Early-onset Exfoliation Syndrome: A Literature Synthesis

Eileen L. Mayro, BA,* Robert Ritch, MD,† and Louis R. Pasquale, MD†

Methods: We conducted a literature review of younger patients with exfoliation syndrome (XFS) in an attempt to identify case similarities and better understand disease etiology.

Purpose: XFS that predisposes to secondary glaucoma is a strongly age-related condition. We performed a literature review of XFS and exfoliation glaucoma (XFG) in patients aged younger than 40 years to examine potential common characteristics and gain clues to its etiology.

Methods: We conducted a broad literature search with appropriate keywords and manually extracted key demographic and ocular features on younger XFS and XFG cases. Articles that did not provide past ocular history on early-onset XFS/XFG were excluded.

Results: We identified 12 cases of XFS and XFG in patients from 13 to 40 years old (8 females; 11 White; 5 from Iran). All had past ocular history remarkable for intraocular surgery for other glaucoma conditions (7 cases), other ocular diseases (3 cases), or ocular trauma (2 cases).

Conclusions: All reported early-onset XFS and XFG cases arise in the setting of events that produced a significant disruption of the blood-aqueous barrier. Understanding the metabolic alterations of aqueous humor from such cases could provide clues regarding how exfoliation material forms.

Key Words: exfoliation, pseudoexfoliation, glaucoma, early-onset (J Glaucoma 2021;30:e164–e168)

Exfoliation syndrome (XFS) was first discovered by Dr John Lindberg in 1917 when examining iris changes in eyes of older patients. He described the presence of grayish flakes at the pupillary border and anterior lens capsule in 50% of patients with glaucoma. Lindberg’s observed associations between XFS, age, and glaucoma remain robust; however, although great strides in the elucidation of this disease have been made in the last decade, the genetic and mechanistic causes of XFS and exfoliation glaucoma (XFG) remain largely unknown.

XFS/XFG primarily affect older individuals. In a US-based study of incident disease, the risk of suspected or definite XFG was 46-fold greater in patients over 75 years of age compared with patients aged 40 to 55 years. The purpose of this study is to examine the characteristics of XFS/XFG in younger patients, which are uncommon, to provide disease insights.

Received for publication October 13, 2020; accepted December 20, 2020.

From the *Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; and †Einhorn Clinical Research Center, New York Eye and Ear Infirmary of Mount Sinai, New York, NY. Disclosure: L.R.P. is a consultant for Verily, Eyenovia, Bausch + Lomb, and Nicox. The remaining authors declare no conflict of interest. Reprints: Eileen L. Mayro, BA, Sidney Kimmel Medical College, Thomas Jefferson University, 1025 Walnut Street #100, Philadelphia, PA 19107 (e-mail: eileen.mayro@jefferson.edu). Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved. DOI: 10.1097/IJG.0000000000001784

METHODS

We performed a literature search of the National Library of Medicine’s PubMed Database in February 2020 using the following keywords “exfoliative,” “exfoliation,” “pseudoexfoliation,” “syndrome,” “glaucoma,” “early-onset,” and “premature.” We manually extracted demographic and ocular features. Articles that did not provide past ocular history on early-onset XFS/XFG were excluded.

RESULTS

In total, 12 cases of XFS in patients age 40 and under were identified. The small sample size precluded statistical analysis. These cases were described between 1967 and 2019 (Table 1). Patients ranged from 13 to 40 years of age. Eight patients were female; 11 patients were White and 1 patient was Asian. Five were from Iran, 3 from the United States, 1 from Germany, 1 from India, 1 from Turkey, and 1 from Greece/Georgia (of Greek ethnicity who was born and raised in Georgia and later moved to Greece at age 16 years).

All cases were unilateral. No case developed exfoliation material (XFM) de novo; all patients had prior intraocular surgery. The mean number of surgeries was 2 (range, 1 to 7). Seven patients had intraocular surgery for pre-existing glaucoma,8,9,11 2 had penetrating keratoplasty (PKP) for keratoconus,9,11 1 had extracapsular cataract extraction for childhood cataract,7 and 2 patients had repair of limbal laceration with excision of prolapsed uveal tissue after ocular trauma.7,10 Ten of the 12 cases involved iris surgery. The remaining 2 cases had PKP, which were performed in 1953 and 1974. At that time, PKPs were routinely completed with a peripheral iridectomy. As a result, it is likely that all 12 cases involved the manipulation of iris tissue. Of the 7 patients with pre-existing glaucoma, 4 had congenital glaucoma, 2 had juvenile open-angle glaucoma, 1 had primary open-angle glaucoma. It was not specified whether any patient had a family history of XFS/XFG. Two patients had a family history of any glaucoma, but the family history of only 6 patients was mentioned.

