Pseudoexfoliation syndrome and glaucoma a dangerous duo

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Disclosure

- Principal investigator for FDA iVue OCT trial
- Principal investigator Topcon FDA trials
  - FDA Topcon NDB Maestro and OCT 2000
  - FDA Topcon OD and Retina study
  - FDA NDB II study
  - FDA Maestro AP II study
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- Consultant for Optovue and Topcon
- Speakers bureau Sanofi- Genzyme and Allergan

Outline

- Background and diagnosis
- Exfoliation syndrome and exfoliation glaucoma
- Pathogenesis
- Other ocular changes
- Systemic disease
- Treatment options
- Cases

Terminology

- "true" exfoliation of lens- exfoliation syndrome
  - Common in glass blowers- no protection against infrared radiation
  - Not commonly associated with glaucoma
  - Also seen in cases of inflammation, trauma and older age group
  - Capsular delamination of lens

Terminology cont…2

- "pseudo-exfoliation" syndrome
- The exfoliation syndrome
- Historically it was considered to be deposits of unknown material on lens and anterior segment.
- Subsequently it was identified to be in part at least from the lens
- The exfoliation syndrome (XFS) or pseudo-exfoliation syndrome mean the same

Characters

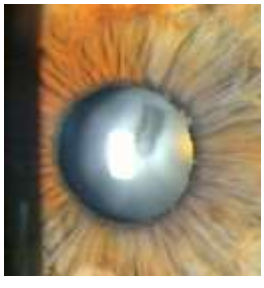
- Deposit of distinctive fibrillar material
- Precise origin unknown (partly lens and iris)
- Hitologically found on lens epithelium and capsule, pupillary margin, ciliary epithelium, iris pigment epithelium, iris stroma, iris blood vessels and subconjunctival tissue

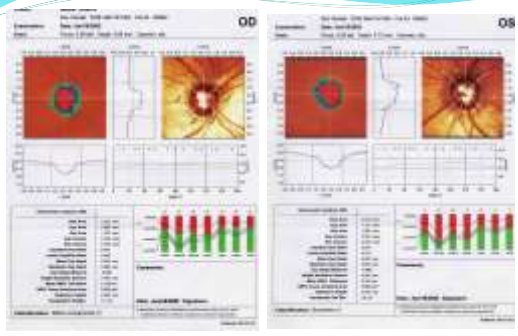
- Best seen post dilation
- Zones of deposit are separated by intermediate clear area
- Material visible on iris at pupillary edge

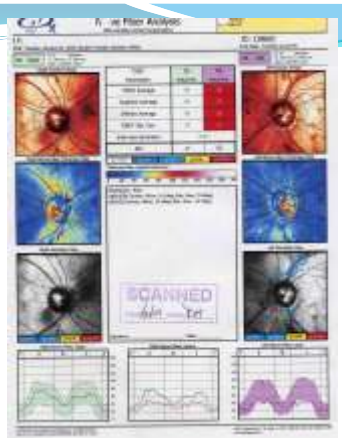
Case 1 -

- 67 year-old woman from Finland
- "White flakes on lens noted in 2000
- IOP elevated OS > OD (24 vs. 19)
- Systemic Hx: HTN, hypercholesterolemia, CAD

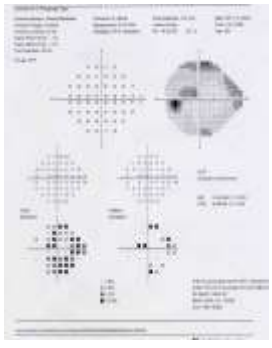
Courtesy Dr. Richard Madonna SUNY

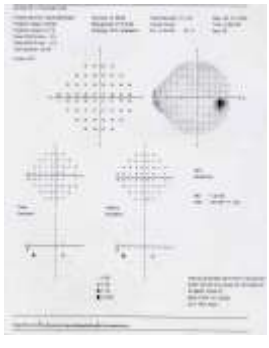




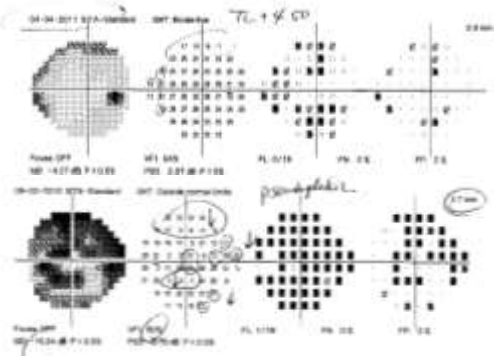


2004





About 7 years later



Epidemiology –exfoliation syndrome

- Not just in Scandinavia, Greece, and Italy – common world wide
- Exfoliation syndrome (XFS) is a significant risk factor for exfoliation glaucoma (XFG)
- About 30% of XFS develop XFG in lifetime

