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Prevalence of Normal-Tension Glaucoma and Primary Open-Angle Glaucoma in Patients With Collagen Diseases

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Purpose: To investigate the prevalence of normal-tension glaucoma (NTG) and primary open-angle glaucoma (POAG) in patients with collagen diseases and determine whether an immunocompromised condition is present in a subset of glaucoma patients.

Methods: Three glaucoma specialists prospectively examined patients with collagen diseases. The diagnostic process included applanation tonometry, slit-lamp examination, gonioscopy, direct ophthalmoscopy, and automated static perimetry. Twenty-four–hour intraocular pressure monitoring was done when necessary. Using the results of a population-based survey conducted in Japan, we calculated an expected number of cases of NTG and POAG, and compared these with the actual number of cases.

Results: Of the 153 patients with collagen diseases examined, we found 6 patients with NTG and 2 patients with POAG. Of these 8 patients, 2 with progressive systemic sclerosis (PSS), one with NTG, and the other, POAG, had a history of being on systemic steroidal therapy. The prevalence of NTG and POAG was significantly higher in women patients having collagen diseases as compared with normal women ($P = .027$).

Conclusion: Women patients with collagen diseases are highly susceptible to NTG and POAG. **Jpn J Ophthalmol 1999;43:539–542** © 1999 Japanese Ophthalmological Society

Key Words: Collagen disease, normal-tension glaucoma, prevalence, primary open-angle glaucoma, scleroderma.

Introduction

The etiology of normal-tension glaucoma (NTG) is still controversial. Some investigators have reported an association of NTG with immune-related diseases, eg, with paraproteinemia and in the presence of autoantibodies.[1–4] Such immunocompromised conditions may be pathophysiologically related to a glaucoma subtype. From the finding of a higher prevalence of immune-related diseases associated with NTG, Cartwright et al[1] attributed the coexistence of the two different diseases to a preexisting vascular immunocompromised condition. Wax et al[2] reported an increased incidence of paraproteinemia and antibodies to extractable nuclear antigens in NTG patients. Other investigators[3] have also noted a high incidence of antibodies to heat-shock proteins in NTG patients. Postmortem histological examination of a patient with NTG revealed the presence of serum antibodies to retinal proteins and retinal immunoglobulin depositions.[4]

Progressive systemic sclerosis (PSS) is a collagen disease that involves the skin and such internal organs as the heart, lungs, esophagus, and kidneys.[5] The etiology of PSS is still unknown. The signs of PSS are Raynaud's phenomenon,[5,6] pitting scars,[5,7] contracture,[5] sclerodactylia,[5] shortening of the tongue frenulum,[5] as well as other conditions. Because PSS is an autoimmune disease, the relationship between this collagen disease and NTG is relevant. In this study, we investigated the prevalence of NTG and primary

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open-angle glaucoma (POAG) in patients with PSS and related autoimmune disorders.

Materials and Methods

We performed ophthalmological examinations on patients with various types of collagen disease in a prospective fashion from June 1996 to September 1996. All patients studied met the following criteria: diagnosis at the Collagen Disease Clinic of the Department of Dermatology, Gifu University Hospital; ocular fundus that was clearly visible by direct ophthalmoscopy; and 30 years of age or older. All patients meeting these criteria during that period were screened for glaucoma.

Three glaucoma specialists (TY, KS, and TT) conducted ophthalmological examinations in a two-step method of screening and diagnosis. The initial screening step included tonometry with a noncontact tonometer, direct ophthalmoscopy, and slit-lamp biomicroscopy with a portable slit-lamp biomicroscope. Each patient was invited to take the diagnostic examination if found to have abnormalities suggestive of glaucoma. These abnormalities were defined as: intraocular pressure exceeding 19 mm Hg measured by a noncontact tonometer; abnormalities of the optic disc and/or retinal nerve fiber layer, such as excavation, rim thinning, and disc hemorrhage; a peripheral anterior-chamber depth grade of 2 or less (van Herick classification); and the presence of pseudoexfoliation, posterior synechia, and other changes visible by slit-lamp biomicroscopy.

