Congress report

1st Ocular Blood Flow Summit in Rigi Kaltbad

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The relationship between ocular circulation and various eye diseases has been studied intensively in recent years which was also made possible by the introduction of new examination methods. This applies to "classical" vascular diseases such as retinal vascular occlusions or diabetic retinopathy but above all to glaucoma. The vascular component of this optic neuropathy has been studied primarily in Switzerland and the pathogenetic concept of glaucoma, developed by Professor Josef Flammer (long-time director of the University Eye Hospital Basel) has led to a better understanding of this disease.

In view of Switzerland's pioneering achievements, it is only logical that the first Ocular Blood Flow Summit took place in the heart of the Central European country - whereby "Summit" was true in two respects: on the one hand, the program director Dr. Katarzyna Konieczka (Basel) had ensured that leading scientists in the field of ocular perfusion came together for this meeting. On the other hand, it took place almost at summit height: on Mount Rigi, not far from Lucerne, at 1400 meters (approx. 4600 feet) altitude. Below are a few practical highlights of the four-day congress.

Glaucoma: The pathogenetic concept of optic nerve damage

Professor Josef Flammer described a part of his medical life's work, the role of blood flow in the pathogenesis of glaucoma. The disease affects the entire optical pathway, from thinning of the optic nerve to cell loss in the lateral geniculate nucleus and the visual cortex. Blood flow is reduced particularly in normal tension glaucoma (NTG) patients but also in those high-pressure glaucoma patients, which progress despite a normalized IOP. A reduction was measured in the retina, the choroid, the optic nerve head and in its vicinity, but also in retrobulbar vessels and even in the nail fold capillaries. The capillary microscopy of the nail fold led to the discovery of the relationship between peripheral vasospasm and

disturbed regulation of ocular blood flow. In glaucomatous eyes, there are signs of hypoxia such as an increase of HIF1-alpha. If, however, glaucomatous optic nerve damage is a hypoxic process, why - Flammer asked - does a glaucomatous optic nerve with its characteristic excavation looks so different from a papilla in an indisputably ischemic condition such as an acute ischemic optic neuropathy (AION)?

The answer is provided by the behavior of the glial cells, particularly the astrocytes. In an acute hypoxia, as in AION, they are activated and proliferate to finally form a glial scar. In glaucoma, increased IOP and/or hypoxia also induce a slight and long-lasting activation of the astrocytes. Simultaneously, an increase of oxidative stress causes these cells to die slowly and therefore prevents the formation of a gliotic scar. The main cause of this local oxidative stress is an instable oxygen supply of the mitochondria, e.g. due to sleep apnea, but particularly due to an instable local blood flow. Blood flow in turn is unstable if IOP fluctuates to a high level - or if the blood pressure drops to a low level; both conditions will from time to time ovestress the autoregulatory capacity. If the autoregulation itself is disturbed, a situation which e.g. is often observed in patients with Flammer syndrome, fluctuation of IOP or blood pressure even in the normal range causes unstable blood flow. As a therapeutic consequence, Flammer recommends to treat the vascular dysregulation and to reduce the challenges for autoregulation by keeping IOP and blood pressure on an ideal level without major fluctuation.

Flammer syndrome: numerous symptoms, striking associations with various diseases

It is rare in medicine that a living researcher or discoverer is honored by having an entity being named after him - for example a syndrome. In the case of the Flammer Syndrome (FS), there was little contradiction within the medical community when the term came up around 2010. The discovery of a certain phenotype, which was partly made with a criminalistic intuition, is too clearly associated with the host of the Summit. Flammer initially coined the term vascular dysregulation for conspicuous perfusion disorders in the eye that are associated with characteristic findings in other parts of the body such as vasoconstriction of

the extremities (cold fingers). The discovery of the syndrome was also made possible by many affected persons who contacted him, suffering from the symptoms that are now described even in Wikipedia where the term “Flammer syndrome” is described in several different languages. Since these patients in many cases often travelled to Basel, Flammer and his colleagues were able to constantly add material to their collection of characteristic findings.

Dr. Katarzyna Konieczka (Basel), a leading researcher in this field of FS, recalled some of the characteristics of affected people:

- Low blood pressure

- Cold hands and feet

- Extended time to fall asleep

- Reduced sensation of thirst

- Slightly increased endothelin 1 levels in plasma

- Increased sensitivity to pain, odors and increased sensitivity to certain drugs

- Reduced blood flow in nail fold microscopy, particularly after cooling

- Reduced autoregulation of ocular blood flow

- Increased retinal venous pressure

- and many more

The reaction pattern to certain stimuli such as cold, physical and emotional stress or fast ascent to high altitudes, is almost typical.