Prevalence and Incidence

- Prevelence: The number of instances of a given disease or other condition in a given population at a designated time.
- Incidence: The number of instances of illness commencing, or persons falling ill, during a given period in a specified population.
  - Very difficult to ascertain.
    - Example Early glaucoma needs to be followed for a long period of time.

Prevalence of exfoliation syndrome

Australia (Aborigines)	> 60 yrs	16.3%	Taylor et al 1977
Australia (Blue mountain)	> 48 yrs	2.3%	Mitchell et al 1999
Iceland (Reykjavik)	> 49 yrs	10.3%	Jonasson et al 2003
Middle Sweden	65-74 yrs	18.0 %	Ekstrom 1987
Middle Finland	> 64 yrs	21.0 %	Krause et al 1988
Saudi Arabia	> 39 yrs	9.3%	Summanen et al 1988
South Africa	> 39 yrs	6.0-7.7%	Rotchford et al 2003
South India	> 39 yrs	6.0 %	Krishnadas et al 2003

Prevalence of exfoliation glaucoma

Location	Age	Prevalence of XFG in XFS	Reference
Finland	> 70	5%	Hirvela 1994
Australia (Blue Mountain)	> 48	14.2 %	Mitchell et al., 1999
Greece	> 39	4. 5%	Kozobolis et al., 2000
Iceland (Reykjavik)	>49	12 %	Jonasson et al., 2003
South Africa	> 39	2.3 to 2.8%	Rotchford et al., 2003
South India	>39	7.5 %	Krishnadass et al., 2003
Middle Norway	> 64	5.0%	Ringvold et al., 1991

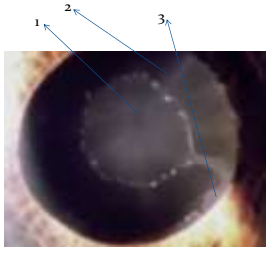
Incidence

- Only one study
- Age and sex adjusted incidence 9.9 per 100,000 per year
- Incidence increases significantly with age
- 0.6 per 100,000 in 40-49 yrs
- 114.3 per 100,000 > 79 yrs
- Incidence greater in females compared to males

- Karger RA et al., J Glaucoma 2003

Features of XFS

- 1 – central disc corresponds to size of pupil, not always seen
- 2- clear zone- removal of material by iris movement
- 3- peripheral granular zone due to undisturbed accumulation



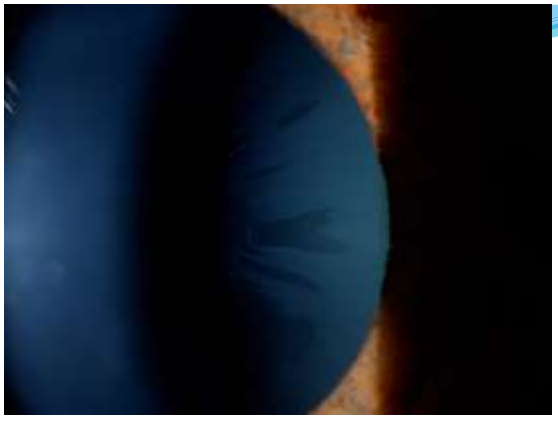


Image courtesy Gabor Hollo

Image courtesy Gabor Hollo

Other lens findings

- Phacodonesis
- subluxation of lens

} Due to degenerative changes in zonular fibers

- Why?
- The XFS material is also found on zonules and it contains proteolytic enzymes

XFS and angle closure

- In prone position anterior lens movement can occur – pupillary block
- thus increased chances of angle closure

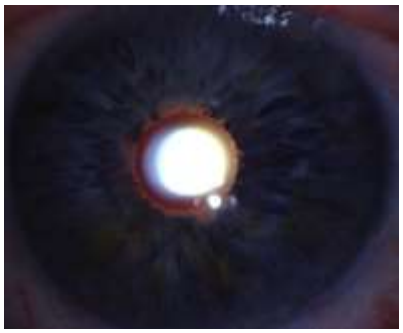
Post-op complications

- Production of XFS material continues after cataract extraction
- May cause late decentration or even subluxation of lens implant

