Review Article

Epidemiology of the pseudo-exfoliation syndrome

A review

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ABSTRACT.
1) Pseudo-exfoliation syndrome (PE syndrome) is a condition with worldwide distribution. 2) Marked geographical variations have been demonstrated. 3) Environmental factors may be of etiological significance for the development of PE syndrome. 4) The PE syndrome's ability to promote glaucoma may vary from one area to another. 5) There seems to be a trend towards lower debut age of PE syndrome at lower latitudes. 6) More *prevalence studies* from different parts of the world are needed. A standardized set-up of such works would facilitate comparison of the results, and so some guidelines have been proposed.

Key words: epidemiology – pseudo-exfoliation syndrome – review

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Information on the distribution of the PE syndrome has been collected for decades, the early papers focusing on its various clinical aspects, mainly observations of glaucomatous eyes. However, it has always been a puzzle that some PE-positive persons apparently do not develop glaucoma.

Initially, only a few ophthalmologists were interested in PE syndrome. Its presence in the anterior eye, particularly in eyes with advanced cataract, is easily overlooked, and its ability to promote glaucoma may vary from one region to another. In addition, since we often see only what we want to see, the impression has arisen that this is a condition confined to certain limited geographical areas. The number of publications describing the occurrence and distribution of PE syndrome has been slowly increasing, and today there are a considerable number of papers.

Sample selection and diagnostic criteria are crucial aspects in every epidemiological study. As to the diagnosis of the PE syndrome, it has traditionally been based on slit-lamp examination. Even today, when many ophthalmologists are convinced that persons showing normal anterior segments still might reveal PE deposits in other parts of the body, it relies on the slit-lamp test. This common basis for the diagnosis is important to ensure comparable results from one study to another, and for larger surveys to come this diagnostic is likely to be unchanged unless reliable tests for systemic involvement are presented. However, it could be confusing if terms for "suggested PE syndrome" ("precursor of PE", "PE-suspects", "initial stage of PE") should be introduced in epidemiology, because these may include various conditions. From consensus regarding diagnostic criteria, things are quite different when it comes to sampling: Different types of patient groups have been examined, random sampling was largely neglected until recently, and so many incomparable results have been created.

From time to time it can be useful to analyse the available data systematically, which is the intention here in grouping the present information in the following categories:

1) Information collected from patients voluntarily attending ophthalmologists for some reason. These are studies documenting the occurrence of PE syndrome and indicating its *frequency* in the particular patient group under examination. Most of these papers present figures concerning the frequency of the PE syndrome in certain groups of glaucoma and/or cataract patients.

2) Screening studies of larger population groups selected on a non-random basis. The observations show the *frequency* of PE syndrome in the examined population, but do not reflect the real distribution in the general population of the area because of the selection bias.

3) *Prevalence studies* on the PE syndrome, i.e. papers presenting the number of PE-positive cases at any given time related to the number of persons in that particular area. This is to say that the information has been compiled from a randomly selected population group or from the total population in the area focused on. Strictly speaking, these are the only reports meeting the modern criteria for epidemiological studies. It should be added that *incidence studies*, i.e. the number of PE- positive cases arising in a given time interval in a certain area, have not so far been published.

Comprehensive surveys on category 1 and 2 studies have been presented elsewhere (Tarkkanen 1962; Aasved 1969; Forsius 1988) and background information on similar subjects, but not mentioned in the previous reviews, has been collected in Table 1. In addition, substantial epidemiological information has also been summarized by Ritch (1994a).

As a whole, this bulk of evidence demonstrates once and for all that PE syndrome is a condition of worldwide significance, perhaps even the most important single risk factor for glaucoma (Ritch 1994b), at least in some areas (see below).

As for the category 3, calculations of the PE distribution in a population, as well as inter-regional comparisons of

Table 1. Studies showing occurrence and frequency estimates of the PE syndrome in various parts of the world. Works quoted in the three reviews mentioned in the text have not been included here.

