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Vitiligo and Glaucoma – An Association or a Coincidence? A Pilot Study

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SUMMARY Our aim was to draw attention of clinicians, dermatovenereologists and ophthalmologists to the possible association of vitiligo and ocular findings characteristic of primary open angle glaucoma (POAG). According to our clinical experience, POAG is relatively often diagnosed or previously diagnosed in patients treated for vitiligo. We found no literature report directly connecting vitiligo and POAG. The articles mentioning glaucoma, i.e. increased intraocular pressure (IOP), are mainly based on secondary type of glaucoma as a direct consequence of vitiligo treated by corticosteroids. On the other hand, there is a substantial number of articles elaborating the association of vitiligo with ocular findings in known clinical syndromes. During a 2-year period, from May 2007 to May 2009, 42 patients with vitiligo were examined at University Department of Dermatology and Venereology and referred for previously appointed ophthalmologic examination at University Department of Ophthalmology, Split University Hospital Center. All patients with vitiligo underwent complete ophthalmologic examination including visual field analysis, in order to treat and follow up or diagnose newly discovered POAG. Of 42 patients with vitiligo suspect of glaucoma, POAG was confirmed in 24 (57%) patients. Age median of all vitiligo patients was 56 (range 19-82) years. In patients with vitiligo and glaucoma, the duration of vitiligo was twofold that recorded in patients with vitiligo alone, the difference being statistically significant ($z=3.3$; $P<0.001$). The risk of developing glaucoma in vitiligo patients was 4.4-fold in >56 age group *versus* <56 age group and 3.5-fold in patients with >13 year *versus* patients with <13 year duration of vitiligo. Multivariate logistic regression for glaucoma development according to vitiligo duration (≤13 years *vs*. ≥13 years) and patient age (≤56 years *vs*. ≥56 years) pointed to the association of glaucoma development and age and yielded a 92% probability for the association of glaucoma development and vitiligo duration. Therefore, we believe that patients treated for vitiligo should regularly undergo complete ophthalmologic examination with special attention paid to POAG irrespective of age, sex, severity, localization and duration of the disease. Although performed in a relatively small sample and over short period of time, the results of this pilot study demonstrated that this association was not accidental. Additional studies in a greater sample of vitiligo patients and POAG are expected to provide definitive answers and conclusion on the association of these two diseases.

KEY WORDS: vitiligo, glaucoma, ocular findings, risk factors

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INTRODUCTION

There are many clinical coincidences between vitiligo and primary open angle glaucoma (POAG) (1,2). One of the basic coincidences is that both diseases are chronic, progressive and irreversible. Vitiligo is an acquired idiopathic disease, and so is POAG. Vitiligo is clinically marked by sharply bordered, oval, depigmented maculae on unchanged skin at various body sites (1). Maculae are usually oval or linear, and with time they grow bigger (1). Glaucoma is chronic optic neuropathy with increased intraocular pressure (IOP), optic nerve loss because of damaged axons of retinal ganglion cells, with subsequent proportional visual field loss, which leads to blindness if left untreated (2,3). The disease is relatively frequently associated with other systemic diseases such as thyroid gland diseases, diabetes mellitus, Addison's disease, arterial hypertension, lipid metabolism deficiencies and vascular dysregulation. Some of them are proved risk factors POAG development (1,4,5). The diseases progress with age and disease duration (1,6). They are found in 0.5%-2% of the population, in both sexes equally, however, POAG is more common in females (7,8). The average age at disease onset is 20 years for vitiligo and above 35 years for POAG (7). A great proportion of patients have a positive family history, pointing to a significant role of the genetic factor in the etiopathogenesis of these two diseases (9,10). It is therefore necessary to extend the preventive measures of early diagnosis of POAG to individuals younger than 35 in order to identify the clinical symptoms of manifested glaucoma on time (7,9).

