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MAJOR REVIEW

A Sick Eye in a Sick Body? Systemic Findings in Patients with Primary Open-angle Glaucoma

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Abstract. Despite intense research, the pathogenesis of primary open-angle glaucoma (POAG) is still not completely understood. There is ample evidence for a pathophysiological role of elevated intraocular pressure; however, several systemic factors may influence onset and progression of the disease. Systemic peculiarities found in POAG include alterations of the cardiovascular system, autonomic nervous system, immune system, as well as endocrinological, psychological, and sleep disturbances. An association between POAG and other neurodegenerative diseases, such as Alzheimer disease and Parkinson disease, has also been described. Furthermore, the diagnosis of glaucoma can affect the patient's quality of life. By highlighting the systemic alterations found in POAG, this review attempts to bring glaucoma into a broader medical context. (**Surv Ophthalmol 51**:179–212, 2006. © 2006 Elsevier Inc. All rights reserved.)

Key words. cardiovascular system • endocrinology • glaucoma • immunology • neurodegeneration • psychology • systemic findings

I. Introduction

Glaucoma, or glaucomatous optic neuropathy (GON), is characterized by a chronic, slowly progressive loss of retinal ganglion cells and their neurons. The disease is associated with remodeling of the optic nerve head and the retina leading to the major clinical signs: characteristic optic nerve head cupping and visual field defects. Elevated intraocular pressure (IOP) is one of the major risk factors for developing GON. By far the most common reason for an increased IOP is the reduced outflow capacity of aqueous humor, usually located at the anterior chamber angle and trabecular meshwork. When the chamber angle is normally developed and not blocked by the iris and there is no other apparent cause for an increased IOP, then the term *primary open-angle glaucoma* (POAG) is used.

However, a number of conditions show that increased IOP does not necessarily lead to GON and that glaucoma can develop even under normal IOP. Other risk factors may be involved as well. Some of these additional risk factors can be found in the eye, such as a thin cornea or disk hemorrhages, whereas other factors are systemic. More than 60 years after the discovery of the causal relationship between GON and elevated IOP by Albrecht von Graefe in 1857,[105] Felix Lagrange of Bordeaux noted that a glaucomatous eye is "a sick eye in a sick body" (1922).[190] This statement, sometimes erroneously attributed to Sir Stewart Duke-Elder, remained a challenge for glaucoma research. A large variety of systemic findings have meanwhile been described and appear to occur in POAG patients more often than in corresponding controls. It automatically raises the question whether such described signs occur indeed more frequently in POAG or are just observed by chance. Furthermore, we may ask whether such systemic factors are primary or

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secondary and whether they do have any causal relationship with GON. Some systemic findings have been confirmed by a number of independent studies, therefore the relationship with POAG is, with high probability, real, whereas other findings need further confirmation. More difficult is the question whether such alterations play a direct role in the pathogenesis of POAG. At present, causality remains often hypothetical. Nevertheless, it is important to know these factors in order to test the hypothesis. Finally, some systemic findings might have therapeutical consequences.

This review aims to summarize the relevant systemic findings in patients with POAG published so far. It will not include systemic conditions associated with secondary glaucoma or ocular hypertension (OHT). Primary open-angle glaucoma patients include patients with high IOP (high tension glaucoma = HTG) and patients with normal IOP (normal-tension glaucoma = NTG). The separation between NTG and HTG is somehow arbitrary and there is no abrupt change in pathophysiology between NTG and HTG.[83,315] Furthermore, the terms are not used uniformly in the literature. Nevertheless, for practical reasons, this review uses all three terms POAG, NTG, and HTG where NTG is defined as POAG with an untreated IOP less than 21 mm Hg.

The following grouping of systemic findings is inevitably somehow arbitrary. There are a number of overlaps and interactions of findings between the groups. To simplify matters these interrelationships will not be discussed in detail. On the other hand, however, additional aspects such as quality of life will be discussed.

II. Cardiovascular System

A large number of studies have demonstrated that GON has a high association with systemic cardiovascular disease, however the literature on the subject reveals some conflicting information, as we will discuss below. An overview of the studies cited herein is given in Table 1.

A. ARTERIOSCLEROSIS

In patients with POAG, both systemic arteriosclerosis and sclerotic changes in the ocular vessels[61,126,131,269,307] and in the internal carotid artery[66,177,178,209,221,338,367] have been observed but also questioned. For example, Schmitz and Salm-Salm compared X-rays of 84 glaucoma patients and 500 controls and found a comparable frequency of sclerotic changes of the internal carotid artery in both groups.[293] Risk factors for arteriosclerosis, its complications and their primary and secondary prophylaxis are important fields of interest, especially because of their relevance for the life expectancy. However in large and well-planned studies concerning this issue, few authors found dysliproteinemia[374,375] and elevated cholesterol levels[330] in glaucoma patients. Both studies included only a small sample size and were not designed to identify arteriosclerosis as an independent risk factor. In a larger cross-sectional study in glaucoma suspects (n = 183), Chisholm et al found neither presence nor absence of dyslipoproteinemia to be associated with glaucoma.[40] In addition, Stewart et al found no correlation between elevated IOP and high-density lipoprotein, total cholesterol levels, and cholesterol/high-density lipoprotein in 25 patients with POAG or OHT.[319]

Smoking, an established and independent risk factor for arteriosclerosis, was not identified as an independent risk for glaucoma in the Beaver Dam Eye Study.[176] Other authors found smoking to be a dependent risk factor in arteriosclerotic glaucoma suspects and glaucoma patients;[360,373] however, this was found only in retrospective case-control studies.

In summary, there is evidence that there is no strong relationship between arteriosclerosis or smoking and glaucoma. The role of diabetes mellitus, another important risk factor for arteriosclerosis, in glaucoma is also contradictory and will be discussed in section V.A. Diabetes Mellitus.

B. BLOOD PRESSURE

Most of the studies undertaken thus far in this field find a certain relevance of altered systemic blood pressure in glaucoma. However, the existing data are contradictory in large part. Some authors find a significant association between POAG and arterial hypertension, others have shown a link between POAG and arterial hypotension. Epidemiologic studies indeed indicate that glaucoma patients can have either low or high blood pressure.[340]

A proper analysis of subgroups, for example, NTG versus HTG, might help to answer the unanswered questions. Some of the studies listed below are biased by a small sample size, their retrospective nature, and potential selection biases. Hopefully in the future, larger epidemiologic studies on this topic will be available.

1. Arterial Hypertension

In the early 20th century, Kümmell described high blood pressure in 30 patients with glaucoma of different types.[189] In Chile, Charlin screened 100 glaucoma patients and found 62 of them to suffer from arterial hypertension.[36] This finding was

TABLE 1

Overview of Studies Showing a Positive or Negative Relationship between Glaucoma and Cardiovascular Risk Factors

	Correlation Found	No Correlation Found
Cardiovascular System	Study, (n), Study type	Study, (n), Study type
Arteriosclerosis		
Dyslipoproteinemia	Winder,[374] (53 NTG, 39 POAG), CCS	Chisholm,[40] (183 glaucoma suspects), CSS Stewart,[319] (25 POAG and OHT), CCS
Hypercholesterinemia	Tanaka,[330] (48 NTG), RCA	Stewart,[319] (25 POAG and OHT), CCS
Smoking	Wilson,[373] (83 POAG, 121 glaucoma suspects), CCS Wang,[366] (147 POAG), CCS	Klein,[173] (4926), ES
Blood pressure		
Arterial hypertension	Kümmell,[189] (30), CCS Charlin,[36] (100), CSS Calhoun,[30] (64), CSS Leighton,[196] (11NTG, 11POAG), CCS Levene,[201] (32 NTG), CR Goldberg,[100] (19 NTG), CCS Klein,[174] (2747), ES Wilson,[373] (83 POAG, 121 glaucoma suspects), CCS Rouhiainen,[282] (30 NTG, 30 POAG), RCA Bonomi,[23] (4297), ES for POAG Kashiwagi,[167] (43 NTG), CCS Wang,[360] (147 POAG), CCS	Elschnig,[65] (141), CCS
Arterial hypotension	Sachsenweger,[285] (240 POAG), CSS Demailly,[56] (51 NTG, 51 POAG), for NTG, CCS Kaiser,[160] (78 POAG, 39 NTG), CCS Hayreh,[134] (166) CCS Graham,[107] (84), CCS Collignon,[50] (70), CCS Graham,[106] (84), CCS	

confirmed by Calhoun, who found high systolic blood pressure in 42%, and high diastolic blood pressure in 57% of 64 examined glaucoma patients.[30] By contrast, Elschnig, examining 141 patients with POAG, did not find a significant difference between glaucoma patients and a control group (cataract patients) with respect to blood pressure.[65] Today, data from several large population and case control studies indicate that POAG patients with high IOP may have an increased chance of systemic hypertension.[23,174,360] It was demonstrated that blood pressure was similar in normals and NTG patients, but higher in HTG patients.[196] In a small and not representative case-control study, Wilson and coworkers, using a health questionnaire, could identify arterial hypertension as an important risk factor for POAG.[373] Some authors have also reported an association between arterial hypertension and NTG,[100,201,282] whereas others failed to demonstrate such an association or even found NTG to be associated with low blood pressure (see below). A recent cross-sectional study from Japan, including 43 patients with NTG and 233 controls, found the blood pressure on the average of NTG patients to be significantly higher. Furthermore, the observed nocturnal dip of blood pressure in NTG patients was similar to the dip of the controls; however, the blood pressure dip was significantly smaller in NTG patients with progressive visual field defects than in patients with NTG with stable visual fields.[167]

2. Arterial Hypotension

A number of studies indicate that in POAG, and especially in NTG, the progression of glaucomatous damage seems to be related to systemic hypotension.[12,23,56,61,62,108,109,159,161,198–200,285] In 1963, Sachsenweger investigated 240 patients with POAG and could demonstrate that low blood pressure accelerated the development of visual field defects and excavation of the ONH. Moreover, he found that the percentage of eyes going blind from glaucoma was higher in hypotensive than in nomo- and hypertensive patients.[285] Demailly demonstrated that the mean difference of blood pressure between supine and upright position was significantly greater in NTG patients than in HTG patients and controls. He therefore suggested that postural hypotension might play a role in the pathogenesis of

NTG.[56] In a series of 4 glaucoma patients with rapid progression of visual field damage and excavation of the optic nerve head despite normal or well-controlled IOP, low systemic blood pressure in tandem with sustained blood pressure drop during sleep was observed (Fig. 1).[159] In a later study, the authors monitored 24-hour blood pressure in 38 POAG patients with decompensated IOP despite maximum treatment, 40 patients with POAG and progressive damage despite controlled IOP, 39 NTG patients, and 32 controls; and they found that both POAG patients with progression despite well-controlled IOP and patients with NTG have a markedly reduced systolic blood pressure during day and night.[161]

Hayreh and coworkers performed 24-hour ambulatory blood pressure monitoring and diurnal IOP curve in 166 patients with AION, NTG, POAG, and other optic nerve head disorders. They noted a significantly lower nighttime mean diastolic blood pressure and a significantly greater mean percentage decrease in diastolic blood pressure in NTG than in acute ischemic optic neuropathy. Moreover, patients with arterial hypertension taking oral hypotensive therapy showed a significant association between deterioration of the visual field and nocturnal hypotension.[132,134]

These studies mainly focused on the relation between low blood pressure and NTG, other groups however have demonstrated that this relationship is not restricted to NTG. Graham and coworkers showed in a case-control setting with a total of 84 patients that blood pressure parameters of NTG and HTG patients did not differ significantly, but that all nocturnal blood pressure parameters were lower in patients with progressive field defects compared with patients whose pressure parameters were stable.[107] In order to determine long-term outcome in these patients, the visual fields of the study patients were reevaluated after 5 years. Those patients who had shown greater nocturnal blood pressure dips were more likely to have visual field deterioration at some stage, despite good IOP control. Patients who had progression of visual field defects showed significantly lower nocturnal blood pressure variables, with significantly larger dips of the systolic, diastolic, and mean arterial blood pressure.[106] Collignon et al recorded 24-hour ambulatory blood pressure and diurnal curve of IOP in 51 HTG and 19 NTG patients and found a high correlation between abnormal nocturnal dipping of systolic blood pressure and disease progression in both groups of patients.[50]

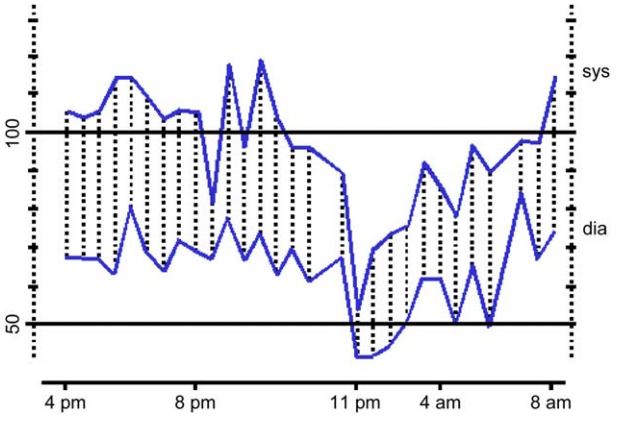

Fig. 1. 24-hour ambulatory blood pressure monitoring in glaucoma patients reveals characteristic drops in nocturnal blood pressure.