Iris changes

- Don't dilate well- deposits on iris stroma muscle and degeneration of sphincter and dilator
- White flecks in pupillary margin
- Loss of pigment in pupillary margin
- Iris transillumination defects – moth-eaten pattern

Retroillumination in exfoliation syndrome



Loss of pupillary ruff

Iris changes Fluorescein angiography

- Hypoperfusion
- And neovascularization
- Increases with age and duration of disease

- Why?
- Vessels blocked with material- causing hypoxia

Parodi et al. Acta Oph Scan. 78(4); 437-442. 2000

Iris pigment and acute rise in IOP

- Dispersion of melanin post pharmacological dilation
- May result in acute IOP rise

- Check IOP post dilation

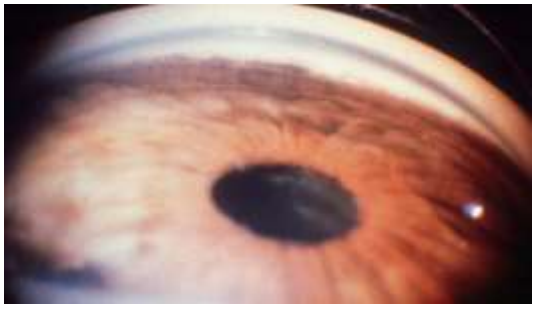
Gonioscopy in exfoliation syndrome

- TM heavily pigments
- Pigment deposition on Schwalbe's line referred as Sampaolesi's line

- Uneven pigmentation

- Chamber narrow presumably due to forward movement of lens–iris diaphragm

Sampaolesi line



Trabecular meshwork

- Chronic pressure elevation due to increased outflow resistance.
- Particularly with deposits juxtacanlicular tissue beneath the inner wall of schlems canal.
- Pigment deposits may also play a role

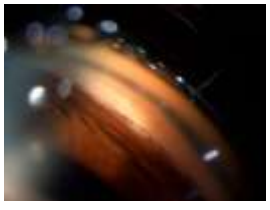
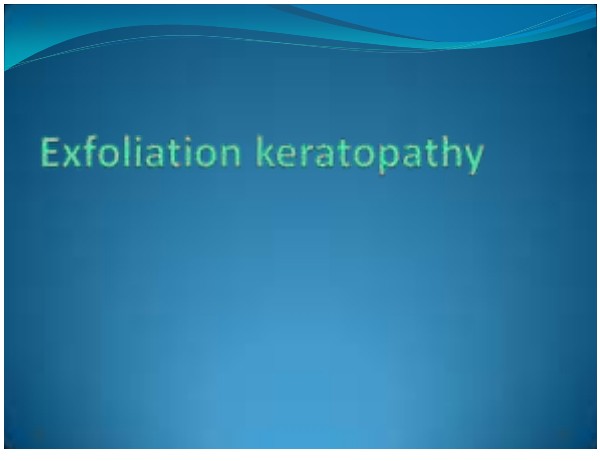


Image courtesy Gabor Hollo

Cornea

- Corneal endothelium may show some adhering XFS material
- Specular microscopy of corneal endothelium- low cell density
- Morphological changes also seen



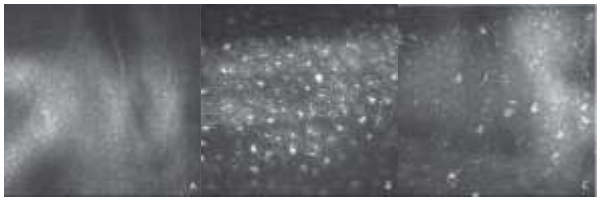
What is Exfoliation keratopathy?

