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Flash Look

Glaucoma beyond the eye: Recent achievements on the systemic dysfunction of this disease.

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INTRODUCTION

Glaucoma is a chronic irreversible optic neuropathy characterized by a slowly progressive loss of retinal ganglion cells. Clinically, it is defined by optic nerve head cupping and visual field defects, both of which are related to optic nerve head (ONH) remodelling. A major risk factor for the development of glaucoma is an elevated intraocular pressure. This discovery led to a clinical and surgical breakthrough for the management of our glaucoma patients where a low target IOP remains our main goal. Nevertheless, a number of studies came through and evolved our basic concept of glaucoma, showing that an increased IOP does not necessarily lead to glaucomatous optic neuropathy. Risk factors as a thin cornea and disk haemorrhages may be involved as well as other systemic factors. A number of studies suggest that primary open angle glaucoma may be a localized, ophthalmological manifestation of a wider, systemic dysfunction. One particular segment of patients in which this may be important are the Normotensional glaucoma (NTG) patients, where disease progression has been linked to a vascular and autonomous nerve system (ANS) dysfunction. Some studies believe that this understanding might have therapeutic consequences in the future. This paper aims to review the relevant systemic findings in POAG published so far.

GLAUCOMA AS A SYSTEMIC DISEASE

I - CARDIOVASCULAR SYSTEM

Pache et al did a major review in 2006 on systemic findings associated with POAG.[1] As described by them, the literature reveals some conflicting information about POAG and associated cardiovascular disease.

A. Arteriosclerosis

No strong relationship exists between arteriosclerosis or smoking and glaucoma.

B. Blood pressure

Most studies show an altered systemic blood pressure in glaucoma. However, the existing data are contradictory mainly because some of the studies are biased by their retrospective nature, a small sample, and methodology misconceptions, as no subgroups analysis of NTG and hypertension glaucoma (HTG) patients were performed.

1. Arterial hypertension

Studies reveal that POAG patients with elevated IOP are predisposed to systemic hypertension. However, blood pressure results are contradictory in NTG patients and controls, with some studies revealing a normal to high/low blood pressure (see below).

2. Arterial hypotension

Several studies show an association between POAG progression and low blood pressure for an accelerated optic nerve cupping and development of visual field defects, particularly in NTG. Markedly reduced systolic blood pressure during day and night is associated with progression despite well-controlled POAG and NTG. A study by Graham et al showed that HTG and NTG patients did not differ according to blood pressure, but all that showed progression had nocturnal lower blood pressure parameters.[2] Tokunaga and co-workers later confirmed this finding suggesting that disturbance in the physiologic dip in nocturnal blood pressure may be involved in the progression of POAG patients.[3] Ghergel et al evaluated the relationship between circadian blood pressure rhythm and retrobulbar blood flow in glaucoma patients. They found that an altered retrobulbar blood flow was present in patients with low nocturnal systemic blood pressure.[4,5] Postural hypotension was also described as a risk factor for the progression of NTG.[1] Kiuchi et al found an association between progression of visual field damage in NTG with IOP in the supine position and the magnitude of IOP elevation accompanying postural

changes. They suggested that deterioration in NTG may occur when patients are lying flat during sleep.[6]

Recently, Charlson et al in a prospective study found that the duration and magnitude of nocturnal hypotension identify the patients with NTG which are more prone for visual field progression.[7] As this finding was statistically significant, they recommended a routine ambulatory evaluation of blood pressure in all NTG patients, especially those who continue to progress despite IOP lowering treatment. They also concluded that blood pressure should be considered as a modifiable risk factor in NTG. Future randomized clinical trials are needed to assess the efficacy of blood pressure management in NTG progression.

