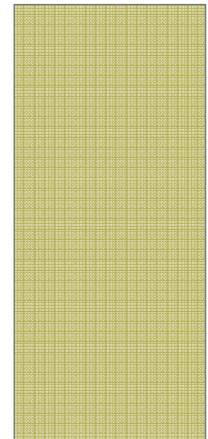




Paediatric glaucoma

Mr John L Brookes



Paediatric glaucoma

- Consultant Ophthalmic Surgeon
 - Glaucoma Service Director – Moorfields Eye Hospital
 - Specialist interest in Congenital Glaucoma
-
- Financial Interest:
 - Consulting: Pfizer

Paediatric glaucoma

- Clinical Overview
 - Clinical features/ Epidemiology/ natural history/ current standards of care
- Evidence base
 - Overview from available paediatric studies
- Unmet needs
- Extrapolating from adult pharmacokinetic data
- Trial designs
- Feasibility of trials in childhood glaucoma

Glaucoma prevalence

- 60.5 million adult population worldwide in 2010 increasing to 79.6 million in 2020¹
- 8.4 million bilaterally blind
- Second leading cause of vision loss
- **Paediatric Glaucoma:**
 - US: 1:10,000 live births for PCG
 - UK: 1:18,500 live births for primary and secondary glaucoma
 - ROI: 1:30,000
- ¹Quigley. Br J Ophthalmol 2006;90:262-267
- ²Papadopoulos et.al. IOVS;2007:48,No. 9

Clinical overview

- Classification:
 - Primary: Primary congenital glaucoma
Juvenile-onset glaucoma
 - Secondary: Ocular
Systemic



Secondary Glaucomas

Associated with anterior segment dygenesis

Axenfeld-Reiger's anomaly
Peter's anomaly
Aniridia
Microphthalmos
Ectropion uvae
Iris hypoplasia

Associated with Phacomatoses

Neurofibromatosis
Sturge-Weber syndrome
port-wine stains
cutis marmorata telangiectasia
Klippel-Trenaunay-Weber syndrome

Associated with Inflammatory/ infective disease

Seronegative arthritides
Congenital rubella, CMN

Associated with Chromosomal/ systemic dis

Down's, Patau's, Turner's
Rubinstein-Taybi
Pierre Robin

Associated with ocular disease/ Rx

Congenital cataract surgery
PHPV
ROP
Trauma
hyphaema/ recession

Associated with Metabolic disease

Lowe's syndrome
Homocystinuria
Mucopolysaccharidoses

Associated with Ocular Tumours

Benign (iris cysts, xantho)
Malignant (Rb, leukaemia)

