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Presentation and long-term follow-up of exfoliation glaucoma in Greece, Spain, Russia, and Hungary

A.G.P. KONSTAS[1], G. HOLLO[2], Y.S. ASTAKHOV[3], M.A. TEUS[4], E.L. AKOPOV[3], J.N. JENKINS[5], W.C. STEWART[5,6]

[1]University Department of Ophthalmology, AHEPA Hospital, Thessaloniki - Greece
[2]Department of Ophthalmology, Semmelweis University, Budapest - Hungary
[3]University Department of Ophthalmology, Saint Petersburg - Russia
[4]Hospital Oftalmológico Internacional de Madrid, Dept. of Ophthalmology, Universidad de Alcalá, Madrid - Spain
[5]Pharmaceutical Research Network, LLC, Charleston
[6]Department of Ophthalmology at the University of South Carolina, Columbia, - USA

PURPOSE. *To evaluate clinical presentation and long-term follow-up of exfoliation glaucoma in separate European population groups.*
METHODS. *A four-center, retrospective, case series analysis in which 200 charts of patients with exfoliation glaucoma or patients with elevated intraocular pressure (IOP) associated with exfoliation syndrome in at least one eye with at least 5 years of follow-up were consecutively reviewed.*
RESULTS. *This study found an average follow-up time of 6.0±2.1 years. Patients in Hungary and Spain statistically presented at an older age (79 years) than Greek patients (67 years). Patients with exfoliation glaucoma in Greece and Hungary had more glaucomatous damage, had more severe glaucoma, had a higher untreated IOP (31.8 to 32.1 mmHg), and were more difficult to control, showing a greater number of changes in medicines during the follow-up period, a greater number of medicines at the end of the follow-up period, and more progression. On long-term follow-up, Greek, Russian, and Hungarian patients also had the highest mean IOP (18.8 to 20.8 mmHg) and the greatest incidence of progression (approximately 50%). Spanish patients demonstrated the lowest mean IOP (17.6±3.6 mmHg) and the lowest rate of progression (28%) during the follow-up period and the fewest number of medications per patient (0.7) to control the IOP at the end of the follow-up period.*
CONCLUSIONS. *The severity of exfoliation glaucoma presentation and its course may differ within distinct geographic populations in Europe. (Eur J Ophthalmol 2006; 16: 60-6)*

KEY WORDS. *Exfoliation glaucoma, Presentation, Long-term follow-up, Progression*

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INTRODUCTION

Clinical findings of the exfoliation syndrome have been well described and are generally characterized by the synthesis and deposition of abnormal extracellular fibrillar deposits on the anterior lens capsule, trabecular meshwork, iris, and cornea (1-3). These proteinaceous deposits have been found throughout the eye and systemically. In the eye, these deposits can be present unilaterally or bilaterally, with or without an associated intraocular pressure (IOP) increase and glaucomatous optic disc or visual field changes (3-6).

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Exfoliation glaucoma has a varied ethnic and regional prevalence worldwide. In general, it presents most often in European countries that border the sea.

An especially high incidence of exfoliation, between 25 and 75%, exists in the Nordic region, but it also commonly occurs in Germany, Great Britain, Italy, Russia, Spain, Turkey, and Greece (3). Hungary has been one European country that has been noted to have a moderately high prevalence without being located by the sea (7, 8). Other isolated populations have been noted, including Navajo Indians in the United Stated and Australian Aborigines, as well as Bantu Indians in Africa (9).

Previously, Konstas and associates observed in a prospective trial that glaucomatous damage presented in a more advanced form in exfoliation patients than with primary open-angle glaucoma (10).

In addition, controlling the IOP was more difficult and patients required more medication long-term than with primary open-angle glaucoma (10). However, although exfoliation presents in distinct populations, little information is available that describes if either the presentation or its course differs across separate population groups.

The purpose of this article was to evaluate both the presentation and progression characteristics of exfoliation glaucoma in four relatively distinct population groups in Europe, including Greece, Spain, Russia, and Hungary.

METHODS

Included in this four-center, retrospective study were patients with newly diagnosed exfoliation glaucoma or elevated pressure associated with exfoliation syndrome in at least one eye (study eye). Sites were chosen that would potentially represent relatively distinct groups of populations known to have exfoliation glaucoma, including Greek, Spanish, Russian, and Hungarian. Patients from the practices of the study investigators were chosen from consecutive charts and reviewed alphabetically. The initial untreated IOP was excluded from long-term follow-up data to allow for adjustment of therapy for presenting elevated IOP. Data were recorded from each available visit included in the follow-up period. Data were gathered regarding stable glaucoma for as long as records were available.