C. Vasospasm

Vasospasm is defined as inappropriate constriction or insufficient dilatation in the microcirculation to stimuli, and has been proposed as an additional risk factor in glaucoma. Gasser et al found that NTG patients showed a significant reduction of blood-flow velocity by nailfold capillaroscopy compared to controls, particularly after cold provocation.[8] The vascular dysregulation interferes with the autoregulation and renders the eye more sensitive to IOP increase and blood pressure decrease. This may be a feature in NTG as well as in HTG. In fact, in glaucoma patients have been found increased plasma levels of endothelin-1 (ET-1), a potent vasoconstrictor. Emre et al found that ET-1 levels were significantly higher in the POAG patients with visual field progression.[9] Another study found abnormal neuro-endothelial mechanisms of vascular tone control in NTG patients, related to the effects of ET-1 and neuropeptide Y, suggesting these findings as secondary to endothelial dysfunction and to autonomic nervous system dysregulation.[10] However, Kunimatsu and co-workers, found no difference in plasma ET-1 level among NTG patients, HTG patients, and normal controls.[11] More recently, Chen et al found no correlation between plasma levels of ET-1 and severity of glaucoma.[12] The effects of ET-1 antagonists on glaucoma still need to be evaluated by clinical studies.

1. Electrocardiographic changes

The existing studies do not have an adequate study design to definitively answer whether ECG changes are an independent risk factor for glaucoma or not. Therefore, routine ECG screening in all glaucoma patients is not recommendable until larger, prospective, confirmatory studies are available.

2. Headache and migraine

The majority of studies available on this topic support an association between POAG (in particular NTG), and migraine. This might be based on the fact that both migraine and glaucoma are associated with systemic vascular dysregulation. Cursiefen and co-workers suggested an association between NTG and migraine and a potential, common vascular aetiology of both diseases.[13] Pache et al concluded that was reasonable to ask glaucoma patients, and especially those with NTG, for symptoms of headache/migraine when taking their medical history.[1]

D.Hemorheology

1. Platelet aggregation

There is evidence that POAG is associated with an altered platelet aggregation. The pathogenic role of an altered platelet aggregation is not yet clear. Theoretically, is assumed that the increased platelet aggregation might have a negative influence on the blood flow in the small branches of the short ciliary arteries supplying the optic disc. Medical interventions studies are needed to confirm this hypothesis.

2. Blood Viscosity

Despite different techniques, assessment of different parameters and small sample size, there is some evidence for an altered hemorheology in POAG. Blood or plasma viscosity are elevated and erythrocyte function and deformability seem to be decreased. For the other factors influencing hemorheology, such as fibrinogen, there are not enough data to draw firm conclusions.

3. Disc Haemorrhages

Recently, Patel et al tried to determine if glaucoma patients with a current optic disc haemorrhage (ODH), a known risk factor for glaucoma progression, had an increased prevalence of nailfold haemorrhages compared with glaucoma patients without history of optic disc haemorrhage. Nailfold capillaroscopy was performed and they concluded that there was no increase in nailfold haemorrhages between the two groups. However, the prevalence of nailfold haemorrhages in patients with glaucoma either with or without an ODH is significantly greater than that identified in normal control subjects in other studies.[14] Park and co-workers found that nail bed haemorrhage and loss of nail capillaries were strongly associated with the presence of optic disc haemorrhage, and the association was stronger with nail bed haemorrhage. No differences were observed between patients with NTG and patients with POAG.[15] We find that recommending a nail cappillaroscopy in glaucoma patients is still in debate.

II - AUTONOMOUS NERVOUS SYSTEM

The influence of the autonomic nervous system on aqueous dynamics and, therefore, on IOP is well established; however, its precise mechanism is still not completely understood.

Some studies, especially those conducted in patients with NTG, reveal that alterations in autonomic nervous system on glaucoma are not necessarily linked to an increased IOP. More likely, these findings support the idea that glaucoma might be a manifestation of more generalized autonomic nervous system dysfunction.[1] Some of the changes seen are, a diminished oculo-cardial reflex, abnormal cardiovascular reflex responses, reduction of the vagal control of the heart, significant reduction in diurnal and nocturnal heart rate variability, a reduced baroreceptor control and vascular dysregulation suggesting a decreased parasympathetic and sympathetic activity as well as sympathetic failure.

Riccadonna and co-workers found a significant reduction in diurnal heart rate variability in NTG compared with the HTG and control groups. They also found that nocturnal diastolic blood pressure variability was also reduced in NTG compared with controls, suggesting blunted blood pressure and heart rate modulation in NTG subjects.[16]

POAG treatment with autonomic agents must therefore be studied prospectively in patients with autonomic systemic disturbances.

