



The Clinical Spectrum and a New Theory of Pathogenesis of True Exfoliation Syndrome

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Purpose: To describe the clinical spectrum and a new theory of pathogenesis of true exfoliation syndrome.

Design: Cross-sectional and prospective, observational case series.

Participants: Consecutive patients with characteristic peeling of the anterior lens capsule.

Methods: After maximal mydriasis, slit-lamp biomicroscopy, and photography, imaging of the anterior capsule and zonules was performed. The condition was classified into 4 clinical stages: annular anterior capsule thickening with a distinct splitting margin (stage 1), an inward detached crescentic flap lying on the anterior lens (stage 2), a floating and folding translucent membrane behind the iris (stage 3), and a broad membrane within the pupil (stage 4). Serial photography was performed at each 3-month follow-up visit. Ultrastructural examination of dislocated lenses and excised anterior capsules was performed.

Main Outcome Measures: Detached membrane morphologic features, zonular defects, pigment deposition, glaucoma, phacodonesis, and cataract.

Results: We enrolled 259 patients (424 eyes). Ages ranged from 52 to 97 years (mean age, 75.2±7.1 years). Eleven patients were associated with trauma (n = 1) or intense heat (n = 10), whereas 248 were idiopathic. Two hundred ten patients were followed up every 3 months, with a mean follow-up of 9.6±6.1 months (range, 3–50 months). The detachment started along the anterior zonular insertions in association with zonular disruption. It progressed centrally to higher stages, manifesting a spectrum of disease. Several stages coexisted in a single eye. At the final visit, including 49 patients who were examined once, there were 70, 87, 85, and 17 patients in stages 1, 2, 3, and 4, respectively. All stages shared common histologic findings consisting of diffuse capsular lamellar separation and anterior zonular disruption. All developed cataract. Pigment deposition on the membrane was present in 178 patients (68.7%). Twenty-six patients (10%) had spontaneous phacodonesis. Eighteen eyes (4.2%) demonstrated secondary delamination.

Conclusions: Capsular lamellar separation and anterior zonular disruption are characteristic findings. Aging, heat exposure, and trauma are risk factors. Initial capsular splits occur along the insertions of disrupted anterior zonules. The peeling progresses centrally in association with iris movement and aqueous flow. A second detachment can occur. *Ophthalmology* 2016;■:1–10 © 2016 by the American Academy of Ophthalmology



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True exfoliation syndrome (TEX) or capsular delamination is characterized by the peeling of a translucent membrane from the anterior lens capsule. Major ocular complications include partial capsulorrhexis masquerade or double-ring sign (DRS)^{1–5} and glaucoma.^{2,6–11} Being exceedingly thin and hidden behind the iris, the membrane tends to be missed on routine examination. Several patients were diagnosed during surgery when the pupil was maximally dilated, allowing a bright red reflex or occurrence of the DRS.^{1,3–5} Since it was first described in 1922,^{12,13} 121 cases of TEX have been reported in 37 English and Japanese articles (85 patients diagnosed by the presence of the membrane, 25 diagnosed by the DRS, and 11 diagnosed by histologic examination).^{1–11,14–39} Most were small case series. The largest series diagnosed by the presence of the membrane comprised 18 patients.¹⁰ Furthermore, those who were diagnosed by the DRS or histologic examination

lacked clinical details. We describe the clinical spectrum and propose a new theory of pathogenesis of TEX in the largest series (259 patients) to date.

Methods

The study was approved by the Ramathibodi Institutional Review Board/Ethics Committee and followed the Declaration of Helsinki. Informed consent was obtained. From January 9, 2012, through April 13, 2016, Thai patients older than 50 years seen in our glaucoma and general eye services, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, underwent complete ocular examination. Maximal mydriasis of more than 7.0 mm was performed in eyes with open angles or angle closure with patent laser iridotomy (LI). Those having characteristic circular anterior lens capsule thickening with a distinct splitting margin or a translucent detached membrane were enrolled. Histories of sustained intense

heat exposure, ocular inflammation, trauma, and radiotherapy were recorded. Patients with pseudoexfoliation (PEX) material or the classic 3-ring sign and intraoperative DRS alone were excluded.

The membrane and the zonules were photographed with a photo slit lamp (Haag-Streit BX900, Haag-Streit AG, Switzerland). Membrane morphologic features, extent, and location were assessed in relation to the adjacent zonules. Pigment deposition on the membrane was recorded. Anterior segment imaging including ultrasound biomicroscopy (UBM; Aviso; Quantel Medical, Inc. France), Scheimpflug photography (Pentacam; Oculus, Optikgeräte GmbH, Wetzlar, Germany), and spectral-domain optical coherence tomography equipped with the Anterior Segment Module external lens kit (Spectralis; Heidelberg Engineering, Inc. Heidelberg, Germany) were performed to evaluate the membrane, lens position, and anterior chamber angles. Dynamic UBM was performed in a dark room when the pupils physiologically dilated, followed by shining a flashlight into the contralateral eye to induce miosis in the examined eye. The condition was classified into 4 successive stages based on characteristic changes in the anterior capsule, including annular capsule thickening with a distinct splitting margin (stage 1), segmental inward detachment along the margin exhibiting a crescentic flap lying on the anterior lens (stage 2), a floating and folding translucent membrane with a serpentine free edge behind the iris (stage 3), and a broad membrane within the pupil (stage 4). The highest stage was counted if several stages coexisted in an eye or the membrane unfolded and reverted to a lower stage. Similarly, the highest stage was counted in patients with bilateral asymmetrical involvement. Lens opacities were recorded as cortical or nuclear cataracts. Lens dislocation or subluxation was diagnosed by the presence of phacodonesis in correlation with A-scan immersion ultrasound biometry and imaging.