Each patient carried, as a diagnosis in at least one eye, exfoliation glaucoma or elevated IOP without damage associated with exfoliation syndrome, as determined by the investigator. All patients demonstrated typical anterior segment findings of exfoliation syndrome in at least one eye (11). In glaucomatous patients typical glaucomatous optic disc (neural rim thinning or notching, saucerization, thin nasal rim, or total cupping) and/or visual field changes (typical nerve fiber layer changes: nasal step or paracentral, Seidel's or arcuate scotoma) were present. Excluded from

TABLE I - BASELINE PATIENT CHARACTERISTICS

Country	Greece	Hungary	Spain	Russia	p Value
Age, yr	67.1±6.3	79.0±7.3	79.3±9.1	70.1±8.1	<0.0001
Sex					0.17
Female	24	33	23	25	
Male	26	17	27	25	
Study eye					0.12
Right eye	17	28	25	22	
Left eye	33	22	23	28	
Visual acuity					0.0005
20/20–20/40	41	33	33	41	
20/50–20/90	2	11	5	5	
20/100–20/190	0	1	4	2	
20/200–20/390	6	0	2	2	
20/400 and above	1	5	6	0	
Cataract present					<0.0001
Yes	16	44	34	28	
No	34	4	16	22	

TABLE II - GLAUCOMA CHARACTERISTICS AT PRESENTATION

Country	Greece	Hungary	Spain	Russia	p Value
Affected glaucoma eye					<0.0001
Right eye	9	11	16	8	
Left eye	12	10	11	6	
Both eyes	14	27	7	36	
Neither	15	2	16	0	
Affected OHT eye					0.01
Right eye	3	2	3	4	
Left eye	13	4	10	3	
Both eyes	2	1	5	0	
Neither	32	43	32	43	
EXG material present					0.007
Right eye	8	10	12	5	
Left eye	19	7	7	6	
Both eyes	23	33	31	39	
IOP at baseline, mmHg	32.3±7.7	31.8±9.6	29.1±7.3	26.7±3.2	0.0005
Baseline visual field rates					<0.0001
0	23	16	16	28	
1	5	0	1	16	
2	11	8	7	6	
3	1	15	4	0	
4	8	5	22	0	
Total	48*	44*	50	50	
Baseline cup/disc ratio					<0.0001
0	2	6	16	0	
1	5	0	8	2	
2	10	16	13	15	
3	0	0	0	32	
4	33	28	13	1	
Total	50	50	50	50	

*Not done due to decreased vision, patient being unreliable, or simply not done
OHT = Ocular hypertension; EXG = Exfoliation glaucoma; IOP = Intraocular pressure

TABLE III - GLAUCOMA CHARACTERISTICS WITH FOLLOW-UP

Country	Greece	Hungary	Spain	Russia	p Value
Progression of study eye					0.04
Yes	21	26	14	26	
No	29	24	36	24	
Time to progression, yr	2.9±1.4	3.1±2.5	4.5±1.0	3.6±1.8	0.08
Medicine changes	3.5±1.7	2.7±1.5	2.1±1.1	1.3±0.6	<0.0001
Medications at end	1.4±0.9	1.4±0.9	0.7±0.6	0.8±0.7	<0.0001
Conventional glaucoma surgery	0.4±0.8	0.4±0.8	0.4±0.5	0.6±0.6	0.34
Laser trabeculoplasties	0.5±0.5	0.6±0.5	0.6±0.5	0.3±0.5	0.06
Average IOP over follow-up, mmHg	18.8±2.5	20.8±4.1	17.6±3.6	18.8±1.0	<0.0001
Follow-up time	5.1±0.4	7.6±3.5	6.3±1.2	5.3±0.8	<0.0001

IOP = Intraocular pressure

this study were patients with congenital, primary, narrow angle, or low-tension glaucoma (untreated pressure never above 21 mmHg). Also excluded from this study were patients thought to have progressive non-glaucomatous visual loss.

Data recorded during the follow-up period from each visit included Goldmann applanation tonometry, evaluation of the ocular adnexa, and slit lamp biomicroscopy. Routine follow-up visits typically were performed every 3 to 6 months. Dilated optic disc and visual field examinations generally were completed yearly or more frequently if required. Visual fields in Spain and Greece were performed with a Humphrey 24-2 program (Humphrey Instruments, San Leandro, CA); in Hungary the Octopus G1 program (Haag Streit International, Koeniz-Berne, Switzerland) and in Russia the Goldmann visual field test (Haag Streit International) were used. At dilated examinations the optic discs were examined by stereoscopic techniques by all authors, optic disc drawings were utilized by some authors (G.H. and A.G.P.K.), and optic nerve head photography was utilized by one author (M.A.T.). The same investigator evaluated each patient during the follow-up period. The optic disc and visual field were graded on a scale from 0 to 4 with 0 being no change, 1 being trace, 2 being mild, 3 being moderate, and 4 being advanced. These terms are not defined for the investigators, but were left to their discretion.

