Glaucoma Specialist Blog: The "Glog"

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THE FLAMMER SERIES

PART V

NORMAL TENSION GLAUCOMA

Introduction

For generations of ophthalmologists, glaucoma was simply defined as a disease characterized by high intraocular pressure (IOP). It was almost forgotten that the eminent German ophthalmologist Albrecht von Graefe (1828-1870) already in 1857 - and thus just seven years after the invention of the ophthalmoscope

which made the hallmarks of the disease like the optic nerve head (ONH) excavation finally visible to physicians - encountered a patient with that characteristic damage but with an IOP that did not seem to be increased at all.

Today, normal tension glaucoma (NTG) is a widely recognized disease though there are still ongoing discussions on whether it is just a special form of primary open-angle glaucoma (POAG) or whether it is a distinct clinical entity with its very own pathogenetic risk factors and with clinical features different from POAG. Professor Josef Flammer has over the years in his many contributions to science strengthened the latter point of view. No doubt: the observation of patients suffering from glaucomatous optic neuropathy (GON) with an IOP within the normal range challenges the traditional pathophysiological concept of glaucoma solely based on elevated IOP.

A number of studies have evaluated the prevalence of normal tension glaucoma - formerly sometimes described by the term "low tension glaucoma" - among the overall glaucoma population. There are marked epidemiological differences between different ethnicities. NTG seems to be much more frequent among Asians than among a European population or one of European heritage. In the Beaver Dam Eye Study, for instance, the prevalence of NTG among glaucoma patients (predominantly white individuals) was 32%, in the Rotterdam Study it was 39%. It was higher among people of African heritage (who are more susceptible to glaucoma in general than other groups) as demonstrated in a study from Zululand where 57% of glaucoma patients had NTG. In Asia, however, it dominates the POAG population: a study from Guangzhou, China, showed an NTG prevalence of 85%; the highest NTG proportion ever reported was from Japan: 92% of POAG patients.

Pathogenesis and Risk Factors

Professor Josef Flammer remembers quite well an experience he had as a young physician who was doing a year-long residency at the eye clinic of the University of British Columbia in Vancouver which at that time was the leading center worldwide when it came to the management of glaucoma and research about its causes. Not only did Flammer encounter patients with characteristic glaucomatous damage at the ONH and the retinal nerve fiber layer (RNFL) while having IOP within the normal range. His mentor and teacher, Professor Stephen Drance, pointed to something that was peculiar about these patients: they often had small hemorrhages at the rim of the optic disc. Drance was convinced that this feature that today is widely regarded as a hallmark of NTG points to an issue of the ocular perfusion - to be sure, POAG patients may have these hemorrhages

as well but they are about five times more frequent in individuals suffering from normal tension glaucoma. Drance therefore ordered a routine cardiovascular check-up for patients with NTG.

Professor Flammer's research has established that the risk factors that lead to IOP increase and thus to the "classical" version of glaucoma and those that initiate GON are not identical but tend to be widely different. Risk factors that lead to artherosclerosis are also risk factors that predispose to elevated IOP like age, smoking, obesity, male gender, dyslipidemia, diabetes mellitus, systemic hypertension. NTG patients who show GON have, however, a very different risk profile than "ocular hypertensives". Risk factors for NTG include female gender, race (i.e. Asian heritage, see above) primary vascular dysregulations (PVD) and low blood pressure. On average, NTG patients tend to be younger than glaucoma patients with an elevated IOP.

Ocular blood flow (OBF) tends to be reduced in glaucoma patients and particularly so in NTG patients. An unstable OBF is supposed to be a major cause of glaucomatous damage; OBF is also significantly more reduced in glaucoma patients showing progression than in patients who do no progress. Normal tension glaucoma patients have a reduced autoregulation: these eyes lack the capacity to properly ensure a stable blood supply which becomes critical when PVD and low blood pressure lead to a diminished blood flow towards the ocular structures.

It has been demonstrated that even more damaging than a continuously low blood pressure are irregularities in blood pressure, excessive "spikes" and equally excessive drops. Sharp decreases - particularly at night - play a pathogenetic role in many NTG patients. The same can unfortunately been said sometimes about medical therapy to lower an increased blood pressure, therapy usually initiated by a general practitioner or specialist in internal medicine. These medications can lead to blood pressure reductions - again, particularly during sleeping hours - that prove to be dangerous to an already compromised OBF in an NTG patient. Some sleeping pills have also the unwanted effect of lowering the blood pressure during sleep in susceptible patients.