Associated with CT abnormality

Marfan's, Weil-Marchesani
Homocystinuria
Ehler-Danlos, S-oxidase def

Topical hypotensive agents

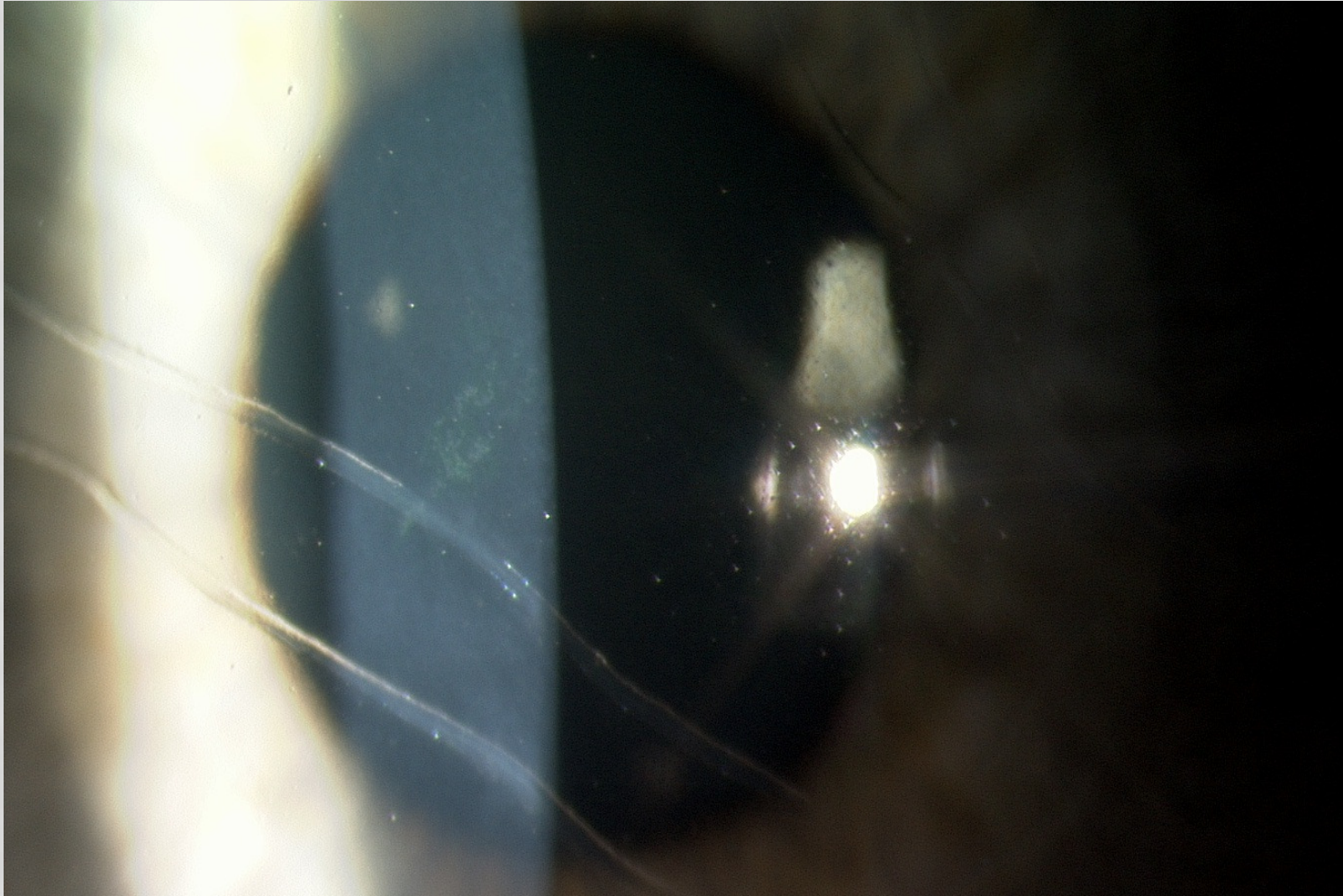
- **Beta-Blockers:**
 - Timolol (0.1%; 0.25%; 0.5%); Betaxolol; Levobunolol
- **Prostaglandin Analogues:**
 - Latanoprost; travoprost; bimatoprost
- **Carbonic anhydrase inhibitors:**
 - Dorzolamide; Brinzolamide
- **Alpha₂-receptor agonists:**
 - Apraclonidine; brimonidine
- **Miotics:**
 - Pilocarpine
- **Combination Therapy:**
 - Xalacom; duotrav; ganfort
- **Systemic Agents:**
 - Acetazolamide

Paediatric glaucoma

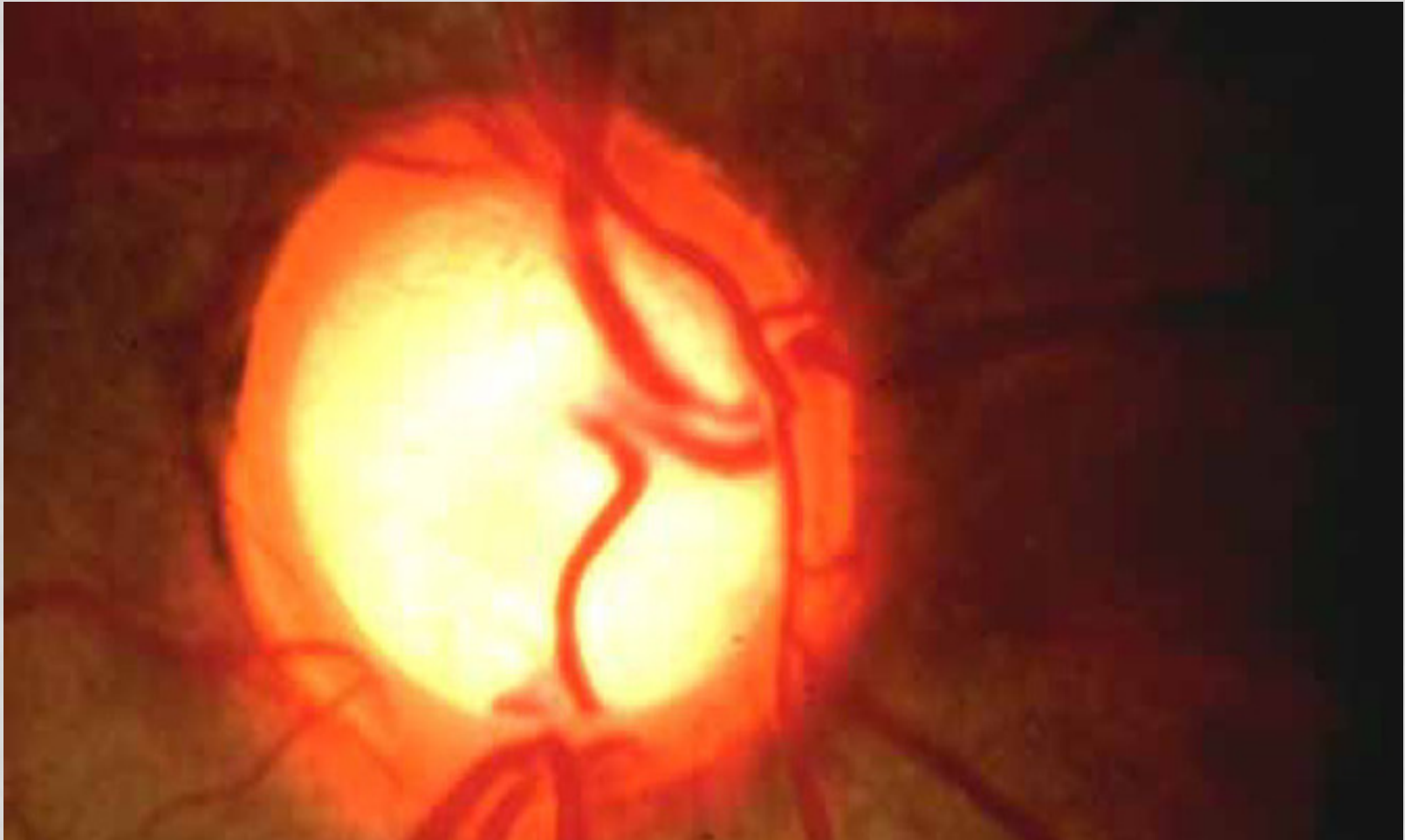
- Rare disease:
 - UK: >720,000 births/ year
 - Incidence of PCG: 1:17-20,000/ year (BOSU study)
- Approx. 40 new cases per year in UK
- Incurable
- Lifelong follow up
- IOP-dependent disease
 - Optic nerve damage results in gradual visual changes and then loss of vision
- >60% of all cases in UK managed at MEH and GOSH



