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Exfoliation syndrome: a disease with an environmental component

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Abstract

Purpose of review—Exfoliation syndrome (XFS), the most common cause of secondary open angle glaucoma, is associated with significant ocular morbidity. Recent studies have pointed toward environmental components that may alter the risk of XFS development. This review focuses on the recent studies elucidating the role of environmental factors that play a role in the development of exfoliation syndrome.

Recent findings—In XFS, aberrant microfibril formation emanating from the cell-extracellular matrix interface admixes with other macromolecules and is cross-linked by lysyl oxidase like 1 (LOXL1) activity. A common gene variant in the LOXL1 enzyme, an enzyme critical for enhancing the tensile strength of collagen and elastin in extracellular matrices, has been found in approximately 90% of XFS cases. However, approximately 80% of controls also have disease-associated *LOXL1* gene variants. These findings point toward other nongenetic factors influencing the development of XFS. Increasing latitude, solar radiation, climatic variables and dietary factors such as high coffee consumption and low dietary folate intake are among the nongenetic factors associated with increased risk of XFS.

Summary—A greater understanding of the environmental components associated with XFS may lead to lifestyle preventive strategies to ameliorate disease burden.

Keywords

coffee consumption; dietary folate; environmental factors; exfoliation syndrome; latitude effect; solar exposure

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Exfoliation syndrome (XFS), the most common cause of secondary open-angle glaucoma [1], is a progressive disease characterized by accumulation of fibrillar extracellular deposits on various anterior segment ocular tissues [2]. XFS is associated with significant ocular morbidity and can lead to multiple ocular sequelae including glaucomatous optic neuropathy secondary to elevated intraocular pressure [3], late-onset spontaneous intraocular lens subluxation [4] and retinal vein occlusion [5-9]. XFS leads to increased cataract formation [10-12] and is associated with increased cataract surgery complications, [13-16] in part due to compromised zonular stability [17,18].

The underlying mechanism of XFS is believed to involve aberrant extracellular matrix metabolism [19] yielding an abnormal aggregation of elastic fiber components [20]. This concept was further supported when the common gene variants in lysyl oxidase-like 1 (LOXL1) enzyme, an enzyme pivotal in enhancing the tensile strength of collagen and elastin in extracellular matrices [21], were found in 99% of XFS cases in Scandinavian populations from Iceland and Sweden [22]. However, up to 80% of controls also had disease-associated *LOXL1* gene variants [22-26]. Similar findings were observed in cases and controls from Australia where disease prevalence is only approximately 1% [27,28]. These findings suggest that other factors in addition to genetics contribute to XFS.

THE LATITUDE EFFECT

The estimates of XFS prevalence tend to increase as a function of latitude in the northern hemisphere. Although certain exceptions exist [29], prior point prevalence studies (Table 1) demonstrate this trend with evidence of hyperendemicity in Northern Europe. This trend holds true in the continental USA using multivariable analyses in two separate study samples [40,41]. Furthermore, Kang *et al.* [41] found that lifetime residence in the middle or lower tier of the USA was associated with reduced risk of XFS compared with lifetime residence in the northern US tier. In this study, the association with latitude was the same in White and non-White cases, indicating that a trend toward genetically predisposed Northern Europeans populating northern tier states does not explain these results [41]. Environmental factors such as climatic variables and solar exposure may be responsible for these findings.

CLIMATIC FACTORS

Colder temperatures in the summer and winter months were found to be independent risk factors for development of XFS [40]. In fact, many of the highest XFS prevalences are from countries with cold mean temperatures such as Iceland, Norway and Sweden. Perhaps the extracellular deposits of XFS represent a precipitation reaction [42] that is more susceptible to develop at colder temperatures. Although the temperature of visceral organs may be close to core body temperature regardless of the ambient temperature, the relatively avascular ocular anterior segment may be more likely to experience a temperature drop in colder environments [43].