The diagnostic examinations were conducted at the Glaucoma Clinic, Department of Ophthalmology, Gifu University Hospital, and included applanation tonometry, slit-lamp examination, gonioscopy, direct ophthalmoscopy, and automated static perimetry with a Humphrey Field Analyzer. If the intraocular pressure did not exceed 21 mm Hg in a patient with apparent disc changes, then the intraocular pressure was measured by applanation tonometry every 2 hours for 24 hours. The diagnosis of NTG was made if: the untreated peak intraocular pressure was equal to or less than 21 mm Hg at all times including during the 24-hour monitoring period; there was a normal open-angle; typical glaucomatous optic nerve head, and visual field changes were present; and the absence of ocular, rhinologic, neurological, or systemic disorders which might be responsible for the optic nerve damage. The primary physicians (YK and TY) made the diagnosis of other types of glaucoma.

We used the results of a population-based survey[8] of glaucoma conducted in seven regions throughout Japan to calculate an expected number of cases of NTG and POAG. We then compared this number with the number of actual cases. A P level of less than .05 was considered to be statistically significant.

Results

One hundred fifty-three consecutive patients with collagen diseases were enrolled in this study; of which, 41 were diagnosed with PSS, 73 with nondefinite cases of PSS with possible Sjögren syndrome [scleroderma Sjögren syndrome-associated spectrum disorders (SSSD)],[9] 22 with Sjögren syndrome, 10 with systemic lupus erythematosus, 4 with dermatomyositis, 2 with mixed connective tissue disease, and one with rheumatoid arthritis (RA). Seventeen were men and 136 were women. The mean (± standard deviation) age was 58.2 ± 12.0 years (range, 30–79 years). All cases of PSS met the criteria proposed by the Scleroderma Research Committee of the Ministry of Health and Welfare of Japan.[10] Twenty-five patients with collagen diseases (men:women = 2:23) were suspected of having glaucoma at the screening step. Of the 25 patients, 23 (men:women = 1:22) underwent the diagnostic step, and 6 were diagnosed as having NTG after detailed examination that included a 24-hour monitoring period. Two cases showed disc hemorrhage. An additional seven patients were diagnosed with glaucoma: two with POAG, three with primary angle-closure glaucoma, one with capsular glaucoma, and one with glaucoma secondary to uveitis. Thus, the total number of patients with glaucoma was 13. The remaining 10 patients did not have glaucoma. The prevalence of NTG, POAG, and other subtypes of glaucoma was 3.9%, 1.3%, and 3.3%, respectively.

All the NTG patients were women: five were subclassified as focal ischemic, one as generalized enlargement according to Geijssen's classification,[11] four were SSSD, one was PSS, and one was Sjögren syndrome. One of the two cases with POAG was a patient with SSSD and the other patient had PSS. One NTG patient with SSSD showed SS-A and SS-B antibody positivity. Antibodies to extractable nuclear antigens were detected in eight patients. At the time of the screening and diagnostic examinations, the eight patients were not receiving systemic corticosteroids. Two PSS patients, one with NTG and one with POAG, had a history of systemic corticosteroid therapy, but the remaining six patients did not. None of the eight patients had ever been on corticosteroid eye drops.

The expected number of glaucoma patients in the subject group was calculated based on a population-

based glaucoma survey[8] after age- and gender-matching (Table 1). The prevalence of NTG and POAG was significantly higher in women patients with collagen diseases than in normal women (P = .027, test based on the Poisson distribution); but this number was not significant when compared to the total number of cases (P = .057). The prevalence of NTG in all the cases or in the women cases was not significantly different from that in the normal population (P = .106 and P = .061, respectively).