III - IMMUNE SYSTEM

Growing evidence suggests an association between POAG and changes in the immune system. Particularly in those with NTG, an autoimmune mechanism may be responsible for the ONH damage either directly or by way of a mimicked autoimmune response to a sensitizing antigen.

A. Autoimmunity

Some studies confirmed the presence of elevated serum levels of antinuclear antibodies (ANAs) and immunoglobulin G. NTG has been associated with a higher prevalence of autoimmune diseases relative to ocular hypertension (OHT) controls. Most studies relative to the immunologic findings in glaucoma are only case reports or small case-control, cross-sectional studies about a specific auto-antibody, their conclusions and relevance are therefore limited to our day practice.[1]

1. Monoclonal Gammopathy

Benign paraproteinemia although not necessarily associated with a systemic disease, it is considered to be a likely causative agent of peripheral neuropathies of various origins. A study revealed that some NTG patients but none HTG presented paraproteinemia.[17]

2. Anti-rhodopsin antibodies

A study by Romano et al found an elevated anti-rhodopsin antibody count in NTG compared to HTG.[18] These autoantibodies were analysed and found to be directed toward the C-terminus of the rhodopsin molecule. Rhodopsin's C-terminus shares sequence identity to some bacterial and viral proteins, what led the authors to speculate about the possible presence of molecular mimicry.

3. Autoantibodies to Heat Shock Proteins (HSP)

HSP play an important role in cell survival both under normal and stress conditions (stress, anoxia, heat, ischemic insults). In general, they have a protective role. They are highly immunogenic. Recent studies demonstrated the presence of serum autoantibodies to HSPs such as HSP27, aB- crystalline, and HSP60 in glaucoma patients. As long as no larger studies on this topic are available, no conclusions should be drawn.[1]

4. Autoantibodies to ONH glycosaminoglicans

Glycosaminoglycans have organizational and space-filling functions in tissue construction. They are also important for the maintenance of various cell functions and cell-to-cell interactions. Tezel et al demonstrated not only the presence of serum autoantibodies against ONH glycosaminoglycans in glaucoma patients, (especially in those with NTG), but also immunostaining of glycosaminoglycans in the lamina cribrosa of postmortem glaucomatous eyes.[19] A physiopathology relationship may be suggested by these findings

5. Neuron-specific Enolase (NSE) Autoantibodies

To date, the mechanism by which anti-NSE antibodies exert their apoptotic effect on retinal ganglion cells is not disclosed. Some studies revealed that anti-NSE antibodies were found significantly more often in glaucoma patients and were significantly higher in the early stages of POAG with visual field deterioration than without it. It has been suggested that the serum NSE autoantibodies might be a risk factor for retinal ganglion cell death in glaucoma.

6. Glutathione S-transferase

Glutathione S-transferases (GST) represent a major group of detoxification enzymes. Yang et al demonstrated increased titters of serum autoantibodies to GST relative to controls.[20] They suggested that up regulation of GST in the glial cells might be a result from the glaucomatous damage,

and in some patients a secondary production of autoantibodies. Whether the circulating antibodies against GST have a pathogenic significance remains to be evaluated.

7. Antiphospholipid Antibodies

Studies are contradictory. According to Pache and Flammer unless larger prospective studies are available, the association between glaucoma and antiphospholipid antibodies remains to be established.[1]

8. Leukocyte activation, and their gene and protein expression in POAG

Some studies suggested that there is leukocyte migration inhibition in patients with POAG. Other studies revealed an increased subpopulation of CD8 and CD3 lymphocytes in the peripheral blood of NTG and HTG patients, suggesting that an autoantigen might be present in some patients with POAG to the retina and/or ONH.

Gene and protein expression in leukocytes was found to be altered in some studies with NTG patients. These revealed that proteins involved in apoptosis as p53 and other regulatory proteins as neural thread protein (NTP), 20S proteasome subunit XAPC7, matrix metalloproteinase 9 (MMP9) were overexpressed. The overexpression found in glaucoma patients may therefore be a consequence of repeated mild ischemia/reperfusion injury. The gene expression profiles observed in these studies indicate the involvement of metabolic pathways characteristic for ischemia/reperfusion injury.[1]

The studies about leukocyte activation and glaucoma are limited by their small sample size and refer mainly to NTG. Larger confirmatory studies are desirable, and possible differences between NTG and HTG should be explored.