Ghergel et al evaluated the relationship between circadian blood pressure rhythm and retrobulbar blood flow in glaucoma patients. They found that glaucoma patients with a marked drop in nocturnal systemic blood pressure had altered retrobulbar blood flow parameters.[97] Analyzing the relation between peripheral vasospasm assessed by nailfold capillaroscopy and circadian blood pressure rhythm, Pache et al failed to demonstrate significant differences between non-dippers, dippers, and over-dippers in respect to peripheral vasospasm.[258] This might indicate that vasospasm and low blood pressure may be two distinct risk factors for glaucomatous damage.[257,258] To summarize, some evidence suggests that especially nocturnal drops in blood pressure may play a role in the pathogenesis of glaucoma, possibly by reducing the ONH blood flow below a crucial level. Only large prospective studies will finally answer the question whether normalization of blood pressure improves the prognosis of GON in such patients.

C. VASOSPASM

The vasospastic syndrome has been proposed as a further risk factor in glaucoma.[78] Vasospasm, or vascular dysregulation, is defined as inappropriate constriction or insufficient dilatation in the microcirculation to stimuli, such as coldness or emotional stress. Vascular dysregulation can occur throughout the body, but some organs might be more prone to spasm.[83] For example, Weinstein could demonstrate vasospasm and atony in the nailfold capillaries of glaucoma patients.[368] Gasser at al compared the capillary blood-cell velocity in the fingertips of 30 patients with HTG, 30 patients with NTG, and 30 control subjects by nailfold capillaroscopy and found a significant reduction of blood-flow velocity in patients with NTG compared with the controls, which was especially pronounced after cold provocation.[90] The presumed role of vasospasm in the pathogenesis of glaucoma has been extensively

reviewed elsewhere.[77,79,81,82,273] Vascular dysregulation interferes with the autoregulation and renders the eye more sensitive to IOP increase and blood pressure decrease.[96,295] Vasospasm is not restricted to patients with NTG but may also be a feature of HTG.[25,83,295]

A number of endothelium-derived vasoactive substances maintain and modulate the vascular tone throughout the body and the eye.[121] In the ophthalmic vascular bed, a constant basal release of nitric oxide (NO) maintains the circulation in constant vasodilation, whereas endothelin-1 (ET-1) has been shown to cause marked vasoconstriction.[118–120,224,225,290,291] Imbalance of the level of these agents, might, possibly in concert with various other vasoactive substances, result in vasospasm.[81,137] Indeed, increased plasma levels of the potent vasoconstrictor ET-1 have been described in glaucoma patients.[326] Moreover, higher ET-1 levels might be an indicator of disease progression: Emre et al retrospectively compared ET-1 plasma levels of 16 patients with POAG who showed progressive visual field defects despite normal or normalized IOP with 15 patients with POAG with stable visual fields. They found the ET-1 levels to be significantly higher in the patients with deteriorating POAG (3.47 vs. 2.59 pg/ml).[67] Some glaucoma patients also present an abnormal ET-1 response to postural changes[162] as well as an altered responsiveness to ET-1 itself.[28,89,137] Impairment in endothelial NO production in glaucoma has not directly been proven thus far.[291] It is also known that NO is a key inhibitor of platelet aggregation, but the involvement of this feature of NO in ocular blood flow of glaucoma patients remains speculative.[291] Impairment in endothelial NO production in glaucoma has not directly been proven thus far;[291] however, in glaucoma, an increased aggregation of erythrocytes[122] as well as an increased platelet aggregate ratio[22] have been observed. Both ET-1[124,125,146,163,325,331,335] and NO[42,237,296,371] are also involved in the regulation of IOP. Moreover, they contribute directly to the local neurotoxic effects that cause axonal degeneration of the retinal ganglion cells.[205,206,243–245,320] Chronic endothelial alteration may lead to raised levels of vascular endothelial growth factor (VEGF) and von Willebrand factor (vWf). Lip et al have recently demonstrated this in a cross-sectional study including 50 NTG and HTG patients, indicating an association between glaucomatous damage and abnormal vascular permeability (VEGF) and endothelial damage and dysfunction (vWf), respectively.[204]

In summary, these findings give some evidence that in glaucoma, we have to consider that to a smaller or larger extent there is a generalized vascular disorder characterized particularly, but not exclusively, by endothelial dysfunction. The vascular dysregulation may partially be due to dysregulation of the autonomic nervous system (see below). Anti-vasospastic treatment modalities for glaucoma patients are still sparse and their beneficial effect is not yet proven. Drugs such as calcium channel blocker (CCB)[207,226,242,248,292,341,342,380] and magnesium[88,376] may reduce vasospasm, but a long-term effect on parameters such as ocular blood flow and visual field has not yet been proven. Some authors even failed to demonstrate a beneficial effect of certain CCBs.[94,127,275]

Recent studies also indicate a positive effect of ginkgo biloba extract on ocular perfusion,[43] and, in a rat model of chronic glaucoma, on retinal ganglion cell survival.[140] Moreover, ginkgo administration improved preexisting visual field damage in some patients with NTG in a small prospective, randomized, placebo-controlled, double-masked cross-over study.[274] However, it remains to be seen if this effect is indeed based on improved retinal function or merely on increased vigilance.

ET-1 antagonists have become available for clinical use in cardiovascular, pulmonal, and renal disease.[208,288] Their effect on glaucoma still needs to be evaluated. Therefore the development of an ideal anti-vasospastic therapy remains a challenge for future research.

1. Electrocardiographic Changes

Various studies have focussed on electrocardiographic (ECG) changes in glaucoma patients. In a study on 212 Finish institutionalized geriatric glaucoma patients (mean age 83.9 years), a negative or isoelectric T-wave was found in 56% of the glaucoma patients compared to 38% of the age-matched control patients. In addition, Q/QS patterns, ST-segment depression, negative or isoelectric T-wave, third- or second-degree AV block, left bundle branch block or right bundle branch block, intraventricular block, or atrial fibrillation or flutter were seen significantly more often in glaucoma patients than in controls (77% vs. 62%). Atrial fibrillation occurred twice as often in glaucoma patients (17% vs. 9%). Arrhythmia, especially atrial fibrillation, was associated with impairment of visual acuity and visual field defects in glaucoma patients.[265] Demailly et al reported the prevalence of rhythm and conduction abnormalities on the ECG to be twice as frequent in glaucoma patients when compared to controls; however, due to the small sample size, this finding was not significant.[56]

Kaiser et al compared the prevalence of silent myocardial ischemia in 13 patients with NTG,

7 patients with HTG, and 20 cataract patients, and found an increased frequency of ischemic episodes in all three groups. Their most striking observation was that the frequency in NTG was twice that of the other two groups.[160] Waldmann et al performed 24-hour ECG monitoring in glaucoma patients (22 with NTG, 27 with HTG) and controls, and found at least one episode of significant asymptomatic ST-T segment depression in 45% of patients with NTG, in 25.9% of patients with HTG, and in 5% of the controls.[356] They reported that the ischemic episodes occurred mainly when patients had been sitting at ease or during sleep. This indicates that the major cause of the silent myocardial ischemia is not explainable by arteriosclerotic changes of the coronary arteries but rather by functional vascular dysregulation.

All studies cited lack 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

Functional vasospasm of brain vessels is linked to the pathogenesis of migraine and, to a lesser extent, to other types of headache. The prevalence of both diseases is strongly age-dependent with a decline with age. As vasospasm is also suspected to play a role in glaucoma, a link between glaucoma and migraine/headache was suspected.[267]

The studies available on this topic thus far give varying results: Using a standardized headache questionnaire, Phelps and Corbett found a higher prevalence of headache and migraine-like symptoms in NTG (87%, n = 54), when compared to HTG (68%, n = 182), OHT (70%, n = 126), and controls (80%, n = 493).[267] A consecutive study in Japanese patients with the same questionnaire failed to demonstrate a significant relationship between migraine and NTG (77 patients) and POAG (73 patients), respectively, but this might be due to the smaller sample size.[347]

The findings of Phelps and Corbett are supported by data from the Blue Mountains Eye Study, which suggests a possible association between migraine headache and POAG in patients of 70–79 years of age, which tended to be marginally stronger in HTG cases.[359] On the other hand, the results of the Beaver Dam Eye Study provide no evidence to support a link between POAG and migraine headache.[173] A French retrospective, multicenter study without a control group investigated 954 glaucoma patients with a standardized International Headache Society (IHS) questionnaire and found 33.5% of the patients to describe a headache (migraine or tension-type headache) and 25.1% to meet the IHS criteria for migraine. In this study, migraine prevalence was not significantly different between patients with NTG and HTG.[272] Cursiefen and coworkers, prospectively analyzing 154 patients with glaucoma (56 patients with NTG and 98 patients with HTG), 55 patients with OHT, and 75 control subjects with the same questionnaire, found no significant variation of the prevalence of headache, migraine, and tension headache among the study groups. Migraine however was significantly more common in patients with NTG (28%) compared with controls (12%) and patients with HTG (10%).[52] The Collaborative Normal-Tension Glaucoma Study Group analyzed the risk factors for progression of visual field abnormalities in NTG and found migraine to be an independent risk factor for faster course of deterioration.[60]

Taken together, the majority of studies available on this topic support an association between POAG, and, in particular, NTG, and migraine. This might be based on the fact that both migraine[91] and glaucoma are associated with systemic vascular dysregulation. It seems therefore reasonable to ask glaucoma patients, and especially those with NTG, for symptoms of headache/migraine when taking their medical history.

D. HEMORHEOLOGY

1. Platelet Aggregation

Several studies have found an altered platelet aggregation in POAG. Already in 1973, Drance et al reported differences in euglobulin lysis time and platelet adhesiveness between patients with NTG and age-matched controls.[62] A study from the Netherlands compared platelet aggregation in 79 patients with POAG with that of 81 patients with OHT and detected a significantly higher incidence of spontaneous platelet aggregation in patients with POAG over 70 years of age.[145] Interestingly, the high incidence of spontaneous platelet aggregation in patients with POAG was found to be independent of the presence or absence of vascular diseases. In a 7-year follow-up study, the same group reported that the percentage of patients with spontaneous platelet aggregation was higher for patients with visual field deterioration than for POAG patients without progression of visual field loss and for glaucoma suspects.[144] No difference in the occurrence of spontaneous platelet aggregation between patients with NTG, HTG, and patients with mid-tension glaucoma were found. A group from Croatia determined circulating platelet aggregates in 32

patients with advanced POAG and 20 healthy volunteers and detected an increased platelet aggregate ratio in the glaucoma group.[22] The same group could, however, not detect a relationship between increased platelet aggregates and progression of visual field loss in a later study.[20] A small study from Japan could also confirm an increased platelet aggregation in patients with NTG (n = 22) and HTG (n = 13).[215] On the contrary, Joist and coworkers, comparing 12 patients with NTG and 12 controls, failed to show a difference in platelet function, blood coagulability, and fibrinolytic activity.[153] Such differences might be explained by the different measurement techniques, but it seems more likely that case selection may help to explain the differing results, as Joist and coworkers tried to match patients and controls for vascular disease.

In summary, there is evidence that POAG is associated with an altered platelet aggregation. Larger prospective, confirmatory studies are desirable. The pathogenetic role of an altered platelet aggregation is not yet clear. Theoretically, one would assume that the increased platelet aggregation has a negative influence on the blood flow in the small branches of the short ciliary arteries supplying the optic disk.[144] A medical intervention study—for example, with acetylsalicylic acid—would help to confirm such a cause–effect relationship.

2. Blood Viscosity

Klaver et al compared blood and plasma viscosity, packed cell volume, plasma fibrinogen, and serum proteins of 83 patients with NTG and 23 patients with HTG with that of 50 cataract patients in a prospective case-control study. They found blood and plasma viscosity and packed cell volume to be significantly higher in the NTG group than in the controls. In the HTG group, only whole blood viscosity was significantly increased compared to controls, but was not different from the HTG group. This might be explained by the fact that smoking was significantly more frequent in the HTG group than in all other groups.[171]

Trope et al measured blood viscosity at three shear rates in 27 patients with POAG and 18 healthy controls matched for sex, mean arterial blood pressure, and smoking habits and found the mean viscosity to be significantly higher in the POAG group than in the control group at all three shear rates.[344] In a similar study, Wolf et al reported increased plasma viscosity in POAG patients (n = 51) but found no difference in erythrocyte aggregation between patients and matched controls.[377] In contrast, Hamard and coworkers found an increased erythrocyte aggregability in POAG; however, no differences in respect to hematocrit, fibrinogen and plasma protein.[122] A French group prospectively compared erythrocyte deformability and aggregability, fibrinogen plasma level, and hematocrit in 21 POAG patients and 18 controls and found erythrocyte rigidity to be significantly increased in POAG; however, no difference with respect to erythrocyte aggregability was observed between the two groups.[214] Vetrugno and coworkers compared erythrocyte deformability and aggregability in 10 patients with POAG, 10 patients with NTG, and 10 controls. They could show that the erythrocytes of glaucoma patients have a reduced elongation index as well as a reduced aggregability index, with both findings being more pronounced in the NTG group.[351] By contrast, Ates et al investigated 16 patients NTG, 17 patients with HTG, and 24 controls and found no altered erythrocyte deformability in their glaucoma patients.[6] A group from Portugal found an increased red blood cell acetylcholinesterase activity in 19 POAG patients, indicating alterations in the membrane integrity of the red blood cells.[385]

A prospective study from Scotland found that patients with HTG (n = 25) had higher levels of prothrombin fragments 1 and 2 and D-dimer than patients with NTG (n = 42) and controls (n = 32).[250] Fibrinogen was found to be higher in the glaucoma groups; however, this finding did not reach statistical significance.