The investigator determined clinical progression from the patient file. In each case progression must have been noted in the chart with the associated reason. Generally, criteria for progression were an increase in thinning of the neural rim or a worsening of glaucomatous visual field loss. In patients with total glaucomatous cupping and diffusely depressed visual fields, worsened visual acuity was used also as a sign of progression. Patients without progression noted were assumed to be stable.

Statistics

All data were two-sided and unpaired. A value of 0.05 was selected to determine statistical significance. A one-way analysis of variance test was used to analyze data for patient age, mean IOP, the number of medicine changes per year, the number of medicines on at the end of the study, the follow-up term in years, and the number of laser trabeculoplasties and trabeculectomies per year (12, 13). Gonioscopy, cataract, sex, affected eye(s) with glaucoma or exfoliation, visual acuity, optic disc, visual field, progression, and study eye were evaluated by a chi-square. A 0 to 4 grading system was used to rank the severity of optic disc and visual field findings. For the follow-up portion of this trial, if both eyes of a patient met the criteria for entrance into the study, only one eye was randomly chosen to be analyzed.

RESULTS

Patient characteristics

Table I characterizes the patients included in this study. Statistical differences existed between sites in several clinical features of the disease. Both the Hungarian and Spanish patients were older at presentation, while the Greek patients were younger. In addition, patients in Hungary and Spain presented with more visual loss, possibly associated with the greater prevalence of cataract. There were no significant differences between study sites in sex and eye laterality. All patients were white at each site.

Exfoliation glaucoma at presentation

Differences also existed among groups in the presentation of the exfoliation glaucoma (Tab. II). A greater percentage of patients in Russia had both eyes involved with exfoliation material, while Greek patients were more often unilateral. Glaucoma presented in the highest percentage of patients in both eyes in Russia, followed by Hungary. Further, the number of patients presenting with glaucoma in at least one eye was also highest in Russia (n = 50) and Hungary (n = 48). In addition, presenting untreated mean IOP was highest and the optic disc cupping was greatest in Greece and Hungary. However, the presenting visual field severity was worse in Spain.

Long-term follow-up

The IOP over the follow-up period was significantly different between groups, with Hungary having the highest (20.8±4.1 mmHg) and Spain the lowest (17.6±3.6 mmHg) (Tab. III). Of all the sites Spain had

the fewest number of progressed patients (n = 14), while at the remaining sites approximately half the patients were progressed. The time to progression did not vary between sites (p=0.08). During the follow-up period Russian patients had the fewest mean changes in study medication per patient (1.3±0.6) and Greek patients had the most (3.5±1.7). In contrast, at the end of the follow-up period Spain had the fewest mean number of medications (0.7±0.6) prescribed per patient, while Greece and Hungary had the most (1.4±0.5). The numbers of conventional glaucoma surgeries (i.e., trabeculectomy, shunt procedures) or laser trabeculoplasties during the follow-up period were not significantly different between the sites. Hungary statistically demonstrated the longest patient follow-up time ($p<0.0001$).

DISCUSSION

Exfoliation is believed by many investigators, although not consistently, to present with more severe findings than with primary open-angle glaucoma, although these findings have not been consistent (14, 15). Jonas et al and Tezel and Tezel showed more loss in neural rim area and peripapillary atrophy in exfoliation patients (16, 17). Hetherington has stated that an impression exists that patients with exfoliation glaucoma are at greater risk for visual loss than those with primary open-angle glaucoma (18). Also, several investigators have noticed that the IOP was higher in patients with exfoliation than in patients with primary open-angle glaucoma (17, 19, 20).

In addition, the long-term management of exfoliation glaucoma is believed by many to be more difficult than primary open-angle glaucoma (1, 18, 21). Specifically, Coburn and Gross stated that the field loss and optic atrophy in exfoliation are more rapid and associated with higher IOP (22). Blika and Saunte showed that exfoliation patients were controlled long-term on a ß-blocker in only 8% of cases compared to 33% of patients with primary open-angle glaucoma (23).

Brooks and Gillies indicated that although exfoliation patients initially had good control on medical therapy they often needed surgery long term (21). Accordingly, Pohjanpelto showed long term that 35% of exfoliation patients required trabeculectomy to control the IOP compared to 18% of primary open-angle glaucoma patients (24).