Paediatric glaucoma



Paediatric glaucoma



Paediatric glaucoma

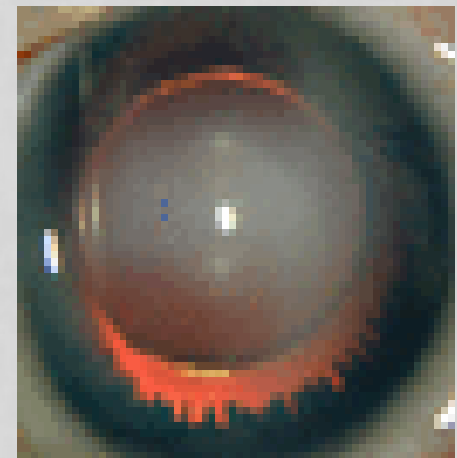
- ***The Epidemiology of Pediatric Glaucoma: The Toronto Experience***

- Taylor RH et al. J AAPOS 1999;**3**:308-15

- *98% of PCG required surgery*
- *50% of aphakic glaucoma*
- *80% of Sturge-Weber glaucoma*
- *73% of ASD*
- *67% of Aniridic glaucoma*
- *71% of Juvenile onset glaucoma*



Secondary Glaucomas



Current standard of care

- Primary Congenital Glaucoma:
- Medical Therapy (prior to angle surgery)
 - 1st Line: Beta-blocker + pilocarpine
- Medical Therapy (after incisional surgery)
 - 1st line: Prostaglandin analogue/ beta-blocker
 - 2nd line: Carbonic anhydrase inhibitor
 - 3rd line: Alpha₂-agonist (avoid in <6 year old)
- NB: Combination agents
- Systemic agents only temporarily prior to surgery

Management

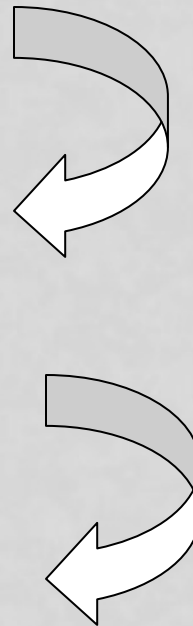
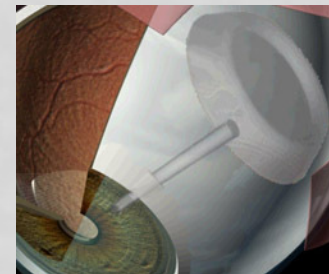
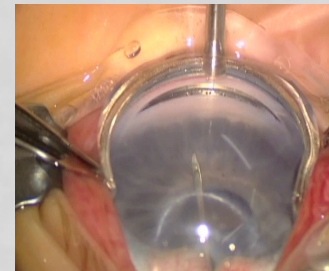
Medical Therapy

