volume regulation, and barrier function. Different parts of the eye have separated vascular systems, which are different both, anatomically and functionally. Primary vascular dysregulation (PVD) is relevant in the context of various diseases such as glaucoma, as this condition leads to a disturbed autoregulation of OBF. People with a PVD tend to have cold extremities, prolonged sleep-onset time, altered drug sensitivity, low blood pressure and higher smell score. The term Flammer-Syndrome (FS) refers to PVD with an additional cluster of symptoms and signs that may occur in healthy people as well those suffering from a disease such as e.g. glaucoma. People with FS have several aspects in common such as like stiffer blood vessels, reduced neurovascular coupling, increased retinal venous pressures and increased levels of systemic oxidative stress. Oxygen supply to the eye fluctuates, either if IOP fluctuates on a high level or blood pressure on a low level or if autoregulation is disturbed as in people with FS. Unstable oxygen supply to tissues such as the optic nerve head leads to oxidative stress, which in turn, leads to the production of free radicals such as peroxynitrite (ONOO-) which finally kills the cells. Thus, interest in diets rich in antioxidants including polyphenolic flavonoids such as tea, coffee, wine and anthocyanosides found in blueberries is increasing.

Keywords: Antioxidants; Flammer Syndrome; Oxidative Stress; Primary Vascular Dysregulation

Abbreviations

OBF: Ocular Blood Flow; SVD: Secondary Vascular Dysregulation; PVD: Primary Vascular Dysregulation; NOS: Nitric oxide Synthase; ABC Transporter Proteins: ATP Binding Cassettes Transporter Proteins; IOP: Intraocular Pressure; FS: Flammer Syndrome; HDL: High density lipoprotein; LDL: Low Density Lipoprotein; MCP: 3-Methyl-1,2-Cyclopentamedione; NO: Nitric Oxide; C: Catechin; EC: Epicatechin; EGC: Epigallocatechin; TFs: Theaflavins; TGs: Thearubigins.

Introduction

Physicians are at times confronted with questions from patients regarding dietary support for their health. This may partly be due to the fact that patients are often dissatisfied with the conventional form of treatment provided because it has been ineffective [1], has produced adverse effects [2,3], is too technologically oriented or because it is less compatible with the patients' values regarding nature and meaning of health and illness [4]. The impact of nutrition on the manifestation and progression of ocular diseases has thus become an important, controversial topic. More recently, interest has been directed to the potential value of dietary support for people with the Flammer- Syndrome, in particular because people suffering from this syndrome are typically healthy, although at higher risk for a variety of disorders [5].

The Flammer-Syndrome, named after the famous clinician and scientist Prof. Josef Flammer describes a combination of symptoms and signs in people who are generally otherwise healthy. These symptoms and signs result from a predisposition to increased sensitivity as e.g. an increased response of the blood vessels to stimuli such as cold result in the person having cold hands [5]. Since people with the Flammer syndrome commonly have higher levels of oxidative stress, dietary support with foods rich in antioxidants is recommended for them [6-8]. The description of the Flammer-Syndrome is given in more detail below. Let's first take a look at the function and regulation of blood flow in the eye.

Function and regulation of blood flow in the eye

Function of blood flow

Blood flow acts primarily as a transport system. It functions similarly to an economic system: if the production and use of a product are not at the same place, we require some kind of a transport. Blood circulation serves not only to transport a large variety

of molecules such as oxygen, cells or heat but, in addition, also serves to exchange information between different organs.

Another function of blood flow is to transport heat. Blood circulation is therefore the reason why our body functions as an intact system and our organs do not function independently [9].

An over-perfusion rarely causes a problem. It can lead to swelling of the corresponding organ and eventually also to damage of blood vessels. Quite often, however, we have to deal with an underperfusion and its consequences. In worst scenario a more or less constant reduction of OBF, can in extreme cases, even lead to infarction. Our organs cannot outlive the strong reduction of the essential nutrients transported to them. A reduction in oxygen supply is particularly detrimental as our organs have no oxygen reserves and rely on the transport of oxygen [10].