Ophthalmologically important is the relatively frequent occurrence of normal pressure glaucoma in people with FS. This is explained by the reduced auto-regulation of ocular blood flow, an increased retinal venous pressure (RVP), a low blood pressure and an increased activation of astrocytes in FS subjects.

Konieczka reported further on a study she conducted together with colleagues in Warsaw, Poland. They found that if glaucoma patients put one hand in cold water, the visual fields worsened temporarily in those patients who were diagnosed with FS, but not in patients without FS. In another study, Konieczka analyzed the

effect of glaucoma drops on the corneal temperature of healthy individuals. Brimonidine but not latanoprost induced a temporary cooling of the cornea. This effect was significantly greater in people with FS than in people without FS. In subjects with FS, even a slight contralateral cooling effect was observed. This impressively demonstrates the greater drug sensitivity of people with FS.

Less well researched yet is the relationship between FS and other eye and general diseases. Konieczka summarized her own work and the present literature: FS is a risk factor for retinal vascular occlusion in young subjects without classical vascular risk factors, FS influences the manifestation and progression of retinitis pigmentosa and of central serous chorioretinopathy. FS is also associated with Susac syndrome, a rather rare microangiopathy characterized by triad of vascular encephalopathy, sensorineural hearing loss and retinal vascular occlusion. Patients with multiple sclerosis also have statistically significantly more often the symptoms and signs of Flammer syndrome. Typically they indicate that they had the FS symptoms already before they were diagnosed with MS. This is also true for other autoimmune diseases, e.g. of the thyroid gland. One hypothesis to explain such associations is the assumption that subclinical microinfarctions, induced by vascular dysregulation, may trigger an autoimmune response. To clarify all these relationships, more research is needed. Under further investigation is the role of FS in the pathogenesis of certain malignant tumors and their metastasis

Central serous chorioretinopathy: RPE detachment and vascular leakage of unknown genesis

It hit an ophthalmic surgeon in the middle of a complicated operation. The colleague felt a sudden vision loss which was particularly dramatic in this situation - another surgeon had to take over for him. This case was one of the most striking that Prof. Christian Prünte (Basel) was able to report. Stress was unmistakably a trigger and indeed the suffering often occurs under such pressure and with type A personalities (which generally includes doctors). According to Prünte, it is a condition that has undergone a change of name, mainly thanks to the efforts of his long-standing Basel boss Josef Flammer: instead of chorioretinitis centralis

serosa, today the international literature speaks of central serous chorioretinopathy (CSC). The pathogenesis is largely unknown, but vascular dysregulation seems to be involved or even causally leading. Patients can often be described as hyperactive, CSC can also be associated with systemic steroid therapy. Indocyanine green angiography (ICG) often shows multifocal congestions of the choroidal veins in the affected but interestingly also in the seemingly unaffected eye. Research from Basel has identified endothelin-1 (ET-1), a potent vasoconstrictor that is significantly elevated in plasma, as one of the triggers for this flow disorder: this was the case at least in a group of 22 patients with acute CSC in whom the ET-1 level in the specific radioimmunoassay was 2.76 pg/ml on average compared to 1.50 pg/ml in a healthy control group of the same age.

The accumulation of ICG and other macromolecular proteins in the area of RPE (retinal pigment epithelium) elevation indicates a collapse of the vascular barrier for high-molecular substances. Elevation of the pigment epithelium was described as characteristic for the clinical picture. This was confirmed by new imaging techniques such as High Definition Fast Scanning OCT. A very typical finding is the chimney-like column of a leakage in angiography, the smokestack in the macula, which is probably due to the lower specific gravity of the fluid escaping from the subepithelial space. It appears that lysosomal enzymes are involved in this collapse of the vascular barriers. Many question marks on pathogenesis remain in this disease for which no causal therapy exists. Prünte also attributed the greatest chance of success in the treatment of the often self-limiting but also recurrent condition to photodynamic therapy (PDT).

Retinitis pigmentosa: The genetic disease is also associated with disorders of ocular perfusion.

According to Dr. Karl-Georg Schmidt (Freienbach, CH), reduced ocular blood flow is also present in retinitis pigmentosa. This phenotypically very heterogeneous clinical picture, in which around 3,000 mutations in more than 70 genes have been detected, shows a decrease in the ocular perfusion parameters depending on the stage. While they are rarely affected in early stages, a reduction in systolic

top speed, among other things, has been shown in advanced stages. Other vascular abnormalities found in RP patients are a decrease in perfusion in the macula and optic nerve, a decrease in parafoveal vessel density but also an increased oxygen saturation in ocular vessels, particularly in retinal veins. Endothelin-1 should also play a pathogenetic role here. Among the (modest) therapeutic approaches documented in the literature against these vascular characteristics of the disease are an improvement of macular blood flow under topical unoproston therapy and a slowing of central visual field progression under systemic administration of the calcium antagonist nilvaldipine.

