Classification of the Glaucomas

&

Epidemiology:

Chronic Open Angle Glaucoma

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Lecture objectives

• *Remind ourselves why glaucoma is important*

• *Consider classification of the glaucomas*
  – Summarise the causes of glaucoma
  – Review the mechanisms by which glaucoma occurs
  – Review the different classification systems for glaucoma

• *Review the epidemiology of COAG*
Context

• **Worldwide blindness**
  – ~67 million people worldwide with glaucoma
  – ~10% ‘blind’ from glaucoma
  – ~50% undetected
  – Second largest cause of ‘legal’ blindness

• **UK blindness**
  – 15% of ‘registrable’ blindness
  – 25% of OPD follow-up visits
  – 15% of new referrals

• **Demographic challenges**
  – Need to provide the service differently
Demographic Challenge 1: Population Growth

- 2004 ~60 million people
- 2031 ≈ 67 million people
- ≈ 12% increase in UK population over next 25 years

www.statistics.gov.uk
Demographic Challenge 2: Ageing Population

- 2002, 16% ≥ 65yrs
- 2031, 24% ≥ 65yrs

8% more people in age strata with higher glaucoma prevalence/incidence

www.statistics.gov.uk
Demographic Challenge 3: Life expectancy

2020 remaining life expectancy @ 65yrs
19yrs M and 23yrs F

23% increase in review duration per patient over next 15 years

www.statistics.gov.uk
Demographic Challenge 4: Impact of life expectancy on prevalence

Incidence same
mortality lower
prevalence increases
Increased demand for glaucoma care provision: Monitoring

- Demographic challenges
  - Population growth, ageing and life expectancy
  - ‘The Bow Wave of Doom’
  - NICE quality standards
    - Service capacity
Classification and Diagnosis
So what is glaucoma?

- Varied group of diseases
- Common denominator is *acquired progressive optic neuropathy*
- Will lead to progressive loss of visual function if undetected, untreated, or insufficiently treated
- Variety of different causes, therefore diverse clinical entities and number of potential diagnoses
Establishing a Diagnosis

Why so important?

• there are many sub-types of glaucoma
• clarifies disease processes at work so stakeholders understand
• provides information to:
  – inform management strategy, e.g. speed of further referral, treatment options, review periods, further tests
  – support the patient, understand their condition, prognosis, expectations, role in care, impact of condition/treatment on QoL

Factors to consider when making diagnosis

• clinical evidence should reasonably exclude differentials
• know the clear, current definition for the condition
• be prepared to refine the diagnosis
Classification of the Glaucomas

- Lots of alternative classification schemes
  - each has a differing (but valid) perspective
- Be aware of all schemes
  - to avoid confusion
  - to aid your understanding of the cause, mechanism and appropriate treatment
- Your colleagues may use a different system!

Three main classifications schemes

- ‘Traditional’ cause-based (1<sup>o</sup> or 2<sup>o</sup>)
- Initial pathological event-based (refined cause-based)
- Mechanism-based (open- or closed-angle)
Three Main Classification Schemes

1. "Traditional" caused-based (1º or 2º) - grouped according to known reasons for IOP elevation  
   **Advantages** – simple to understand; widely used  
   **Disadvantages** – over-simplification; not adaptive to increasing knowledge; doesn’t account for glaucomas without raised IOP

2. **Initial pathological event-based** – grouped by knowledge of cause leading to glaucomatous damage  
   **Advantage** – systematic, promotes understanding of disease processes; accepts IOP-independent causality  
   **Disadvantage** – ignores mechanisms that results in glaucoma; not practical, generally as does not assist choice of treatment

3. **Mechanism-based (open- or closed-angle)** – grouped according to how aqueous outflow reduction occurs that leads to raised IOP  
   **Advantage** - useful to assist with approaches to treatment  
   **Disadvantage** – ignores underlying cause(s); does not account for IOP-independent causality; more than one mechanism can exist
**“Traditional” Cause-Based Classification**