All patients were examined, photographed, and imaged at the initial examination by the first author (C.T.). Patients were followed up every 3 months and serial photography with or without imaging was performed at each visit. Patients with symptomatic cataracts underwent phacoemulsification and intraocular lens implantation. Capsulorrhexis was performed with a cystotome after trypan blue staining of the anterior capsule. Extreme care was taken to avoid iatrogenic injuries. Those with symptomatic anteriorly dislocated or subluxated lenses underwent intracapsular cataract extraction and scleral-fixated intraocular lens implantation. To preserve the delicate membrane, lenses were expressed manually through an oversized scleral incision. Cryoextractor and capsule forceps were avoided. The excised anterior capsules or extracted lenses were processed for light and transmission, for scanning electron microscopy, or both. The extracted lenses were halved and fixed in a position for scanning electron microscopy of the equator and the anterior and posterior surfaces. A search for TEX in the English and Japanese literature was performed. Incomplete clinical data in past reports were obtained formally from authors when possible.^{14,26,37,40}

Results

Patient Characteristics

We enrolled 259 patients (424 eyes) comprising 118 men and 141 women. Mean age at initial presentation was 75.2 ± 7.1 years (range, 52–97 years). Forty-nine patients were seen once and were either lost to follow-up or underwent cataract surgery. The others ($n = 210$) were followed up every 3 months. Mean follow-up was 9.6 ± 6.1 months (range, 3–50 months). Ten patients had worked for more than 30 years in oven burning ($n = 4$), steel ($n = 3$) or gold ($n = 1$) smelting, steel welding ($n = 1$), or glass blowing

($n = 1$) without heat protection. A patient with unilateral TEX had an ipsilateral blunt contusion. The remaining 248 patients (138 women and 110 men) had idiopathic TEX. Fifty-five patients had undergone LI before presentation. At least 6 patients underwent LI with a neodymium:yttrium–aluminum–garnet laser. Initial location and extent of TEX did not correspond to the LI site in 31 patients; the others ($n = 24$) were not examined. None had uveitis or radiotherapy.

Laterality

On initial examination, 94 patients were phakic unilaterally and 165 patients were phakic bilaterally. Of the 94 unilaterally phakic patients, 2 had a history of heat exposure and 92 had idiopathic disease. Of the 165 bilaterally phakic patients, 8 had undergone heat exposure and had bilateral TEX, 1 had sustained blunt trauma and had ipsilateral TEX, and 156 had idiopathic disease. Of these 156 patients, 17 (9 in stage 1 and 8 in stage 2) had unilateral TEX and 139 had bilateral TEX. Mean age of the 17 unilateral patients was 69.7 ± 6.2 years (range, 61–80 years) and mean age of the 156 bilateral patients was 75.2 ± 7.4 years (range, 52–97 years). The 17 unilateral patients were significantly younger than the 156 bilateral ones ($P = 0.004$, Student's *t* test). Three of the 17 unilateral patients showed TEX in the contralateral eye during follow-up. Most of the 156 bilateral patients demonstrated TEX symmetrically in both stage and location between eyes (Table 1, available at www.aaojournal.org).

Clinical Spectrum of True Exfoliation Syndrome

The clinical spectrum of TEX is outlined in Table 2 (available at www.aaojournal.org).

Stage 1. The initial lesion appeared as a pale sector on the anterior lens with a curved distinct margin along the innermost anterior zonular insertions (Fig 1A). It typically occurred first in the nasal or temporal quadrant(s), or both, and progressively involved the inferior and superior quadrants successively, until a complete disc with a smooth sharp margin was formed. Disc diameters varied with anterior zonular insertions and patient age, ranging from 6.0 to 8.0 mm. The central disc appeared hazy, contrasting with the outer capsule, and could wrinkle. Specular reflection of the central capsule abruptly terminated along the disc margin (Fig 2A). Trypan blue staining of extracted dislocated lenses clearly accentuated the central disc (Fig 3, available at www.aaojournal.org). Slit-lamp biomicroscopy at high magnification ($\geq \times 25$) of the disc margin revealed microscopic splitting and peeling of the anterior capsule. Tangential examination with a gonioscopy lens demonstrated subtle elevation of the splitting margin and missing anterior zonules (Fig 4A, available at www.aaojournal.org). Retroillumination highlighted the disc margin in locations whose anterior zonules were either sparse or absent (Fig 5, available at www.aaojournal.org).

Stage 2. Inward segmental peeling developed along the disc margin. It typically occurred before the central disc of stage 1 was formed completely. The detached membrane flipped centrally and lay flat on the central disc capsule, showing a characteristic narrow crescent with tapered, sharp ends (Fig 1B). The crescent typically occurred first in the nasal or temporal quadrant, or both, with the sharp ends situated at the 2-o'clock and 4-o'clock positions, the 8-o'clock and 10-o'clock positions, or both. Segmental peeling distorted the central disc and exposed the deeper layer of the capsule as a gray crescent exhibiting a mirror image of the flipped flap (Fig 2B). The denuded capsule slowly faded out and blended with the outer capsule. The peeling occurred exclusively in the locations whose anterior zonules were missing and terminated wherever the zonules remained. Bordering zonules were always

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