SOLAR EXPOSURE

The relative immunity of Arctic-dwelling Inuit people to develop XFS [44] suggests that other climatic factors contribute to the disease. The idea that solar exposure might contribute to XFS was suggested in 1979 based on a review of the ocular characteristics found in an Australian Aboriginal population and the increased prevalence among those who worked with livestock [45]. Similar findings from rural India confirmed that XFS was more common in those participating in outdoor occupations [46]. Recently, Kang *et al.* [41] found that greater time spent outdoors during the summer months from high school to age 24 was independently associated with greater risk of incident XFS, supporting a possible causal relationship of early exposure to outdoor climatic factors on XFS risk. Furthermore, there have been strong associations between XFS and other ultraviolet (UV) associated ocular diseases such as climatic droplet keratopathy [47]. In-vitro studies of human Tenon's capsule fibroblasts provide some support for a role of UV light in XFS cause. UV-light exposure has been found to upregulate the expression of LOXL1 and major elastic fiber proteins found in the exfoliation extracellular deposits [48].

Most recently, Pasquale *et al.* [49▪▪] found that more time spent outdoors in the summer over a lifetime was associated with XFS in case–control groups from the USA and Israel. Furthermore, work over reflective surfaces such as water or snow in the USA was associated with increased odds of XFS [49▪▪]. Interestingly, Sydenham *et al.* [50] found that ambient UV exposure does not fully account for ocular solar exposure and it is known that snow reflects as much as 80% of UV-B during midday [51]. These findings provide insight into the data reported by Pasquale *et al.* [49▪▪], suggesting that ocular exposure to light from reflective surfaces may be an important UV source in the pathogenesis of XFS.

ELEVATED HOMOCYSTEINE LEVELS, DIETARY FOLATE AND COFFEE CONSUMPTION

Elevated homocysteine may increase exfoliation material (XFM) formation by contributing to vascular damage [52], oxidative stress [53,54] and changes in the extracellular matrix [19]. Homocysteine levels are higher in the serum [55-57], aqueous humor [58] and tear [59] samples of XFS patients compared with controls. The synthesis of methionine from homocysteine requires folic acid enzymes and so a deficiency of folic acid leads to elevated homocysteine plasma levels [60]. Low serum folate levels are associated with increased risk of XFS [61]. Kang *et al.* [62▪] found lower risk of XFS with higher folate intake but not with vitamin B6 or vitamin B12 intake. Meanwhile, the Reykjavik Eye study showed that higher consumption of fruits and vegetables was associated with a reduced risk of XFS [63]. Interestingly, fruit and vegetables serve as a major source of dietary folate.

Coffee consumption may be yet another dietary factor that alters XFS. In a prospective study performed in the USA, heavy coffee consumption is associated with increased risk of XFS [64]. A possible etiologic factor explaining this finding may be that coffee consumption produces increased homocysteine levels [65]. The exact mechanism by which homocysteine enhances XFM formation remains unclear but may rely on the complex interaction between extracellular matrix metalloproteinase regulation [66].

CONCLUSION

LOXL1 genotype markers have served as the springboard to investigate environmental factors associated with XFS. Environmental factors may alter LOXL1 activity, which in turn increases the predisposition of individuals already at risk to accumulate XFM. Climatic variables operative at higher residential latitude are environmental factors that appear to contribute to XFS. Furthermore, dietary factors such as folate intake and coffee consumption have been found to alter the risk of XFS, possibly by affecting homocysteine levels. Further studies are needed to elucidate the exact mechanism by which homocysteine alters the development of XFM. These findings suggest that alterations in environmental factors could lead to disease modification in persons who may be genetically predisposed to develop XFS.

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KEY POINTS

- Environmental factors may play a role in the development of XFS.
- XFS prevalence tends to increase as a function of latitude.
- Ocular exposure to light from reflective surfaces may be an important environmental factor in the pathogenesis of XFS.
- Dietary factors such as folate intake and coffee consumption may increase the risk of XFS.

Table 1.

Published exfoliation syndrome prevalence

	Disease prevalence			
Country	**% Men**	**% Women**	**Age range (years)**	**Latitude**
Sweden [30]	17.0	31.0	70-79	64.4°N
Norway [31]	16.9 total		64+	64.3°N
Iceland [32]	13.4	21.6	70–79	64.1°N
Finland [33]	17.0	31.0	70–79	59.6°N
Greece [34]	10.9	13.2	60+	39.0°N
Pakistan [35]	13.0 total		70+	29.4°N
Upper Egypt [36]	4.3	4.1	70–79	25.7°N
Nigeria [37]	2.7 total		30+	7.3°N
Sri Lanka [38]	3.8 total		70+	7.0°N
Australia [39]	2.9	1.7	70–79	37.0°S