- Active involvement of corneal endothelium
- Clinically
  - Reduced endothelial count (800-1500 cells/mm^2)
  - Changes in cell size and shape
  - Retrocorneal flakes
  - Pronounced melanin deposits on corneal endothelium
  - Irregular thickening of Descemet's membrane
  - No corneal guttata

In Vivo Confocal Microscopic Evidence of Keratopathy in Patients with Pseudoexfoliation Syndrome

Zheng et al IOVS

Normal control | Pseudoexfoliation syndrome | Fellow eye of XFS



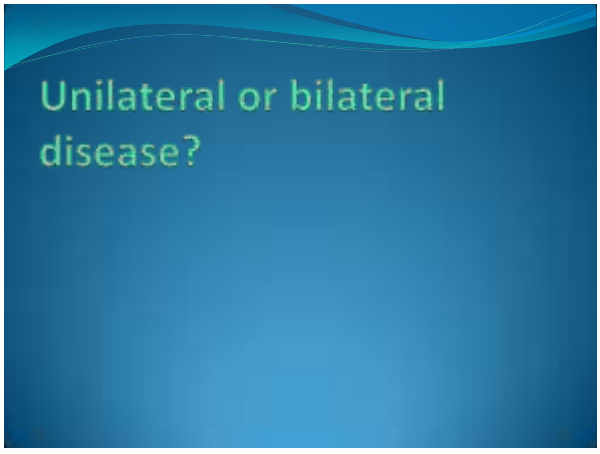
Clinical and histopathological features

	Fuch's dystrophy	Exfoliation keratopathy
Corneal guttata	+++	atypical
Endothelial cell loss	+++	++
Decompensation pattern	Central	diffuse
Melanin dispersion	+	+++
Iris atrophy	absent	+ to +++
Nuclear cataract	++	++
Secondary glaucoma	absent	Absent /+++
Descemet's membrane	Focal guttata	Diffuse thickening
Thickness of Descemet's	14-30 microns	16- 45 microns
Exfoliation material	Absent	Absent to +++
Melanin phagocytosis	+	+++

+ mild; ++ moderate; +++ marked

Clinical significance of exfoliation keratopathy

- Corneal decompensation may develop in both normotensive and hypertensive eyes
- Lowering IOP may reverse decompensation effects in early stages
- Later stages may need penetrating keratoplasty
- Edematous cornea higher risk of infection and ulceration
- Pre-operative counseling



Clinically

- Often appears unilateral
- May remain so for a long periods
- Tarkkanen 48% of Caucasians unilateral
- Shimizu et al 85% of Japanese population unilateral

- Signs may be subtle and even experienced observers miss 15% of cases
- First signs to typical presentation 5-10 years.

Unilateral to bilateral

- 11-14% in 5 years
- 16-32% in 7 years
- 36 -52 in 10 years

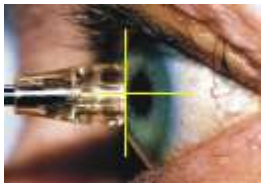
- XFS possibly asymmetric rather than unilateral

Ocular hemodynamics in exfoliation syndrome and glaucoma

Impaired blood flow

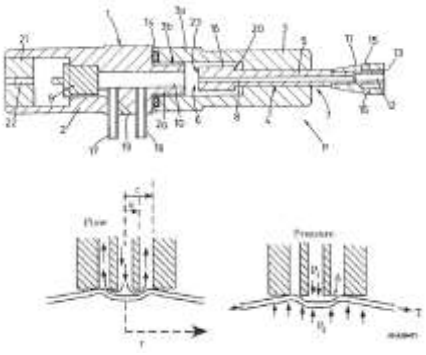
- XFG > XFS
- Blood flow could be low because of elevated IOP
- Sibour et al., POBF decreased
  - Affected eyes when compared to fellow eyes
- Mistlberger et al., POBF same in eyes with and without XFS
  - But XFG low POBF

Pneumotonometer



- IOP: 200 /sec
- Up to 20 seconds
- Measures 7 pulses and selects 5 best to calculate IOP and POBF
- Also gives pulse amplitude and calculates pulse volume

Pulsatile ocular blood flow



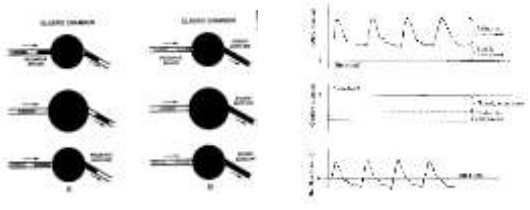


Table 3 Comparison of the mean pulsatile ocular blood flow reported in different studies