In the discussion, Flammer remarked that although the reduction of blood flow, e.g. in the choroid, is obseved in RP patients mainly in the late phase, a disturbed regulation of the retinal blood vessels can already be observed in the very first stage.

Calcium channel blocker to improve ocular microcirculation

The potent vasoconstrictor endothelin-1 is also elevated in other ocular vascular diseases - such as, for example, Prof. Teruyo Kida (Osaka) explained, in retinal vein occlusions. In contrast to former assumptions, the veins are not mechanically compressed but rather actively constricted, a phenomenon which Flammer explained in his work with a local diffusion of vasoactive substances from the arterial wall and its surroundings to the veins. According to the Japanese ophthalmologist, anti-VEGF therapy in retinal branch vein occlusions often leads also to a reduction in ET-1 levels, but not always: in some patients, these levels even increase, which is accompanied by a lack of functional therapy success. In an animal model it was shown that the choroidal blood flow decreased after intravenous injection of ET-1 and the retinal veins near to the optic nerve head constricted.

The effect of endothelin-1 can be counteracted by administering calcium channel blockers, as Prof. Stephan Krähenbühl, pharmacologist at the University of Basel, explained. These substances, especially the group of dihydropyridines, appear to improve ocular microcirculation in people with high ET-1 levels. In Krähenbühl's view as an internist, it is however questinable whether this leads to a functional benefit. The most recent publication from 2017 documented a slower visual field progression in a group of 39 patients with NTG under nimodipine and nifedipine

therapy compared to a control group not treated with calcium channel blockers. Possible side effects of dihydropyridines include: reddening of the skin due to the vasodilatation which is desired in the eye, possibly in combination with headache; peripheral edema, constipation and reflex tachycardia may also occur.

In the discussion Flammer noticed the following: a) In patients with vascular dysregulation, CCBs should be dosed very low, e.g. 1 to 3 mg nifedipine per day. A very low dose has even a better effect with much less side, b) water-soluble CCBs, such as nifedipine or amlodipine, although they do not cross the blood-brain barrier, reach the optic nerve head via the choroid and usually have a better effect than fat-soluble CCBs, c) CCB studies using visual fields as their main parameter were practically always positive, while studies with blood flow blood flow as main parameter were partly negative. The reason for this is the fact that (low dose) CCBs do not, ore only slightly increase baseline blood flow but rather improve the regulation of blood flow, which is the important factor in the protection of the visual fields.

According to Prof. Richard Stodtmeister (Dresden), other drugs also have a positive effect, particularly on retinal venous pressure (RVP), which is increased in many diseases including glaucoma. RVP has recently risen to the rank of an independent risk factor for the progression of glaucoma damage. Stodtmeister presented the results of a Dresden study in which 14 glaucoma patients were treated for 4 months with 50 mg pentaerithrityltetranitrate, a prodrug used in cardiology to dilate the coronary vessels. The initial RVP was reduced under therapy from approximately 45 mm Hg to an average of 28 mm Hg, resulting in an improvement in ocular perfusion pressure, a desirable effect especially in NTG patients.

Calcium channel blockers: a therapeutic option for glaucoma beyond pressure reduction?

Dr. Maneli Mozaffarieh (Zürich) explained the role of calcium channel blockers in glaucoma in more detail. This option is particularly suitable in situations in which classical glaucoma therapy - the reduction of IOP - reaches its limits, for example in patients with visual field progression despite an OP in the low teens. The active substances are applied at a central point of the pathogenetic concept of glaucomatous optic neuropathy after Flammer, the unstable blood flow in many

glaucoma patients (especially those with NTG) and the resulting processes of tissue remodeling and cell apoptosis. Mozaffarieh further demonstrated that CCBs also reduce the retinal venous pressure, a pressure that is particularly often increased in glaucoma patients with FS. This can also be explained by the fact that the vasoconstrictive effect of ET-1 on the optic nerve and other regions of the eye may be counteracted by calcium channel blockers.

Flammer and co-authors documented an improvement of the visual field, best visible on the Bebie curves (the eponym, Hans Bebie, emeritus professor of theoretical physics in Bern, was one of the participants of the Summit) under short-term nifedipine therapy for the first time in 1987. A few years later, a slight but lasting improvement in visual fields was observed, especially in patients with Flammer syndrome under long-term nifedipine therapy. The patient group of a Japanese study was comparatively large; 36 glaucoma patients received calcium channel blockers and 74 patients formed a control group without this therapy - the perimetric deterioration over a period of almost ten years was significantly less pronounced with this medication than in the control group. According to Mozaffarieh, calcium channel blockers also reduce oxidative stress, probably by keeping the blood flow more constant.