Vascular dysregulation

Functional vascular dysregulation

The need of blood flow to different organs tissues varies quite rapidly over time which is why there's a need for a sophisticated local regulation of blood flow [11]. Dysregulation simply means that blood flow is not properly adapted to this need. Dysregulative mechanisms can therefore lead to an over- or an underperfusion. Such an over- or underperfusion does normally not induce long-term damage. Under certain circumstances, however, repeated underperfusion can lead to damage. An underperfusion occurs when a vessel constricts in responding to a stimulus. This is known as a vasospasm [12]. At times, vasodilation which are of necessity either do not occur or do not occur sufficiently. For this reason the term "vasospasm ", also known as "vasospastic syndrome" (if more than one organ is involved) was replaced with the more global term "vascular dysregulation" [12]. There are a number of causes that lead to local or systemic vascular dysregulation. Vascular dysregulation can be due to other diseases; quite often, autoimmune diseases. This is known as a secondary vascular dysregulation (SVD). Vascular dysregulation, however, can also be primary of nature. In this review we will focus on primary vascular dysregulation. Primary vascular dysregulation (PVD) is an inborn tendency to respond different to different stimuli. PVD has an inherited component. Subjects often indicate that their parents, in particular their mothers, also suffered from cold hands and other symptoms [5]. The term Flammer-Syndrome Figure 1, refers to PVD with an additional cluster of symptoms and signs that may occur in healthy people as well those suffering from a disease such as e.g. glaucoma [13,14].

Figure 1: The spectrum of a population: Whereas people with a metabolic syndrome in general have an increased body mass index (BMI), high blood pressure (BP), diabetes mellitus type 2 (DM type II) and are less active, those with the Flammer syndrome have low BMI, low BP values, no diabetes and are generally quite active.

Josef Flammer. Glaucoma. 3rd revised edition. Hogrefe and Huber publisher (2006), page 104.

General symptoms of flammer syndrome

There are certain signs and symptoms that occur more commonly in people with the Flammer Syndrome. The more signs and/or symptoms that accumulate, the higher the chance that these subjects suffer from Flammer Syndrome. The symptoms also depend on the person's age. Most of the symptoms occur in puberty and mitigate with age. During menopause these symptoms generally attenuate and may even completely disappear. Some of these symptoms are described in more detail below as it helps to distinguish those suffering from this particular syndrome from others anamnestically.

Flammer Syndrome and temperature

Very classical is the response to cold [15]. People with Flammer Syndrome generally have cold hands even when there is only a moderate decrease in the temperature outside. Interestingly, an association has been observed between cold hands in these people and their optic nerve head blood flow [5]. Some of them even complain of being cold at all times whereas others get cold hands under psychological stress. Again, others suffer rather from cold feet.

Flammer Syndrome and sleep behaviour

People with Flammer Syndrome have trouble falling asleep particularly when they are cold. The reason is because we need to

warm up before we can fall asleep. These people have colder feet in comparison to others and therefore require a longer time to warm them up [16]. Sleep onset time is reduced if they take a warm bath before they go to bed or if they warm up their feet by wearing socks. Moreover, these people have a shifted circadian rhythm [17]. In other words, they are awake longer late in the evening and need a longer time in the morning to fully wake up.

Flammer Syndrome and thirst

People with Flammer Syndrome are often less thirsty than others [16]. Normally, they drink enough but rather because of the necessity to drink, rather than driven by thirst. This symptom can be explained by a slight increase in the hormone Endothelin in the circulating blood [17]. Endothelin is a peptide produced by endothelial cells. It is secreted abluminally to regulate local vascular tone. A small part of it is secreted intraluminally. One of the effects of Endothelin is to suppress the center of thirst in the brain (via an upregulation of another hormone, namely prostaglandin E2) [16-18].

Flammer Syndrome and blood pressure

People with Flammer Syndrome tend to have a low blood pressure especially at night and particularly when they are young [19]. The major cause for systemic hypotension in these patients is reduced reabsorption of sodium in the proximal tubule of the kidneys (ie, subjects with PVD loose more salt in the kidneys). This dysfunctional management of sodium in the kidney, which is partially dependent on Endothelin-1, has also been seen in patients with normal tension glaucoma.

Flammer Syndrome and smell

People with the Flammer Syndrome in general identify odours much better than other [20]. Indeed they are quite more sensitive to smells than others. A differential expression of odorant binding proteins may explain why the people are more susceptible to various different smells.