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, established parameters for chronic vascular disease, 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.

III. Autonomic 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. As early as 1906, it was shown that stimulation of the superior cervical ganglion results in an increase of IOP.[337] Further evidence of the association between autonomic nervous system and IOP is demonstrated by the fact that many IOP-lowering drugs consist of autonomic agents, such as cholinergic agonists, sympathomimetic, and sympatholytic agents.[47] Reports of glaucomatous degeneration of the ciliary ganglion lend additional support to this hypothesis.[72,73,165,346]

Based upon these findings, it has been suggested that POAG is associated with systemic autonomic nervous dysfunction, and numerous studies in this field have been undertaken.[19,21,27,44–47,74,168,188] Faupel and Niedermeier noted a diminished oculocardial reflex response in glaucoma patients, indicating a decreased parasympathetic activity. Moreover, they found pilocarpine to increase the oculo-cardial reflex in both glaucoma patients and controls.[74] Also, Clark and Mapstone, using tests based upon cardiovascular reflex responses, could clearly demonstrate the presence of parasympathetic neuropathy in POAG patients.[46] Their findings were later confirmed and extended by other researchers: Kumar and Ahujy assessed autonomic nervous system function in 50 patients with POAG and 50 normal subjects using several well established cardiovascular reflex response tests. Their results showed decreased activity of both sympathetic and parasympathetic divisions of the autonomic nervous system in POAG. Sympathetic under-activity was seen in 73% of the POAG patients while parasympathetic activity was found to be decreased in 86% of the POAG patients.[188]

A recent study from Japan, analyzing the heart-rate variability of 32 patients with NTG, found the sympathetic activity of their patients to be more accentuated during the resting night span.[168] A consecutive case-control study on 29 German glaucoma patients demonstrated an impaired baroreflex-mediated heart rate in patients with both NTG and HTG using spectral analysis of heart rate and blood pressure signals.[27] The data from the latter study show a clear reduction of the vagal control of the heart both in patients with HTG and NTG. A second main finding of the study was that the baroreceptor control of the blood vessels were reduced in glaucoma patients. It is interesting in this context that a study from Croatia found venoconstriction responses to physiologic stimuli such as Valsalva maneuver to be significantly decreased in glaucoma patients.[21] Findings like these add further weight to the concept of vascular dysregulation as a risk factor for glaucomatous damage. Riccadonna et al performed 24-hour blood pressure monitoring in patients with NTG, HTG, and controls.[277] They found a significant reduction in diurnal and nocturnal heart rate variability as well as reduced nocturnal diastolic blood pressure variability in NTG. The differences among NTG, HTG, and controls even tended to become more prominent in the more severe forms of NTG, thereby suggesting a correlation between the extent of autonomic nervous system disorder and severity of the disease.

Gherghel et al performed a modified cold pressor test in 24 patients with POAG and 22 controls and found a differing blood pressure, and ocular blood flow response in patients with POAG suggestive for a systemic autonomic failure and ocular vascular dysregulation. The patients with POAG demonstrated an increase in diastolic blood pressure, heart rate, and mean ocular perfusion pressure during immersion of the tested hand in 40 °C water. During cold provocation, the patients demonstrated a significant decrease in finger and ocular blood flow. In contrast, the controls did not demonstrate any blood flow or finger temperature changes during immersion of the tested hand in 40 °C water. During cold provocation, they exhibited increases in systolic blood pressure and pulse pressure and a decrease in finger blood flow, and ocular blood flow remained unchanged at all times.[95]

The latter studies, especially those conducted in patients with NTG, show us that alterations of the autonomic nervous system of glaucoma patients are not necessarily linked to increased IOP alone. More likely, these findings support the idea that glaucoma might be a manifestation of more generalized autonomic nervous system dysfunction. Other observations, such as disturbances of the physiologic circadian change in blood pressure in glaucoma patients, provide additional evidence for the concept of autonomic nervous system dysfunction. Further studies are warranted to determine the relevance of the autonomic nervous system disturbances to disease progression in glaucoma. It should also be examined whether treatment with autonomic agents is more effective after assessment of the patient's individual autonomic nervous system function, and it should be addressed whether glaucoma patients with autonomic nervous system disturbances might benefit from alternative treatment methods, such as autogenic exercises or acupuncture.

IV. Immune System

Even though not traditionally linked, mounting evidence suggests a true association between POAG and alterations of the immune system (see Table 2). Wax suggested that the role of the immune system in glaucoma might be two-fold. In some patients, especially 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. Second, that the signal pathways of the immune system can cause neuronal cell death in response to stress factors such as high IOP, ischemia, and excessive excitatory amino acids.[361]

TABLE 2

Summary of the Immunologic Findings Described in Glaucoma Patients

Increased frequency of autoimmune disease[33]
Elevated antinuclear antibodies and IgG[236, 358]
Monoclonal gammopathy[362,*]
Different complex autoantibody repertoires[114]
Anti-rhodopsin antibodies[279,280,361,*]
Autoantibodies against heat shock proteins[262,334,336,363,364,*]
Autoantibodies against ONH glycosaminoglycans[333,361,*]
Autoantibodies against neuron-specific enolase (NSE)[148,212,213]
Autoantibodies against Glutathione S-transferase (GST), GST polymorphism[158,382]
Antiphospholipid antiboides [186,187,*]
T-Lymphocytes:
Increased expression of CD8 and MHC class II antigen (HLA-DR)[381,*]
Simultaneous expression of CD8 and CD3[381]
Increased level of cytokine interleukin-2-receptor (sIL-2R)[381]
Leukocytes:
Leukocyte migration inhibition[136,324]
Overexpression of genes coding for p53-protein, neural thread protein, 20S proteasome subunit XAPC7[103,378,*]
Underexpression of genes coding for Xeroderma pigmentosum gene, survivin protein[103,*]
Overexpression of lymphocyte IgE receptor (Fc epsilon RII/CD23), T cell specific tyrosine kinase, thromboxan-A2-receptor, alkaline phosphatase[101]
Overexpression of matrix metalloproteinase 9 (MMP9) and its upregulator MT1-MPP[102,*]

*Findings more pronounced or exclusively found in normal-tension glaucoma.

A. AUTOIMMUNITY

In 1974, Waltman and Yarian reported a high percentage of positive antinuclear antibody reactions in patients with POAG,[358] a finding that was soon confirmed in a larger study by Nagasubramian et al, who found elevated serum levels of antinuclear antibodies (ANAs) and immunoglobulin G in 225 glaucoma patients.[236]

In 1992, Cartwright performed a retrospective chart analysis of 67 NTG patients and compared them to a matched group of OHT patients. He found that 30% of patients with NTG had one or more autoimmune disease(s) compared with 8% in the OHT group.[33] More recently, Grus and coworkers described differences between the complex autoantibody repertoires of glaucoma patients and controls.[114]

To date, a considerable number of studies dealing with immunologic findings in glaucoma patients can be found in the literature. However, most of them are only case reports or small case-control, cross-sectional studies about a specific auto-antibody with limited momentous to the relevance of autoimmunity and glaucoma. It should also be emphasized in this context that there are various autoimmune diseases, such as multiple sclerosis, fibromyalgia, and rheumatoid arthritis, which do not seem to be associated with glaucoma.

1. Monoclonal Gammopathy

Monoclonal gammopathy represents a clonal expansion of antibodies generated by specific B lymphocytes. Wax and coworkers, assessing 44 patients with NTG and 41 controls with HTG, found 18% of the NTG patients, but none of the patients with HTG, to have a monoclonal paraproteinemia.[362] Even though benign paraproteinemia is not necessarily associated with systemic disease, it is considered to be a likely causative agent of peripheral neuropathies of various origins. This is especially striking as these peripheral neuropathies share some characteristics with glaucomatous neuropathy, such as symmetry, slow progression, and occurence in patients with a median age of 55–60 years.[361]

2. Anti-rhodopsin Antibodies

Romano et al examined the sera of patients with 28 NTG and 26 patients with HTG for the presence of antibodies directed toward retinal antigens, and they found an elevated anti-rhodopsin antibody count to be related to NTG.[279] This result seemed surprising, as glaucoma is associated mainly with ganglion cell damage rather than affecting photoreceptors. In order to further explore the role of the anti-rhodopsin antibodies, the authors also examined their epitopic specificity.[280] They discovered that the serum autoantibodies in patients with NTG are directed toward the C-terminus of the rhodopsin molecule. This is of special interest as the rhodopsin's C-terminus shares sequence identity to numerous bacterial and viral proteins, what led the authors to speculate about the possible presence of molecular mimicry. This would mean that an inappropriate immune response to a plain viral or bacterial infection could lead to destruction of retinal ganglion cells. It was also speculated that rhodopsin

shares a protein sequence to other, still unknown, autoantigens in the retina of glaucoma patients that accounts for a mimicked rhodopsin antibody response.[361] In this context it is interesting that the heat shock proteins (HSPs) αB-crystallin and Hsp27, which are expressed in photoreceptors and may participate in rhodopsin processing, are also target of autoantibodies of glaucoma patients[336] (see below).

3. Autoantibodies to Heat Shock Proteins

Heat shock proteins, also called stress proteins, are a group of highly conserved proteins classified into families based on their molecular weight, including HSP90, HSP70, HSP60, HSP27, and αB-crystallin.[128] Heat shock proteins play an important role in cell survival both under normal and stress conditions such as heat, anoxia, and other metabolic stress. In the central nervous system, constitutive HSP expression occurs in a variety of cell types, thus implying a neuroprotective role for HSPs. In fact, HSPs have been shown to increase neuronal tolerance to ischemic insults.[41] Due to the high degree of sequence conservation between human and bacterial HSPs, HSPs are highly autoimmunogenic.

Recent studies demonstrated the presence of serum autoantibodies to HSPs such as HSP27, αB-crystallin, and HSP60 in glaucoma patients, especially in those with NTG.[336,363,364] Moreover, increased immunostaining of HSP27 and HSP60 has been demonstrated in retina and optic nerve head of glaucomatous eyes, thereby suggesting that HSPs are components of a local defense mechanism that is upregulated in glaucoma (Fig. 2).[334] Experimental application of antibodies against HSPs led to apoptotic cell death of both neuronal cells and cells of the retinal vasculature.[336] This indicates that HSP antibodies may be a direct cause rather than an epiphenomenon of retinal cell death. Vice versa, induction of HSP72 protected retinal ganglion cells from heat stress in a rat glaucoma model.[262] Intriguingly, Fellman et al recently reported a patient with NTG whose serum immunoreactivity to retinal proteins regressed after methotrexate treatment for rheumatoid disease.[75] During the treatment period of 3 years, the patient's visual field appeared to improve. Such a case report persuades us to speculate about an immune-based intervention in some glaucoma patients. However, as long as no larger studies on this topic are available, no rash conclusions should be drawn.

4. Autoantibodies to ONH Glycosaminoglycans

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. Autoantibodies against glycosaminoglycans are thought to play a role in tissue injury in various autoimmune diseases such as systemic lupus erythematodes, scleroderma, thyroid disease and thyroid-associated orbitopathy.[123,157,294]

By means of Western blotting, Tezel et al demonstrated the presence of serum autoantibodies against ONH glycosaminoglycans in glaucoma patients, especially in those with NTG.[333] In this study, increased immunostaining of glycosaminoglycans in the lamina cribrosa of postmortem glaucomatous eyes was also observed. The authors therefore suggested that increased local deposition of glycosaminoglycan antibodies may disadvantageously change the structural properties of the lamina cribrosa. This would increase the susceptibility of the optic nerve head to nerve fiber damage at least in a subgroup of glaucoma patients.[333,361]

5. Neuron-specific Enolase Autoantibodies

Three recent studies from Japan deal with the role of autoantibodies against neuron-specific enolase (NSE) in glaucoma.[148,212,213] In a study including 79 patients with glaucoma (NTG: 23 cases; POAG: 56 cases) and 60 age-matched healthy subjects, serum NSE autoantibodies were found significantly more often in glaucoma patients than in controls (25% vs. 12%).[213] The same group also examined serum NSE autoantibodies in a larger study group including 143 patients with glaucoma (NTG: 45 cases, POAG: 98 cases) and related it to IOP, visual field, ONH cupping, and other clinical factors. Maximum IOP in the serum anti-NSE antibody-positive patients was significantly lower than that found in the negative patients. No statistical differences were observed in visual field loss, disk cupping, or other clinical factors. Interestingly, during the clinical course, rates of the presence of anti-NSE antibody were significantly higher in the early stages of POAG with visual field deterioration than without it. Although it was not statistically significant, the positive rates of serum anti-NSE antibody were relatively higher in the later stages of POAG and NTG with visual field deterioration than without it.[148] In further immunocytochemical studies, the same group showed that serum from glaucoma patients specifically reacts with the retinal ganglion cell layer.[213] It was therefore assumed that the antibodies in glaucoma patients differ from those found in controls either in affinity, avidity, specificity, or class. It was demonstrated in an animal model that intravitreal administration of anti-NSE antibodies induced a decrease of ERG response and an increase of TUNEL

