Pseudoexfoliation Syndrome: The Puzzle Continues

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Pseudoexfoliation (PXF) syndrome is a genetically determined, age-dependent generalized disorder of the elastic fiber system, characterized by excessive production and accumulation of an elastotic material within a multitude of intra- and extracellular tissues. Accumulation of this abnormal material in the aqueous humor outflow pathways predisposes to ocular hypertension and development of a severe type of open-angle glaucoma, known as PXF glaucoma, which represents the most common identifiable cause of open-angle glaucoma. Systemic manifestations of this abnormal matrix process appear to be associated with increased cardiovascular and cerebrovascular morbidity. PXF syndrome is generally considered as a complex, multifactorial, late-onset disease involving a combination of genetic and non-genetic factors in its etiopathogenesis. Genetic studies in multiple populations have provided conclusive evidence that single nucleotide polymorphisms in the LOXL1 (lysyl oxidase-like 1) gene, encoding a cross-linking matrix enzyme, represent the principal genetic risk factor for both PXF syndrome and PXF glaucoma. Moreover, a number of non-genetic factors, including ultraviolet light exposure, dietary factors, infectious agents, and trauma as well as several stress conditions, such as oxidative stress, hypoxia, and inflammation, have also been suggested to act as co-modulating external factors.

The fibrotic PXF process may affect up to 25% of the general population over 60 years of age worldwide. In all populations, the frequency rises with age, with its incidence doubling every decade after the age of 50, however the diagnosis is rarely made below the age of 50. There are exceptional populations in which PXF develops at an earlier age including Icelanders, Australian Aborigines and South African Bantu, which may be attributed to genetic or environmental causes. In typical late-onset populations, however, only few cases have been reported with onset below 50 years of age. To date, only 6 cases of PXF manifestation in patients younger than 40 years have been described in the literature. In each of these cases, intraocular surgery, including iris surgery, had been performed prior to development of PXF after a latent phase of several years. The youngest reported patient with signs of PXF deposits, who underwent cataract surgery in infancy, was 13 years of age. However, confirmation by electron microscopy of typical PXF fibrils in conjunctival biopsies has been performed in only one of these patients, a 17-year-old girl.

In this issue of the Journal of Ophthalmic & Vision Research, Amini et al report on another 4 patients with congenital or juvenile glaucoma who presented with clinical signs of PXF syndrome at young age (18-43 years) following multiple surgical procedures. Signs of PXF were consistently observed in the eye subjected to repeated surgeries, and the time interval between the last surgery and diagnosis of PXF varied from 6 months to 4 years. Thus, this report represents the largest series of exceptionally young patients developing PXF syndrome subsequent to intraocular surgery or trauma to the anterior segment. In accordance with the existing literature, the authors suppose that such traumatic events, particularly to the iris, may serve as a trigger for premature development of PXF syndrome in genetically predisposed individuals. Although the causal relationship between PXF manifestation and iris surgery remains to be clarified, it can be
hypothesized that injury to anterior segment structures, particularly to the iris, causes damage to iris blood vessels with concomitant breakdown of the blood-aqueous barrier and inflammatory reactions leading to an influx of pro-inflammatory cytokines and fibrogenic growth factors into the anterior chamber. In fact, iris tissue alterations are an early and consistent feature in all PXF eyes and include a pronounced vasculopathy associated with chronic defects in the blood-aqueous barrier and degeneration of blood vessels. Ultrastructural alterations of iris vessels have been shown to represent the earliest histopathological signs of PXF syndrome, which can be detected in clinically unaffected contralateral eyes in cases with unilateral disease. Moreover, previous studies have provided evidence for a crucial role of growth factors, such as transforming growth factor (TGF)-β1, and pro-inflammatory cytokines, such as interleukin-6 (IL-6), in the initial phase of the fibrotic PXF process. Increased levels of IL-6 in the aqueous humor of eyes with early PXF have been shown to result from increased production by iris vasculature, to adversely affect blood-aqueous barrier integrity, and to stimulate the expression of elastic matrix components in vitro. Therefore, it is reasonable to assume that a chronically activated stress response by trauma to the iris in combination with a specific genetic background may result in an exceptionally early onset of PXF-associated fibrosis.