<table>
<thead>
<tr>
<th>Primary – unrelated to ocular or systemic disease</th>
<th>Secondary – known contribution from ocular/systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open Angle</strong></td>
<td></td>
</tr>
<tr>
<td>i. juvenile</td>
<td></td>
</tr>
<tr>
<td>ii. POAG (high pressure type)</td>
<td></td>
</tr>
<tr>
<td><strong>Angle Closure</strong></td>
<td></td>
</tr>
<tr>
<td>i. acute</td>
<td></td>
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<tr>
<td>ii. intermittent</td>
<td></td>
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<tr>
<td>iii. chronic</td>
<td></td>
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<tr>
<td><strong>Congenital</strong></td>
<td></td>
</tr>
<tr>
<td>i. primary congenital</td>
<td></td>
</tr>
<tr>
<td>ii. primary infantile</td>
<td></td>
</tr>
<tr>
<td>iii. associated with congenital anomalies</td>
<td></td>
</tr>
<tr>
<td><strong>Open Angle</strong></td>
<td></td>
</tr>
<tr>
<td>i. to ophthalmic conditions</td>
<td></td>
</tr>
<tr>
<td>ii. iatrogenic</td>
<td></td>
</tr>
<tr>
<td>ii. to extra-ocular conditions</td>
<td></td>
</tr>
<tr>
<td><strong>Angle closure</strong></td>
<td></td>
</tr>
<tr>
<td>i. with pupil block</td>
<td></td>
</tr>
<tr>
<td>ii. ‘pulling’ without pupil block</td>
<td></td>
</tr>
<tr>
<td>iii. ‘pushing’ without pupil block</td>
<td></td>
</tr>
<tr>
<td><strong>A. Open-angle glaucomas without ocular or systemic disorders</strong></td>
<td><strong>D. Glaucomas associated with other ocular and systemic disorders</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>i. ‘Primary’ open angle glaucoma</td>
<td>i. Associated with disorders of the corneal endothelium</td>
</tr>
<tr>
<td>ii. Normal tension glaucoma</td>
<td>ii. Associated with disorders of the iris and ciliary body</td>
</tr>
<tr>
<td><strong>B. Angle closure glaucomas without known ocular or systemic disorders</strong></td>
<td>iii. Associated with disorders of the lens</td>
</tr>
<tr>
<td>i. Pupillary block mechanism glaucoma</td>
<td>iv. Associated with disorders of the retina, choroid and vitreous</td>
</tr>
<tr>
<td>ii. Combined mechanism glaucoma</td>
<td>v. Associated with intraocular tumours</td>
</tr>
<tr>
<td><strong>C. Developmental glaucomas</strong></td>
<td>vi. Associated with elevated episcleral venous pressure</td>
</tr>
<tr>
<td>i. Congenital glaucomas</td>
<td>vii. Associated with inflammation</td>
</tr>
<tr>
<td>ii. Developmental glaucomas with associated ocular or systemic anomalies</td>
<td>viii. Steroid induced glaucoma</td>
</tr>
<tr>
<td>iii. Secondary glaucomas in childhood</td>
<td>ix. Associated with ocular trauma</td>
</tr>
<tr>
<td></td>
<td>x. Associated with haemorrhage</td>
</tr>
<tr>
<td></td>
<td>xi. Following intraocular surgery</td>
</tr>
</tbody>
</table>
# Mechanism-based classification

<table>
<thead>
<tr>
<th>Open angle</th>
<th>Closed angle</th>
<th>Developmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Pre-trabecular (membrane overgrowth)</td>
<td>A. Anterior (‘pulling’) mechanisms</td>
<td>A. High insertion of anterior uvea</td>
</tr>
<tr>
<td>i. fibrovascular membrane (neovascular glaucoma)</td>
<td>i. contracture of membranes</td>
<td>i. congenital glaucoma</td>
</tr>
<tr>
<td>ii. endothelial layer</td>
<td>ii. contracture of inflammatory precipitates</td>
<td>ii. juvenile glaucoma</td>
</tr>
<tr>
<td>iii. epithelial downgrowth</td>
<td></td>
<td>iii. associated with other developmental anomalies</td>
</tr>
<tr>
<td>iv. fibrous ingrowth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>v. inflammatory membrane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Trabecular (occlusion of inter-beam spaces)</td>
<td>B. Posterior (‘pushing’) mechanisms</td>
<td>B. Incomplete development of trabecular meshwork and Schlemm’s canal</td>
</tr>
<tr>
<td>i. idiopathic</td>
<td>i. with pupil block</td>
<td>i. Axenfeld-Rieger syndrome</td>
</tr>
<tr>
<td>ii. ‘clogging’ of meshwork</td>
<td>ii. without pupil block</td>
<td>ii. Peter’s anomaly</td>
</tr>
<tr>
<td>iii. alterations in meshwork structure</td>
<td></td>
<td>iii. associated with other developmental anomalies</td>
</tr>
<tr>
<td>C. Post-trabecular</td>
<td></td>
<td>C. Iridocorneal adhesions</td>
</tr>
<tr>
<td>i. occlusion of Schlemm’s canal</td>
<td></td>
<td>i. broad strands (Axenfeld-Rieger syndrome)</td>
</tr>
<tr>
<td>ii. elevated episcleral venous pressure</td>
<td></td>
<td>ii. Fine strands contract and close angle (Aniridia)</td>
</tr>
</tbody>
</table>
Glaucoma Epidemiology
Definition of Epidemiology