Professor Flammer and his co-workers have over the years developed a pathogenetic concept of glaucoma based on the role of OBF and led to the discovery of Flammer syndrome which supports the hypothesis of "glaucoma as a sick eye in a sick [from a vascular point of view] body". Both OBF and Flammer syndrome have been discussed earlier in this series. Suffice it here to say that vascular factors like recurrent hypoxia due to increased vascular resistance or

PVD as well as the so called reperfusion injury (the damage done to cells that have for some time been deprived of adequate blood flow and then sometimes virtually "drown" in re-established OBF and in oxygen) lead to oxidative stress and inflammation, resulting in damage to the retinal ganglion cells, the astrocytes and other layers at the ONH and the RNFL.

A possible link between NTG and general disease has been the focus of a number of studies. There is so far no established significant association between NTG and diabetes mellitus. There are indications of a link between NTG and obstructive sleep apnea (OSA), both having a multifactorial pathogenesis in which recurrent hypoxia obviously plays a major role.

Diagnosis

The basic diagnostics in glaucoma management apply also for NTG patients - with one probable exception: IOP readings are no reliable predictors of progression. For diagnosis and to draw a line versus POAG, IOP should always be below 21 mm Hg before we speak of normal tension glaucoma. It has to be kept in mind, though, that this is a rather arbitrary boundary - we are dealing with a continuum, not with a clear distinction between NTG and POAG. The lower the IOP value that is associated with glaucomatous damage and/or with progression, the higher is the likelihood of vascular factors as a primary pathogenetic mechanism.

Structural and functional measurements are valuable in establishing the diagnosis and performing controls. Like in other fields of ophthalmology, the advent and increasing sophistication of OCT has improved the diagnosis of glaucoma in general and of NTG in particular. Dynamic retinal vessel analysis (DVA) may add further valuable information on the status of the patient's ocular vasculature.

Measuring retinal venous pressure (RVP) can point to NTG: it is more frequently increased in these eyes than in POAG.

Therapy

In general, therapy of NTG has much in common with therapy of POAG: ophthalmologists try to lower the patient's IOP as good as they can. IOP reduction improves the prognosis in all types of glaucoma. This can be done pharmacologically, by laser treatment or with a surgical intervention.

Nevertheless, some patients are known to progress despite an IOP level regarded as appropriate ("target pressure") has been reached.

In NTG patients in which OBF seems to be a major factor, other treatment options in addition to IOP lowering have been tried to achieve functional stability and to prevent further progression. Since low blood pressure is common among NTG patients, further reductions should be prevented or, in some cases, even raising the blood pressure moderately will be tried. This requires a close cooperation between ophthalmologist and general practitioner or internal medicine specialist or cardiologist - the latter disciplines are traditionally concerned with lowering blood pressure, not elevating it. In daily practice, informing these colleagues about the dangers of low blood pressure in NTG patients and convincing them to stabilize blood pressure at a somewhat higher level as well as avoiding fluctuations has often proven to be quite a challenge for ophthalmologists.

In Basel, Professor Flammer and his team have been able to improve vascular regulation locally by carbonic anhydrase inhibitors and systemically with low dose magnesium and low dose calcium channel blockers. Evening eals with a higher-than-average dose of salt can be helpful in preventing nighttime blood pressure dips. Oxidative stress can potentially be reduced by gingko biloba. The elucidation of IOP-independent risk factors will most likely add therapeutic options in the future - and will challenge the in many places still-dominant concept of glaucoma therapy: IOP reduction alone.

AUTHOR

Ronald D. Gerste, born in Magdeburg, Germany, grew up and studied medicine (M.D.) and history (Ph.D.) at the University of Düsseldorf, Germany. He has worked as an ophthalmologist, but over the years moved to the field of medical publishing. Work for a number of journals and publishers, based since 2001 near Washington DC where he is acting as a science correspondent. Have the privilege of being associated with and a friend of Prof. Flammer for more than 20 years; was part of the team that translated his great book "Glaucoma" into the English language. He has written repeatedly on Flammer Syndrome in German-language journals. Also the publicist for the Swiss Academy of Ophthalmology (SAoO), the German Society for Cataract and Refractive Surgery (DGII) and the German Glaucoma Awareness Association (Initiativkreis Glaukom).

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