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Exfoliation Syndrome and Solar Exposure: New Epidemiological Insights into the Pathophysiology of the Disease

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Abstract

Recent epidemiological studies have revealed new insights into the pathophysiology of exfoliation syndrome (XFS). These studies found that lifetime and most recent residence in the northern tier of the United States (versus the middle and southern tiers) and with increasing latitude away from the equator are associated with increased risk of XFS.[14,21,31] Ambient low temperature, ambient solar exposure, time spent outdoors (particularly in youth), and leisure or work activity over water or snow are associated with elevated risk of XFS.[21,31,32] Sunglass, but not brimmed hat, wear decreases the risk of XFS.[21]

These environmental factors could influence the risk of XFS in several ways. Ultraviolet radiation (UVR) can upregulate exfoliation material (XFM) components and colder temperatures could enhance the precipitation of XFM out of the aqueous. Activity over water or snow may elevate the risk of XFS because of the high solar reflectivity off of these surfaces. Sunglasses are likely protective because they shield the eye from solar rays reflected off the ground. Residence with increasing latitude away from the equator increases risk of the disease likely because the sun is more angulated with respect to the earth's surface, allowing for greater UVR reflectivity.[32] That time spent outdoors in youth increases the risk of the condition suggests that lifestyle patterns in young adulthood can increase the risk of XFS and common gene variants execute a plan that results in manifest disease.

New evidence indicates that XFS is associated with environmental risk factors such as solar exposure.

Exfoliation Syndrome: A Brief Overview

Exfoliation Syndrome (XFS) is characterized by flaky white deposits of abnormal fibrillar extracellular material in the anterior segment of the eye, notably on the pupillary border of the anterior lens capsule. XFS is responsible for approximately 20–25% of open-angle glaucoma worldwide and over half of glaucoma cases in certain countries.[1] It is thought that XFS causes open-angle glaucoma through the following mechanism: exfoliation material, along with iris pigment liberated when iridolenticular friction scrapes exfoliation material from the lens and disrupts iris pigment epithelium, can accumulate in the trabecular

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meshwork.[2,3] This can lead to an increase in intraocular pressure, a well-known risk factor for the development of glaucoma. Additionally, XFS is associated with increased cataract formation[4] and cataract surgery complications such as capsular rupture from zonular instability.[5–7] XFS has also been linked to central retinal vein occlusion[8–9] as well as climatic droplet keratopathy[10,11]

XFS has historically been thought of as a disease of "Scandinavian" heritage, owing to the high prevalence (i.e., approximately 20% of people over the age of 60) of the condition in northern Europe.[12–14] However no study has been performed to date that proves that Scandinavian ethnicity increases the risk of developing XFS.[14]

Exfoliation material primarily contains, among other extracellular matrix components, elastin, fibulins, fibrillin-1 and latent transforming growth factor binding proteins.[18] It also contains lysyl oxidase-like 1 (LOXL1), a critical enzyme required for proper elastogenesis.[15] LOXL1 has been identified in various parts of the eye including the lens capsule, iris, cornea, ciliary processes and optic nerve.[16,17] Elastin has also been found in these components, as well as in zonular fibers[16,18] and the trabecular meshwork.[16,19]

Single nucleotide polymorphisms (SNPs) in the LOXL1 gene have been found in up to >99% of XFS and exfoliation glaucoma (XFG) cases.[16, 20] However, LOXL1 SNPs are also detected in up to 88% of controls.[16] Additionally, the ratio of LOXL1 gene variants in those with XFS to those without XFS is similar in areas where the disease is prevalent[21,22] and in areas where the condition is uncommon.[13,21] This indicates that there are likely environmental factors that work to influence the development of XFS.[21]

Exfoliation Syndrome and Solar Exposure: Conflicting Evidence in the Literature

There is conflicting evidence in the literature regarding the relationship between solar exposure and XFS/XFG. The Reykjavik Eye Study explored the relationship between solar exposure and the disease in Icelanders who were at least 50 years old.[23] Questionnaires assessed for most recent time spent outdoors and eyewear behaviors (i.e., wearing of eyeglasses, hats or sunglasses).[23] The authors found that time spent outdoors and eyewear behaviors did not change the risk of developing the condition.[23] Additionally, *Forsius et al.* found that the Eskimos or Inuits were not afflicted with the disease at all, despite residing in a region with high ambient solar exposure.[24,21]