Study	Total subjects	POBF (ul/min)	Instrument	Male/female
Massey et al[27]	668	668 (Mean POBF)	OBF system (Software version unknown)	Not known
Yang et al[28]	167	776 (Mean POBF)	OBF system (Software version unknown)	73/94
Pemarta et al[31]	777 (1554 eyes)	624 (Median POBF)	OBF system (Software version 3.01)	347/430
Goldstein et al[11]	135	645 (Mean POBF)	Langham Blood Flow system	86/49
Mori et al[29]	80	395.3 (Median POBF)	Langham Blood Flow system	27/53
Lam et al[8]	76	661.2 (Mean POBF)	OBF system (Software version unknown)	35/41
Morgan et al[9]	36	1190 (Mean POBF)	OBF system (Software version unknown)	Not known
Indians	250	1076.3 (Mean POBF)	OBF system (Software version 16.2)	122/130
(Present study in India)				

P Gunvant, M Baskaran, L Vijaya, BC Hansen, IS Joseph, RJ Watkins, DC Broadway, DJ O'Leary: Comparison of pulsatile ocular blood flow in Indians and Europeans ***Eye***, 2005, 19, 1163-1168.

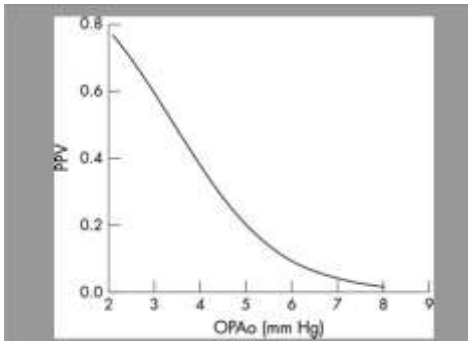
Pascal -Dynamic Contour Tonometer

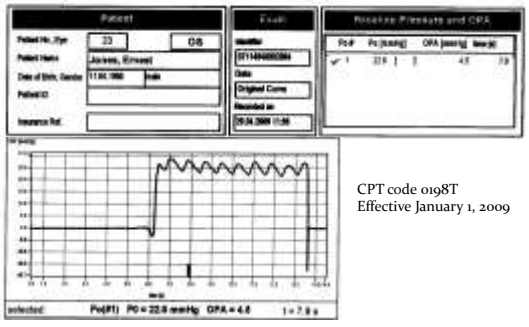
Ocular Pulse Amplitude in Normal Tension and Primary Open Angle Glaucoma

Ingeborg Stalmans, MD, PhD, Alon Harris, PhD,† Veerle Vanbellinghen, BSc,* Thierry Zeyen, MD, PhD,* and Brent Siesky, PhD†*

Conclusions: OPA is reduced in normal tension and POAG patients compared with healthy controls. OPA is influenced by IOP, but not by corneal thickness.

OPA and NTG



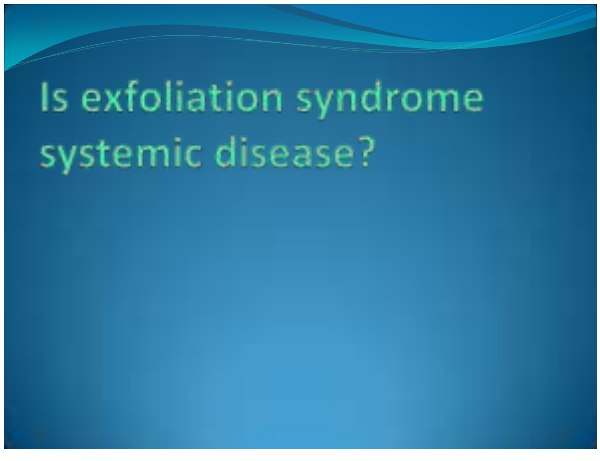


CPT code 0198T
Effective January 1, 2009

- Vesti et al., macular capillary blood flow decreased
  - XFG compared to controls
- Ocakoglu et al., scanning laser doppler flowmetry decreased blood flow in optic nerve heard and peripapillary retina (XFS compared to controls)
- Variability seen with POBF are also seen with measurement of capillary blood flow using both entoptic phenomenon and doppler flowmetry

Summary ocular hemodynamics – XFS and XFG

- Blood flow may be decreased in these conditions
- Measurement variability of blood flow makes it not ideal for use clinically.