DISCUSSION

Although XFS is the most common identifiable cause of open-angle glaucoma,12 the pathogenesis leading to its development is unclear. Several risk factors have been identified including environmental, most notably climatic,3,13-15 and genetic factors, most notably, harboring-specific LOXL1 alleles.16 We undertook an analysis on the basis of early chronological age to gain further insights into XFS. All cases present convincing clinical evidence for the presence of XFM and in 1 case, conjunctival biopsy provided ultrastructural confirmation of the disease.8 All patients with early-onset XFS had a significant past ocular history of prior ocular surgery. There is insufficient evidence that a family history of glaucoma could play a role in these cases. Certainly, there is no mention of genetics in the XFS/XFG cases summarized here. Our sample is too small to draw inferences regarding geographic or other environmental predisposition to the disease. During our
| References       | Country   | Year of Birth | Patient Age at Diagnosis (y) | Type of Glaucoma | Examination Findings of Exfoliation Syndrome | Patient Age at Exfoliation Syndrome Diagnosis (y) | Race | Sex | Affected Eye | Family History of Glaucoma | Ocular History (y) |
|------------------|-----------|---------------|-------------------------------|------------------|---------------------------------------------|-----------------------------------------------|------|-----|--------------|--------------------------|------------------|
| Kumar et al⁴     | India     | 1991          | 2 (1993)/ congenital OU       |                  | “Exfoliation material on the pupillary margin and anterior lens capsule” | 28 (2019)                                    | Asian| F   | OS           | No                       | 1. Glaucoma filtration surgery OU (1993) 2. Presenile cataract OS (2019) |
| Yuksel et al⁵    | Turkey    | 1989          | No glaucoma diagnosis        |                  | “Whitish, dandruff-like deposits along the pupillary margin and the inferior chamber angle” | 13 (2002)                                    | White| F   | OS           | Unknown                 | 1. Developmental cataract OU (1996) 2. Extracapsular cataract extraction with sulcus fixed posterior capsule intraocular lens implantation OU (1996) 3. Nd:YAG posterior capsulotomy OU (1998) |
| Amini et al⁶     | Iran      | 1987          | 10-d old (1987)/ congenital OU |                  | “Exfoliative deposits on the anterior lens capsule and pupillary border” | 18 (2005)                                    | White| F   | OS           | Yes                     | 1. Trabeculotomy OU (1987) 2. Trabeculectomy OU (1993) 3. Trabeculectomy OU (1997) 4. Blebitis OS (2001) 5. Blebitis OS (2001) 6. Trabeculectomy OS (2004) 7. Ahmed glaucoma valve implant OS (2005) 8. Posterior subcapsular cataract OS (2010) |
| Amini et al⁶     | Iran      | 1967          | 27 (1994)/juvenile OU        |                  | “Exfoliative deposits on the anterior lens capsule, pupillary margin, and angle structures” | 40 (2007)                                    | White| F   | OS           | Yes                     | 1. Trabeculectomy OU (1994) 2. Trabeculectomy OS (1994) 3. Ahmed glaucoma valve implant OS (2003) |
| Amini et al⁶     | Iran      | 1966          | 36 (2002)/primary open-angle OU |                  | “Exfoliative material on slit lamp and gonioscopic examinations” | 40 (2006)                                    | White| M   | OS           | No                      | 1. Argon laser trabecuoplasty OU (2002) 2. Trabeculectomy OS (2003) 3. Anterior chamber reformation OS (2003) |
| Fakharie et al⁷  | Iran      | 1999          | 6-mo old (1999)/ congenital OU |                  | “Flaky white material on the anterior lens capsule” | 13 (2012)                                    | White| F   | OD           | Unknown                 | 1. Unspecified angle surgery OU (1999) 2. Trabeculectomy OD (2001) 3. Needling bleb revision OD (2010) |
| Fakharie et al⁷  | Iran      | 1982          | 30 (2012)/ secondary OD      |                  | “Whitish, dandruff-like material on the anterior lens capsule and pupillary border” | 30 (2012)                                    | White| F   | OD           | Unknown                 | 1. Penetrating trauma with iris prolapse and limbusceral laceration OD (1986) 2. Prolapsed iris excision with laceration repair OD (1986) |
| References   | Country          | Patient Year of Birth | Patient Age at Glaucoma Diagnosis (y)/Type of Glaucoma | Examination Findings of Exfoliation Syndrome                                                                 | Patient Age at Exfoliation Syndrome Diagnosis (y) | Race | Sex | Affected Eye | Family History of Glaucoma | Ocular History (y) |
|-------------|------------------|-----------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------|-----|-------------|--------------------------|-------------------|
| Konstas et al<sup>8</sup> | Georgia/Greece   | 1980                  | 8-mo old (1980)/congenital OD                           | “White, fluffy deposits on the pupillary margin, a large central disc of white material on the lens capsule, and a dense band of granular material on the lens periphery connected by bridges to the central disc … Fibri...” | 17 (1997)                                    | White | F   | OD          | Unknown                 | 1. Trabeculectomy OD (1980) 2. Peripheral iridectomy OD (1980) |
| Kückle and Naumann<sup>9</sup> | Germany          | 1943                  | No glaucoma diagnosis                                  | “Typical exfoliation material on the anterior lens capsule”                                                 | 37 (1980)                                    | White | M   | OD          | Unknown                 | 1. Keratoconus OU 2. Penetrating keratoplasty OD (1974) 3. Penetrating keratoplasty OD (1989) 4. Penetrating keratoplasty OS (1990) |
| Sugar<sup>10</sup>           | United States    | 1951                  | No glaucoma diagnosis                                  | “Fuzzy whitish deposits on the pupil border and capsular exfoliative material arranged in streaks that occurred only where iris folds were in contact with the lens capsule” | 22 (1973)                                    | White | M   | OS          | Unknown                 | 1. Penetrating trauma with iris prolapse OS (1952) 2. Prolapsed iris excision OS (1952) |
| Horven and Hutchinson<sup>11</sup> | United States    | 1934                  | 16 (1950)/juvenile OU                                  | “Exfoliative material on the anterior lens surface and pupillary margin with a clear intermediate zone in the surgical coloboma area” | 31 (1966)                                    | White | F   | OD          | No                      | 1. Iridencleisis OD (1950) |
| Horven and Hutchinson<sup>11</sup> | United States    | 1929                  | 35 (1964)/secondary                                   | “Peripheral exfoliation band on anterior lens surface and flakes of exfoliative material on pupillary margin” | 35 (1964)                                    | White | M   | OD          | No                      | 1. Keratoconus OU (1945) 2. Penetrating keratoplasty OD (1953) 3. Penetrating keratoplasty OS (1960) |