IV. ENDOCRINOLOGICAL SYSTEM

A. Diabetes Mellitus

There is some controversy about the association of diabetes mellitus and POAG and ocular hypertension. Ellis and co-workers failed to confirm this association stating that at this moment we can not affirm that diabetes is a risk factor for the development of POAG.[21,22]

B. Thyroid disease

Pache and Flammer suggested that unless larger epidemiological studies are available, a systematic screening for thyroid dysfunction in POAG patients seems unjustified, but may be indicated in selected patients, as the relationship between glaucoma and thyroid dysfunction is still in debate.[1]

1. Thyroid-associated orbitopathy (Graves Disease)

Thyroid-associated orbitopathy associated glaucoma can occur by several mechanisms, including elevated episcleral venous pressure, impaired outflow facility, and fibrosis of the extraocular muscles compressing the globe. Cockerham et al found that a subgroup of patients with thyroid-associated orbitopathy, might have an elevated IOP and that the duration of active orbital involvement is statistically associated with the progression of glaucomatous damage.[23] Ohtsuka and coworkers found a significantly higher prevalence of POAG and OHT among the patients with Graves disease when compared to the general population in Japan.[24] However a recent review by Haefliger and co-workers found that in thyroid eye disease, glaucoma prevalence does not seem significantly increased, and from a a pathophysiological standpoint the long term IOP increase is essentially due to episcleral venous pressure elevation and it should be differentiated with POAG.[25,26]

Therefore suggesting an association between thyroid eye disease and POAG seems unreasonable.

2. Hypothyroidism

The association between POAG and hypothyroidism is still controversial. No conclusions can be drawn to suggest a routine screening of hypothyroidism in glaucoma patients.

C. Pituitary system (Acromegaly)

There are few studies describing the association of elevated levels of growth hormone and POAG. Howard and English reviewed 74 cases of acromegaly, and found among them an incidence of POAG of 10%.[27] According to Pache and Flammer the observation of POAG in patients with acromegaly might suggest that the somatotropic hormone may promote a condition of glaucoma.

D. Cushing syndrome

Cushing syndrome occurs when there is increased levels of glucocorticoids from and endogenous or exogenous source. The outflow of aqueous humour is decreased up to 50% in these patients. Recent studies refer that this effect is partially mediated by trabecular meshwork inducible glucocorticoid response (TIGR) gene expression.[1]

Case studies report an association of Cushing syndrome and POAG. Rozsival and co-workers found the highest plasma and aqueous humour cortisol levels in patients with POAG who suffers also from systemic hypertension.[28] McCarty and Schwartz found that both ocular hypertension (OHT) and POAG are associated with elevated levels of plasma free cortisol which were related to a reduced cortisol binding capacity to albumin.[29]

Schwarts and co-workers later found that compared with normals, the OHT plus POAG subjects showed lower plasma cortisol levels in response to intramuscular ACTH, suggesting adrenal suppression in the OHT plus POAG group.[30] Future research into the influence of glucocorticoids on aqueous outflow may elucidate a possible association between these two disorders.

V. NEURODEGENERATIVE DISEASES

There is evidence that glaucomatous damage extends beyond the optic neuropathy also affecting the central nervous system (CNS): lateral geniculate nucleous and visual cortex. A direct consequence from the degenerative damage of the visual pathway.[1]

A. Alzheimer Disease

Alzheimer is a dementia characterized by the accumulation of large extracelular beta-amyloid plaques and intraneuronal neurofibrillary tangles in the SNC.