Flammer Syndrome and drug sensitivity

People with the Flammer Syndrome often don't tolerate certain classes of drugs. One of the reasons for the intolerance to certain drugs is that PVD subjects have a different expression of the so-called ABC (ATP-binding – cassettes) transporters proteins [21]. These are proteins, which, amongst other things, are involved in the transmembranal transport of drugs. When treated for example, systemically with calcium channel blockers or beta blockers they often feel sick and suffer from more side-effects than expected. If these drugs are given to these patients at a very low dose the drugs exert their beneficial effects and the patients suffer from barely any or no side-effects and thus the drug can exert beneficial effects [22]. In contrast, these patients may require a higher dose of other drugs, such as for example pain killers.

Flammer Syndrome and other signs

Laboratory results in people with the Flammer Syndrome often differ in comparison to other people. Endothelin value in blood is increased in these people [23]. We also mentioned that the ABC transport proteins are expressed differently [21]. Several studies have shown that the genetic expression of leucocytes in blood is altered [24]. In other words, some proteins are expressed more than others.

People with Flammer-Syndrome do not react well to trigger factors [5]. Various trigger factors include cold, medications, migraine attacks, hunger, mechanical stress, emotional stress etc. In our experience cold and psychological stress are important trigger factors as well as IOP and low blood pressure which play an important role in ocular blood flow. If there's a sudden drop in IOP or blood pressure the endothelial cells would have to react rapidly to make sure that ocular blood flow is not decreased. In other words, there's a demand on the regulation [25]. People with Flammer Syndrome lack healthy endothelial cells in their vessels and cannot react well towards this demand; in other words they have a disturbed autoregulation of blood flow. This is well observed by means of dynamic vessel analysis. The vessels of people with Flammer syndrome respond to flickering light (stress) with a reduced reaction (reduced neurovascular coupling) [26]. Moreover, their blood vessels are irregular [27].

The retinal venous pressure as measured by means of ophthalmodynamometry is also increased in these people [28,29]. It is also worthy to note that systemic oxidative stress values are increased in these people [30].

Since oxidative stress is increased in people with Flammer Syndrome we would like to discuss the value of nutrition with potential antioxidative effects [7,8].

Nutritional recommendations

Nutritional recommendations for individuals with Flammer Syndrome revolve around reducing oxidative stress. This could possibly improve the condition and lower the potential risk of certain diseases such as glaucoma [8].

Antioxidative Molecules

Most of these foods and beverages with antioxidative properties contain either polyphenolic flavonoids or anthocyanosides [31]. Both are natural antioxidative molecules that have the ability to neutralise oxygen radicals either by donating a proton or withdrawing an electron [9]. The most relevant examples of oxygen radicals are: reactive oxygen species, the superoxide anion, hydrogen peroxide and reactive nitrogen species. All of these are generated during physiological metabolism in the body [8].

Green or black tea, coffee, dark chocolate or wine are examples of foods containing polyphenolic compounds [8]. The hydroxyl group of a polyphenol enables these compounds to readily donate a proton to free radicals to neutralize them (Figure 2). Foods containing anthocyanosides possess a positively charged oxygen atom which can scavenge electrons from free radicals [8] (Figure 3).

Figure 2: The general chemical structure of a polyphenol with a phenol ring depicted in yellow. Alongside are foods rich in polyphenols.

Mozaffarieh M and Flammer J. Ocular blood flow and glaucomatous optic neuropathy. 2007 Springer. Page 45.

There are many examples of foods and beverages that contain molecules capable of reducing oxidative stress in the body, of which a few examples are named here.

Examples of foods and beverages

Anthocyanosides

Bilberries and blueberries

In general these foods are coloured, such as blue coloured fruits and berries. Bilberry (*vaccinium myrtillus*) and blueberry both belong to the genus vaccinium. The main difference is the flesh of the fruits, with the flesh of blueberries being white or green and the flesh of bilberries dark red or purple. This is why bilberries have a higher content of anthocyanosides [32].

Figure 3: Right: The general chemical structure of an anthocyanoside with a positively charged oxygen atom in the central ring which has the capacity to scavenge a free radical. Left: Blueberries rich in anthocyanosides.