F indicates female; M, male; Nd:YAG, neodymium-doped yttrium aluminum garnet; OD, right eye; OS, left eye; OU, both eyes.
these patients were excluded from our study. Cases occurred in Iran, Pakistan, Australia, Saudi Arabia, Greece, South Africa, Iceland, Russia, India, and Ethiopia. Patients’ ocular findings at the time of diagnosis and ocular histories are unknown. As a result, it is possible that a major traumatic insult in a young individual causes excessive secretion of transforming growth factor-β1 and CTGF into the aqueous humor, leading to the formation of XFM.

Ideally, future research would compare the biochemical composition of aqueous humor in XFS, early-onset XFS, young controls, and older controls. However, this approach may prove impossible on the basis of how rare early-onset XFS seems to be. Instead, a prospective study of younger patients with a history of trauma and/or intraocular surgery could be conducted. The study could include thorough clinical examination and documentation of XFS findings, as well as ultrastructural analysis and aqueous humor biochemical profiles. Future research could also compare the XFM in early-onset XFS with the XFM of older patients with XFS. Previous research has suggested that early-onset XFM aggregates may be smaller and less compact than aggregates of older XFS patients. Konstas et al inferred that this finding could be caused by decreased aggregate accumulation time. However, additional ultrastructural analyses with biopsies performed at diagnosis and periodically thereafter are needed to confirm this hypothesis.

We studied the characteristics of patients with early-onset XFS as an age-based phenotype analysis to better understand the pathogenesis of XFS. All patients with early-onset XFS had prior intraocular surgery. Although any conclusion should be taken with caution, the present literature suggests that surgical trauma in younger patients may trigger XFS in some cases. Although the exact mechanism by which surgery causes early-onset XFS is unknown, an aqueous humor biochemical profile may provide disease insights.