One limitation of the present study is lack of histopathological confirmation of the clinical diagnosis, because the characteristic fibrillar morphology of PXF deposits, e.g. in conjunctival tissue biopsies, remains the gold standard for a definite diagnosis. It is also regrettable that the authors were not able to determine the LOXL1 genotype of their patients in order to assess the genetic risk of developing PXF, which quite unusually appeared in eyes initially diagnosed as having congenital glaucoma or juvenile primary open-angle glaucoma.

Considering the frequency of PXF in aged populations, such early onset cases, as presented by Amini et al., are certainly rare. However, they can provide further clues to the pathophysiologic mechanisms involving stress-related triggering factors in addition to genetic predisposition. They further underline the need for a careful ophthalmological examination in young patients with a history of intraocular surgery.

PXF patients can present with unilateral or bilateral involvement with unilaterality rather being the rule than the exception. In these cases, the involved eye often has poorer visual acuity, more advanced lens opacity, a smaller pupil, higher intraocular pressure (IOP), more trabecular meshwork pigmentation and more pronounced glaucomatous damage than the unaffected fellow eye. Histopathologically, however, both eyes are involved supporting the concept that PXF syndrome is a generalized, basically bilateral disorder with often markedly asymmetric clinical presentation. This is also reflected by highly asymmetric manifestation of concomitant iris abnormalities, particularly loss of pigment from the iris sphincter region and its dispersion and deposition on anterior chamber structures. The reason for this asymmetric appearance is not known, but may involve subtle differences in ocular blood flow, aqueous humor dynamics, blood-aqueous barrier function, or anterior segment anatomy. In fact, significant differences in anterior segment morphology, including chamber angle width and iridolenticular contact, have been reported between PXF eyes and unaffected fellow eyes in an optical coherence tomography (OCT) analysis.

In another cross-sectional study of this issue of the Journal of Ophthalmic and Vision Research, Rao compared clinical findings and retinal nerve fiber layer (RNFL) thickness measured by OCT in affected eyes of clinically unilateral (n=32) and bilateral cases (n=59) of PXF syndrome without manifest glaucoma. He found that bilateral cases were significantly older, had smaller discs, larger cup disc ratios (CDR), thinner RNFL, and higher frequency of pupillary ruff atrophy (PRA) than unilateral cases. The differences may reflect early glaucomatous damage in bilateral PXF cases, especially since a CDR greater than 0.7 is highly suspicious of glaucoma. These findings are consistent with the existing literature, in
which patients with bilateral PXF tend to be slightly older and to have a higher prevalence of glaucoma than those with unilateral disease. Thus, unilateral involvement is often considered a precursor to bilateral disease.

More interestingly, Rao also evaluated the predictive value of PRA, one of the most striking, though not specific, features of PXF eyes, for early glaucomatous damage as indicated by RNFL thinning. He found that the presence of PRA predicted RNFL thinning with high sensitivity (80-89%) but only low specificity (46%) in both unilateral and bilateral PXF cases. Yet, the author concluded that the clinical sign of PRA may indicate early glaucomatous damage in PXF eyes. This notion has in fact been confirmed in a recent prospective study on 103 glaucoma patients without PXF syndrome examining the correlation between PRA and glaucoma-related parameters. The authors found that asymmetric PRA changes were significantly correlated with both IOP and CDR asymmetry between eyes. They also provided a plausible explanation for such a relationship since pigment liberation from the peripupillary iris pigment epithelium and its accumulation in the chamber angle is a well recognized risk factor for increased IOP and glaucoma development.

Taken together, the findings of both studies seem to suggest a relationship between the presence of PRA and glaucoma-related clinical parameters in glaucomatous eyes with and without PXF syndrome. Although the clinical significance of this observation has to be evaluated in further studies, PRA may be a useful, readily apparent clinical indicator for glaucoma risk or early glaucomatous damage in eyes with PXF syndrome and may thus contribute to an increased awareness and timely management of a challenging and severe type of glaucoma.

REFERENCES