Exfoliation material

- Presence of exfoliation material is not restricted to intraocular tissues
- Conjunctiva, orbital tissue, extraocular muscles, optic nerve, ciliary arteries
- Systemically- skin, lungs, heart muscle, vessel walls, liver, kidney, gall bladder and cerebral meningies

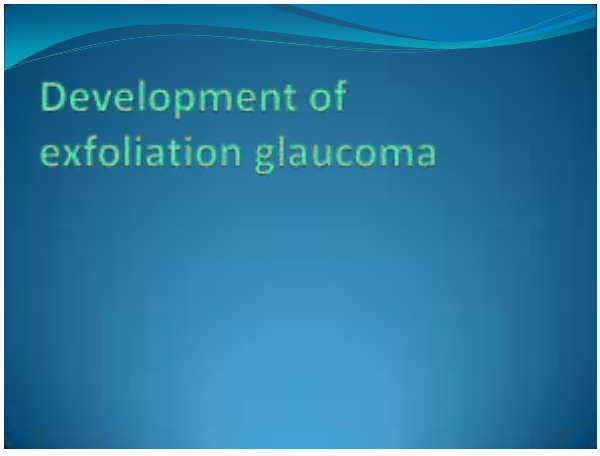
XFS and XFG- systemic diseases

- Not clearly understood
- Increased rate of morbidity of cardiovascular, cerebrovascular disease and alzheimers disease and XFS
- But not increase in mortality

- Elevated plasma homocystein levels- related to increased risk of venous occlusion
- Mild sensory hearing loss is also reported

Summary

- XFS is a systemic disease
- But the role of exfoliation material in causing or exaggerating the systemic diseases remains to be clarified.



Risk of glaucoma in XFS

- Exfoliation increases the relative risk of glaucoma
  - Ekstorm et al., - 9.8 fold
  - Mitchell et al., - 5 fold
  - Even after adjusting for IOP the relationship between XFS and glaucoma was unchanged
  - XFS without high IOP is an independent risk factor in glaucoma development

So if IOP is not "the" mechanism on normotensive XFG what is?

- Exfoliation material found in posterior ciliary artery and vortex veins
  - Disturbance in perfusion in posterior ocular tissues

Ocular hypertension with and without XFS

- Risk of glaucoma due to ocular hypertension was 3.7 times
- XFS and ocular hypertension increases the risk much higher up to 67 fold

Role of pigment dispersion

- XFG has greater pigment accumulation in angle compared to XFS
- **Degree of pigmentation and exfoliation material in angle correlates positively with IOP**

Development of glaucoma in normotensive and hypertensive eyes

- Normotensive eyes with XFS show elevation of IOP over time
- Likelyhood of development of ocular hypertension
  - 5.3% over 5 years
  - 15.4% over 10 years
- Glaucoma twice as common in XFS with ocular hypertension when compared to only ocular hypertension
  - 35% vs 18% in 9 years (Puska et al., 1995)

Conversion rate XFS to XFG

- 32% 10 years (Puska et al., 1995)
- Conversion was rapid- 2/3rd in 3 years
- 94% in 5 years
- Most eyes high pressure glaucoma
- All patients except one with high pressure developed glaucoma
- Baseline parameters- rim area is lesser in converters when compared to non-converters
- XFS shows greater diurnal variations

Fellow eye of unilateral XFG

- 21-26% risk of developing glaucoma in 5 years (Puska et al., 1995)
- Almost all became bilateral over time

Onset of glaucoma related to exfoliation material

- No set pattern
  - Simultaneous
  - After
  - Long after
  - May precede

Intraocular pressure and XFG

- Higher mean IOP compared to POAG
  - Often exceed 35 mmHg
- Greater 24 hour IOP fluctuations both in in XFS and XFG
  - Normals <5 mmHg vs normotensive XFS 50% 5 mmHg
  - 10% normotensive XFS showed 10 mmHg fluctuations

Intraocular pressure and XFG-2

- Significant diurnal IOP fluctuations may differentiate XFG from POAG
- 50% of XFG show peak IOP outside office hours
- Greater IOP fluctuations may account for faster progression in XFG

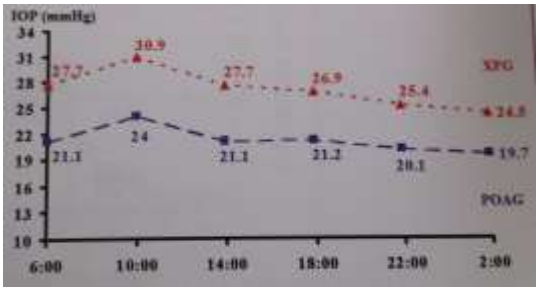
Summary

- Presence of XFS represents risk of development of XFG
- In eyes with XFS but normal IOP risk of conversion to XFG is 30% in 10 years
- Most convert in 5 years
- XFS and ocular hypertension combined has twice the chances of developing glaucoma when compared to only ocular hypertension
- 24-hour diurnal variations may be greater in XFS and XFG patients compared to controls.