REFERENCES

1. Lindberg JG. Kliniska undersökningar över Depigmentering av Pupillarränder och Genomlysbarheten av Iris vid Fall av Ålderstar samt Normala Ögon hos Gamla Personer [Clinical Studies on Depigmentation of the Pupillary Border and Translucency of the Iris in Cases of Senile Cataract and in Normal Eyes of Elderly Persons] [thesis]. Helsinki, Finland: University of Helsinki; 1917.
2. Pasquale LR, Borras T, Fingert JH, et al. Exfoliation syndrome: assembling the puzzle pieces. Acta Ophthalmol. 2016;94:e505–e512.
3. Kang JH, Loomis S, Wiggs JL, et al. Demographic and geographic features of exfoliation glaucoma in 2 United States-based prospective cohorts. Ophthalmology. 2012;119:27–35.
4. Kumar PS, Rao A, Senthil S. Premature expression of pseudoexfoliation syndrome with pseudoexfoliated cataract in a 28-year-old lady. J Glaucoma. 2019;28:e115–e117.
5. Yuksel B, Schlotez-Schrehardt U, Pehlivan O, et al. A 13-year-old girl with pseudoxfoliated pseudoexfoliation. Acta Ophthalmol. 2005;83:626–627.
6. Amini H, Daneshvar R, Eslami Y, et al. Early-onset pseudoexfoliation syndrome following multiple intraocular procedures. J Ophthalmic Vis Res. 2012;7:190–196.
7. Fakhraie G, Mohammadi M, Latifi G, et al. Unilateral pseudoexfoliation in two young patients with history of iris trauma and associated intraocular surgery. Iran J Ophthalmol. 2012;24:57–60.
8. Konstas AG, Ritch R, Bufidis T, et al. Exfoliation syndrome in a 17-year-old girl. Arch Ophthalmol. 1997;115:1063–1067.
9. Küchle M, Naumann GO. Occurrence of pseudoexfoliation following penetrating keratoplasty for keratoconus. Br J Ophthalmol. 1992;76:98–100.

10. Sugar HS. The exfoliation syndrome: source of the fibrillar material on the capsule. Surv Ophthalmol. 1976;21:59–64.

11. Horven I, Hutchinson BT. Exfoliation syndrome. Case reports of 31 and 35-year-old patients. Acta Ophthalmol. 1967;45:294–298.

12. Ritch R. Exfoliation syndrome-the most common identifiable cause of open-angle glaucoma. J Glaucoma. 1994;3:176–177.

13. Stein JD, Pasquale LR, Talwar N, et al. Geographic and climatic factors associated with exfoliation syndrome. Arch Ophthalmol. 2011;129:1053–1060.

14. Pasquale LR, Jiwani AZ, Zehavi-Dorin T, et al. Solar exposure and residential geographic history in relation to exfoliation syndrome in the United States and Israel. JAMA Ophthalmol. 2014;132:1439–1445.

15. Kang JH, Wiggs JL, Pasquale LR. Relation between time spent outdoors and exfoliation glaucoma or exfoliation glaucoma suspect. Am J Ophthalmol. 2014;158:603–614.e1.

16. Thorleifsson G, Magnusson KP, Sulem P, et al. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science. 2007;317:1397–1400.

17. Aminisaraye H, Fekrat N. The prevalence of glaucoma secondary to exfoliation syndrome in Iran. Proceedings of the XXV International Congress of Ophthalmology. Rome, Italy; May 4–10, 1986.

18. Khazaie A. Exfoliation syndrome in Pakistan. J Glaucoma. 1999;8:18–23.

19. Schlotzer-Schrehardt U, Zenkel M, Konstas AG. The role of lysyl oxidase-like 1 (LOXL1) in exfoliation syndrome and glaucoma. Invest Ophthalmol Vis Sci. 2019;60:4205–4211.

20. Horven I, Hutchinson BT. Exfoliation syndrome. Case reports of three cases. Klin Monatbl Augenheilkd. 1995;206:8–99.

21. Taylor HR, Hollows FC, Moran D. Pseudoexfoliation of the lens. Surv Ophthalmol. 1976;21:59–64.

22. Tham YC, Wong W, Chan W, et al. The global burden of ocular diseases: a systematic analysis. Invest Ophthalmol Vis Sci. 2014;55:7778–7802.

23. Als E. Lens exfoliation and related problems in Iceland. South Africa. II. Occurrence and prevalence. Br J Ophthalmol. 1978;62:1037–1040.

24. Summanen P, Tonjum AM. Exfoliation syndrome among the Sami of Northern Norway. Statens Sygepleiekommisjon. 1978;17:103–109.

25. Joannides T, Katsourakis N, Velissaropoulos P. Glaucoma capsulare. Graefes Arch Exp Ophthalmol. 1985;2:7–9.

26. Summanen P, Tonjum AM. Exfoliation syndrome among Saudis. Acta Ophthalmol Suppl. 1988;184:107–111.

27. Tham YC, Wong WL, Chan W, et al. The global prevalence of ocular diseases: a systematic analysis and meta-regression analysis for 2010 and 2020. Invest Ophthalmol Vis Sci. 2014;55:7778–7802.