The etiopathogenesis of vitiligo and POAG has not yet been completely elucidated. Three theories of the possible vitiligo origin are most frequently mentioned (autoimmune, neural and melanocyte self-destruction theory) (10), whereas two theories have been accepted for POAG (mechanical and vascular theory) (2,9). Current researchers only agree about the fact that glaucomatous disease is the result of action of a number of known and as yet unknown risk factors (4,5).

Skin lesions are asymptomatic in most cases (1), which also holds for POAG clinical symptoms and signs (6). Although vitiligo may occur in any part of the body, on the face it most frequently appears around the eyes with or without leukotrichia, poliosis and depigmentation on oral mucosa and genitals (10). According to localization, vitiligo is clinically classified as focal, generalized, or universal (1).

The course of either disease usually cannot be predicted. Vitiligo progresses with the formation of new maculae and centrifugal widening the existing ones (1), and glaucoma by the loss of the field of vision (2). In most cases, the natural course of the disease is slow progression while on therapy, however, rapid and unexplained deterioration (progression) may also occur (1-3).

Vitiligo associated with uveitis, central nervous system disturbances and premature grey hair is referred to as Vogt-Koyanagi-Harada syndrome (11) and Alezzandrini's syndrome (12,13), with characteristic findings on eye fundus but demonstrated not to be associated with glaucoma (13).

The diagnosis of vitiligo is based on the clinical symptoms and signs and Wood's lamp examination (1), whereas the diagnosis of glaucoma is made on the basis of history data with target interview questions and general ophthalmologic examination (2,3). Expanded diagnosis of vitiligo may include histology (1), and that of glaucoma visual field and IOP measurement (3).

Systemic therapy by psoralens in combination with UV lamp is only efficacious in some patients (14,15). Topical corticosteroids may sometimes prove more efficacious, however, this therapeutic option may result in skin atrophy and in IOP increase (secondary glaucoma) if applied for a long time in periocular area (16). Currently, neither vitiligo nor POAG treatment can be considered satisfactory (14-16). It is therefore necessary to look for new risk factors and explain the etiopathogenesis of the disease, so that new and better therapeutic modalities can be found. In addition, the importance of systemic association of local skin (1) and eye changes in vitiligo and POAG (10,17) should be emphasized.

PATIENTS AND METHODS

During a two-year period (May 2007 to May 2009), 42 patients recruited from the specialist dermatologic outpatient clinic of the University Department of Dermatology and Venereology were referred to the outpatient clinic for glaucoma and neuro-ophthalmology with perimetry of the University Department of Ophthalmology, Split University Hospital Center. All patients were diagnosed with vitiligo by a dermatovenereologist, received no topical corticosteroid therapy, and underwent complete ophthalmologic examination to detect POAG. All patients were systemically healthy. POAG was established by the following diagnostic methods: gonioscopy with Goldmann's lens to identify eye

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angle openness (anterior chamber angle, from I to IV according to Shaffer) and pigmentation (from 1 to 4 according to Scheie). Goldmann's applanation tonometry (GAT) was performed in all patients using a Haag Streit 900 slit lamp. Measurement of optic nerve head excavation (C/D vertically higher than 0.5) was performed by a Heine 2000 ophthalmoscope and ocular background biomicroscopy by use of three mirror lens according to Goldmann in medicamentous mydriasis. As a mydriatic we used 10% solution of phenylephrine. Visual field was analyzed by the classic method of quantitative kinetic perimetry on Goldmann perimeter according to Aulhorn classification. Brightness of the VF cupola was 1000 Abs (Apostilb, brightness unit). Visual acuity was determined by eye chart (optotype) for visual examination according to the international method at 5-m (20 feet) distance, with or without correction by glasses or contact lenses (6).

The diagnosis of vitiligo is based on clinical symptoms and signs, by Wood's lamp and patient history. Histologic analysis of depigmented maculae reveals complete loss of melanin, while DOPA-reaction (dihydroxyphenylanine) is negative (1).

Statistical comparison was done by use of χ^2-test and Mann-Whitney test. Data were considered statistically significant at $P<0.05$.