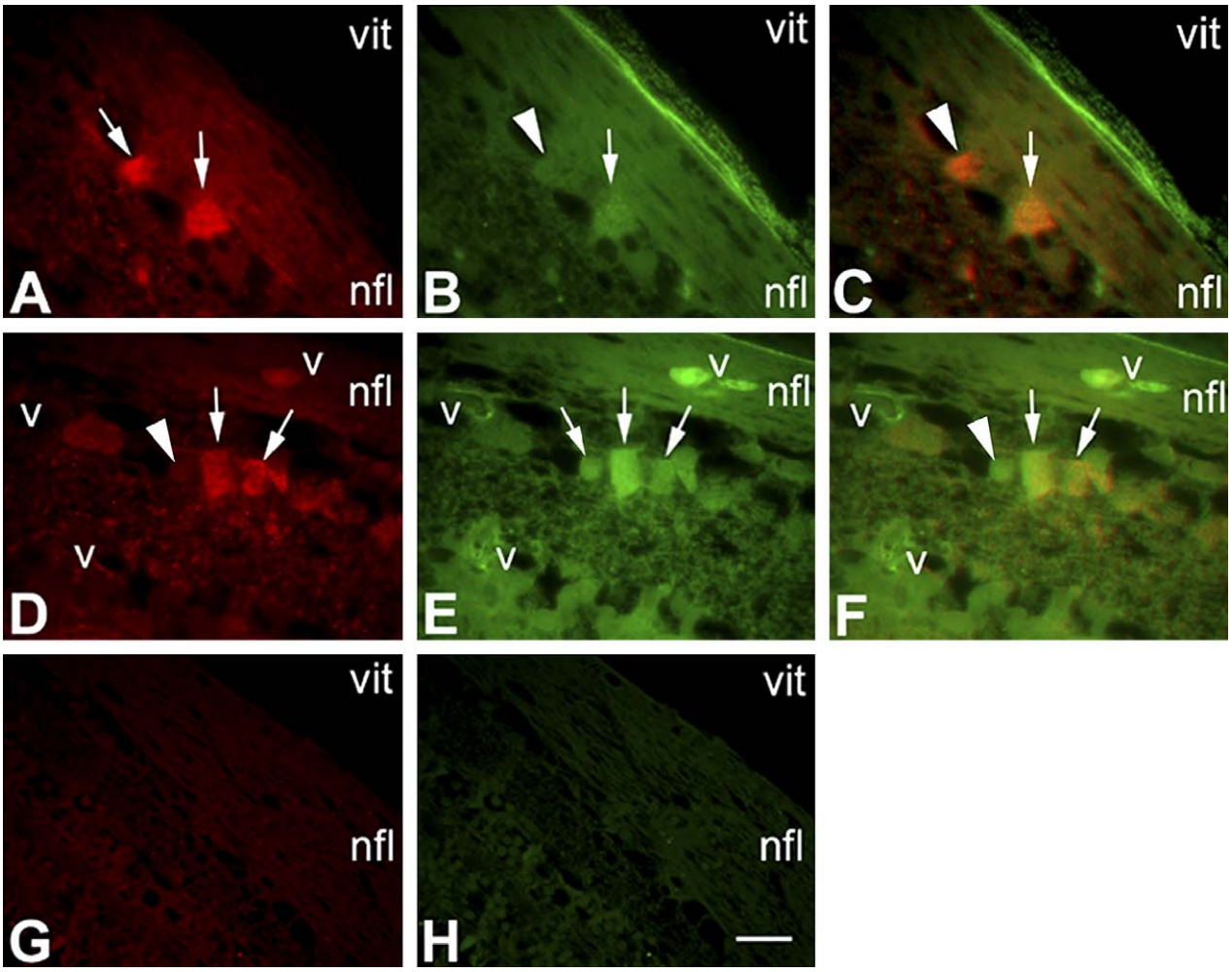

Fig. 2. Double immunofluorescence labeling for heat shock proteins (HSP) 60 (red) and HSP 27 (green) in retinal sections from an eye with moderate glaucomatous damage. *A, D:* Immunostaining of HSP 60. *B, E:* Immunostaining of HSP 27. *C, F:* Colocalization of HSP 60 and HSP 27. *G, H:* Negative controls. Immunostaining of HSP 60 was negative, but immunostaining of HSP 27 was positive around the blood vessels and in glial cells lining the internal limiting membrane. Most of the retinal ganglion cells were stained for both HSP 60 and HSP 27 (arrows). (Reprinted with permission from Tezel et al.[334])

(TdT-dUPT terminal nick-end labeling)–positive staining of the retinal ganglion cells.[213] Therefore it was suggested that the serum NSE autoantibodies might be a risk factor for retinal ganglion cell death in glaucoma. In another series of experiments, the same authors demonstrated that anti-NSE antibody-induced retinal dysfunction was comparable to the excitotoxic retinal dysfunction caused by N-methyl-D-aspartate (NMDA).[212] However, to date, the precise mechanism by which anti-NSE antibodies exert their apoptotic effect on retinal ganglion cells is not disclosed.

6. Glutathione S-transferase

The glutathione S-transferases (GST) represent a major group of detoxification enzymes. Glutathione S-transferases catalyze the conjugation of reduced glutathione with a wide variety of electrophiles, which include known carcinogens as well as various compounds that are products of oxidative stress including oxidized DNA and lipid.[129,130]

The polymorphic GST enzymes are susceptibility candidates for several systemic diseases as well as for eye disease such as cataract. Juronen and coworkers examined whether polymorphisms at the GSTM1, GSTM3, GSTT1, and GSTP1 loci are associated with increased susceptibility to glaucoma, and found a significant association between GSTM1 polymorphism and glaucoma in an Estonian population.[155] Yang et al demonstrated increased titers of serum autoantibodies to GST in 52% of 65 patients with glaucoma. Only 20% of the age-matched controls (n = 25) presented autoantibodies to GST. They suggested that the glaucomatous damage might lead to an upregulation of GST in the glial cells and, at

least in some patients, to a secondary production of serum antibodies to GST.[382] Whether the circulating antibodies against GST have a pathogenic significance remains to be evaluated.

7. Antiphospholipid Antibodies

Antiphospholipid antibodies are a heterogeneous group of immunoglobulins originally thought to recognize anionic phospholipids, which were first documented in SLE patients with an increased risk of thrombosis. The antibodies are directed against cardiolipin, b2 glycoprotein, and phosphatidylserine. Clinical features besides thrombotic events include pulmonary hypertension, thrombocytopenia and migraine.[350] There are indications that some of the vascular occlusions might be due to vasospasm.[249] Abnormalities in nailfold capillary microscopy have been observed,[327,350] and endothelin-1 is increased in these patients.[7] An association of antiphospholipid antibodies with retinal vascular occlusions has also been described.[197]

In a prospective study, Kremmer et al measured serum concentration of antiphosphatidylserine antibodies, a subspecies of antiphospholipid antibodies, in 43 NTG patients, 40 POAG patients, and 40 healthy controls.[187] They could demonstrate an increased serum concentration of antiphosphatidylserine antibodies in the NTG group. In addition, about 35% of the NTG patients demonstrated both elevated IgG and IgM antiphosphatidylserine antibodies antibodies, pointing toward an active (IgM) and persistent (IgG) autoimmune process. The 40 NTG patients showed a high frequency of circulatory disturbances, with 10 having a history of thromboembolism. The authors therefore suggested that apoptotic events outside the eye may have accounted for the induction of the autoimmune process.

Because antiphosphatidylserine antibodies can also be associated with progressive sensorineural hearing loss, Kremmer et al also looked for a possible association between NTG and progressive sensorineural hearing loss. In a small case-control study, they evaluated 34 patients with NTG and found 23 of them to suffer from hearing loss (progressive sensorineural hearing loss n = 11; presbyacusis n = 12). Moreover, the NTG patients had significantly higher antiphosphatidylserine antibodies levels than controls, and the elevated antiphosphatidylserine antibodies concentrations were significantly more frequent in patients with NTG and hearing loss compared with NTG patients with normacusis, thus indicating a high coincidence of NTG and hearing loss, possibly due to similar systemic autoimmune processes.[186]

In contrast, Tsakiris et al prospectively studied 22 patients with NTG, 23 with HTG, and 25 controls and found no significant difference in the antiphospholipid antibody levels of the three groups.[345] Therefore, unless larger prospective studies are available, the association between glaucoma and antiphospholipid antibodies remains to be established.

B. LEUKOCYTE ACTIVATION

In 1973, Henley and coworkers demonstrated a lack of cell-mediated immunity, as indicated by leukocyte migration inhibition in patients with POAG.[136] This finding was later confirmed and extended by Stukalov et al, who described an increased microprecipitation and lysis reaction as well as leukocyte migration inhibition in 42 patients with POAG.[324]

In theory, studies on blood leukocytes may provide new insights into the pathomechanism of glaucoma, and they may allow early noninvasive diagnostics in the future. The studies listed below 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. We need to learn whether there is a clearly definable subgroup of patients with POAG with leukocyte activation, and, if yes, whether this activation shows a characteristic pattern. If so, this would greatly facilitate the diagnosing of glaucoma.

1. Analysis of T cell Subsets

Examining potential alterations in the cellular immune system, Yang and coworkers looked at differences in subpopulations of lymphocytes in patients with NTG (n = 20) and HTG (n = 18).[381] They reported that T lymphocytes in the peripheral blood of NTG patients express both CD8 and MHC class II antigen (HLA-DR) with increased frequency, whereas others simultaneously express antigens CD8 and CD3 and are more frequent in both patients with NTG and HTG. Interestingly, the increased presence of HLA-DR molecules on lymphocytes has been described in various organ-specific autoimmune diseases.[34,216,253] This led the authors to suggest that a retina and/or ONH specific autoantigen might be present in some patients with NTG. Because cytokines are involved in acute and chronic pathology of the central nervous system, the authors also assessed the concentration of the cytokine interleukin-2 (IL-2) and its receptor (sIL-2R). They found increased levels of sIL-2R in patients with both NTG and HTG. This is of special interest as sIL-2R is also elevated in some autoimmune diseases.[211,310] It was therefore concluded that the high sIL-2R levels observed in some glaucoma

patients may occur in response to aberrant humoral or cellular immunity.

2. Gene and Protein Expression in Leukocytes

Golubnitschaja et al compared mRNA expression in lymphocytes of six NTG patients with vasospastic diathesis to six healthy controls.[103] They demonstrated that genes coding for p53-protein, neural thread protein (NTP), and 20S proteasome subunit XAPC7 were overexpressed, whereas genes coding for Xeroderma pigmentosum gene (XPGC), and survivin protein were underexpressed in NTG (Fig. 3).

As p53 is considered to be a key determinant in the promotion of apoptosis in ischemia-reperfusion injury,[154] its upregulation in NTG is not necessarily surprising. The same holds true for NTP, which is upregulated in perifocal neurons of focal injury and stroke,[54] as well as in Alzheimer disease.[53,55] Proteasomes play a central role in the turnover of various regulatory proteins, and it is known that the 20S proteasome is upregulated during oxidative stress. The upregulation of 20S proteasome subunit XAPC7, which encodes the 20S proteasome α-subunit, has meanwhile also been confirmed on the protein level of NTG patients.[378]

To date, it is still unknown why leukocytes of these patients enhance their synthesis of 20S proteasome α-subunit. It can however be speculated that this upregulation might somehow be linked to a complex pathway of tumor necrosis factor (TNF)α-/ET1/nuclear factor (NF)-κB-activation, thus leading to apoptotic glaucomatous damage.[378] XPGC is a member of the family of the DNA repair proteins. The fact that it is underexpressed might be interpreted in a way that NTG patients have an increased sensitivity to free oxygen radicals, which in turn, might add to the increased expression of p53.[48] Survivin is an apoptosis inhibitor similar to bcl-2,[203] and it can be speculated that its downregulation might be induced by reperfusion damage.

In another series of experiments, an increased expression of the lymphocyte IgE receptor (Fc epsilon RII/CD23), T cell specific tyrosine kinase (ITK), thromboxan-A2-receptor, and alkaline phosphatase in peripheral leukocytes of glaucoma patients was demonstrated.[101] It was hypothesized that the enhanced expression of the lymphocyte IgE receptor observed in this study could be due to an increased synthesis of IL-4. ITK plays a crucial role in IL-2 production. As mentioned before, increased levels of sIL-2R have been found in glaucoma patients.[381] The increased expression of the thromboxan-A2-receptor is interesting as it is well known that thromboxan-A2-receptor antagonists reduce myocardial damage and leukocyte accumulation following coronary arterial occlusion and reperfusion in animal models.[85,318] Upregulation of alkaline phosphatase has also been demonstrated in patients with chronic ischemic heart disease and myocardial infarction, indicating the involvement of the same metabolic pathways. More recently, the authors demonstrated an overexpression of matrix metalloproteinase 9 (MMP9) in combination with its upregulator MT1-MPP in 6 patients with NTG.[102] Matrix metalloproteinases are a family of highly regulated peptidases that are collectively responsible for the degradation of extracellular matrix—for example, during tissue remodeling, embryonic development, morphogenesis, and reproduction.[309] Upregulation of MMP-9 after ischemia/reperfusion injury has been described in the eye, brain, lung, and in muscles.[386] The upregulation found in glaucoma patients may therefore be a consequence of repeated mild ischemia/reperfusion injury.[82] The gene expression profiles observed in these studies indicate the involvement of metabolic pathways characteristic for ischemia/reperfusion injury. Moreover, the profile seems to be characteristic for adherent leukocytes, which could contribute to the blood-brain barrier breakdown described in some glaucoma patients.[381,383]

V. Endocrinological System

A. DIABETES MELLITUS

The association of diabetes with POAG is not new, but still controversially discussed. Although numerous studies demonstrated a positive correlation between both conditions,[2,5,13,58,172,174,175,229,247] other researchers failed to demonstrate such an association[8,113,158,195,198,339,373] (Table 3).

