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Cataract Surgery in Eyes with Pseudoexfoliation (PEX) Syndrome

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Abstract

Pseudoexfoliation (PEX) syndrome is a common age-related systemic disorder characterized by a huge production and deposition of fibrillogranular amyloid-like extracellular material within many ocular tissues. Pseudoexfoliation is a risk factor for glaucoma and also correlated to an increased incidence of cataract formation. Cataract surgery in eyes with pseudoexfoliation is connected with many complications and presents challenges that require careful preoperative planning and intraoperative care to ensure safe surgery and successful postoperative outcome. Zonular weakness and poor pupillary dilation are two major risk factors for surgical complications and poor visual acuity after surgery. With proper preparation and use of specialized adjunctive devices, phacoemulsification (PHACO) is the preferred procedure of cataract extraction in this group of patients. Postoperatively pseudoexfoliation patients require frequent and detailed follow-up to monitor for complications such as intraocular pressure rise, inflammation and intraocular lens dislocation. In conclusion, with appropriate preoperative, intraoperative and postoperative care the risks of complications can be minimized and favourable outcomes can be achieved in cataract surgery in eyes with pseudoexfoliation syndrome.

Keywords: Pseudoexfoliation syndrome; Cataract surgery; Phacoemulsification

Introduction

Pseudoexfoliation (PEX) syndrome is an age-related systemic disease with primarily ocular manifestations characterized by deposition of whitish-gray pseudoexfoliation fibrillogranular amyloid like material on the anterior lens capsule, zonules, ciliary body, pupillary margin of the iris, corneal endothelium, anterior vitreous and trabecular meshwork [1,2]. The most important and easily recognizable diagnostic sign of pseudoexfoliation is whitish-grey flaky material on the pupillary border of the iris or on the anterior surface of the lens. The lens frequently demonstrates a "three-ring sign" on the anterior lens capsule which consists of a relatively homogenous central zone and a granular cloudy peripheral zone with a clear zone in between. Whilst the characteristic signs of manifest pseudoexfoliation have often been described the early stages of exfoliation have not been well defined. Pigment loss from the iris sphincter region and its deposition on anterior chamber structures support the diagnosis. Detection of these signs requires a careful clinical examination using dilated slit-lamp biomicroscopy and additionally undilated gonioscopy but frequently undiagnosed pseudoexfoliation can lead to unexpected problems in management and during surgery. The awareness of the significance of pseudoexfoliation has increased considerably in the latest decade. Pseudoexfoliation is a risk factor not only for open-angle glaucoma, but also for angle-closure glaucoma, lens subluxation, blood-aqueous barrier impairment serious intraoperative and postoperative complication and has been correlated with an increased incidence of cataract formation. Exfoliation of fibrillogranular amyloid-like material has been found in many organs such as skin, heart, lungs, liver, kidney, gall bladder, blood vessels, extraocular muscle, connective tissue in the orbit, optic nerves and meninges suggesting that the pseudoexfoliation syndrome is not only an ocular disease but also a general disorder that involves the abnormal production of extracellular matrix material [3,4]. Recent investigations have shown the positive link between pseudoexfoliation and transient ischemic attacks, stroke, heart disease and aneurysms of the abdominal aorta [4,5]. Although the exact etiology of this condition as well as the exact structure of the material is still unknown it is presumed that the production of pseudoexfoliation material is associated with abnormal metabolism of glycosaminoglycans and thus abnormalities of the basement membrane in the epithelial cells. Pseudoexfoliation syndrome occurs in all areas of the world with varying frequency. There is a high prevalence of pseudoexfoliation syndrome in Scandinavian countries, Arabic populations and in Oman [6,7] whilst it is relatively rare among African Americans, Eskimos and Canadian Arctic populations. Pseudoexfoliation syndrome is more common in females than in males [8] and its prevalence increases steadily with age and is rarely seen before the age of 50. Jonasson et al. reported a 10% annual increase for both open-angle glaucoma and pseudoexfoliation in persons of 50 years and over in Iceland 9]. The reported mean age ranges from 69-75 years. Genetic factors influencing pseudoexfoliation has been explored considerably in the latest decade [10]. Recent genetic studies in multiple populations have identified the lysyl oxidase-like 1 (*LOXL1*) gene as a major contributor to the risk of developing pseudoexfoliation syndrome and pseudoexfoliation glaucoma. *LOXL1* belongs to the lysyl oxidase family of extracellular enzymes that have multiple functions including the synthesis and maintenance of elastic fibres. However, the exact relationship between *LOXL1* polymorphisms and the development of pseudoexfoliation has not been completely elucidated and thus the value of genetic testing for this disorder for the time being has not been validated [11]. In addition to heritable a number of nongenetic factors such as ultraviolet light, autoimmunity, slow virus infection, and trauma are supposed to have an implication in the development of pseudoexfoliation. It is possible that a combination of genetic and nongenetic factors may be involved

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in etiopathogenesis of pseudoexfoliation and thus it may be considered as a multifactorial disorder [12].