Location	Reference
Finland/Åland Islands	Forsius & Eriksson 1961
India/Pondicherry	Sood & Ratnaraj 1968
South Africa (Bantus)	Bartholomew 1973
Iceland	Sveinsson 1974
Greece/Peloponnes/Euboea/Attica	Tragakis et al. 1978
Japan	Kinoshita 1979
Papua New Guinea	Dethlefs 1982
Russia	Frolova & Khamitova 1984
Italy/Messina	Romeo et al. 1984
Pyrenees	Barthe et al. 1985
Iran	Aminisarduei & Fekrat 1986
Northern Syria	Antaki 1986
Northwestern Pakistan	Khanzada 1986
India/New Dehli	Lamba & Aurora 1986
Pakistan	Mohammad & Kazmi 1986
Japan	Ueno et al. 1986
France	Colin et al. 1988
Japan	Okamura et al. 1988
Southeastern United States	Cashwell & Shields 1988
USA/Southern Louisiana	Ball et al. 1989
Eastern Algeria	Boukoffa et al. 1989
Japan/Kumamoto	Futa et al. 1989
Northwestern Spain	Montañés et al. 1989
China	Ye et al. 1989, 1992
Tunisia	Ayed et al. 1990
Greece/Epirus	Stefaniotou et al. 1990
Switzerland/Zürich	Esmail 1991
New Mexico	Jones et al. 1992
Turkey/Eastern Mediterranean area	Yalaz et al. 1992
USA/Baltimore/Russian immigrants	Levey et al. 1995
Portugal	Alfaiate et al. 1996
Greece/Thessaloniki	Konstas et al. 1996
USA/New York/Russian immigrants	Ritterband et al. 1998

Table 2. The presently available prevalence studies on the PE syndrome have been listed.

Location	Age (years)	PE prevalence	Reference
Australia (Aborigines)	>60	16.3%	Taylor et al. 1977
USA/Framingham Eye Study (Mass)	52–85	1.8%	Hiller et al. 1982
Middle Sweden	65–74	18%	Ekström 1987
Middle Norway	≥65	16.9%	Ringvold et al. 1987, 1988
Middle Finland	>60	8.4%	Aine 1988
Middle Finland/Kuusamo	>60	2.1%	Krause et al. 1988
Saudi Arabia	≥40	9.3%	Summanen & Tönjum 1988
Japan	≥40	■ 1.02%	Shiose et al. 1991
		1.24%	Futa et al. 1992
Finland/Kuopio Eye Survey	=65	○ 8.5%	Rouhiainen & Teräsvirta 1992
	=75	○13.2%	Rouhiainen & Teräsvirta 1992
Western Ireland	≥50	■ 1.3%	Coffey et al. 1993
Finland/Oulu	>70	22.1%	Hirvelä et al. 1995
Northern Mongolia	≥40	■ 0.3%	Foster et al. 1996
Australia/Blue Mountain eye study	≥49	2.2%	Mitchell et al. 1996
Greece/Crete	≥40	16.1%	Kozobolis et al. 1997
Greece/Thessaloniki	55–59	5.4%	Bufidis 1998
Central Iran	≥50	13.1%	Sahebghalam et al. in press.

○ Aphakic and pseudophakic eyes not included.
■ Pupil not routinely dilated.

such numbers, make sense only when based on prevalence studies. Otherwise fictional differences are observed. It is striking that PE syndrome, as both biological phenomenon and risk factor for glaucoma development, has been ignored in many well-publicized glaucoma prevalence surveys performed over the last two decades. Indeed, in some reports capsular glaucoma has been identified, but since only some PE-positive persons have glaucoma, varying from 7 to 30% (Taylor et al.1977; Ringvold et al. 1991; Hirvelä et al. 1994–95; Sahebghalam et al., in press), PE prevalence cannot be deduced from prevalence numbers for capsular glaucoma. It is a challenging question why only 7–8% of PE-positive eyes in Iran and Australia had glaucoma versus 27–30% in Finland and Norway. (The various inclusion criteria for glaucoma have not been evaluated here). One of the reasons is obviously that the results have been collected from different age groups. However, in the Middle Norway material 26.5% of the PE-positive cases had glaucoma in one region versus 34.5% in another (Ringvold et al. 1991), and the mean age of the PE-positive cases in the respective areas were 75.4 and 73.9 years. Together these observations might indicate that the eye's ability to cope with the PE-material is different from one area to another. Further prevalence studies are needed to verify the observation and, in case, to evaluate which factors may be responsible for it.

The first PE prevalence studies were presented about two decades ago, and the currently available reports are summarized in Table 2. As seen in the survey among Australian Aborigines over 60 years of age (210 persons from different regions) a PE prevalence of 16.3% was observed (Taylor et al. 1977). On the other hand, the comprehensive Framingham Eye Study (Mass) revealed an overall prevalence rate of 1.8% for the age group 52–85 years (Hiller et al. 1982). The results from these two excellent studies are, of course, incomparable because of the age difference between the examined groups: Much more "young", presumably PE-negative persons have been included in the latter study. This problem of incomparability was one of the reasons why the Middle-Norway survey was performed (Ringvold et al. 1987): Similar age groups from three different areas (Hi/Hå/Re) were examined, and 10.2%, 21.0%, and 19.6% of the populations were PE-positive, respectively. Ac-

cordingly, there are marked variations in PE prevalence from one area to another, and this conclusion has recently been supported by a similar study from Crete (Kozobolis et al. 1997).