Clinical features of XFG

- High IOP, open angle
- Exfoliative trabeculopathy
- Iridopathy, phacopathy, zonulopathy
- Significant diurnal fluctuations
- IOP spikes
- Pigment dispersion
- Acute IOP rise after pupillary dilation
- Aggressive course, rapid progression
- Poor response to medications
- Need for surgery common

Diurnal variation of IOP



Konstas et al., 1997 ArchOphthalmol

Temporary devices contact lenses

Leonardi M, Leuenberger P, Bertrand D, et al. First steps toward noninvasive intraocular pressure monitoring with a sensing contact lens. *Invest Ophthalmol Vis Sci*. 2004;45: 3113-3117.

Wireless contact lens sensor for intraocular pressure monitoring: assessment on enucleated pig eyes

Matteo Leonardi,[1] Elie M. Pitchon,[1,2] Arnaud Bertsch,[1] Philippe Renaud[1] and André Mermoud[2]

Temporary devices

Advantages

- Non invasive
- not permanent
- can be used on ad-hoc basis

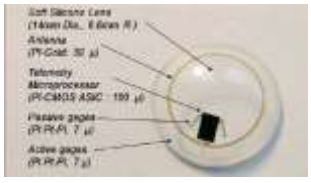
Disadvantages

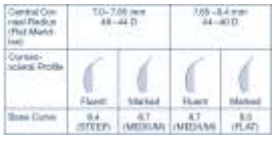
- Eye movement may have greater effect when compared to permanent devices
- Surface tension, light exposure, temperature
- Reproducibility

SENSIMED

innovation in medical micro-technology

Triggerfish





Cost 500 Euro. Not available for sale in USA

Cataract surgery and XFS

- Careful pre-operative evaluation to identify XFS and weak zonules
- Max pupil dilation should be noted as pupils tend to not dilate well
- Risk of surgical complications should be discussed
  - Capsular tear, vitreous loss
  - Dislocation of IOL

Medical therapy in XFS and XFG

- Generally medical therapy is not very effective
- May be due to worst IOP characteristics rather than lack of response to medications
  - High mean IOP
  - IOP fluctuations greater
  - High IOP spikes

Target IOP in XFG

- Like in all glaucoma IOP lowering decreases the chances of progression but does not guarantee it
- XFG patients with mean IOP less than 17 mmHg only 28% progressed compared to 70 %mean IOP ≥20mmHg

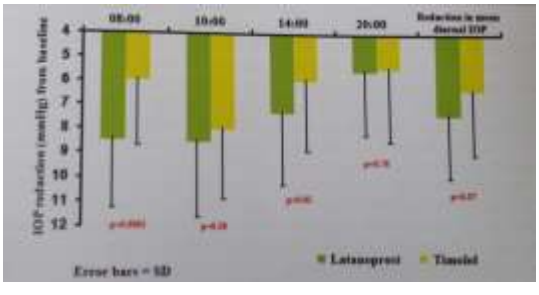
Protocols of treatment

- Similar to POAG
- But monotherapy not always successful
- Maximal therapy required
- Miotics may have a role to play-
  - pupil is fixed so less pigment dispersion
  - May help outflow and removal of materials
- Systemic aqueous suppressants not suitable- decreases trabecular function over time
- Often early surgery

Medical therapy- timolol

Konstas et al., 1997 ArchOphthalmol

Medical therapy- timolol versus latanoprost

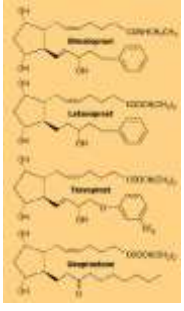


Konstas et al., 2004 Eye

Which prostaglandin?

- Structurally all prostaglandins are similar
- One study shows that Travoprost works better than latanoprost
- Another studyshowed 3 months IOP control better with Bimatoprost versus latanoprost

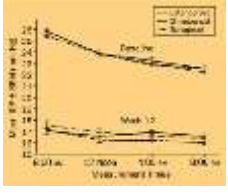
- Latanoprost, travoprost and unoprostone are ester prodrugs
- Bimatoprost described as prostamide (nitrogen attached to carbonyl group)



A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study

RICHARD K. PARRISH, MD, PAUL PALMBERG, MD, PhD, AND WANG-PUI SHELL, MA, FOR THE XLT STUDY GROUP

• CONCLUSIONS: Latanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in OAG and OHT patients. Latanoprost exhibited greater ocular tolerability. (Am J Ophthalmol 2003;135: 688–703. © 2003 by Elsevier Inc. All rights reserved.)