Implications for Cataract Surgery

Many resent studies have shown that patients with pseudoexfoliation syndrome have higher rates of complications during and after cataract surgery compared to patients without this disorder [13,14]. As a systemic disorder of the extracellular matrix pseudoexfoliation syndrome involves all structures of the anterior segment of the eye causing many clinical and surgical complications (Table 1). Local production and deposition of pseudoexfoliation fibers may lead to characteristic changes of the corneal endothelium [15], trabecular meshwork [16], iris [17], lens [1], ciliary body [18], zonules [19] and structures of blood-aqueous barrier [17,20]. These alternations of tissues of the anterior eye segment make cataract surgery potentially challenging and thus surgeons must be aware of numerous intraoperative and postoperative problems in managing the patient with pseudoexfoliation syndrome. Two pathological manifestations of pseudoexfoliation, zonular weakness and poor pupillary dilation have been identified as the most significant risk factors for surgical complications. Zonular weakness can be attributed to the deposition of pseudoexfoliation material on the zonular fibers and ciliary processes resulting in a proteolytic disintegration of the zonules that can lead to spontaneous devastation. Thus, a significant zonular instability can cause phacodonesis [21], spontaneous subluxation of the lens [22] and angle-closure glaucoma due to pupillary and ciliary block 23]. The incidence of phacodonesis and/or subluxation of the lens in eyes with pseudoexfoliation syndrome have been reported to be between 8.4% and 10.6% [13,21]. Furthermore, pupils of patients with pseudoexfoliation show a reduced response to mydriatic agents due to infiltration of the iris stroma with excessive exfoliation of the extracellular matrix causing mechanical obstruction during mydriasis and adhesion of the exfoliation material to the iris pigment epithelium and anterior lens capsule causing mechanical restriction of pupillary movements. The small pupillary diameter and zonular fragility are presumed to be the most important risk factors for capsular rupture and vitreous loss during cataract surgery [24-26]. According to some authors zonular instability is more essential than poor pupil dilation [24,27]. Zonular instability increases the risk of lens subluxation, zonular dialysis or vitreous loss up to ten times [28]. Vitreous loss in patients with pseudoexfoliation has been reported to be five times more common than in patients without this disorder (9.0% vs.1.8%) [29] which is related to an increased incidence of zonular dialyses, lens subluxation and capsular rupture. Despite the involvement of the lens capsule in pseudoexfoliation some authors found no significant differences in the mean capsular thickness between the eyes with pseudoexfoliation and normal eyes. Although the posterior capsule is of normal thickness, capsular rupture is more common in the eyes with pseudoexfoliation with an occurrence of up to 27% as compared to 2% in the control eyes [1]. Küchle found an intraoperative complication rate of 13.4% in the eyes with an anterior chamber depth less than 2.5 mm and 2.8% in eyes with an anterior chamber depth of 2.5 mm or more [13]. This finding suggests that preoperative reduced anterior chamber depth indicates zonular instability and should therefore alert the surgeon to the possibility of intraocular complications related to zonular dialysis. Pseudoexfoliation syndrome influences the development of synechiae between the iris pigment epithelium and the anterior lens capsule due to blood-aqueous barrier breakdown. Posterior synechiae extend postoperatively between the iris and intraocular lens (IOL). Posterior synechialysis or lysis of more peripheral iridocapsular adhesions and pupillary enlargement are often necessary [30]. Due to chronic sphincter fibrosis it is advisable not to overexert the pupil because it will often remain dilated, predisposing it to pupillary capture [31].

Postoperative decentrations of IOLs were reported to be significantly higher in eyes with pseudoexfoliation due to zonular rupture or capsular bag decentration. Lens decentration is even more common when the lens is entirely in the capsular bag primarily due to decentration of the entire bag [32]. Posterior chamber lenses may be implanted in the ciliary sulcus despite the presence of a small capsular break or area of zonular dehiscence providing that enough support still exists for the implant [33]. Postoperatively, patients with pseudoexfoliation are at a greater risk of developing an immediate elevation of intraocular pressure (IOP) and thus all viscoelastic should be removed from the eye at the time of surgery. Patients with extensive visual field loss or severe glaucomatous optic atrophy should have tonometry performed 4-6 hours after surgery and an acute rise in IOP should also be promptly treated [34]. In glaucomatous patients combined cataract and glaucoma surgery decreases the incidence of an acute postoperative rise in IOP and may improve long-term control of IOP [33,35]. Posterior capsular opacification is increased in pseudoexfoliation eyes most probably due to an aggravated blood-aqueous barrier breakdown [36]. Both the increased rate of vitreous loss during surgery and the frequent need of Nd:YAG capsulotomy for posterior capsular opacification enhance the risk of retinal detachment