The Middle-Norway survey also indicated a significantly higher number of married couples with PE syndrome in both spouses than was expected from calculations based on random combination. Along with the observation of two homozygote pairs of twins, one concordant and one discordant for the presence of PE syndrome, this was taken to indicate an environmental influence on the distribution of the PE syndrome (Ringvold et al. 1988). However, as indicated recently by Damji et al. (1998), it is possible that a combination of genetic and nongenetic factors may be involved in the etiology and pathogenesis of the PE syndrome, i.e. it may be a multifactorial disorder. Further details concerning prevalence studies on the PE syndrome and open angle glaucoma in Northern Europe have recently been reviewed elsewhere (Ringvold 1996).

A brief summary of the large Scandinavian series shows PE prevalences of 18% (65–74 years) in Middle Sweden (Ekström 1987) and 16.9% (above 64 years of age) in Middle Norway (Ringvold et al. 1988), whereas a population over 60 years of age in Middle Finland show 8.4% (Aine 1988) and 2.1% in Kuusamo/Middle Finland (Krause et al. 1988). Further to the north in Finland/Oulu 22.1% was observed in a population over 70 years of age (Hirvelä et al. 1995). The Kuopio Eye Survey from central-eastern Finland reveals prevalences of 8.5% and 13.2% in 65-year-old and 75-year-old individuals, respectively (Rouhiainen & Teräsvirta 1992). However, since aphakic and pseudophakic eyes were excluded in the latter study, the real figures may have been a bit higher. Unfortunately, reliable prevalence figures seem to be lacking for Southern Sweden, Denmark, and Iceland. It may be concluded that the age groups are rather similar in most of these Scandinavian studies, whereas the corresponding prevalence figures are very different.

A further extension of our summary to PE prevalence studies from the rest of the world reveals a number of interesting papers: A population-based survey among Saudis comprising 376 persons aged 40 years or more showed an overall PE prevalence of 9.3% (Summanen & Tönjum 1988). In a new study from Central Iran 13.1% PE prevalence was observed in people aged 50 years or more (Sahebghalam et al., in press). The overall prevalence was 16.1% in a population aged 40 years or more in Crete, varying between 11.5 % and 27% in different regions of the island (Kozobolis et al. 1997). Considering the age range, these studies seem to present the highest rates ever reported.

The studies from Crete, Iran, and Saudi Arabia indicate a trend towards lower debut age at lower latitudes compared to what has been observed in Scandinavia. In addition, the former countries are roughly located at the same latitude, and so the high prevalence figures could be taken to support Taylor (1979), who observed that PE occurred more commonly at lower latitudes, and was seen more frequently with higher levels of global radiation. On the other hand, the association between PE prevalence and radiation effects was not confirmed in the Middle Norway material (Ringvold et al. 1988).

In the Blue Mountains eye study, performed in another region of Australia, 2.2% PE-positive residents were found in a population 49 years of age or older (Mitchell et al. 1996). This figure is not so very different from a PE-prevalence of 1.3% reported in persons aged 50 years or more in Western Ireland (Coffey et al. 1993). A feature of this latter study was that the participant's pupils were not routinely dilated, which means that some 10% of PE-positive cases may have been missed (Aasved 1969).

In Northern Mongolia the PE-prevalence was 0.3% in a population 40 years and older (Foster et al. 1996), but again, the pupil was not routinely dilated before examination.

In two comprehensive studies from Japan, PE prevalences of 1.02% and 1.24% were observed in populations 40 years or older (Shiose et al. 1991; Futa et al. 1992, respectively). Shiose et al. added that their figures were based on observation through undilated pupil.

The PE prevalence in the age group 55–59 years in Thessaloniki was found to be 5.4% (Bufidis 1998), which may bear comparison fairly well with the 2.9% found in the 50–59 age group in the Cretan survey.

Some of the conclusions that may be drawn from this review are:

1) It is hard to see how interesting epidemiological knowledge may be added by further *frequency* studies (i.e. categories 1 and 2).

2) On the other hand, *prevalence* surveys are very much needed, because they may be useful in the search for etiological factors.

3) As can be seen in Table 2, however, comparison from one country to another poses difficulties, even when based on prevalence studies, since the various surveys cover different age ranges.

Therefore, in order to facilitate comparison of PE prevalence results worldwide, a consensus-based set-up should be used in forthcoming studies, the most important criteria for which would be:

- random sampling of the recruited persons
- mydriasis during slit-lamp examination
- results presented for fixed age intervals; for instance, half-decades from 50 years of age.

It is hoped that researchers will adopt a prevalence approach rather than a frequency approach when aiming to provide new epidemiological information.

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