A comparable effect on retinal venous pressure was also achieved by a natural active ingredient: borage, a medicinal and aromatic plant cultivated since the Middle Ages. In patients with Flammer syndrome, RVP was reduced on average from 38.9 mm Hg to 32.5 mm Hg with virtually no change in IOP.

Retinal venous pressure: a reliable measurement method

If ophthalmologists look at the central fundus, they usually detect a spontaneous vein pulse on the papilla. If this is not the case, the RVP is significantly higher than the intraocular pressure, a predisposing situation for glaucoma, which is estimated to be present in one third of glaucoma patients, as Gabriele Fuhrmann (Jena) pointed out. However, increased retinal venous pressure is not only a risk factor for glaucoma damage, but also for patients with diabetic retinopathies and retinal vein occlusion. This parameter can be measured reliably by gently increasing the eye pressure from the outside for a few seconds with a dynamometer and the examiner documents the IOP at which the pulsation of the

veins starts – this artificially induced IOP corresponds to the retinal venous pressure. Fuhrmann presented also a new method to increase IOP. A small balloon resting in a frame, similar to a pair of glasses, is pressed into the (anaesthetized) corner of the patient's eye. This balloon is gradually inflated in order to increase the IOP. With this new method no contact with the cornea is necessary and the optic is free for a simultaneous observation of the fundus. A study in Dresden tests presently the application under clinical conditions.

Vascular dysregulation, optic nerve compartment syndrome and increased retinal venous pressure: Aspects of the same underlying disease?

Dr Katarzyna Konieczka (Basel) demonstrated that these three clinical pictures often occur together, especially in NTG patients with Flammer syndrome. The good news is that, at least in her study, these three entities improved simultaneously under a combination therapy with magnesium and a very low dose of Nifedipine.

Retinal Vessel Analysis: Helpful Tool for Cardiologists as well

The response of arterioles and venules in the retina to flickering light allows a statement on vascular health in other organs. Dynamic retinal vascular analysis has made the high-tech investigation, actually developed for ophthalmologists, a helpful tool for cardiologists. According to Prof. Henner Hanssen (Basel), alterations of the small retinal vessels measured with the Retinal Vessel Analyzer are a warning signal. Both reduced responses to flickering light as well constricted arteries and or dilated veins are risk indicators for arterial hypertension, diabetes mellitus and obesity which may predict an increased occurrence of heart attack, stroke and cardiac mortality. The dynamic retinal vascular analysis (DVA), developed by Walthard Vilser (Jena), measures the diameter of certain small retinal arteries and veins. With a 12.5 Hz or 8 Hz optoelectrical flicker light, a stimulation is exercised which induces in healthy retinal arteries and veins a dilatation.

According to Hanssen's experience, the retinal vascular analysis not only detects vascular alterations corresponding to already exiting diseases but

also allow a prediction of future cardio-vascular diseases and enable monitoring of the effect of therapeutic interventions. For example, the Basel study group imposed a 20-minute exercise program on children during school breaks, five days a week for four weeks, and at the end of this period, compared with an inactive or normally active control group (36 participants each), found a clear improvement in the vascular parameters CRAE (central retinal vein equivalent)
and, in parallel, improved cognitive function.

Another study focused on physically inactive seniors. A total of 160 participants between 50 and 69 years of age underwent 12 weeks of High Intensity Training (HIT); the first results of this yet unpublished study showed an improvement in retinal vascular parameters after the program. According to the speaker, this analysis is sensitive to the effect of treatment strategies and can also document the success of an ADAM strategy (aggressive decrease of atherosclerosis modifiers, a combination of diet, exercise and medication) in cardiovascular high-risk patients.

Dr. Matthias Nägele from the Department of Internal Medicine (Baden CH) documented in patients with a well-adjusted, compensated heart failure a significantly reduced flicker-induced arteriolar dilatation in the retina, without clear changes in the width of brachial arteries after stimulation. This points, according to Nägele, to a limited microvascular endothelial function in patients with a normal macrovascular endothelial function. The reduction in venous flicker-induced dilatation compared to dilatation in healthy individuals was associated with echographic evidence of left ventricular stiffness and pulmonary hypertension. An important cardiovascular risk factor, hypercholesterolemia, was also associated with a significant reduction of flicker-stimulated arteriolar dilatation. According to Nägele, retinal vascular analysis may be a useful tool for cardiologists to assess the success of vascular-targeted therapies in patients with heart failure.