28. Detorakis ET, Kozobolis VP, Pallikaris IG, et al. Detection of Helicobacter pylori IgG antibodies in aqueous humor and serum of subjects with primary open-angle glaucoma, exfoliation glaucoma, and cataract. Invest Ophthalmol Vis Sci. 2014;55:7778–7802.

29. Als E. Lens exfoliation and related problems in Iceland. Br J Ophthalmol. 1977;61:473–475.

30. Summanen P, Tonjum AM. Exfoliation syndrome among Saudis. Acta Ophthalmol Suppl. 1988;184:107–111.

31. Joannides T, Katsourakis N, Velissaropoulos P. Glaucoma capsulare. Graefes Arch Exp Ophthalmol. 1985;2:7–9.

32. Bartholomew RS. Pseudoocular exfoliation in the Bantu of South Africa. II. Occurrence and prevalence. Br J Ophthalmol. 1973;57:41–45.

33. Als E. Lens exfoliation and related problems in Iceland. Nordic Council Arct Med Res Rep. 1980;26:48–53.

34. Kivela ST, Virolainen M, Kaski JP, et al. Elevated IgG antibody titers against Helicobacter pylori in patients with exfoliation syndrome. Acta Ophthalmol Scand. 1998;76:278–280.

35. Bhandari AK, Kansal RK, Garg A. The occurrence of exfoliation syndrome after penetrating keratoplasty: a report of three cases. Clin Exp Ophthalmol. 2013;41:767–770.

36. Bedri A, Alemu B. Pseudoexfoliation syndrome in Ethiopian glaucoma patients. East Afr Med J. 1999;76:278–280.

37. Kansal RK, Garg A, Bedri A. Pseudoexfoliation syndrome in Ethiopian glaucoma patients. Clin Exp Ophthalmol. 2013;41:767–770.

38. Bedri A, Alemu B. Pseudoexfoliation syndrome in Ethiopian glaucoma patients. East Afr Med J. 1999;76:278–280.

39. Kansal RK, Garg A, Bedri A. Pseudoexfoliation syndrome in Ethiopian glaucoma patients. Clin Exp Ophthalmol. 2013;41:767–770.

40. Sajapulil HJ, Anilkumar VT, Gopinath MG. The occurrence of pseudoexfoliation syndrome following penetrating keratoplasty: a report of three cases. Klin Monatbl Augenheilkd. 1995;206:8–99.

41. Detorakis ET, Kozobolis VP, Pallikaris IG, et al. Detection of herpes simplex virus in pseudoexfoliation syndrome and exfoliation glaucoma. Acta Ophthalmol. 2002;80:612–616.

42. Kountouras J, Mylopoulos N, Konstas AG, et al. Increased levels of Helicobacter pylori IgG antibodies in aqueous humor of patients with primary open-angle and exfoliation glaucoma. Graefes Arch Clin Exp Ophthalmol. 2003;241:884–890.

43. Deshpande N, Lalitha P, Krishna das SR, et al. Helicobacter pylori IgG antibodies in aqueous humor and serum of subjects with primary open angle and pseudo-exfoliation glaucoma in a South Indian population. J Glaucoma. 2008;17:665–670.

44. Zhang J, Liu H, Liu X, et al. The relationship between helicobacter pylori infection and open-angle glaucoma: a meta-analysis. Invest Ophthalmol Vis Sci. 2015;56:5238–5245.

45. Ritch R, Schlotzer-Schrehardt U. Exfoliation (pseudoexfoliation) syndrome: toward a new understanding. Proceedings of the First International Think Tank. Acta Ophthalmol. 2001;79:213–217.

46. Bernstein AM, Ritch R, Wolosin JM. Exfoliation syndrome: a disease of age, eye and LOXL1 proteopathy. J Glaucoma. 2018;27(suppl 1):S44–S53.

47. Konstas AG, Williamson TH. Co-existence of exfoliation syndrome, previous iris surgery, and heterochromia. Acta Ophthalmol. 1993;71:850–852.

48. Zeng J, Liu H, Liu X, et al. The relationship between Helicobacter pylori infection and open-angle glaucoma: a meta-analysis. Invest Ophthalmol Vis Sci. 2015;56:5238–5245.

49. Ritch R, Schlotzer-Schrehardt U. Exfoliation (pseudoexfoliation) syndrome: toward a new understanding. Proceedings of the First International Think Tank. Acta Ophthalmol. 2001;79:213–217.

50. Bernstein AM, Ritch R, Wolosin JM. Exfoliation syndrome: a disease of age, eye and LOXL1 proteopathy. J Glaucoma. 2018;27(suppl 1):S44–S53.