However, there is also evidence demonstrating higher prevalence of XFS/XFG in people who presumably spend more time outdoors. *Vojnikovic et al.* found that the prevalence of the disease on the island of Rab in the Northern Adriatic Sea varied, as the authors did not find the condition in any of the 60 urban residents but found the disorder in 110 of the 480 fishermen or agriculturists.[21,25] Similarly, *Taylor et al.* found that the prevalence of the disease in aboriginal Australians who presumably were outdoors for a considerable amount of time was about 16.3%,[26] compared to the 0.98% overall prevalence of the condition in Australians who were at least 40 years old.[21,27] *Faulkner* found that the prevalence of the disorder in Arizonian Navajo Indians who were at least 60 years old was quite high at

38%.[28] Additionally, there is evidence that people engaged in occupations that presumably involve more time spent outdoors are linked with XFS/XFG. *Taylor et al.* revealed that Australian stockmen had a significantly higher prevalence of the disease.[21,29] The Southern India Andhra Pradesh Eye Disease Study found that subjects who worked outdoors had a significantly higher odds ratio of the condition.[30]

Is Exfoliation Syndrome Associated with Solar Exposure? New Epidemiological Evidence

In just the past three years, four key epidemiological studies have been published and provide new evidence linking XFS to environmental risk factors such as solar exposure.

In 2011, *Stein et al.*[31] published a retrospective study exploring environmental factors associated with XFS/XFG. The study identified 626,901 beneficiaries of eye care in a managed health care network across the United States from 2001 to 2007 and who were at least 60 years old and did not have XFS/XFG at baseline. Statistical analyses adjusted for socio-demographics and medical co-morbidities.

The authors found that, compared to the most recent residence in the middle tier of the United States, most recent residence in the northern tier was associated with an elevated hazard of ES (adjusted hazard ratio [HR] of 2.14 with a 95% confidence interval [CI] of 1.94–2.35) while residence in the southern tier was associated with a decreased hazard of the condition (adjusted HR of 0.83 with a 95% CI of 0.75–0.93). When Caucasians were removed from these analyses, the associations were not materially changed. Furthermore climatic data analysis revealed that the hazard of XFS/XFG increased by 1.5% for each additional sunny day per year (adjusted HR of 1.02 with a 95% CI of 1.01–1.02). There was a 3% reduction in hazard of the disease (adjusted HR of 0.97 with a 95% CI of 0.96–0.98) for every one-degree elevation in January low temperature. There was a 9% reduction in the hazard of the condition with every one-degree elevation in July high temperature (adjusted HR of 0.91 with a 95% CI of 0.89–0.93).

The authors concluded that solar exposure, ambient temperature, and living at more northern latitudes within the United States may be environmental risk factors of XFS. Strengths of this study included the large number of subjects and socio-demographically diverse participant pool. Limitations of the study include that only the most recent residence, rather than lifetime residence, was examined. Additionally only state-wide climatic exposure was analyzed, rather than individual ocular solar exposure which more accurately captures the amount of sunlight that reaches each subject’s eye.

In 2012, *Kang et al.*[14] published a prospective cohort study evaluating the relationship between environmental and residential factors and XFG or XFG suspect status. Subjects included 78,955 females in the Nurses’ Health Study (NHS) from 1980 to 2008 and 41,191 males in the Health Professionals Follow-up Study (HPFS) from 1986 to 2008. Participants were at least 40 years old and did not have glaucoma at baseline. Three hundred and forty-eight XFG or XFG suspect cases were identified. Statistical analyses accounted for socio-demographics and medical co-morbidities.

The authors found that lifetime residence in the southern (multivariate rate ratios [MRR] 0.25 with a 95% CI of 0.09–0.71) or middle tier (MRR 0.53 with a 95% CI of 0.40–0.71) was associated with a decreased risk of developing XFG or XFG suspect as compared to lifetime residence in the northern tier. Northern tier residence at age 15 years old was associated with increased risk of XFG/XFG suspect compared to residence in the middle tier (MRR 0.55 with a 95% CI of 0.32–0.94) in the southern tier (MRR 0.40 with a 95% CI of 0.16–0.99). The study also found that male gender was associated with decreased risk of XFG/XFG suspect (MRR 0.32 with a 95% CI of 0.23–0.46). The authors confirmed that age and family history of glaucoma are risk factors for the condition. However the study demonstrated that eye color and Scandinavian heritage were not risk factors for the disease.

The authors concluded that living in more northern latitudes within the United States may be a risk factor for the development of XFG/XFG suspect. They also concluded that Scandinavian heritage was not significantly associated with the disease. Strengths of this study included the large sample size, socio-demographically diverse subject population and evaluation of lifetime residence. Limitations of the study include that neither time spent outdoors nor individual ocular solar exposure was examined.