Recently, Konstas and associates prospectively compared the presentation and initiated response to the treatment of exfoliation glaucoma and primary open-angle glaucoma patients (10). This study indicated that, after accounting for age, patients with exfoliation glaucoma present with a higher IOP and greater visual field loss than patients with primary open-angle glaucoma. Furthermore, exfoliation patients on average needed more medication and surgical intervention (laser or trabeculectomy) to gain initial control of the IOP than patients with primary open-angle glaucoma (10).

The purpose of this study was to evaluate the presentation and long-term treatment of exfoliation glaucoma in four genetically distinct European populations.

This study found that the presentation of exfoliation glaucoma differed between European population groups. Patients in Spain and Hungary presented at a mean age of up to 12 years older than patients in Russia and Greece. The Spanish and Hungarian patients also had greater visual loss at presentation. However, the greater prevalence of visual loss may have been associated with the higher prevalence of cataract associated with the older age of patients at these sites. Although controversial, increasing evidence has linked a higher prevalence of cataract in exfoliation patients (1). Our data may indicate that the prevalence may vary across populations.

In contrast, the Hungarian and Greek patients generally demonstrated more severe glaucoma at presentation, despite the mean difference in age between these sites. Both these sites had higher presenting IOP, more optic nerve damage, and a higher percentage of patients with glaucoma (along with the Russians) as compared to the Spanish site.

It is not clear why the patients in Greece and Hungary generally presented with more advanced glaucoma, especially with the 12-year mean difference in presenting age between these two sites. Genetic factors may have played a role in the differences between age and the presenting severity of glaucoma between various ethnic populations. Whether such a supposed genetic difference was based on the time of onset of the production of exfoliation material or the susceptibility of the optic nerve to damage is not known. It also remains unclear if environmental factors or associated systemic medical conditions could

have influenced the age and severity of presentation of the exfoliation glaucoma.

Similarly, over long-term follow-up, glaucoma was more difficult to control in the Hungarian and Greek sites. During the follow-up period the greatest number of medication changes to control IOP, the highest percentage of progression (along with the Russian site), and at the end of the follow-up period the most number of medications required per patient were in Greece and Hungary. Also, during the follow-up period the Hungarian site showed the highest mean IOP.

In contrast, the Spanish site, during the follow-up period, demonstrated the lowest rate of progression, the least required medication, and the lowest mean IOP. Again, genetic factors may have played a role in this difference to response in therapy. However, it remains unclear whether the genetic factors could be associated with susceptibility to optic nerve damage or response to medical or surgical treatment. Further, compliance could play a role in Hungary or Greece if patients were less willing to be compliant with the prescribed treatments and follow-up due to cultural reasons. In addition, differences in the long-term follow-up could have resulted from differing treatment endpoints between study sites. Currently the most effective treatment endpoints for exfoliation glaucoma are not known.

The follow-up time was statistically greater for the Hungarian site. The longer follow-up interval at this site theoretically could have increased the number of several parameters, including procedures performed, progressed patients, and medicine changes. However, the time to progression was statistically similar among sites, usually occurring before 5 years of follow-up. Afterwards, patients should have been better controlled with less additional therapy changes and progression would be less likely to occur. Consequently, the longer follow-up in Hungary probably did not allow for extra progression or treatment alterations.

These data are potentially important because they indicate that exfoliation glaucoma patients may present differently in age and the extent of the disease among relatively distinct population groups. In addition, this study showed that the ocular hypertensive patient response and the results of the treatment could differ among populations. Consequently, these data may suggest that characterizing the severity and age of diagnosis as well as defining specific treatment regimens and endpoints among geographically distinct areas may better assure timely detection and long-term vision retention in exfoliation glaucoma patients.

The public health system in Greece, Hungary, Russia, and Spain is free and no obvious impediments exist to keep patients from health care. Consequently, the status of the health care system should not have influenced the results of this study. However, since this was a retrospective study, patients could not be evaluated on an individual basis to determine if obstacles to medical care existed that were not accounted for in this study.

This study suggests that differences in exfoliation glaucoma prevalence, clinical presentation, and long-term follow-up may exist between geographic populations.

This study did not evaluate long-term follow-up in a prospective manner. Such a prospective evaluation with consistent uniform ophthalmic examination techniques (including optic disc photographs, automated perimetry, and digital optic disc analysis techniques) along with treatment regimens among groups would better define differences between populations. In addition, the representative sites included in this study may not reflect all population groups within their individual countries. Further research should help clarify the differences between populations of exfoliation patients and the presentation and response to treatment.

