“Masked” Pseudoexfoliation Syndrome in Unoperated Eyes With Circular Posterior Synechiae

Clinical–Electron Microscopic Correlation

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Objective: To investigate the prevalence of “masked” pseudoexfoliation (PEX) syndrome in eyes with circular posterior synechiae receiving antiglaucomatous therapy with miotics.

Design: Cross-sectional prospective study.

Methods: Twenty-eight eyes of 27 consecutive patients with circular posterior synechiae and a history of miotic drug use without previous intraocular surgery, inflammation, or trauma, and without conventional signs of PEX material in the anterior chamber were included in the study. All eyes were investigated by slitlamp biomicroscopy and gonioscopy of the anterior chamber before extracapsular cataract surgery for the presence of typical PEX-associated iris pigment epithelial changes, such as peripupillary atrophy and trabecular meshwork melanin granule deposition. The anterior chamber depth, lens thickness, and axial lengths of the eye were measured by A-scan immersion sonography. The excised anterior lens capsules obtained during extracapsular cataract surgery were investigated for the presence of precapsular fibrillar PEX deposits by electron microscopy.

Main Outcome Measure: The prevalence of masked PEX syndrome in eyes with circular posterior synechiae receiving antiglaucomatous therapy with miotics.

Results: Transmission electron microscopy of unselected nonserial sections revealed a precapsular layer consisting of typical PEX fibers or microfibrils, which indicated early stages of PEX syndrome in 18 (64%) of 28 eyes with circular posterior synechiae. Melanin granules were frequently found adhering to the fibrillar layer. Eyes with precapsular fibrillar deposits showed significantly greater trabecular meshwork pigmentation than eyes without such deposits. Differences in age, lens thickness, axial length of the eye, anterior chamber depth, and degree of peripupillary atrophy were, however, not statistically significant between the groups with and without electron microscopic evidence of PEX deposits.

Conclusions: Circular posterior synechiae were more frequently associated with manifest or early stages of PEX syndrome. However, the formation of broad posterior synechiae in miosis prevented a definite clinical diagnosis based on the classic changes of the anterior lens capsule. In eyes with spontaneous or miotic-induced circular posterior synechiae without other obvious cause, the masked variant of PEX syndrome should always be considered.

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Among a wide spectrum of clinically recognizable ocular manifestations and complications,1 pseudoexfoliation (PEX) syndrome predisposes eyes to the formation of posterior synechiae, particularly during miotic therapy for secondary open-angle glaucoma (Figure 1). Factors contributing to the development of iridocapsular adhesions are sticky PEX material accumulations on the iris pigment epithelium and the anterior lens capsule,2,3 decreased iris mobility and elasticity, and an increased aqueous humor protein concentration4 leading to elevated viscosity. Attempts to remove the posterior synechiae by mydriasis or mechanical separation may lead to spontaneous hyphema after pupillary dilation.1,3,6

Broad posterior synechiae may hide PEX deposits on the anterior lens capsule, thus hampering a conventional PEX diagnosis; circular posterior synechiae make it impossible to recognize PEX. We describe this variant as “masked” PEX syndrome.1 In this study, we investigated the prevalence of this masked variant of PEX syndrome in eyes with circular posterior synechiae receiving miotic therapy in a cross-sectional, clinicohistopathologic design.
PATIENTS AND METHODS

The study included 28 (18 right, 10 left) eyes of 27 consecutive patients (mean ± SD age, 73.0 ± 9.0 years) undergoing extracapsular cataract extraction and having circular posterior synechiae and a history of using miotic eye drops (pilocarpine, carbachol) for at least 2 years to treat primary open-angle glaucoma. Informed consent was obtained from the patients undergoing surgery. The eyes had no biomicroscopic signs of PEX material on anterior segment structures. Eyes with a history of surgery, trauma, diabetes, or inflammatory disease were excluded. All eyes were investigated preoperatively by slitlamp examination and gonioscopy of the anterior chamber for the presence of typical PEX-associated clinical signs of secondary melanin dispersion, such as atrophy of the peripupillary pigment epithelium and trabecular meshwork pigmentation. Both of these PEX-related signs were semiquantitatively scored, ranging from 0 to 3 by slitlamp biomicroscopy and gonioscopy. The prevalence of PEX in this situation may be even higher than 64%. This suggests a clear correlation between fibrillar deposits on the anterior lens surface, to represent a precursor of typical PEX fibers, and therefore, to characterize early stages of PEX syndrome. Such a microfibrillar layer was shown to be present in up to 70% of eyes with suspected PEX syndrome by electron microscopy. Its occurrence seems to be associated with clinically observed pigmentary abnormalities of the anterior segment, such as peripupillary atrophy, trabecular meshwork pigmentation, and melanin dispersion after mydriasis.