Tissue involvement	Clinical signs	Clinical complications	Surgical complications
Cornea	- atypical cornea guttata	- endothelial decompensation - endothelial proliferation	- endothelial decompensation
Trabecular meshwork	- pigment deposition - marked asymmetry of IOP - marked IOP rise after pupillary dilation	- intraocular hypertension - open-angle glaucoma	- postoperative IOP rise
Iris	- peripupillary atrophy and iris sphincter region transillumination - melanin dispersion associated with pupillary dilation - poor mydriasis, asymmetric pupil sizes	- melanin dispersion - poor mydriasis - iris rigidity - blood-aqueous barrier impairment - pseudouveitis - anterior chamber hypoxia - posterior synechiae	- miosis/poor surgical access - intra- and postoperative hyphema - postoperative inflammation - prolonged blood-aqueous barrier breakdown - posterior synechiae and pupillary block
Lens, ciliary body, and zonules	- diffuse precapsular layer - phacodonesis - PEX deposits on zonules	- cataract - phacodonesis - lens subluxation - angle-closure glaucoma due to pupillary and ciliary block	- zonular rupture/dialysis - vitreous loss - posterior capsule rupture - decentration of the lens implant - anterior capsule fibrosis - secondary cataract

Table 1: Clinical signs and complications of pseudoexfoliation (PEX) syndrome.

in these eyes. Thus, the pseudoexfoliation syndrome may also be considered as a risk factor for the development of retinal detachment.

Pseudoexfoliation Syndrome and Phacoemulsification

Improved by both technology and new surgical procedures, phacoemulsification (PHACO) of the nucleus has become increasingly important in extracapsular cataract surgery. PHACO within the capsular bag has confirmed to be a valuable surgical technique yielding predominantly good results. PHACO in the presence of pseudoexfoliation presents a particular challenge for cataract surgeons. The frequency of intraoperative and postoperative complications such as zonular dialysis, capsular rupture, vitreous loss and IOL decentration may be reduced with careful attention and precise surgical technique [36]. Many studies showed a lower complication rate during PHACO than extracapsular extraction in eyes with pseudoexfoliation [13,27,35,37], but still with a greater complication rate than in eyes without this disorder [1]. Potential preoperative and intraoperative measures to avoid or minimize complications of cataract extraction in pseudoexfoliation eyes require an increased awareness of potential intraoperative problem that this disorder may induce. Excepting eyes with very hard nuclei, PHACO is the preferred surgical technique but its use should be directed by the experience of the surgeon. Before surgery it is important to determine the presence of zonular instability with careful examination to assess the subtle lens subluxation, zonular dialysis, iridophacodonesis or shallow anterior chamber [13,25].

Small pupils make cataract surgery particularly demanding. Considering that the stretching of the small pupil could lead to micro ruptures, increased postoperative inflammation and sometimes even sphincter damage that can cause permanently dilatated pupils after surgery avoiding this procedure is advisable. Since, PHACO can be performed in the central space, the stretching of the pupil may therefore be unnecessary in most cases. However, with pupil diameter less than 4 or 4.5 mm additional dilatation is required. Pupil dilation could be improved by preoperative usage of NSAIDs (nonsteroidal anti-inflammatory drugs) eye drops. Pupils may be further enlarged by using highly cohesive viscoelastic (viscomydriasis) whilst taking care of avoiding over-inflation of the anterior chamber. If present, posterior synechiae should be released with capsulorhexix forceps before further maneuvers. For stretching of small pupils we usually use iris hooks and do not stretch the pupil larger than 5 mm square since overstretching could produce an irregular atonic pupil postoperatively. If zonular weakness is significant the use of iris hooks can additionally support the anterior capsulotomy. A more sophisticated pupil expanding device that exerts less iris trauma is the Malyugin ring which adequately dilates the pupil and simultaneously prevents iris sphincter damage. It is easy to insert and remove, sufficiently expands the pupil, protects the iris sphincter during surgery and allows the pupil to return to its normal shape, size and function after the operation [26,38].