Laser therapy in exfoliative glaucoma

Argon laser trabeculoplasty

- Well tolerated and well established procedure
- Considerable pressure lowering effect
- ALT better response in exfoliation glaucoma (XFG) compared to POAG
  - Why?
- Later failures are common in XFG

Argon laser trabeculoplasty cont…2

- ALT a choice after medical therapy failure
- ALT may be first choice in older or non-compliant individuals
- A degree of pigmentation is must for procedure to be effective
  - Not a problem in XFG as pigment is released from iris

Pre -operative care

- Pre-op apraclonidine or brimonidine is used
- Systemic acetazolamide is also recommended
  - These prevent laser induced early IOP spikes
- Untreated eyes timolol may also help in lowering IOP
- Topical anesthesia is sufficient for ALT

Post-operative care

- Ideally IOP check 6 hours after procedure
- Topical steroids or non-steroidal anti-inflammatory q.i.d. 4-7 days
- Re-evaluate 4-6 weeks to assess the success

Complications

- Transient blur –gonioscopic fluid
- Early and transient IOP spike
- Anterior uveitis (more common in XFG than POAG)
- Formation of peripheral synechiae
- Late loss of effect.

Selective laser trabeculoplasty

- Similar principle to ALT but selectively targets intracellular melanin in trabecular meshwork
- Shorter exposure time
- Very low power
- Wide area of application

} thermal damage and disruption decreased

- Because of non-destructive nature can be repeated
- Pre-and post-op similar to ALT

Main points

- Frequently needed in XFG
- In cases of very low target IOP- trabeculectomy surgery of choice
- Non-penetrating surgeries if cataract progression is a concern
- Trabecular aspiration may be considered in XFG if cataract surgery is performed

Case 2

- 73 YO W/F
- H/O XFS OU on multiple medications
- SP SLT OS 180degree
- Referred for additional SLT

Case courtesy of Drs. Jay Katz and Robert Goulet

Ocular history

- Narrow angle PI OD
- OS not done
- IOP Max 30 OD 34 OS

- Difficulty with ocular medications
- Alphagan (Brimonidine)
- Lumigan (Bimatoprost)
- Xalatan
- Preserved timolol

Slit lamp and other anterior segment findings

- Mild injection in conjunctiva
- Iris
- OD patent peripheral iridotomy, loss of ruff, transillumination defects
- OS Loss of pupillary ruff

- CCT 502 and 503 OD and OS respectively
- IOP 23 mmHg OU 2:34 PM


Gonioscopy

- OD C30 r 2 + pigment
- OS B25 r 2 + pigment

A = Above Schwalbe line, totally occluded angle.
B = Behind the Schwalbe line, peripheral iris is in contact with TM.
C = Scleral spur Iris root at the level of scleral spur
D = Deep anterior ciliary body seen.
E = extremely deep


Iris insertion


Angle approach


Curvature of periheral iris

Optic nerve

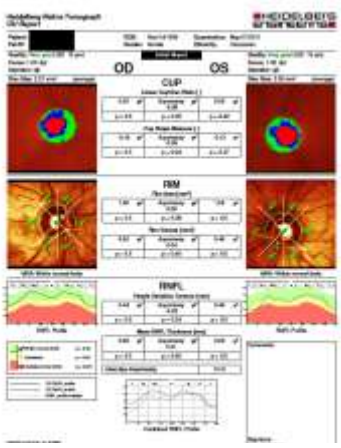
- OU pink with good rim
- CD ratio
- OD .5 V and H
- OS .6 V and H

- DDLS OU 4

Overall Within normal limits.
Optic disc size average
Asymmetry between optic nerve heads visible

Moorfields Regression Analysis within normal limits

RNFL - measured just outside the disc margin



Management

- 1) Ocular hypertension, monitor for progression
- Treatment continue
- Travatan Z OU qhs
- Trusopt 2% OU t.i.d
- Timoptic ocudose 0.5% OU t.i.d
- 2) Narrow angle Laser PI OS first, then SLT
- 3) Cataract and XFS observe