Armstrong and coworkers were the first to describe an increased incidence of glaucoma in diabetic patients, and vice versa, of diabetes in glaucoma patients. Of 393 diabetics screened, 4.1% were found to have glaucoma, compared to 1.4% in a control group of non-diabetics. In an additionally performed retrospective chart analysis (n = 844), the overall-incidence of glaucoma was found to be at least 5.9% of the diabetics. The authors also screened 53 unselected glaucoma patients for diabetes and found 5.7% of the patients to have previously unsuspected diabetes.[5] Also Becker stated that "diabetes occurs more often in patients with primary open-angle glaucoma than in non-glaucomatous populations."[13] Dielemans and coworkers reported an association between newly diagnosed diabetes mellitus and high levels of blood glucose with elevated IOP and HTG when analyzing the data of the Rotterdam study.[58]

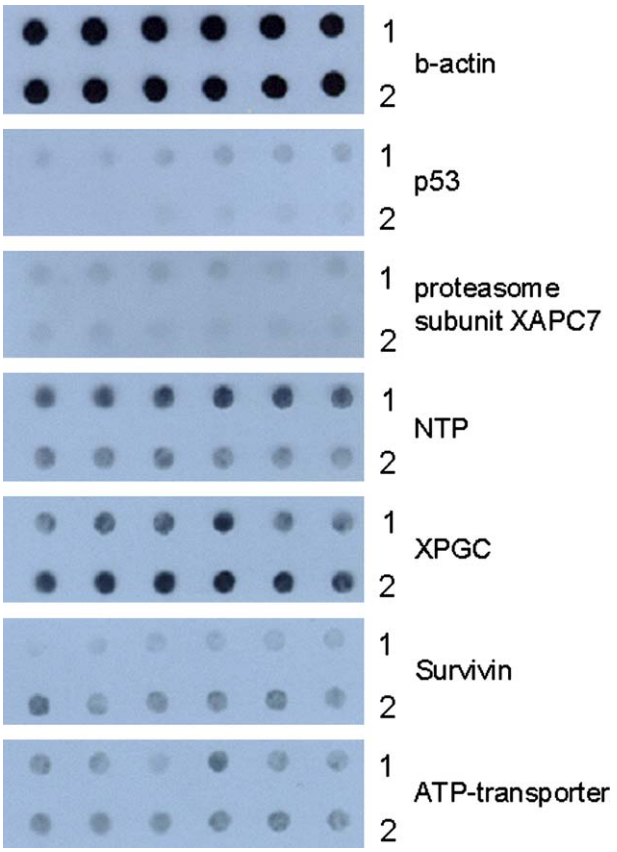

Fig. 3. Dot-blots with mRNA-pools from individual subjects, used to quantify specific transcripts hybridized with labeled subtracted cDNAs. In each dot-blot, the top and bottom dots represent specific mRNA-signals from NTG-patients and healthy subjects, respectively. (Reprinted with permission from Golubnitschaja-Labudova et al.[103])

In the Wisconsin Study of Diabetic Retinopathy, IOP values of 2,366 diabetic persons and 381 nondiabetic persons tended to be higher in diabetic persons. Moreover, a higher rate of glaucoma among diabetic persons was found through health questionnaires.[174] The Beaver Dam Eye Study found a twofold increase of both definite and probable glaucoma in diabetic subjects, and also found twice as many subjects to have an IOP > 21 mm Hg in at least one eye among diabetic patients.[172] A study exploring the relationship between diabetes and POAG in an older Australian population demonstrated an increased glaucoma prevalence in diabetic patients (5.5% vs. 2.8%). Vice versa, diabetes was present in 13.0% of people with glaucoma, compared with 6.9% of those without glaucoma.[229]

In contrast to these findings, the Framingham Study failed to demonstrate an association between diabetes and POAG.[158,195] Also, the Baltimore Eye Survey, which included a total of 5,308 subjects, found no evidence for an association between diabetes and POAG. However in the latter study,

TABLE 3

Survey of the Large Epidemiological Studies Dealing with the Relationship between Glaucoma and Diabetes Mellitus

Positive Relationship
Rotterdam Study[58]
Wisconsin Study of Diabetic Retinopathy[174]
Beaver Dam Eye Study[172]
Blue Mountains Eye Study[229]
No or Negative Relationship
Framingham Study[158,195]
Baltimore Eye Survey[339]
Barbados Eye Study[198]
Ocular Hypertension Treatment Study[104]

diabetes was associated with higher IOP.[339] In the Barbados Eye Study, including 4,709 subjects, logistic regression analyses revealed that age, male sex, high IOP, and family history of POAG were major risk factors for glaucoma. However, although hypertension and diabetes were common in the study participants, they were found to be unrelated to the prevalence of POAG.[198] The Ocular Hypertension Treatment study (OHTS) even found diabetes to be significantly protective against developing POAG.[104] It is interesting in this context that obesity, a common hallmark of diabetes, seems not to be associated with glaucoma. Gasser et al compared the body mass index (BMI) of 42 patients with HTG, 87 patients with POAG who were progressive despite IOP less than 21 mm Hg, and 57 patients with NTG with the BMI of 288 control subjects and found no statistical difference in BMI between patients with glaucoma and control subjects.[92] In a cohort study of 137 patients with POAG, Soares and coworkers evaluated potential risk factors associated with optic disk hemorrhages and found them to be significantly associated with diabetes.[313]

Interpretation of the data from the studies listed above harbors some difficulties. Most of the earlier studies were small, used differing definitions of glaucoma, and examined selected populations. But even the newer studies show discrepancies in population and diabetes definition. Ellis and coworkers, recently asking "Should diabetic patients be screened for glaucoma?" critically reviewed all existing studies on this topic and came to the conclusion that a meta-analysis of the available data is impossible due to the above-mentioned differences and shortcomings in study design. The authors state that it is momentarily insufficient to claim that diabetes is a risk factor for the development of POAG because of a lack of conclusive evidence. They suggest that information from a prospective, general population–based, incidence study of all subjects in a community with full

ascertainment of diabetes is warranted before any recommendations for a general screening should be given.[64]

B. THYROID DISEASE

One of the earliest reports on the association between glaucoma and thyroid disease appeared in 1897, when Brailey and Eyre described 5 cases of thyrotoxicosis in young women who all exhibited signs of glaucoma.[24] Today, despite a considerable number of studies on this subject, the relationship between glaucoma and thyroid dysfunction is still unresolved. Study results differ, sometimes are actually contradictory, and leave an impression of considerable confusion. Unless larger epidemiological studies are available, a systematic screening for thyroid dysfunction in POAG patients seems unjustified, but may be indicated in selected patients.

1. Thyroid-associated Orbitopathy (Grave Disease)

Patients with thyroid-associated orbitopathy present with hyperthyroidism and with one or more of the triad of goiter, dermopathy, and ophthalmopathy. 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. In clinical practice, it is important but also difficult to differentiate glaucomatous visual field and ONH changes from changes caused by orbitopathy-related compressive optic neuropathy.[314]

Cockerham et al, who analyzed the charts of 500 consecutive patients with thyroid-associated orbitopathy, found 24% of the patients to have an IOP between 22 and 30 mm Hg. Seven patients were identified as glaucoma suspects, and two patients demonstrated progressive visual field defects and cupping. The mean duration of thyroid-associated orbitopathy was 3, 8, and 12 years for ocular hypertensives, glaucoma suspects, and patients with glaucomatous damage, respectively. These data indicate that the duration of active orbital involvement is statistically associated with the progression of glaucomatous damage. It was therefore suggested that patients with chronic, long-standing thyroid-associated orbitopathy deserve close follow-up to prevent optic nerve damage.[49,76] Ohtsuka and coworkers performed a prospective study in 104 consecutive patients with graves' disease and found a significantly higher prevalence of POAG and OHT among the patients when compared to the general population in Japan.[254] Pohjanpelto examined 187 Finish patients with various disturbances of thyroid function for glaucoma, amongs them 127 patients with hyperthyroidism and 37 cases of hypothyroidism (see below). The incidence of glaucoma for the total series of 127 patients with hyperthyroidism was 6.3% (with glaucoma suspects 9.4%), and for patients over 40 years of age 8.3% (with glaucoma suspects 11.5%).[270]

In contrast, Kalmann and coworkers found POAG to have the same prevalence in the general Dutch population as in thyroid-associated orbitopathy patients.[164] Their results are weakened by the fact that they performed a retrospective chart analysis of thyroid-associated orbitopathy patients without differentiating between active and inactive disease stage. In conclusion, there is convincing evidence that longstanding, active thyroid-associated orbitopathy is associated with glaucoma. Therefore, regular screening for glaucoma in thyroid-associated orbitopathy patients is recommended.

2. Hypothyroidism

The association between POAG and hypothyroidism is still controversial (see Table 4). In 1966, Becker and coworkers demonstrated low values of protein-bound iodine in POAG patients,[14] a finding that was later confirmed by Cherniavskii et al. The latter group measured the level of protein-bound iodine in the blood serum of 85 patients with glaucoma, their relatives including glaucoma suspects, and in 10 normal controls and found significantly lower levels of protein-bound iodine in glaucoma patients and in their relatives suspectible of glaucoma.[38] In contrast, Cheng and Perkins found no association between thyroid disease and glaucoma. They screened 155 patients with thyroid disease (including both patients with hyper- and hypothyroidism), and found only two to suffer from glaucoma, which was considered to be in the same rate as in the general population. Also, no difference in IOP when compared to the general population was found, and the mean IOP value did not differ between the hyperthyroid and the hypothyroid group.[37] Vice versa, McLenachan and Davies screened 100 patients with POAG and found signs of thyroid dysfunction in 45 cases (myxoedema: 16; Hashimoto disease: 10; thyrotoxicosis: 16; thyroidectomy: 15; goitre: 22; carcinoma of the thyroid: 1).[222] Cartwright and coworkers reviewed the charts of 67 NTG patients and found 11.9% to have previously diagnosed hypothyroidism. Moreover, 30% of the patients with NTG had one or more immune-related disease. The authors therefore speculated that individuals with inclinations to autoimmunity, including hypothyroidism, have a predisposition for glaucoma.[33] Smith et al reported the reversal of POAG in a 62-year-old

TABLE 4

Overview of Studies Showing a Positive or Negative Relationship between Glaucoma and Hypothyroidism

	Correlation Found	No Correlation Found
Glaucoma and Hypothroidism	Study, (n), Study type	Study, (n), Study type
Hypothyroidism in POAG	McLenachan and Davies,[222] (100 POAG), CSS Becker,[14] (56 POAG), CCS Cherniavskii,[38] (85 POAG, glaucoma suspects, relatives), CCS Cartwright,[33] (67 NTG) RCA Smith,[312] (1 POAG), CR Smith,[311] (64 POAG), CCS Girkin,[99] (590 OAG), CCS	Gillow,[98] (100 POAG), CSS Munoz-Negrete,[235] (75 POAG), CCS
POAG in hypothyroidism	Lee,[191] (324), ES	Cheng,[37] (155), CSS Pohjanpelto,[270] (187), CSS Karadimas,[166] (100), CSS

CR = case report; CCS = case control study; CSS = cross-sectional study; RT = randomized trial; ES = epidemiological study; FS = follow-up study; RCA = retrospective chart analysis.

woman after 1 year of thyroxin therapy.[312] In a later case-control study, the same authors evaluated 64 patients with POAG and found 23.4% to suffer from hypothyroidism. A diagnosis was made previously in 12.5% of the patients, and 10.9% were newly diagnosed, thus indicating that there might be a large group of patients with POAG with undiagnosed hypothyroidism.[311] Also, data from the Blue Mountains Eye Study indicate a relationship between glaucoma and thyroid disease. Lee et al found a significantly higher frequency of open-angle glaucoma in subjects reporting current thyroxine use or a history of thyroid surgery. The authors, however, could not properly categorize the thyroid disorder for all cases, but assumed that the use of thyroxine suggests a prior hypothyroid stage.[191]

In a cohort study in Alabama, 590 patients with newly diagnosed glaucoma between 1997 and 2001 were compared with 5,897 age-matched controls with respect to the association between prior diagnosis of hypothyroidism and the risk of developing glaucoma. After adjustment for other potential risk factors, such as diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, arterial disease, and migraine, patients were significantly more likely to have prior hypothyroidism than controls (OR, 1.40; 95% confidence interval, 1.01–1.97).[99]

In contrast to these findings, Gillow et al found no increased prevalence of hypothyroidism in British POAG patients.[98] Similarly, a Spanish group was unable to demonstrate a relationship between hypothyroidism and POAG. When comparing 75 consecutive patients with a previous diagnosis of POAG and 75 controls, hypothyroidism was revealed in two patients with POAG and in three controls.[235] Pohjanpelto examined 187 Finish patients with various disturbances of thyroid function for glaucoma, among them were 37 cases of hypothyroidism. In this subgroup were one patient with glaucoma and three glaucoma suspects, and the author concluded that the incidence of glaucoma in this group was not very high compared with the incidence in the general population.[270] Additionally, a recent study from Greece failed to demonstrate an association between hypothyroidism and glaucoma. In this study, 100 consecutive patients with newly diagnosed hypothyroidism underwent a complete ophthalmologic examination, however none of them was found to have glaucoma. Furthermore, in this study, no correlation between IOP and either thyroid stimulating hormone or free tri-iodothyronine was found, and no difference between IOP levels before and after treatment of the hypothyroidism was observed.[166]

C. PITUITARY SYSTEM

Various smaller case series indicate an association between POAG and pituitary tumors such as prolactinoma and somatotropic adenoma, even though the mechanism by which this occurs is not yet clear. Van Bijsterveld and Richards stated that they have seen 14 cases of chromophobic adenoma within a period of 2.5 years among which three were associated with POAG.[348] In 1955, Arén and Skanse reported 5 Swedish patients with acromegaly, of which 3 were found to have "simple glaucoma."[4] Howard and English reviewed 74 cases of acromegaly, and found among them an incidence of POAG of 10%.[143] The observation of POAG in patients with acromegaly might suggest that the somatotropic hormone may facilitate a condition of glaucoma.