In this study, the excised anterior lens capsule specimens showed ultrastructural alterations (ie, deposits of microfibrils or mature PEX fibers) typical of PEX syndrome or its early stages in 64% of eyes with circular posterior synechiae. No other obvious cause was found, such as previous surgery, trauma, inflammation, or diabetes. The formation of broad synechiae prevented a precise biomicroscopic evaluation of the anterior lens capsule for the presence of classic PEX deposits and confirmation of a frosted appearance of the lens surface characterizing early stages of the disease. Similarly, the biomicroscopic observation of the zonules, which may be coated with PEX material early in the process, was impossible in these eyes. Ultrasound-biomicroscopy may demonstrate PEX deposits on the zonular fibers in advanced cases but was not systematically applied here. The prevalence of precapsular fibrillar deposits in this selected group of patients (64%) was higher than the prevalence in patients with cataract (38%). This suggests a clear correlation between fibrillar deposits on the anterior lens surface and the presence of posterior synechiae while receiving miotic therapy. Discontinuities in the precapsular layer and mechanic effects of stripping the loosely adhering layer off during surgery may account for an underestimation of the prevalence of early or manifest PEX syndrome in these eyes. Since serial sections were not performed, the effect of sampling artifacts could not be determined. We therefore assume that the prevalence of PEX in this situation may be even higher than 64%.

RESULTS

Transmission electron microscopy of unselected sections of anterior lens capsules revealed a precapsular layer consisting of microfibrils in 16 (57%) of 28 eyes and typical PEX fibers in 2 (7%) of 28 eyes with circular posterior synechiae. The presence of typical PEX fibers or a microfibrillar layer, suggested to be a precursor to typical PEX fibers on the surface of the anterior lens capsule, was indicative of a manifest or early stage of PEX syndrome. Melanin granules were frequently found adhering to or embedded within the microfibrillar layer (Figure 2). Ten (36%) of 28 capsular specimens did not show any deposits on their surfaces and were listed as non-PEX.

Eyes with and without evident precapsular fibrillar deposits showed no significant differences in age, lens thickness, and axial length of the eye. The difference in anterior chamber depth, which was shallower in eyes without precapsular deposits, was almost statistically significant between both groups (P = .06) (Table). Eyes with a precapsular layer showed a statistically significantly higher trabecular meshwork pigmentation score than eyes without a precapsular layer (P = .02), whereas the degree of peripupillary atrophy was not statistically different between groups (Table).
In advanced stages of ocular PEX, the iris pigment epithelium and the anterior lens capsule tend to adhere to each other because of the sticky PEX material accumulations on both surfaces, particularly when pupillary movement is inhibited by miotic therapy.\(^1\) Adhesive components of the microfibrillar layer, such as laminin, fibronectin, and fibrillin-1,\(^8\)\(^9\) may facilitate the formation of iridocapsular adhesions during miotic therapy in the early stages. A significantly increased protein concentration of aqueous humor\(^4\) (including adhesive glyco-proteins such as plasma fibronectin\(^12\)\) caused by disruption of the blood-aqueous barrier could contribute to the tendency to form posterior synechiae. Further factors predisposing to the development of posterior synechiae in eyes with early or manifest PEX syndrome may include a relatively shallow anterior chamber compared with that found in normal eyes,\(^13\) a reduction of iris elasticity and mobility,\(^14\) and degenerative pigment epithelium of the iris.\(^15\)