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Reprint requests to:
William C. Stewart, MD
Pharmaceutical Research Network, LLC
1 Southpark Circle
Suite 110
Charleston, SC 29407
info@prnorb.com

REFERENCES

1. Ritch R, Schlotzer-Schrehardt U. Exfoliation syndrome. Surv Ophthalmol 2001; 45: 265-315.
2. Ritch R, Schlotzer-Schrehardt U, Konstas AGP. Why is glaucoma associated with exfoliation syndrome? Prog Retin Eye Res 2003; 22: 253-75.
3. Stewart WC. Clinical practice of glaucoma. In: Hoffman J, ed. Thorofare, NJ: Slack; 1990: 162-6.
4. Schlötzer-Schrehardt UM, Küchle M, Naumann GOH. Electron-microscopic identification of pseudoexfoliation material in extrabulbar tissue. Arch Ophthalmol 1991; 109: 565-70.
5. Streeten BW, Li ZY, Wallace RN. Pseudoexfoliative fibrillopathy in visceral organs of a patient with pseudoexfoliation syndrome. Arch Ophthalmol 1992; 110: 1757-62.
6. Schlötzer-Schrehardt UM, Koca MR, Naumann GOH. Pseudoexfoliation syndrome. Ocular manifestation of a systemic disorder? Arch Ophthalmol 1992; 110: 1752-6.
7. Sziklai P, Suveges I. Glaucoma capsulare in patients with open-angle glaucoma in Hungary. Acta Ophthalmol Suppl 1988; 184: 90-2.
8. Sziklai P. Data of the frequency of incidence of glaucoma associated with pseudoexfoliation (glaucoma capsulare). Ophthalmologica Hungarica 1976; 113: 149-52.
9. McCarty CA, Taylor HR. Pseudoexfoliation syndrome in Australian adults. Am J Ophthalmol 2000; 129: 629-33.
10. Konstas AGP, Hollo G, Astakhov YS, et al. Factors associated with long-term progression or stability in exfoliation glaucoma. Arch Ophthalmol 2004; 122: 29-33.
11. Ritch R. Exfoliation syndrome and occludable angles. Trans Am Ophthalmol Soc 1994; 92: 845-944.
12. Book SA. Essentials of statistics. In: Arthur AA, Rogers JL, Bradley JW, eds. Testing Statistical Hypotheses. New York: McGraw-Hill Book Company; 1978: 117-22.
13. Swinscow TDV. Statistics at Square One, 10th ed. London: BMG Books; 1976: 54-7.
14. Aasved H. The frequency of optic nerve damage and surgical treatment in chronic simple glaucoma and capsular glaucoma. Acta Ophthalmol (Copenh) 1971; 49: 589-600.
15. Linnér E, Schwartz B, Araujo D. Optic disc pallor and visual field defect in exfoliative and non-exfoliative, untreated ocular hypertension. Int Ophthalmol 1989; 13: 21-4.
16. Jonas JB, Fernández MC, Naumann GOH. Papillenmorphometrie in Glaukomaugen mit und ohne Pseudoexfoliationssyndrom. Fortschr Ophthalmol 1990; 87: 150-2.
17. Tezel G, Tezel TH. The comparative analysis of optic disc damage in exfoliative glaucoma. Acta Ophthalmol (Copenh) 1993; 71: 744-50.
18. Hetherington J Jr. Capsular glaucoma: management philosophy. Acta Ophthalmol Suppl 1988; 184: 138-40.
19. Futa R, Shimizu T, Furuyoshi N, Nishiyama M, Hagihara O. Clinical features of capsular glaucoma in comparison with primary open-angle glaucoma in Japan. Acta Ophthalmol (Copenh) 1992; 70: 214-9.
20. Lindblom B, Thorburn W. Functional damage at diagnosis of primary open angle glaucoma. Acta Ophthalmol (Copenh) 1984; 62: 223-9.
21. Brooks AMV, Gillies WE. The presentation and prognosis of glaucoma in pseudoexfoliation of the lens capsule. Ophthalmology 1988; 95: 271-6.
22. Coburn AG, Gross RL. Pseudoexfoliation syndrome. Clin Signs Ophthalmol 1990; 12: 2-15.
23. Blika S, Saunte E. Timolol maleate in the treatment of glaucoma simplex and glaucoma capsulare. Acta Ophthalmol (Copenh) 1982; 60: 967-76.
24. Pohjanpelto P. Influence of exfoliation syndrome on prognosis in ocular hypertension greater than or equal to 25 mmHg. Acta Ophthalmol (Copenh) 1986; 64: 39-44.