In 2014, *Pasquale et al.*[21] published a case-control study investigating the relationship between XFS (with or without glaucoma) and solar exposure and lifetime residence in the United States (118 cases and 106 controls) and Israel (67 cases and 72 controls). Socio-demographic information and medical co-morbidities were collected. Subjects were at least 60 years old and were administered a validated questionnaire by masked interviewers. Participants recounted their entire residential history (city, state and country) from birth to age 60. Additionally, for each decade of life from age 10 to 60, subjects reported: (1) the percent of time from 10am to 4pm during the summer (when the sun shines the most brightly) that they wore any kind of sunglasses, brimmed hat, non-tinted eyeglasses, and contact lenses; and (2) regular leisure or work activity over snow or water.[21] Subjects also disclosed the age of their first sunburn.

In multivariate analyses, every one degree of "weighted lifetime average residential latitude away from the equator was associated with an 11% increased odds of XFS (pooled odds ratio = 1.11; 95% CI: 1.05–1.17; p = .0003)."[21] Additionally, every one hour spent outdoors between 10am and 4pm during the summertime week, "averaged over a lifetime, was associated with a 4% increased odds of XFS (pooled odds ratio = 1.04; 95% CI: 1.00–1.07; p = .03). For every 1% of average lifetime summer time between 10 a.m. and 4 p.m. that sunglasses were worn, the odds of XFS decreased by 2% (odds ratio = 0.98; 95% CI: 0.97–0.99; p = .00003) in the United States, but not in Israel (odds ratio = 1.00; 95% CI: 0.99–1.01; p = .92; p for heterogeneity = .005). In the United States, after controlling for important environmental covariates, history of work over water or snow was associated with increased odds of XFS (odds ratio = 3.86; 95% CI: 1.36–10.9)."[21] There were too few subjects with a history of work or snow in Israel for meaningful analysis. "Brimmed hat wear was not associated with XFS (p>.57)."[21]

The authors concluded that latitude away from the equator, solar exposure, sunglass wear and leisure or work activity over water or snow may be environmental risk factors of XFS.

Advantages of this study included examining the lifetime residence and near lifetime (each decade of life from age 10 to age 60) individual solar exposure of each subject. Drawbacks to this study include but are not limited to possible subject recall bias.

In 2014, *Kang et al.*[32] published a prospective cohort study examining the relationship between time spent outdoors and risk of XFG/XFG suspect. Subjects included 49,033 females from the NHS and 20,066 males from the HPFS. Participants were at least 60 years old and without cataracts or glaucoma at baseline. Questionnaires were administered every two years over a 30 (NHS) or 24 (HPFS) year period and asked the subjects to recall "time spent outdoors in direct sunlight at midday"[32] from high school to age 24, age 25–35, and age 36–59.

In multivariate analyses, while “no association was observed with greater time spent outdoors in the ages of 25–35 or ages 36–59 years, the pooled multivariable-adjusted rate ratios for ≥11 hours per week spent outdoors in high school to age 24 years compared with ≤ 5 hours per week was 2.00 (95% CI = 1.30, 3.08; P for linear trend = .001). In women, this association was stronger in those who resided in the southern geographic tier in young adulthood (P for interaction = .07)."[32]

The authors concluded that more time spent outdoors in high school to 24 years old was associated with an elevated risk of XFG/XFG suspect. Strengths of the study include the large sample size, collection of individual solar exposure data prior to the development of the disease, and incorporation of a per tier analysis whereby subjects within a tier who spent more times outdoors were found to be at an increased risk of XFG. Limitations of the study include that the subjects were generally healthy European Caucasians residing in the United States instead of a more diverse subject population.

Understanding Solar Exposure as Risk Factor for Exfoliation Syndrome

Taken together, new studies suggest that lifetime and most recent residence, and in particular residence at age 15 years old, in the northern tier of the United States (as compared to the middle and southern tiers) and with increasing latitude away from the equator are associated with increased risk of XFS.[14,21,31] Additionally ambient low temperature, ambient solar exposure, time spent outdoors, sunglass wear and leisure or work activity over water or snow may be environmental attributes associated with XFS.[21,31] There is also evidence that more time spent outdoors in earlier years is associated with the disease.[32] And notably, there is a well-designed study with a large number of participants demonstrating that there is no association between Scandinavian heritage and XFS.[14]

How do we make sense of this evidence? How can solar exposure play a role in increasing the risk of XFS? The anterior segment of the eye, where exfoliation material is found, may be vulnerable to solar ultraviolet radiation (UVR). Indeed, UVR has been known to cause anterior segment disease in the form of climatic droplet keratopathy and pterygium,[33,34] and these disorders have been associated with XFS as well.[10,11,35–37] UV radiation has also been demonstrated, using *in vitro* human Tenon capsule fibroblasts, to upregulate the expression of genes responsible for key components of exfoliation material: LOXL1, elastin, fibulins, fibrillin-1 and latent transforming growth factor binding proteins.[15] It is therefore possible

that UV radiation that reaches the eye upregulates these components and triggers the development of exfoliation material. In essence, although it is often said that ‘genetics loads the gun and the environment pulls the trigger, the exact opposite may be true for XFS. The LOXL1 genetic marker studies motivated the discovery of environmental risk factors. Lifestyle patterns in young adulthood may accumulate to increase the risk XFS and common gene variants may serve to execute a plan that results in manifest disease.