Studies reveal a possible relationship between Alzheimer disease and glaucoma. Bayer and co-workers found a high occurrence rate of visual defects and/or optic disk cupping among patients with Alzheimer disease compatible with the diagnosis of glaucoma.[31] It was also identified in the aqueous humour of glaucoma patients Alzheimer disease specific proteins, such as Alzheimer peptide (Ab) and alpha-1-antichymotrypsin. Apolipoprotein E (APOE) is involved in neuronal degeneration in Alzheimer disease. Inheritance of the APOE gene polymorphism, 34 allele, has been shown to be associated not only with an elevated risk for Alzheimer disease, but also for NTG in the Tasmanian population.[32]

Recently Tsilis et al did a major review about this topic suggesting that large and high-quality association studies, preferably with long follow-up, are needed to clarify the existence and nature of possible associations between POAG and Alzheimer disease.[33] Because an Alzheimer diagnosis can only be verified histologically, Pache and Flammer suggested the need of larger prospective post-mortem studies to assure an association between Alzheimer disease and glaucoma. A recent large cohort study by Keenan and co-workers found that the coexistence of these two disease is no different from that expected by chance. However, the diagnosis of POAG was modestly associated with later development of vascular dementia, which the authors suggested as a consequence of shared vascular risk factors.[34]

B. Parkinson disease

The review of existing studies does not reveal a sustained association between the two diseases. Lin et al recently did a retrospective study of POAG patients that were followed for 8 years to determine if there was an association between these two diseases. They found that POAG is not a predictor of PD.[35]

VI. SLEEP DISTURBANCES

A. Sleep apnea syndrome

Recent meta-analysis found that obstructive sleep apnea/hypopnea syndrome (OSAHS) patients have an increased risk of glaucoma.[36,37] Pérez-Rico and co-workers also reviewed this topic suggesting that patients with severe OSAHS should have an ophthalmic evaluation, and that in glaucoma patients, especially those with NTG and disease progression despite treatment, a screening for sleep apnea syndrome should be recommended.[38] However, as recommended by Shi et al, prospective cohort and interventional studies are needed to confirm whether OSAHS is an independent risk factor for glaucoma.[39]

VII. MISCELLANEOUS

A- Empty sella: Glaucomatous excavation is observed in empty sella syndrome and possible associations between NTG and this syndrome have been described. Two mechanisms purposed were first the resulting mechanical traction and second, vascular ischemia, induced by downward pulling of the optic chiasm and by retraction of the posterior communicating arteries, respectively.
Until date is unclear whether there is an association between NTG and empty sella syndrome.

B- Ischemic brain lesions: A study found imagiologic signs of ischemic changes in brain MRI in 32 of 94 NTG patients.[44] Supported by other studies these findings reflect a vascular cause in some glaucoma patients possibly due to cerebral small-vessel ischemia. But until larger confirmatory studies are performed a routine MRI is not recommended in glaucoma suspects.

C- Hearing Loss: Various studies suggest a relationship between POAG and neurosensorial hearing loss. After reviewing the existing studies Pache and Flammer concluded that larger epidemiological studies are necessary before a true relationship can be established.

D- Helicobacter Pylori: H. pylori is thought to be associated with the development of autoimmune sequelae observed in neuropathies and with some

autoimmune conditions such as Sjogren syndrome. Kounturas et al found that H. pylori infection was histologically confirmed in 87.5% of the POAG patients, but only in 46.7% of the controls.[45] Moreover, 68% of glaucoma patients and 30% of anaemic control participants were seropositive for H. pylori. In a more recent prospective, non-randomized, comparative study, the same group demonstrated higher levels of H. pylori-specific IgG antibody levels in the aqueous humour and serum of patients with POAG when compared to age-matched cataract patients. The authors hypothesized that H. pylori antibodies may circulate in the bloodstream and enter the aqueous humour via the blood-aqueous humour barrier. In the aqueous, the antibodies might reach a level sufficient to impact the development or progression of glaucoma.[45]

In contrast, Galloway et al could not establish an association between H. pylori infection and POAG. Seropositivity for H. pylori was found to be higher in patients with glaucoma (26.0%) than in controls (20.2%), this finding, however, did not reach statistical significance.[46]

H. pylori infection may be linked to glaucoma, nevertheless experimental and prospective multicenter epidemiologic evaluation studies are needed to validate this hypothesis.

CONCLUSIONS

POAG is a multifactorial disease that nowadays is seeing a change of spectre. Besides affecting the eye, several studies show an association with systemic findings, particularly in NTG. This is important, as these patients might need a more profound evaluation with future implications in observation, follow-up and treatment. Further clinical trials, especially randomized clinical trials, are necessary to confirm newly developed medications safety and utility.

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