As previously emphasized the complications during PHACO surgery are mostly related to zonular weakness and therefore require particular attention. Depending on zonular weakness or dialysis a capsular tension ring (CTR) could be inserted prior to PHACO or after nucleus PHACO and prior to cortical irrigation-aspiration. In difficult cases Cionni modified-CTR (mCTR) or capsular tension segments (CTS) could be inserted either alone or in combination. When the degree of zonular weakness is mild, a CTR may be enough to support intraopeative manoeuvres and to stabilize an IOL in the capsular bag. If obvious phacodonesis is present it is advisable to insert a CTR early after completing the capsulorhexis to stabilize the capsular bag for PHACO and cortical removal. For more advanced zonular instability the mCTR or CTS both of which can be sutured to the sclera for improved fixation should be considered. Unlike the CTR the CTS does not require a dialing technique during insertion and therefore creates less stress on the zonules. With respect to all these facts the entire surgical procedures should be conducted with precise care [26,37,39].

During the operation it is also important to avoid overinflating the anterior chamber with saline solution or viscoelastics. Putting a blunt instrument on the lens and gently rocking it to and fro may be useful to test for any weakness of the zonules. Likewise, excessive lens movement during capsulorhexis should alert the surgeon to this complication. To perforate the anterior capsule at the beginning of the capsulorhexis a sharp instrument should be used since zonular weakness results in less anterior capsular tension and reduced resistance which makes the initial puncture more difficult. If necessary counterpressure could be additionally exerted using a needle or chopper. Capsulorhexis size is important and should be performed within the limits of the outer pseudoexfoliation ring. Too small a diameter will add further stress to loose zonules during the operation whereas too large a diameter may engage the zonular attachments. Due to the tendency for anterior capsular phimosis and further zonular stress a large capsulorrhexis should be performed with recommendation of at least 5.5 mm in diameter.

Hydrodissection/hydrodelineation should be performed very carefully with minimal stress on the zonule. However, the degree of dissection must be balanced since too aggressive an injection of fluid can lead to further loosening. During hydrodissection it is essential that the anterior chamber not be overfilled as this would cause excessive zonular stress. To avoid this situation gentle burping of the incision during hydrodissection can allow release of fluid and keep the anterior chamber at normal pressure.

With regards to the PHACO technique, it is recommended that each surgeon applies his technique of preference. For denser nucleus horizontal chop is our preferred technique whilst for softer nucleus we utilise anterior phaco technique. To avoid zonular stress we adjust machine settings in the medium range (vacuum 250-300 mm mercury, aspiration flow rate 20-30 cc/min, US power 50-60% continuous). Cortex removal is a critical step and should therefore be done with tangential stripping rather than centripetal movements aiming to avoid promoting pressure to zonules and posterior capsule. In cases with inserted CTR, cortical remnants could be entrapped which presents an additional obstacle for cortical removal.

The selection of IOL form is also important in eyes with pseudoexfoliation syndrome. Heparin surface modified posterior chamber IOLs were found to be associated with fewer postoperative fibrinoid reactions, less frequent pigment and cellular deposits on the lenses and lower incidence of the posterior synechiae formation than other forms of IOLs [30]. Furthermore, flexible silicone IOLs should not to be used to prevent capsular contraction syndrome and valuating of intraocular lens optic [1]. Although unfolding one-piece acrylic PCIOL is considered by some surgeons as the best choice for minimal capsular and zonular stress, we more often insert a three-piece acrylic PCIOL (with PMMA haptics) as an equally safe procedure. Additionally the springy nature of the PMMA haptics can provide tension to help support smaller areas of zonular dehiscence without insertion of additional CTR. In the case of severe zonular instability and dialysis or loss of vitreous the alternative option is scleral or iris-fixated IOL. An angle-supported anterior chamber IOL should be

avoided particularly in the cases of eyes with glaucoma or corneal endothelial cell abnormalities.

After surgery, the pseudoexfoliation patients should undergo thorough and frequent examinations for early detection of an increase of IOP, inflammation and IOL dislocation. Administering acetylzolamide immediately after surgery and using topical glaucoma mediators in the postoperative period can effectively control the rise of IOP. In addition, topical use of steroids and NSAIDs is important to control inflammation which tends to be higher in these patients [25,39].

It should be kept in mind that the pseudoexfoliative process will continue even after the surgery thus the patient should be monitored for possible development of glaucoma, capsular phimosis syndrome or decentration of IOL. There is also a possible risk of future IOL-CTR capsule complex dislocation which may require surgical intervention.

Conclusion

Pseudoexfoliation syndrome presents challenges that need careful preoperative planning and intraoperative care to ensure safe surgery and a successful postoperative outcome. With appropriate preparation and use of specialized adjunctive devices, phacoemulsification is the preferred method of cataract extraction in eyes with pseudoexfoliation syndrome. In addition, proper follow-up of patients after surgery is needed to evaluate endothelial cell function, intraocular pressure rise, inflammation and intraocular lens dislocation. Conclusively, the risks associated with cataract surgery in the pseudoexfoliation eyes can be minimized with appropriate preoperative, intraoperative and postoperative care.

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