Angle Surgery

+ Medical Therapy

Incisional Glaucoma Surgery

+ Medical Therapy



Evidence

- Need to ensure new agents are efficacious and safe for a defined group of patients
- Demonstrate lack of inferiority through comparative assessment

Evidence base

- Observational Studies:
 - **Timolol:** Safety and Efficacy of Timolol in Paediatric Glaucoma. Zimmerman et. al. Surv Ophthalmol 1983;28:262-264
 - **Latanoprost:** Latanoprost in port wine stain related paediatric glaucoma. Ong et.al. Br J Ophthalmol 2003;87:1091-1093
 - **Brimonidine:** Is brimonidine ophthalmic a safe therapy for infants? Daubert. J Clin Pharm and Therapeutics 2006;31:289-292

Evidence base

- Latanoprost:
 - Prostaglandin F2 alpha
 - Increases uveoscleral outflow through an induced turnover and remodelling of ECM adjacent to ciliary muscle cells¹
 - First marketed in 1996 as second-line therapy; subsequently approved for first-line therapy
- Paediatric studies including a PK and phase 3 studies completed in EU in 2009
- First PGA to be evaluated prospectively as monotherapy in paediatric glaucoma

¹Surv Ophthalmol Feb 1997,S53-S59

Evidence base

- PANDA Study
 - A phase 3 Prospective, Randomised, Double masked 12-week, Parallel Group Study Evaluating the Efficacy and Safety of Latanoprost and Timolol in Paediatric Glaucoma
- Purpose:
 - To assess the relative efficacy and safety of the adult dose of once-daily latanoprost compared with twice-daily timolol in paediatric glaucoma
 - Latanoprost (n=68); Timolol (n=69)

Evidence base

- PANDA Study
 - 0-18 years old; glaucoma requiring IOP-lowering treatment
 - Stratified into 3 age groups
 - 0 to <3; 3 to <12; 12 – 18 years
 - Diagnosis: PCG vs non-PCG
 - Baseline: <27; 27-31; >31mmHg
 - Staged enrollment (oldest group first)
 - Randomised 1:1; follow up at weeks 1,4 and 12
 - Primary endpoint: mean change in IOP from baseline at week 12; latanoprost not inferior to timolol
 - Responder rates = >15% IOP reduction from baseline at weeks 4 and 12

Evidence base

- PANDA Study (cont.)
 - Responder rates:
 - Population: Latanoprost = 60%, Timolol = 52% (p=0.3315)
 - In subgroups: PCG (Lat) = 50%, PCG (Tim) = 46%
 - Non-PCG: Lat = 72%, Tim = 57%
- Conclusion:
 - Latanoprost was safe and well tolerated
 - Safety and efficacy of latanoprost support its usefulness for glaucoma patients aged 0-18 years, including those with either PCG or non-PCG
 - European commission approval for the treatment of elevated IOP in paediatric population in Oct 2010

Evidence base

- Long Term Study of Xalatan in Paediatric Populations (ongoing)
 - Primary Objective:
 - To evaluate the long term impact of treatment xalatan on ocular development and neurodegenerative diseases, changes in eyelashes and hyperpigmentation of the eye and corneal endothelial function/corneal thickness, by comparing paediatric subjects treated with xalatan with those not treated with topical PGA
 - Secondary Objective:
 - Characterise risk factors and identify risk subgroups eg. age

Evidence base

- Prospective, non-interventional, longitudinal cohort study
 - 200 paediatric patients (<18 years)
 - 150 treated with xalatan
 - 50 untreated with any topical PGA
 - Follow up period for each patient: 3 years

Unmet need

- PCG: Most common glaucoma in infants
 - Evidence only obtained with latanoprost
- Secondary Glaucoma:
 - Aphakic Glaucoma – need for safety of efficacy studies of IOP-lowering drugs
- Pharmacokinetic Studies:
 - PK studies done for PANDA study
 - Children treated with adult doses of drugs NB. Brimonidine
 - Challenging to carry out in paediatric population
- Biggest obstacles are the relative rarity of each subtype of glaucoma and consent for studies in children

Trial designs

- Randomised controlled trial (RCT):
 - Traditionally gold standard
 - Large sample size; costly and takes long time
 - Adaptive/pragmatic/ meta-analyses
- Observational:
 - Patients receiving a particular treatment are observed rather than being assigned to a treatment randomly
 - Adv:
 - Representative of routine clinical practice/ low cost/ high speed/useful for relatively rare conditions
 - Disadv:
 - Prone to confounding factors eg. underlying differences in patient groups

Conclusion

- Paediatric glaucoma is a relatively uncommon disease with poor visual prognosis
- Poor evidence base for most ocular hypotensive agents used in its treatment
- Many challenges to obtaining robust evidence in this group of patients