Greco and coworkers reported that glaucoma patients display plasma human growth hormone (HGH) levels twice as high as controls after administration of arginine. They hypothesized that the increased HGH level might interfere with the regulation of IOP by modifying the outflow via changes in the sclero-corneal trabecular meshwork.[111] A small case-control study on 11 hyperprolactinemic patients and 5 healthy volunteers showed that hyperprolactinemic patients have increased IOP levels both at baseline as well as after water load. The authors therefore suggested a possible role of prolactin in the hormonal regulation of IOP.[59] Due to the small sample size, however, these results should be interpreted with caution.

D. CUSHING SYNDROME

Cushing syndrome may be associated with corticotropic adenomas of the pituitary gland, the adrenal gland, or with exogenous hormone administration. The outflow facility is decreased up to 50% in patients with Cushing syndrome,[117,314] and it is well known that long-term systemic or local steroid application can increase IOP in predisposed subjects.[31] Recent evidence suggests that this effect is at least partially mediated by Trabecular meshwork Inducible Glucocorticoid Response (TIGR) gene expression.[246,322]

First case reports about an association of Cushing syndrome and POAG arose with Dérer and Kopf,[57] Tatar,[332] and Schmelzer.[289] Vice versa, in patients with POAG, increased plasma cortisol levels as well as disturbances of the hypothalamo-hypophyseal-adrenal gland system have also been described.[202,217,218,283,297,299,300] Rozsival et al examined aqueous humor and plasma cortisol levels in 35 patients with various types of glaucoma (including 15 patients with POAG), and 35 cataract patients and found the highest plasma and aqueous humor cortisol levels in patients with open-angle glaucoma who suffered also from systemic hypertension.[283] Moreover, Schwartz and coworkers tested the stress response to pyrogen and vasopressin in glaucoma patients and normals. With pyrogen, a significant response of elevation of plasma cortisol levels was positively correlated with IOP and changes of the ONH. With vasopressin, a decreased response of plasma cortisol levels was negatively correlated with the degree of elevated IOP.[298] Weinstein et al demonstrated an accumulation of 5 beta-Dihydrocortisol in cells cultured from trabecular meshwork specimens from patients with POAG. The group could also show an abnormal metabolism of cortisol[316] and a marked increase in delta 4-reductase and a decrease in 3-oxidoreductase[366] in trabecular meshwork specimens of patients with POAG. Moreover, they found a decreased activity of 3α-hydroxysteroid dehydrogenase (3α-HSD), a key enzyme of cortisol metabolism, in peripheral blood lymphocytes of patients with POAG.[365] This led the authors to hypothesize that a similar reduction of 3α-HSD in ocular tissue may, at least in part, be responsible for the OHT and steroid sensitivity of a subgroup of glaucoma patients.

Becker and coworkers demonstrated a relationship between HLA antigens and corticosteroid response. They studied 25 randomly chosen patients with POAG and 30 controls and found that the gaucoma patients demonstrated an increased prevalence of HLA-B7 and HLA-B12. Testing of the in vitro prednisolone inhibition of lymphocyte transformation in these patients revealed that the individuals with HLA-B12 antigen respond to significantly lower concentrations of prednisolone than patients with other antigens.[15] Stokes and coworkers evaluated the central and peripheral sensitivity to glucocorticoids in patients with POAG, OHT, and healthy controls and found patients with POAG to exhibit a greater cutaneous vasoconstrictor response to glucocorticoids than patients with OHT and normal subjects. Moreover, a change in the balance of 11-beta-hydroxysteroid dehydrogenases, regulators of the glucocorticoids activity at a prereceptor level, was found in patients with POAG, thus indicating an increased sensitivity of glucocorticoid receptors in these patients.[321]

Future research into the stress response of glaucoma patients, as well as into the influence of glucocorticoids on aqueous outflow, and on MYOC gene expression may further elucidate the above mentioned observations.

VI. Neurodegenerative Diseases

There is increasing evidence that glaucomatous damage extends from retinal ganglion cells to the lateral geniculate nucleus and to the visual cortex in the brain.[115,384] These degenerative alterations are however a direct consequence of glaucoma, and are therefore not discussed in detail here.

A. ALZHEIMER DISEASE

Alzheimer disease is the most prevalent progressive dementia, mainly characterized by large extracellular beta-amyloid plaques and intraneuronal neurofibrillary tangles. The severity of dementia in Alzheimer disease is closely related to the degree of the associated neuronal and synaptic loss.[32] Various visual abnormalities like deficits in stereopsis, color vision, contrast sensitivity, and motion detection, have been described in Alzheimer disease patients.[141]

Recent studies also indicate a possible relationship between Alzheimer disease and glaucoma. Chandra and coworkers, who studied all death certificates of the United States from 1978, were the first to describe a high frequency of glaucoma in senile and presenile dementia.[35] Hinton and coworkers found widespread axonal and retinal ganglion cell degeneration in the optic nerves of 8 of 10 patients with Alzheimer disease.[139] Sadun and Bassi showed in 10 patients with Alzheimer disease that this loss was predominant in the largest class of retinal ganglion cells (M cells), and they reported a dropout of retinal ganglion cells ranging from 30% to 60%.[286]

In a retrospective analysis, Nesher and Trick compared the pattern-electroretinography recordings of 42 patients with glaucoma, 13 patients with Alzheimer disease, 58 patients with diabetes mellitus, and 92 control subjects, and observed a similarity of the changes of recordings in patients with Alzheimer disease and glaucoma.[241] In 2002, Bayer et al described a series of 49 patients with Alzheimer disease, of whom 12 patients (24.5%) presented with glaucomatous visual field defects or cup-to-disk ratios of 0.8 or greater.[10] This finding was confirmed and extended in a larger series of patients: In 112 Alzheimer disease patients of four nursing homes in Upper Bavaria, Germany, 29 (25.9%) were found to have visual field defects and/or optic disk cupping compatible with the diagnosis of glaucoma.[9]

These observations bring up the idea of a pathogenetic similarity between Alzheimer disease and glaucoma, two diseases in which neuronal cell death via apoptotic mechanisms plays a major role. It is interesting in this context that Alzheimer disease-specific proteins, such as Alzheimer peptide (Aβ) and alpha-1-antichymotrypsin have been identified in the aqueous humor of glaucoma patients.[151] Moreover, caspase activation and abnormal processing of amyloid precursor protein, both important events in Alzheimer disease, were observed in retinal ganglion cells of rats with experimental glaucoma.[220] More recently, Apolipoprotein E (APOE), crucially involved in neuronal degeneration in Alzheimer disease, has been reported to act as a potent modifier for glaucoma.[51] Inheritance of a particular APOE gene polymorphism, namely the ε4 allele, has been shown to be associated not only with an elevated risk for Alzheimer disease, but also for NTG in the Tasmanian population.[353]

Despite these attractive theories, it must be said that the listed studies are not sufficient to establish a real relationship between Alzheimer disease and glaucoma. Each study is limited either because of its small sample size, its retrospective nature, or by potential selection bias. Because the diagnosis of Alzheimer disease can only be verified histologically, we need larger prospective postmortem studies before we can speak of a true association between Alzheimer disease and glaucoma.

B. PARKINSON DISEASE

Parkinson disease is a progressive neurodegenerative disorder characterized by degeneration of the nigrostriatal dopaminergic pathway and the appearance of cytoplasmic proteinaceous aggregates, the so-called Lewy bodies. Biochemical analysis has implicated mitochondrial dysfunction in Parkinson disease. The mitochondrial dysfunction, resulting from genetic defects, environmental toxins, or a combination of both, may cause selective neurodegeneration through mechanisms involving oxidative stress and excitotoxicity.[303] In a recent study, Bayer and coworkers reviewed the ophthalmologic charts of 38 patients with Parkinson disease and found 23.7% of them to suffer from glaucoma.[10] Such a result raises questions about whether a common basis process underlies glaucoma and neurodegenerative diseases such as Parkinson disease; however, the study is limited by its retrospective nature, its small sample size, and by potential selection bias. Unless prospective epidemiologic studies with adequate sample size confirm the finding of Bayer et al, it is not justified to speak of an association between the two diseases.

VII. Sleep Disturbances

A. SLEEP-ONSET DISTURBANCES

A recent study demonstrated a self-reported prolonged sleep onset latency in NTG patients with vascular dysregulation.[259] A relationship between thermoregulatory processes and the initiation of sleep has long been implicated. It has been shown that the degree of dilation of blood vessels in the skin of hands and feet, which increases heat loss at these extremities, is a good physiological predictor for the rapid onset of sleep.[185] As patients with vasospastic syndrome often suffer from cold hands and cold feet, and respond to cold stimuli or even emotional stress with inappropriate constriction or insufficient dilation in the microcirculation,[83] it was proposed that these patients might have difficulties to prepare physiologically for sleep due to an impaired ability to initiate distal vasodilation. In fact, these patients revealed a prolonged sleep onset latency both in the evening as well as after nocturnal sleep interruption when rated with a sleep questionnaire. Moreover, 62% of the patients named "cold feet" among their reasons for sleep onset difficulties, whereas no subject in the control group marked this item.[259] This suggests a link between the prolonged sleep-onset latency and the frequent

rating of "cold feet," which might be explained by an impaired ability of distal vasodilation in these patients. The cited study, however, has a limitation that deserves comment: The self-reported sleep-onset latency found in a sleep-questionnaire may not necessarily reflect the real sleep-onset latency of the patients. Therefore, larger confirmatory studies, e.g., in a sleep laboratory under a constant routine protocol, are warranted before such a link can be definitely established.

B. SLEEP APNEA SYNDROME

A different set of complaints that might reach the ophthalmologist in connection with NTG and sleep disturbances are the symptoms of sleep apnea syndrome (Fig. 4, Table 5). These patients frequently suffer from headache, mainly in the morning, from daytime sleepiness, and often report a long history of loud snoring and obstructive breathing.[230–232] In contrast to the above-mentioned vasospastic NTG patients, who are mainly women with a low body mass index (BMI),[259] sleep apnea syndrome typically affects men with a high BMI.[230–232]

Walsh and Montplaisier reported a combination of familiar glaucoma and sleep apnea syndrome in five members of two generations of a family.[357] Robert et al, studying eyelid hyperlaxity and sleep apnea syndrome, could show an incidental but significant association between sleep apnea syndrome and POAG.[278] Mojon and coworkers studied the prevalence of glaucoma in 114 white patients consecutively referred for polysomnographic evaluation of suspected sleep apnea syndrome. Of 69 patients with confirmed sleep apnea syndrome, 5 patients (7.2%) were found to have POAG, and 2 of them fulfilled the criteria of NTG.[232] Moreover, the Respiratory Disturbance Index (RDI) during night sleep correlated positive with IOP, visual field loss variance and glaucomatous optic disk changes. In another series of experiments, the same authors studied 30 consecutive glaucoma patients and found 6 (20%) of them to suffer from SAS.[231] Onen and coworkers rated 212 outpatients with and 218 without POAG with a sleep questionnaire and found a significantly higher prevalence of sleep-disordered breathing in patients with POAG.[255] In a comparative case series, Marcus et al examined the prevalence of SAS in NTG patients both by means of a questionnaire and by polysomnography of selected patients and also found a significant association between glaucoma and sleep apnea syndrome.[210] These findings led to the hypothesis that sleep apnea syndrome may aggravate or possibly even cause glaucoma in some cases. It was hypothesized that the glaucomatous damage may result from impaired perfusion of the ONH secondary to repetitive prolonged apneas, or, alternatively, from sleep apnea syndrome-induced arterial hypertension and arteriosclerosis.[230–232] Sleep apnea syndrome patients, like glaucoma

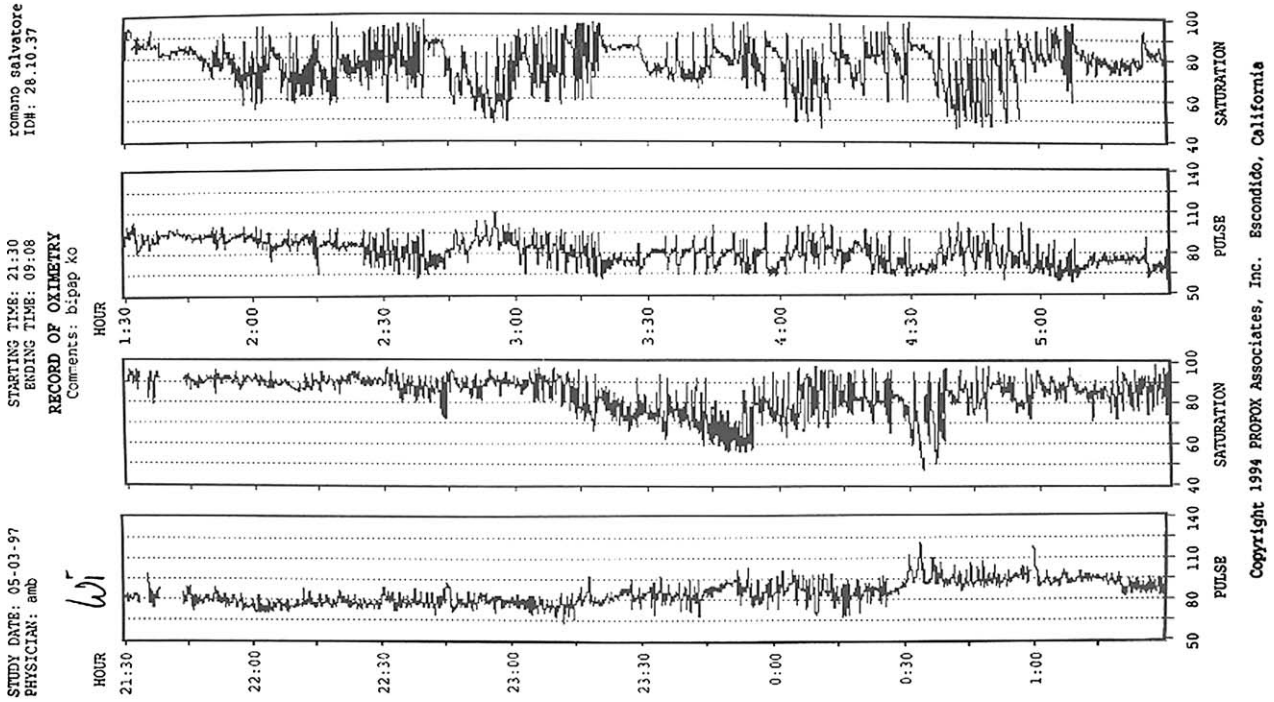

Fig. 4. Pulsoxymetry of a patient suffering from sleep apnea syndrome. (Courtesy of Jürg Leuppi, MD, University Hospital Basel, Switzerland.)

