Glaucoma Specialist Blog: The "Glog"

THURSDAY, AUGUST 15, 2019

THE FLAMMER SERIES

PART III

OCULAR BLOOD FLOW IN GLAUCOMA

1. INTRODUCTION

Glaucoma was initially presented as a mechanical process due to relatively high intraocular pressure (IOP) compressing the optic nerve. However, cases of ocular hypertension, normal tension glaucoma and those individuals who continue to progress despite apparently adequate lowering of IOP put a question mark over the mechanical theory for the development of glaucomatous optic neuropathy (GON). Subsequently, a number of researchers have presented alternative theories such as the vascular, biochemical, genetic and abnormalities in translaminar pressure, among others.

The vascular theory considers GON as a consequence of insufficient blood supply due to either increased IOP or other risk factors reducing ocular blood flow (OBF). Fluctuations in OBF cause oxidative stress to ocular structures such as the mitochondria and trabecular meshwork, causing damage and glaucomatous degeneration. Prof Josef Flammer is a pioneer among those who elucidated the concepts of vascular theory. This article takes a brief look at his research on “ocular blood flow”.

2. ANATOMY AND PHYSIOLOGY OF OCULAR BLOOD FLOW

Ocular circulation is complex because of the necessity to supply different ocular structures with nutrients without interfering with the visual pathway.

OBF is highly regulated in order to adapt to changing metabolic needs during changing visual function, to compensate for varying perfusion pressures and finally to keep the temperature at the back of the eye constant.

Retinal vessels are supplied by the central retinal artery, which in turn is a branch of the ophthalmic artery.

The anatomy and physiology of the retinal circulation resembles the brain circulation with the exception that retinal circulation has no autonomic innervations.

Retinal circulation is characterized by a low level of flow and high oxygen extraction.

Circulation is auto-regulated i.e. within a certain range; flow being independent of perfusion pressure.

Endothelial cells have a major role in local regulation of OBF.

Factors involved in this regulation are:

- Partial pressure of oxygen.
- Carbon dioxide levels.
- Circulating and locally produced hormones such as angiotensin-II.
- Local metabolites like adenosine diphosphate.

In contrast, choroidal circulation is characterized by very high flow and low oxygen extraction. It accounts for 85% of the total blood flow in the eye.

Choroidal circulation seems to be important for maintaining temperature and volume in the eye.

The choroid is supplied by the posterior ciliary arteries. It has rich autonomic innervations as well.

Due to poor autoregulation choroidal blood flow is more dependent on perfusion pressure.
The superficial layer of the optic nerve head (ONH) receives its blood supply via small branches of the central retinal artery. The prelaminar region is supplied by branches from recurrent choroid arterioles and the short posterior ciliary arteries.

There is some diffusion from the surrounding choroid to the ONH. The ONH capillaries have an inadequate blood-brain barrier and are leaky. This makes ONH circulation especially sensitive to circulating molecules like endothelin-I and angiotensin-II.

Autoregulation in this area is less efficient than in the retina, but better than that in the choroid.

3. OCULAR BLOOD FLOW IN GLAUCOMA

A number of studies have shown reduced ocular perfusion in glaucoma. These blood flow disturbances are especially pronounced in normal tension glaucoma (NTG) than high tension glaucoma (HTG).

Reduced pulsatile OBF has been reported in NTG and POAG patients, often, prior to development of visual field defects.

Angiographically there is reduced blood flow in the retina, choroid and ONH in glaucomatous eyes. This is evident by delayed filling and prolonged passage time.

Changes observed around the ONH include:

- Local filling defects.
- Slow filling.
- Increased leakage.

Laser Doppler velocimetry analyses also showed reduced OBF velocities in POAG and NTG patients. Heidelberg retina flowmetry also showed reduced OBF in the ONH and reruns of glaucoma patients. Color Doppler imaging studies have demonstrated reduced peak systolic and diastolic velocities and increased resistivity indices in the retrobulbar vessels of glaucoma patients. Blood flow in the nail fold capillaries and in skin microcirculation is reduced in glaucoma patients, especially after cold provocation.

When peripheral blood flow in glaucoma patients was compared with normal controls, baseline blood flow was on average slightly decreased, the difference however became very clear after cold provocation, especially in NTG patients.

Indirect signs of reduced OBF are also seen in conjunctival capillaries, vasoconstriction of retinal vessels, ONH hemorrhages, increased prevalence of venous thrombosis and gliosis like alterations in glaucoma patients. Ischemic lesions in other organs such as hearing problems, silent myocardial ischemia and small ischemic lesions in the brain have also been described. Increased levels of endothelin-1 in plasma and aqueous humor have been described.

It is not clear whether alterations in blood flow are a consequence of glaucomatous disease (increased IOP or GON) or a primary vascular component is involved in the pathogenesis of GON. Since the vascular changes are not limited to the eye there is high possibility of a primary vascular disease. IOP also does not appear to be the main factor, since altered blood flow is more common in NTG rather than HTG.