Discussion

In the present study, we found that the prevalence of NTG and POAG was higher for women patients with a variety of collagen diseases than for the general population when the two subtypes are combined. Although the results of this study were compared with those of a population-based survey,[8] the diagnostic steps of the two studies were almost identical; that is, a screening step with slit-lamp microscopy, tonometry with a pneumatonograph and a fundus examination, followed by a detailed second diagnostic step. Moreover, the examiners in the current study had participated as active investigators in the previous population-based survey.[8] Thus, the uncontrolled nature of the study probably affected the validity of the results only minimally.

Collagen diseases sometimes cause POAG, an emerging concept that covers both glaucomas, via a yet unknown but presumably intraocular pressure-related mechanism. It could be that local vascular abnormalities at the level of the optic nerve head sometimes accompany collagen disease. Wax et al[2,3] reported that humoral immune mechanisms are involved in the pathogenesis of optic neuropathy in patients with NTG because autoantibodies to extractable nuclear antigens, most often the Sjögren syndrome A antigen (SSA[Ro]), are found more frequently in NTG patients than in control subjects. The presence of Raynaud's phenomenon, a localized vascular abnormality that is well-recognized as one of the most important initial signs of PSS,[5] demonstrates that capillary alteration is one of the initial changes of PSS.[12,13] Maricq et al[14] reported that the scleroderma pattern of capillary abnormalities can be divided into two types: an inactive type characterized by many giant loops often accompanied by capillary hemorrhage; and an active type, characterized by capillary loss with avascular areas. Maeda et al[9] demonstrated hemorrhagic patterns in the cuticles distal to the proximal nailfolds of the fingers of patients with systemic scleroderma. The results of the capillaroscopical abnormalities found in the study may be compatible with the fact that hemorrhage is easily seen in peripheral areas, such as the capillary loops of the proximal nailfolds. Interestingly, Nishida et al[15] have already reported a relationship between transient global amnesia and Raynaud's phenomenon in patients with scleroderma, and the stated transient ischemic change that occurs in a local portion of the central nervous system following cold water-evoked Raynaud's phenomenon of both hands. These facts suggest that these collagen diseases may induce vascular abnormality in the optic nerve head, especially in nondefinite cases of PSS with possible Sjögren syndrome.[9]

In conclusion, based on the higher prevalence of NTG and POAG found in the current study, we suggest that local infarction or ischemic changes can occur in any part of the human body in patients with collagen diseases, except in peripheral areas, such as fingers and toes. These vascular abnormalities can then lead to certain types of glaucoma.

Table 1. Prevalence of Normal-Tension Glaucoma (NTG) and Primary Open-Angle Glaucoma (POAG) in Patients With Collagen Diseases

	Women				Men				Total			
Age (y)	30–49	50–69	70+	Total	30–49	50–69	70+	Total	30–49	50–69	70+	Total
Number of subjects	30	92	14	136	1	11	5	17	31	103	19	153
NTG prevalence* (%)	0.90	2.18	3.39		0.93	1.86	4.89					
Expected patient number	0.27	2.01	0.47	2.75	0.01	0.20	0.24	0.45	0.28	2.21	0.71	3.20
Actual patient number	0	4	2	6	0	0	0	0	0	4	2	6
POAG prevalence* (%)	0.00	0.60	1.69		0.28	0.52	0.70					
Expected patient number	0.00	0.55	0.24	0.79	0.00	0.06	0.04	0.10	0.00	0.61	0.28	0.89
Actual patient number	0	2	0	2	0	0	0	0	0	2	0	2
Prevalence of both* (%)	0.90	2.78	5.08		1.21	2.38	5.59					
Expected patient number	0.27	2.56	0.71	3.54	0.01	0.26	0.28	0.55	0.28	2.82	0.99	4.09
Actual patient number	0	6	2	8	0	0	0	0	0	6	2	8

*Data from Shiose et al.[8]

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