TABLE 5

Overview of Studies Showing a Positive or Negative Relationship between Glaucoma and Sleep Apnea Syndrome

	Correlation Found	No Correlation Found
Sleep Apnea Syndrome (SAS)	Study, (n), Study type	Study, (n), Study type
SAS in POAG patients	Walsh,[357] (5), CR Mojon,[231] (30), CSS Onen,[255] (212), CCS Marcus,[210] (23 NTG, 14 NTG suspects), CCS	
POAG in SAS patients	Walsh,[357] (5), CR Robert,[278] (69), CR Mojon,[232] (69), CSS	Geyer,[93] (228), CSS

CR = case report; CCS = case control study; CSS = cross-sectional study.

patients, have increased plasma levels of the potent vasoconstrictor endothelin-1.[268,284] Interestingly, it has been demonstrated in an animal model that sleep deprivation increases plasma ET-1 levels.[260]

In contrast to these findings, the largest group of patients with sleep apnea syndrome investigated thus far in order to determine the prevalence of glaucoma among these patients was negative. In a cross-sectional study on sleep apnea syndrome patients, Geyer et al found the prevalence of glaucoma to be comparable to that in the general white population.[93]

Further studies must clarify if there is indeed a link between sleep apnea syndrome and POAG, and, if yes, whether treatment of SAS slows down the progression of glaucomatous damage. For the time being, a general screening for SAS in glaucoma patients is not recommended; however, asking suspicious patients about the above-listed symptoms of sleep apnea syndrome seems reasonable.

VIII. Psychological Aspects

A. PSYCHOLOGICAL CHARACTERISTICS

The role of psychic factors in glaucoma is widely recognized among ophthalmologists. Whereas the earliest studies focused mainly on the influence of emotions on angle-closure glaucoma, it is now evident that psychic factors also play a role in patients with POAG. It was shown that in healthy individuals stress results in an increase of IOP, whereas relaxation techniques have an IOP-lowering effect.[26,70,112,343] The diencephalon, which is responsible for emotional behavior, plays an important role in the regulation of IOP. Therefore it seems not unlikely that unstable emotions are associated with a disturbed central IOP control in glaucoma patients.[71] This might explain a phenomenon frequently observed in clinical routine: Patients who had high IOP when they were outpatients have low IOP when they are admitted as inpatients.

Various studies describe emotional instability in patients with POAG. Hibbeler, who administered the Minnesota Multiphasic Personality Inventory (MMPI) to 27 white POAG patients, found that two-thirds of the patients exhibited marked deviations on personality scales. The observed trend was in the direction of "depression" and "hysteria" for the male patients and in the direction of "paranoia" and "schizophrenia" for the female patients.[138] A similar observation was made by Holtmann, who administered the MMPI to 34 hospitalized POAG patients and to 34 hospitalized controls and found glaucoma patients to have a personality distributions similar to that of clinically proved neurotics with a psychosomatic behavior.[142] Böhringer analyzed the personality of 13 relatively young glaucoma patients by means of an interview and the Rorschach test and found them to suffer from psychopathological symptoms such as depression, hypochondriasis, obsession, phobia, sexual disturbances, and pronounced affectional instability.[18]

Using the Yatabe-Guilford personality test and the Rorschach test, Kato found glaucoma patients to be generally more depressive, anxious, meticulous, introverted, submissive, arbitrary, and emotionally unstable than healthy controls. Moreover, the patients seemed to have more perfectionism, obsessive ideas, inferiority feelings, difficulties in personal relations and a tendency to take a subjective view on matters.[169] Floru and Floru investigated the psychological profile of 50 glaucoma patients with the Freiburg inventory test sheet and the Giessen test and found glaucoma patients to be depressive, nervous, irritable, emotionally unstable, and to have a decreased coping capacity.[84] Their results are comparable to those of Erb, who rated 48 glaucoma patients with the Beck depression inventory, the Zerssen symptom list, and the Maudsley personality inventory and found two-thirds of the patients to show psychiatric symptoms, and to have higher scores for depression and psychosomatic complaints, as well as reduced emotional stability.[68] In

a different study, Erb studied the psychological characteristics of patients with NTG only, and found them to have an insufficient coping capacity, but none of the aforementioned symptoms.[69]

In summary, all studies indicate an increased frequency of psychological disturbances in glaucoma patients. However, the existing data do not allow us to sketch a psychological portrait of the glaucoma patient. Due to the heterogeneity of methods and patients, the studies failed to reveal a characteristic personality pattern. Some of the older studies used test strategies that are no longer common in modern psychology, such as the Rorschach test, and should be interpreted with caution. It is also unclear whether the observed psychological disturbances contribute to the development of glaucoma or whether they are merely a consequence of the disease. Larger studies, using comparable, standardized, and validated questionnaires in this field are desirable.

B. QUALITY OF LIFE

During the past decade, increased efforts have been made to assess the quality of life in glaucoma patients.[116,147,150,152,192,228,239,240,251,252,263,266,355] Whereas in the past, outcome of glaucoma treatment focused mainly on the level of IOP, visual field, and progression, these newer findings put more emphasis on the patient's psychological well-being.

Glaucoma can affect the patient's quality of life for several reasons: the diagnosis itself, the visual deterioration, the treatment[147] and its potential side effects. Severity of visual field loss, decrease in visual acuity, and complexity of therapy were found to correlate significantly with a diminished quality-of-life perception.[304] The most frequent problems related directly to decreased vision are mobility, glare, and lightning, as well as activities such as reading, walking on stairs, household tasks, and personal care.[147,239,251] Questions such as "Do you notice variations in color sensitivity?, Do you bump into things sometimes?, Do you trip on things or have difficulty with stairs?, Do you have difficulty finding things that you have dropped?" were found to be the most useful questions to evaluate patient's limitations.[147,228,355]

In a Norwegian study of 589 glaucoma patients, more than 80% of the patients reported feelings like anxiety, depression, or fear of going blind when being told about their disease, whereas at the same time 83% of the patients reported good or excellent vision, and half of them had no visual problems at all. The elderly patients, despite having more visual problems, seemed less concerned about the disease than the younger ones.[251] Another aspect is that women were generally more dissatisfied than men both with vision and treatment.[251,370] It was concluded from these data that from the patient's point of view, the diagnosis of glaucoma should not be given before it is confirmed, and that the term *pre-perimetric* should not be overly stressed.[135,251]

Adequate knowledge of the disease is rather lacking in a large number of patients; [63,170,179,251] therefore, more time should be spent on information once the diagnosis is made.[251,317] It was found that even a brief, simple education program can significantly improve levels of knowledge about glaucoma, but that patient education must be repeated to maintain a useful effect.[170] It seems that there is a clear need to find out more about the questions and problems of visual disability in glaucoma. More sophisticated tools both for assessment and improvement of quality of life in glaucoma patients are warranted in the future.[192]

IX. Miscellaneous

A. EMPTY SELLA

The term *empty sella* applies to the appearance of the sella turcica in which the diaphragma sellae is incomplete and the pituitary gland appears to be anatomically absent (Fig. 5).[29] One distinguishes between a primary (without surgical or radiotherapeutical procedures) and a secondary (following such procedures) empty sella syndrome.[369] Whereas some authors report cases of primary empty sella syndrome with glaucoma-like visual field defects without glaucomatous changes of the ONH,[16,238] others report single cases[281,379] and small case-series[11] of co-existing NTG and primary empty sella. Two mechanisms have been supposed to be involved in the pathogenesis of the glaucomatous excavation observed in empty sella syndrome: First, mechanical traction, and second, vascular ischemia, induced by downward pulling of the optic chiasm and by retraction of the posterior communicating arteries, respectively.[379] To date, it is still unclear whether NTG and empty sella syndrome occur independently of each other, or whether there is a real link between both diseases. The data existing thus far are anecdotal, and we lack studies with a larger sample size to establish a genuine association between both diseases.

B. ISCHEMIC BRAIN LESIONS

To date, three studies have been undertaken to evaluate the presence of ischemic brain lesions in glaucoma patients. Stroman and coworkers performed magnetic resonance imaging (MRI) in 20 consecutive patients with NTG, and found

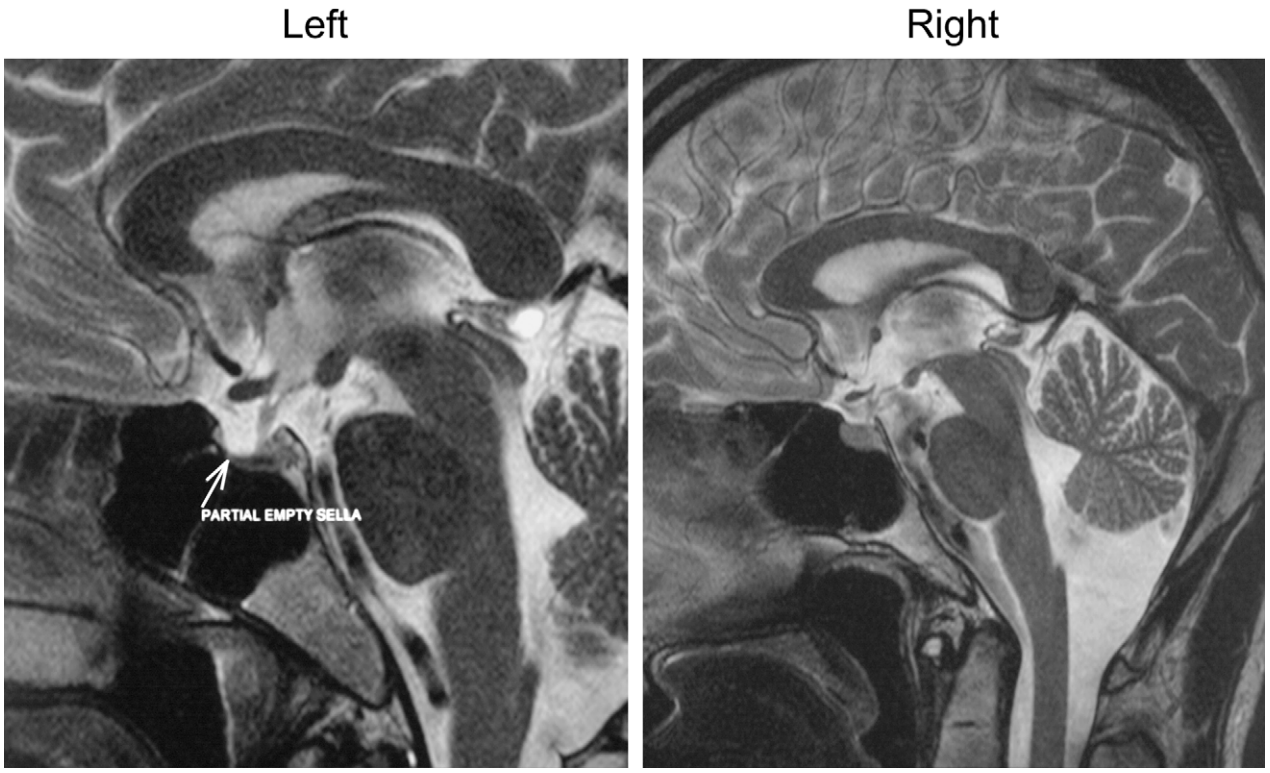

Fig. 5. *Right:* Normal MRI finding. *Left:* MRI showing a partially empty sella (arrow). (Courtesy of Carlos Buitrago Téllez, MD, University Hospital Basel, Switzerland.)

significantly more diffuse cerebral small-vessel ischemic changes when compared to controls.[323] This consecutive case-control study, however, lacks the masking of the two observers and their rate of agreement. In another consecutive case-control study, an Australian group demonstrated a significantly greater extent of cerebral infarctions in 10 patients with NTG when compared to 10 controls, but the rate of interobserver agreement was poor (Kw = 0.23). In addition, the thickness of the body and genu of the corpus callosum were found to be thinner, and the corpus callosum cross-sectional area to be smaller in patients with NTG, but the interobserver agreement was only fair (Kw = 0.4).[256]

In a single center, cross-sectional study, Suzuki and coworkers performed brain MRI and visual field tests in 94 consecutive NTG patients. The MRI images were evaluated for the presence of ischemic changes by two masked neuroradiologists. Signs indicative of ischemic changes in brain MRI were found in 32 of the 94 patients (34.0%). In addition, NTG patients with ischemic MRI changes had a relatively deeper depression in the inferior pericentral visual field.[329]

It has been proposed that these findings reflect a vascular cause in some glaucoma patients, possibly due to cerebral small-vessel ischemia (Fig. 6).[323] Larger confirmatory studies with masked observers and standardized grading systems are however desirable. To date, routine MRI in glaucoma suspects cannot be recommended.