Potential causes of OBF reduction include:

- Increased resistance to flow.
- Reduced perfusion pressure.
- Increased blood viscosity.

4. VASCULAR DYSREGULATION

All cells in the body are under influence of vascular endothelial cells. This regulation by the endothelial cells is crucial to the cells' ability to adapt to changes in perfusion pressure, which is known as autoregulation.

The vessels of the retina and ONH are also under the influence of neural and glial cells which regulate the size of retinal vessels. This phenomenon is known as "Neurovascular coupling".

Blood flow through an organ is regulated by perfusion pressure and local resistance to flow. This regulation ensures adequate supply of oxygen and nutrients to the target tissues.

Patients with primary vasospastic syndrome often have diffuse or glaucomatous-like visual field defects, which are often not obvious to the patient. This is attributed to a reduced OBF in the choroid. These ocular changes have led to the coining of the term "ocular vasospastic syndrome" by Prof Flammer.

Primary vasospastic syndrome may be a significant risk factor for GON. Vasospastic syndrome could affect OBF in two ways: (a) these patients have lower than average blood pressure, thus they may have periods of low perfusion pressure (b) Glaucoma patients have disturbed autoregulation which might be a manifestation of the primary vasospastic syndrome. Reduced OBF could be the consequence of insufficient adaptation to low perfusion pressure.

Vasospastic syndrome can be considered as a risk factor occurring independently of IOP, but acting in concert with IOP by rendering the eye more sensitive to IOP.

Chronic dysregulation of blood flow may lead to GON and also damage aqueous humor outflow. Development of GON is significantly associated with unstable blood circulation. This leads to oxidative stress in the affected mitochondria. Oxidative stress makes the difference between pure hypoxic atrophy and glaucomatous atrophy. Individuals with primary vascular dysregulation have reduced auto-regulation. This group of people experience particularly frequent

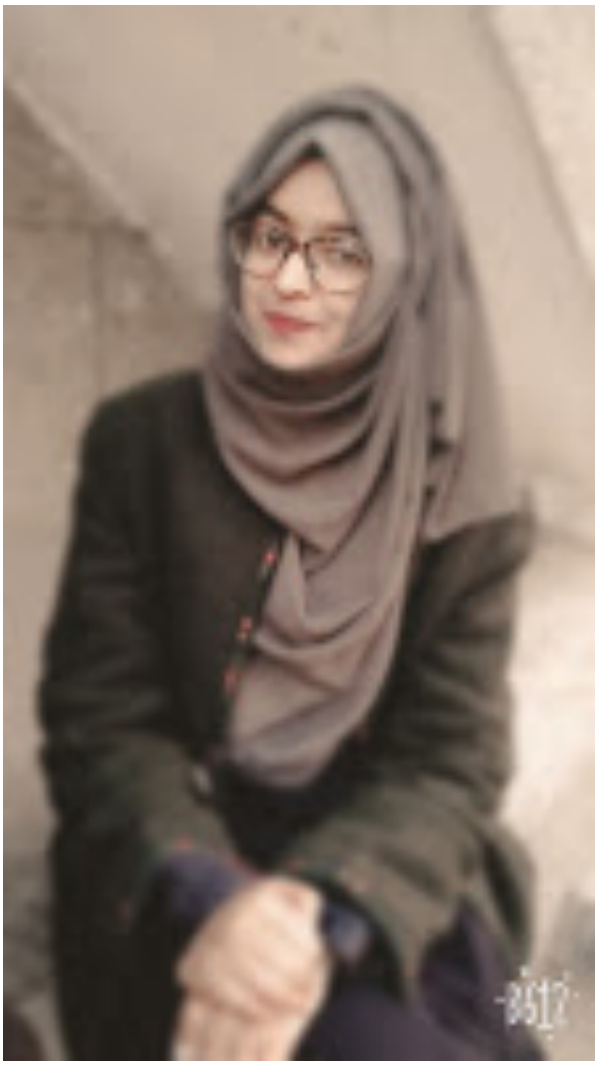
and strong fluctuations in blood supply (due to fluctuations in IOP or BP) and thus, also fluctuations in oxygen supply.

5. TREATMENT

Carbonic anhydrase inhibitors have been shown to improve visual field defects independent of their IOP reduction. This is attributed to their beneficial influence on ocular perfusion and increased optic nerve oxygen tension.

New treatment options are being investigated which improve ocular perfusion dynamics, influence vascular dysregulation or protect neural cells directly.

AUTHOR



I am **Ghuncha Khatoon**, a final year BUMS student at the prestigious Ajmal Khan Tibbiya College in Aligarh, India. My hometown is the historic city of Sasaram, Bihar.

For me humbleness and humility are very important qualities in an individual. My ideal is Mother Teresa. And inspired by her, I love to care for and help old age people.
My hobbies are poetry, writing diaries and reading novels. Traveling to new places also interests me immensely. Whenever I find some free time I love to spend in gardening.
Being a part of the Flammer Series has given me immense satisfaction as I got to learn a lot about Prof Flammer and his work.

Posted by Syed Shoeb Ahmad