Additionally, exfoliation material could form by the hypothesized “protein sink model,” in which increased iris vessel permeability leaks a nucleation protein which allows for a larger protein matrix to be formed.[38] Clusterin, an abundant chaperone protein in the iris, may participate in this process.[39,40] These aggregates can then precipitate out of the aqueous humor and form the exfoliation material that then coats the structures in the anterior segment of the eye.[38] It is possible that UVR plays a role in this model by triggering or enhancing iris vessel leakage.[31] Furthermore, *Stein et al.* found that lower ambient temperature was also a risk factor for the development of ES.[31] It is possible that the anterior segment of the eye may be susceptible to ambient temperature, and that colder temperatures could enhance the precipitation process of the material out of the aqueous humor in the anterior segment of the eye.[31]

Why may work or leisure activity over water or snow increase the risk of XFS? Solar reflectivity off of these surfaces can be quite significant, reaching as high as 88% for fresh snow and up to 30% off of water.[41] This can considerably increase the amount of UVR that reaches the eye. Sunglasses can attenuate this effect, which could explain why *Pasquale et al.* found sunglasses to be a protective factor against the development of XFS.[21] However wearing a brimmed hat still allows the solar rays from the surface of the earth to reflect towards the eye, which could explain why the aforementioned authors did not find brimmed hat wear to be a protective factor against the disease.[21]

Solar reflectivity may also explain why residing at increasing latitude away from the equator and in the northern tier of the United States (as compared to the middle and southern tiers) is associated with an elevated risk of XFS. With increasing latitude away from the equator, the sun is more angulated with respect to the earth’s surface, allowing for greater UVR reflectivity into the eye.[32] Additionally, such regions are more likely to have snow, with its high solar reflectivity, and are more likely to have colder temperatures to enhance the precipitation of exfoliation material in the eye.

Additionally, available evidence suggests that solar exposure early in life may be important to the development of XFS. *Kang et al.* found that residence at age 15 years old elevated the risk of developing the condition in the northern United States tier compared to the middle and southern tiers[14] and that more time spent outdoors in high school to 24 years old was associated with elevated risk of XFG/XFG suspect.[32] *Pasquale et al.* found significant associations between solar exposure and sunglass wear by examining individual ocular solar exposure starting at age 10.[21] Certainly, people spend more time outdoors when they are younger,[21,42] and pupil size is known to be larger with younger age.[21,43] Taken together, it is possible that more solar rays can reach the eye during the earlier decades of life and that this time period plays an important role in the development of the disease.[21]

How can we reconcile some of the conflicting evidence published in the literature about XFS and solar exposure? For example, the Reykjavik Eye Study found that time spent outdoors and sunglass wear were not risk factors for the disease. However, this study only examined most recent,[23] rather than lifetime,[21] solar exposure and sunglass wear behavior. Also, *Forsius et al.* examined 99 Inuits or Eskimos who were at least 50 years old and found no XFS/XFG in this population.[24] It is unclear why the Inuit do not appear to be afflicted with the disease based on this study. Certainly more work is needed to replicate this XFS/XFG prevalence result. Given that the Inuit live in regions known for high solar exposure, and that the Inuit are afflicted with other ocular solar related conditions including pterygium, climatic keratopathy and pinguelcua,[24] ultraviolet radiation certainly appears to be reaching at least the ocular surface of the eye. Perhaps the Inuit have ocular features that could help elevate ocular temperature to prevent the precipitation and formation of exfoliation material.[31] Such features could include a shallow anterior chamber[44, 45] that has been long been hypothesized in the literature to serve as a "thermoregulatory role" as an adaptation to their extreme cold climate,[46,47] as well as ocular adnexa features such as increased periorbital fat.

Future Directions

Certainly more work is needed to further elucidate the relationship between XFS and solar exposure and UVR, as well as between XFS and other conditions that are linked to solar exposure (i.e., pterygium and skin cancer).[17] This will further our understanding of the pathophysiology of the disease in efforts to better treat this condition. Furthermore, modification of lifestyle behaviors to decrease solar exposure may help prevent the development of XFS.

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