C. HEARING LOSS

Various lines of evidence suggest that neurosensorial hearing disorders are associated with microcirculatory disorders.[80,193,194,233,301,349,354,372] It was even shown that sudden hearing loss can be caused by ET-1 induced vasospasm of the spiral modiolar artery.[287] As discussed before, ET-1 also seems to play an important role in vasospasm-induced glaucomatous damage. It may therefore be possible that the same kind of vascular dysregulation which contributes to glaucomatous damage might also affect cochlear function.

Indeed, various studies suggest a relationship between POAG and neurosensorial hearing loss[17,39,156,184,328,352] (Fig. 7). Bietti showed a frequent lowering of the audiometric curve at frequencies > 4 kHz in glaucoma patients; however, he did not specify whether the hearing loss was conductive or neurosensorial.[17] Another study found an abrupt high-frequency hearing loss in glaucoma patients, but the authors did not control for the effects of presbyacusis.[39] In a more recent case-control study, Susanna and Basseto demonstrated a high

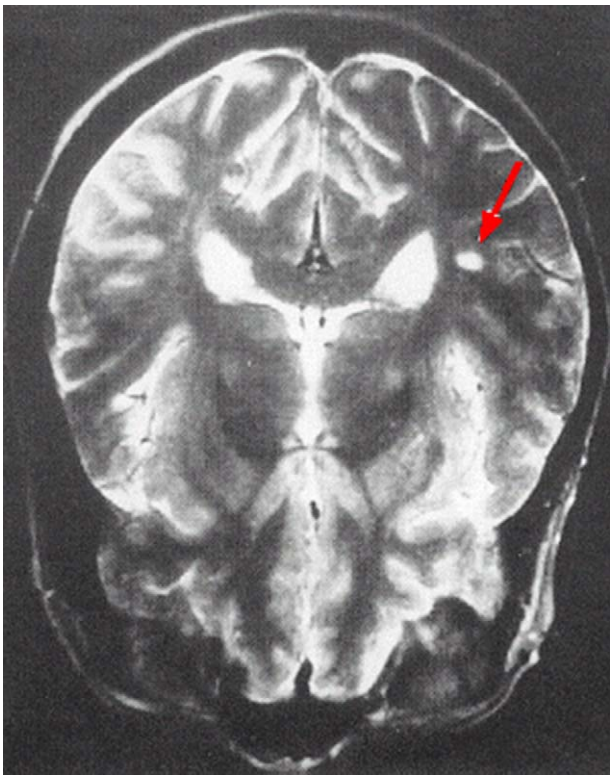

Fig. 6. Magnetic resonance imaging showing an ischemic brain lesion (arrow) in a patient with normal-tension glaucoma.

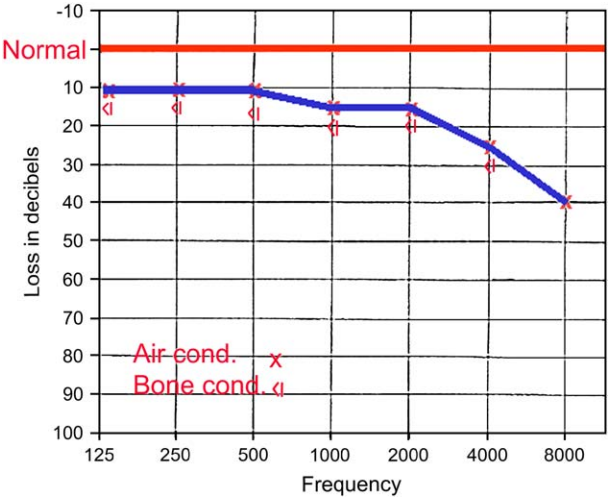

Fig. 7. Audiometric curve of a glaucoma patient demonstrating a lowering of the frequencies >4 kHz (blue line).

frequency of neurosensorial dysacusia in both patients with NTG (n = 16) and HTG (n = 41), with a tendency to a greater frequency of occurrence in patients with NTG.[328] The frequency of neurosensorial dysacousia was found to be highest in patients with hemorrhages of the optic disk. Optic disk hemorrhage is known to be significantly associated with disease progression.[149,276,305,308] As discussed previously, Kremmer et al also found a high coincidence of NTG and hearing loss, possibly due to similar underlying autoimmune processes.[186]

Other authors, however, found no association between POAG and hearing loss.[133,302] Shapiro et al prospectively examined 67 patients with glaucoma and found no evidence of neurosensorial hearing loss greater than expected for age. However, this study included patients with various types of glaucoma apart from POAG, such as pigmentary glaucoma, congenital glaucoma, and ocular hypertensives, which might explain its different outcome. Hayreh et al prospectively investigated 36 patients with NTG, 138 patients with HTG, and 142 patients with other types of glaucoma, and they also failed to demonstrate an association between hearing loss and glaucoma. Due to the obvious discrepancies of the studies listed above, it must be concluded that even though an association between POAG and neurosensorial hearing loss seems attractive when assuming vascular dysregulation and, possibly, immune processes as an underlying cause of both diseases, larger epidemiological studies are necessary before a true relationship between hearing loss and glaucoma can be established.

D. HELICOBACTER PYLORI

Helicobacter (H.) pylori is a curved spiral Gram-negative bacterium that colonizes the gastric mucosa. It has been associated with various upper gastrointestinal diseases[1,219] and, moreover, with numerous extra-digestive conditions, such as ischemic heart disease,[223,264] cerebrovascular disorders,[110,271] and vascular disorders.[87,227] Apart from the association between H. pylori infection and gastric autoimmunity, H. pylori is thought to be associated with the development of autoimmune sequelae observed in neuropathies[234,261] and with some autoimmune conditions such as Sjogren syndrome.[3,306]

Kountouras and coworkers determined the frequency of H. pylori infection in Greek glaucoma patients and in anemic controls. Interestingly, H. pylori infection was histologically confirmed in 87.5% of the POAG patients, but only in 46.7% of the controls. Moreover, 68% of glaucoma patients and 30% of anemic control participants were seropositive for H. pylori. When compared with anemic control participants, glaucoma patients exhibited less often endoscopically normal gastric mucosa and more often antral gastritis or peptic ulcer disease.[180] In a 2-year clinical follow-up study, the group found H. pylori eradication to have

a positive influence on mean IOP and visual field parameters.[181] In a more recent prospective, nonrandomized, comparative study, Kountouras demonstrated higher levels of H. pylori-specific IgG antibody levels in the aqueous humor and serum of patients with POAG when compared to age-matched cataract patients. Moreover, the mean vertical cupping of the ONH correlated significantly with the titer of anti-H. pylori-specific IgG in the aqueous humor in the POAG patients.[183] The authors hypothesized that H. pylori antibodies may circulate in the bloodstream and enter the aqueous humor via the blood–aqueous humor barrier. In the aqueous, the antibodies might reach a level sufficient to impact the development or progression of glaucoma.

In contrast, Galloway et al could not establish an association between H. pylori infection and POAG. The group examined pylori-specific IgG antibody levels in the serum of 97 consecutive glaucoma patients (38 patients with POAG, 19 with NTG, 16 with pseudoexfoliation glaucoma, and 24 with OHT) and 94 age-matched controls. 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.[86] Differences between the examined populations, the severity of glaucoma, the examined type of glaucoma, and the H. pylori detection method may account for the differing results.

It is tempting to speculate that H. pylori infection may be linked to glaucoma. Possible mechanisms may be molecular mimicry-related toxicity by H. pylori autoantibodies and various H. pylori toxic antigens to endothelium and proteins in retina and/or ONH, release of H. pylori-related vasoactive substances into the circulation, or increased susceptibility of neurons to H. pylori various substances.[182,183] However, these hypotheses require validation by both experimental and prospective multi-center, multi-country epidemiologic evaluation studies.

X. Conclusion and Perspective

Even though POAG is well characterized phenomenologically, the exact pathogenesis of the disease is still not completely understood. Besides elevated IOP, there is mounting evidence for the involvement of both vascular and immunological factors in the development of glaucomatous damage, with ischemia/reperfusion injury and inflammatory stress sharing a common outcome. Moreover, an association between glaucoma and various endocrine disorders has been described, and alterations of the autonomic nervous system were found. In addition, parallels with other neurodegenerative diseases, such as Alzheimer disease and Parkinson disease, have been observed. Sleep disturbances, psychological characteristics, and quality of life of glaucoma patients, mostly consequences of the disease, are also listed herein (Table 6).

Taken together, such findings suggest that glaucoma is not just a process involving the visual system, but more likely the manifestation of a more generalized systemic dysfunction. We are dealing with a multifactorial disease, and a complex cascade of events and interactions between IOP, vascular, immunological, and various other systemic factors must be postulated to explain the development of glaucomatous damage.

Momentarily, some studies on systemic findings in glaucoma patients give contradictory results, and further research is necessary in order to clarify their

TABLE 6

Assessment of the Likelihood of Relationship between Glaucoma and Systemic Alterations

	Relationship with Glaucoma Is	
	…Likely	…Possible
Arteriosclerosis		+
Blood pressure		
Arterial hypertension		+
Arterial hypotension	+*	
Vasospasm		
Electrocardiographic changes	+*	
Headache and Migraine	+*	
Hemorheology		
Platelet aggregation	+	
Blood viscosity	+	
Autonomic nervous system	+	
Immune system		
Autoimmunity		+
Leukocyte activation		+
Diabetes mellitus		+
Thyroid disease		
Thyroid-associated orbitopathy (graves' disease)	+	
Hypothyroidism		+
Pituitary system		+
Cushing syndome	+	+
Neurodegenerative diseases		
Alzheimer disease		+
Parkinson disease		+
Sleep disturbances		
Sleep onset disturbances		+*
Sleep apnea syndrome		+(*)
Psychological alterations		+
Empty sella		+
Ischemic brain lesions		+
Hearing loss		+
Helicobacter pylori		+

*Relationship more pronounced or exclusively found in NTG.

exact role in the pathogenesis of the damage. The disclosure of the complex interaction between the multiple systemic factors remains a challenge for future research, thus hopefully leading to a better understanding of glaucoma and to earlier diagnosis, treatment, and prevention of the disease.

XI. Method of Literature Search

A systematic search of the MEDLINE database using the PubMed website for the years 1966 through January 2005, was conducted using the following key words: *POAG, glaucoma, normal tension glaucoma, vasospasm, vascular dysregulation, arteriosclerosis, endothelin, nitric oxide, blood pressure, ECG, heart, headache, migraine, brain, ischemia, hemorheology, platelet aggregation, blood viscosity, autonomic nervous system, immunology, autoimmunity, lymphocytes, endocrinology, diabetes, thyroid, pituitary system, Cushing, cortisol, neurodegeneration, Alzheimer's disease, Parkinson's disease, sleep, psychology, quality of life, empty sella, hearing loss, helicobacter pylori.* All articles read were in English and German, and when articles in other languages were of relevance, their abstracts in English were read. Articles in Russian were translated if the abstract did not provide sufficient information.

The Old Medline was searched for articles published between 1953 and 1965 using the same keywords. All articles in English and German were read; however, due to the lack of abstracts, articles in other languages were not included.

The reference section of the articles was reviewed for articles not captured by Medline search, especially for articles published before 1953. Selected articles published before 1953 were included for historical purposes, but the review is based mainly on articles published after 1952.

The textbook *Du glaucome et de l'hypotonie; leur traitement chirurgical* by F. Lagrange, Paris, Librairie Octave Doin 1922, was cited for historical reasons. Other textbooks reviewing the systemic aspects of glaucoma were not cited, but screened for original articles, especially those published before 1966. We reviewed: 1) *System of Ophthalmology,* Vol. XI, by Sir Stewart Duke-Elder, London, Henry Kimpton, 1969; 2) *Glaukom. Ein Handbuch,* 2nd edition, by W. Leydhecker, Springer Verlag, Berlin, Heidelberg, New York, 1973; 3) R.A. Stone's "Systemic diseases associated with elevated intraocular pressure and secondary glaucoma" in *The Glaucomas*, by R. Ritch, M. B. Shields, and T. Krupin, The C.V. Mosby Company, St. Louis, Baltimore, Philadelphia, Toronto, 1989; and 4) J. B. Soltau's "Glaucoma associated with systemic disease" in *Clinical Pathways in Glaucoma* by Th. Zimmerman and K. S. Kooner, Thieme, New York, Stuttgart, 2001.

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