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The reason for its antioxidant properties lies in the chemical structure as explained above. The high anthocyanoside content is the reason for scavenging properties. Neuroprotective effects through radical scavenging have been shown in animal studies [8].

Polyphenolic flavonoids

Coffee

Coffee might also have antioxidant effects due to its high content of polyphenols [7]. These molecules act as scavengers for free radicals and are capable of chelating metal [33]. They also inhibit lipid peroxidation and possibly have an effect against mutagenicity [34]. Especially the molecule 3 methyl-1,2 cyclopentanedione (MCP) acts as a scavenger selectively for peroxynitrite (ONOO-) [35]. which plays an important role in the pathogenesis of glaucoma [8].

Tea

Tea has long been an important part of many cultures and has been appreciated not only for its taste but also for its health benefits. Both green tea and black tea are products of the *Camellia sinensis* plant and contain polyphenols [7]. Black tea, by oxidation, develops theaflavins and thearubigins which have the ability to scavenge the superoxide anion and nitric oxide. This could help in-

hibit damage in glaucoma patients aswell as UV induced damage of oxidative stress. They also inhibit LDL peroxidation and formation of lipid peroxyl radical species [7]. Green tea, which does not go through oxidation thus has a higher content of polyphenols such as catechin (C), epicatechin (EC), epigallocatechin (EGC) and their gallate esters [36].

Wine

Endothelial dysfunction plays an important part in Flammer-Syndrome and can be improved by polyphenols in red wine which stimulate nitric oxide synthase (NOS) production that induces vasodilatation [7]. Polyphenols also inhibit oxidation of LDL [37] as well as Endothelin-1 production which also leads to increased ability for vasodilatation [38]. The polyphenolic content is much higher in red wine compared to white wine [7]. Some studies also show that flavonoids of wine have an effect against atherosclerotic plaque development [39] and VEGF reducing capabilities of certain molecules found in grapes and wine [40].

Borage

In eastern cultures, especially Iran, Borage (*boragio officinalis*) is known and appreciated for its flowers and seeds that contain different ingredients with medical properties [41]. The flowers are rich sources of vitamin A and C, carotenoids and polyphenols [42]. They have been shown to have a calcium- antagonising effect. Some health benefits include: cardio depressant effects [43], improving skin condition [44], reducing atherosclerosis [45] and dilating both blood vessels [41] and bronchial tubes [42].

The seeds of borage are rich in gamma linolenic acid which is an essential fatty acid that is converted into the endogenous vasodilatator Prostaglandin E1 [42,46]. A study has shown that Borage tea consumption lowers retinal venous pressure. Since retinal venous pressure is increased in people with the Flammer-Syndrome, borage tea could be brought up as nutritional recommendation for these patients [42].

Gingko biloba

Gingko leaves and fruits have a long history of being used for their medical properties in Chinese medicine. They contain high amounts of flavonoid glycosides which have antioxidant effects on the mitochondrial level, thus stabilizing its function [7]. They are also rich sources of terpenoids which inhibit platelet activating factor [47]. Many positive effects of gingko extracts were shown: LDL oxidation is inhibited, vascular walls are relaxed, systemic oxidative stress could be reduced for glaucoma patients and visual field progression slowed [7].

Cacao

Cacao is rich in polyphenolic flavonoids and has been proven to lower risk for vascular diseases [48] by decreasing blood pressure, reducing blood platelet stickiness and clotting, increasing HDL and increasing insulin sensitivity [7]. This effect is due to the action of flavan-3-ols which boosts endothelial NOS, and thus benefits endothelium dependant vasorelaxation [49].

Conclusion

It is not entirely clear to which extent antioxidative supplementation can benefit individuals with FS. The listed positive effects have been shown mainly *in vitro* and in animal studies and may not be representative yet [8]. As explained previously, oxidative stress caused by FS could increase the risk for diseases such as glaucoma. The recommendation to reduce oxidative stress is reasonable but should certainly be supported by scientific knowledge in further research. The effect of a diet is not easily measured or monitored, which makes it hard to design and carry out significant and conclusive studies.

The advantages of a nutritional recommendation for FS are numerous. It is usually well accepted by patients, accessible and cost effective. There are also rarely adverse effects. As for now we would recommend not to withhold this information from patients that show interest and to invest in further investigation whether antioxidants could benefit these conditions.

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