RESULTS AND DISCUSSION

During the two-year study period (May 2007 to May 2009), 42 vitiligo patients were examined at specialist dermatologic outpatient clinic of the University Department of Dermatology and Venereology, Split University Hospital Center. After clinical examination and under suspicion of glaucoma, they were referred to the outpatient clinic for glaucoma and neuro-ophthalmology with perimetry of the University Department of Ophthalmology, Split University Hospital Center, for detection or control of POAG. Out of 42 vitiligo patients suspect of glaucoma (POAG), glaucoma was confirmed in 24 (57%) patients. The ocular parameters significant for confirming the diagnosis of glaucoma, which were observed in all study patients, are shown in Table 1.

There was no statistically significant difference between the group of patients that developed glaucoma and those that did not according to sex ($\chi^2=1.05$; $P=0.307$) or age ($z=1.35$; $P=0.178$) (Table 2). The duration of vitiligo was statistically significantly (nearly twofold) longer in patients with both vitiligo and glaucoma than in those with vitiligo alone ($z=3.3$; $P<0.001$) (Table 3). Age median of all vitiligo patients was 56 (range 19-82) years. Median vitiligo duration was 13 (range 1-50) years. Classification of patients according to age median and vitiligo duration showed the number of patients

Table 1. Ocular parameters in vitiligo patients referred from dermatology clinic to ophthalmology clinic for suspicion of glaucoma (POAG)

Ocular findings		Glaucoma No (n=18)	Glaucoma Yes (n=24)
Peripapillary atrophy n (%)	No	17 (94)	10 (42)
	Yes	1 (6)	14 (58)
Eye fundus: C/D* of ONH n (%)	Proper	12 (67)	6 (25)
	Changed	6 (33)	18 (75)
Right eye: angle pigmentation according Scheie, n (%)	<2	8 (44)	19 (79)
	≥2	10 (56)	5 (21)
Left eye: angle pigmentation acc. Scheie, n (%)	<2	8 (44)	18 (75)
	≥2	10 (56)	6 (25)
Right eye: IOP§ (mm Hg) (median; range)		15 (10-18)	18 (14-20)
Left eye: IOP§ (mm Hg) (median; range)		15 (13-18)	17.5 (15-21)
Duration of glaucoma (years) (median; range)			8 (1-27)

*C/D: vertical disk diameter (excavation) of optic nerve head; §IOP: intraocular pressure

Table 2. Demographic characteristics of vitiligo patients according to glaucoma development

		Glaucoma		
		No (n=18)	Yes (n=24)	*P*
Sex n (%)	Female	10 (56)	17 (71)	0.307*
	Male	8 (44)	7 (29)	
Age (median; range) (yrs)		62 (41-78)	65.5 (41-82)	0.178†

*χ^2-test; †Mann-Whitney test

older than 65 to be twofold in the glaucoma group as compared with glaucoma-free group (χ^2=3.66; *P*=0.017), and the number of patients with glaucoma to be 1.8-fold that of glaucoma-free patients in the group of patients with vitiligo duration >13 years (χ^2=4.18; *P*=0.041) (Table 4).

In vitiligo patients aged >56, the risk of developing glaucoma was 4.4-fold that recorded in patients aged <56. In patients with vitiligo duration >13 years, the risk of developing glaucoma was 3.51-fold that recorded in patients with vitiligo duration <13 years (Table 5).

Multivariate logistic regression for glaucoma development according to vitiligo duration (≤13 years or >13 years) and patient age (≤56 years or >56 years) pointed to an association of glaucoma onset with age and yielded 92% probability of association with vitiligo duration (Table 6). In patients with vitiligo duration >13 years, the risk of glaucoma development was 3.51 as compared with patients with vitiligo duration ≤13 years (Table 5). It is known that age also influences glaucoma development, so the risk of glaucoma associated with vitiligo duration was corrected for age, which pointed to a 92% probability of association and risk of 3.1 (Table 6). These findings pointed to the necessity of additional studies of vitiligo duration and glaucoma, which should also include the role of positive family history, all clinical symptoms and signs of both diseases presented, and known risk factors. Their possible association should be seriously considered. The hypothesis of an association of these two diseases is based on the fact that melanocytes and pigment cells of the choroid (uveal tract) originate from the mesenchyma (18,19). This report may indirectly give a partial clue to a new theory on the risk factors or the mechanism of origin of these two diseases.