Pigment loss from the peripupillary pigment epithelium of the iris and its deposition on anterior segment structures—particularly the trabecular meshwork—is a hallmark of PEX syndrome.\(^7\)\(^16\) In this study, eyes with electron microscopic evidence of early or manifest PEX syndrome had a statistically significantly higher score for trabecular pigmentation and a higher but not statistically significant score for peripupillary atrophy than eyes without such evidence. This is in concordance with previous studies demonstrating a significant association between clinical signs related to melanin dispersion with both manifest PEX syndrome and early stages without clinically visible PEX material.\(^5\)\(^7\)\(^8\)\(^10\)\(^17\) These pigment-related signs also correlated with the presence of PEX fibrils in extraocular tissues (eg, in conjunctival biopsy specimens\(^17\) and eyelid skin specimens\(^18\)\) in suspect eyes without clinically visible intraocular PEX deposits.

The formation of broad posterior synechiae prevented the biomicroscopical examination and conventional diagnosis of the subtle alterations of the anterior lens surface. Therefore, in eyes with spontaneous or miotic-induced circular posterior synechiae without other obvious cause, PEX syndrome should be considered or even ruled out by methods such as high-resolution ultrasound biomicroscopy, which may detect PEX deposits on the peripheral zonules.\(^1\) Indications of the presence of masked PEX syndrome in eyes with circular

### Table: Electron Microscopic Evaluation of Anterior Lens Capsules With and Without PEX Deposits\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>Eyes Containing Lens Capsules With PEX Deposits (n = 18)</th>
<th>Eyes Containing Lens Capsules Without PEX Deposits (n = 10)</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.7 ± 9.5 (57-88)</td>
<td>71.8 ± 8.2 (58-83)</td>
<td>.6</td>
</tr>
<tr>
<td>Peripupillary atrophy</td>
<td>1.9 ± 0.8 (0-3)</td>
<td>1.8 ± 0.8 (1-3)</td>
<td>.6</td>
</tr>
<tr>
<td>Trabecular meshwork pigmentation</td>
<td>2.1 ± 0.6 (1-3)</td>
<td>1.4 ± 0.5 (1-2)</td>
<td>.02</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>22.9 ± 1.4 (20.9-26.7)</td>
<td>22.4 ± 0.7 (21.3-23.9)</td>
<td>.3</td>
</tr>
<tr>
<td>Depth of anterior chamber, mm</td>
<td>2.4 ± 0.5 (1.5-3.2)</td>
<td>2.1 ± 0.4 (1.5-2.9)</td>
<td>.1</td>
</tr>
<tr>
<td>Lens thickness, mm</td>
<td>5.0 ± 0.2 (4.6-5.4)</td>
<td>5.0 ± 0.4 (4.4-5.5)</td>
<td>.8</td>
</tr>
<tr>
<td>Lens thickness-axial length ratio</td>
<td>22.1 ± 1.7 (17.2-24.4)</td>
<td>22.4 ± 2.0 (19.2-25.5)</td>
<td>.6</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD (range) unless otherwise indicated. PEX indicates pseudoexfoliation.
†Nonparametric Mann-Whitney \(U\) test and \(t\) test.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Transmission electron microscopic findings of a normal anterior lens capsule (A), of an anterior lens capsule with a precapsular layer (PCL) and adhering melanin granules (B), and an anterior lens capsule with typical pseudoexfoliation fibrils within the PCL and melanin granules on the capsular surface (C) (C indicates lens capsule; bar=2 µm). Inset in (B) shows microfibrils (arrows) within the PCL (bar=0.1 µm).
posterior synechiae may include an increased and asymmetric trabecular meshwork pigmentation and peripupillary atrophy of the iris pigment epithelium. Since elderly patients with early or manifest PEX syndrome often have a coexisting cataract, and since PEX syndrome is associated with a higher incidence of complications in extracapsular cataract surgery, this masked variant of PEX syndrome should always be considered preoperatively to prepare for intraoperative complications. Intraoperatively, posterior synechiolysis and mechanical pupillary dilatation may be necessary and particular attention should be paid to the consequence of subtle or pronounced phacodonesis caused by PEX zonulopathy.

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REFERENCES


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From his own experience, Jonnesco commends highly this operation first performed by Kronlein. Axenfeld also had good results in 3 cases. Panus prefers it to Lagrange’s method, but the latter method is favored by Dransart.