As we found glaucoma in 57% of our patients, we believe it is less damage from one control

Table 3. Vitiligo localization and median (range) of vitiligo duration according to glaucoma (POAG) development

		Glaucoma		
		No (n=18)	Yes (n=24)	*P*
Vitiligo localization	Extremities	5	6	
	Extremities and eyes	7	8	
	Extremities and trunk	4	4	
	Extremities, eyes and trunk	2	6	
Duration of vitiligo (yrs)		6.5 (1-35)	17 (3-35)	0.001*

*Mann-Whitney test

Table 4. Number of vitiligo patients (%) with/without glaucoma (POAG) according to age and vitiligo duration

		Glaucoma No (n=18)	Glaucoma Yes (n=24)	*P**
Age (yrs)	≤56	14 (70)	9 (35)	0.017
	>56	6 (30)	17 (65)	
Duration of vitiligo (yrs)	≤13	13 (65)	9 (35)	0.041
	>13	7 (35)	17 (65)	

*χ^2-test

Table 5. Risk of glaucoma development in vitiligo patients according to age and vitiligo duration

		Odds ratio	95% CI*	*P*
Age (yrs)	≤56	4.4	1.3-15.4	0.02
	>56			
Duration of vitiligo (yrs)	≤13	3.51	1.03-11.9	0.044
	>13			

*CI, confidence interval

ophthalmologic examination in those that have not developed glaucoma, than missing those that have developed it, from both health and socio-economic aspects. Therefore, the question has arisen whether the individuals with vitiligo should regularly undergo ophthalmologic examination for early detection and timely treatment of glaucoma (POAG), since unrecognized glaucoma along with other risk factors can lead to blindness. To the best of our knowledge, there are no articles on this clinical problem, although there are articles associating vitiligo with diseases and findings on the eyes (11-13,16,17). This clinical observation, i.e. pilot study, may serve as a timely warning to physicians, especially clinicians, and offer a new algorithm in the diagnosis, follow up and management of these two diseases.

Future studies in a greater number of patients with vitiligo and POAG should give definitive answer and conclusions on the association of these two diseases.

CONCLUSION

In our opinion, patients treated for vitiligo should be regularly subjected to complete ophthalmologic examination with special reference to POAG diagnosis, irrespective of age, sex, severity, localization and duration of the disease. This is supported by the fact that glaucoma tends to progress with age and duration of vitiligo, and leads to blindness and reduced working ability if left untreated.

Although the present study included a relatively small patient sample and short period of examination (pilot study), it strongly indicated that this association was not accidental. Additional studies including larger samples of vitiligo and glaucoma patients should provide definitive answer and conclusions on the association of these two diseases. Consequently, vitiligo and glaucoma could be connected with several pathomechanisms and/or risk factors that have not yet been fully clarified.

This clinical observation and our conclusions confirmed the hypothesis, however, these two diseases may also be underlain by some systemic, immune factors that should be additionally examined because of the known destruction of pigment cells in the skin (18,19) and eye, retina and optic nerve in particular, that are connected by retinal nerve fiber layer. It is just the retinal nerve fiber layer decay in glaucoma that is important to monitor the progression of visual field loss (2,3).

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Table 6. Risk of glaucoma (POAG) development in vitiligo patients according to age and vitiligo duration (multiple regression analysis)

		Odds ratio	95% CI*	*P*
Age (yrs)	≤56	4.0	1.1-14.6	0.036
	>56			
Duration of vitiligo (yrs)	≤13	3.1	0.083-11.4	0.083
	>13			

*CI, confidence interval

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