- Study of the distribution and determinants of diseases and injuries in human populations
  - Concerned with frequencies and types of injuries and illness in groups of people
    - *Focus is not on the individual*
  - Concerned with factors that influence the distribution of illness and injuries
Fundamental Assumptions in Epidemiology

- Disease doesn’t occur at random
- Disease has causal and preventive factors
  - Disease is not randomly distributed throughout a population
    - Epidemiology uses systematic approach to study the differences in disease distribution in subgroups
    - Allows for study of causal and preventive factors
Components of Epidemiology

• Measure of disease frequency
  – Quantification of existence or occurrence of disease

• Distribution of disease - three questions
  – Who is getting disease?
  – Where is disease occurring?
  – When is disease occurring?
  ➔ Formulation of hypotheses concerning causal and preventive factors

• Determinants of disease
  – Hypothesis are tested using epidemiologic studies
Prevalence

• Number of existing cases of disease or other condition
  – Proportion of individuals in a population with disease or condition at a specific point of time
    • Diabetes prevalence, smoking prevalence
  – Provides estimate of the probability or risk that one will be affected at a point in time
  – Provides an idea of how severe a problem may be – measures overall extent
    • Useful for planning health services (facilities, staff)
Incidence

- Measure of **new cases** of disease (or other events of interest) that develop in a population during a specified period of time
  - E.g. Annual incidence, five-year incidence
- Measure of the probability that unaffected persons will develop the disease
- Used when examining an outbreak of a health problem
Prevalence of POAG
Risk factors for POAG

- Age (~4-10x higher in older age)
- IOP (1 modifiable factor)
- Race (~6x)
- Family history (sibling ~3.7x, parent ~2.2x)
- High myopia (~2-3x)
- Corneal thickness
- Diabetes Mellitus (controversial)
- Vascular factors
Risk factors for NTG

• Variant of POAG, mean IOP ≤ 21 on phasing, with glaucomatous VF defects and optic neuropathy

• Open drainage angle/absence of 2 cause

• ~16% of all cases of COAG

• Risk factors
  – Older age, females, Japanese race, family history

• Features
  – IOP in high teens, larger discs, more frequent disc haemorrhages, VF loss more localized, deeper, steeper and closer to fixation
Race as a risk factor for POAG

- POAG has a devastating impact in blacks
- Prevalence ~6x as high compared to whites
- More likely to result in blindness
- Appears ~10 years earlier
- Progresses more rapidly
- Larger optic discs (?IOP)
- Prevalence of diabetes & hypertension higher
- Less responsive to drug/surgical treatment
- Reduced accessibility to diagnosis/treatment?
TABLE 1
Prevalence of POAG at different levels of screening IOP and the relative risk at specific levels of IOP, from the population-based Baltimore Eye Study (Sommer et al, 1991)\textsuperscript{9}

<table>
<thead>
<tr>
<th>IOP (mmHg)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>1.0</td>
</tr>
<tr>
<td>16-18</td>
<td>0.8</td>
</tr>
<tr>
<td>19-21</td>
<td>0.6</td>
</tr>
<tr>
<td>22-24</td>
<td>0.4</td>
</tr>
<tr>
<td>25-29</td>
<td>0.2</td>
</tr>
<tr>
<td>30-34</td>
<td>0.1</td>
</tr>
<tr>
<td>&gt;35</td>
<td>0.0</td>
</tr>
</tbody>
</table>

IOP as a risk factor
Screening

• Directed to early disease detection
• Does not arise from patient initiated contact
• ‘Case-finding’ versus screening
• ‘….presumptive identification of disease or defect by the application of tests, examinations or other procedures which can be applied rapidly’
• Sorts out those who probably have a condition Vs those who probably don’t
Diagnostic accuracy

- Sensitivity
- Specificity

![Graph showing Diagnostic accuracy with Sensitivity and Specificity](image-url)
Sensitivity and specificity ‘trade-off’

- Tests with continuous score, sensitivity and specificity can be calculated for different test / cut-off criteria

- move criterion to ‘normal’
  score ↑ sens but ↓ spec

- move criterion to ‘abnormal’
  score ↓ sens but ↑ spec

- “Trade-off” visualised by plotting “ROC curve”
IOP and Glaucoma Detection

Sensitivity

Specificity

Intraocular Pressure (mmHg)

Sensitivity/Specificity

Intraocular Pressure (mmHg)
### IOP at presentation: epidemiological study data

<table>
<thead>
<tr>
<th>Study</th>
<th>Nº POAG</th>
<th>% with Normal IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Des Moines, USA</td>
<td>189</td>
<td>68</td>
</tr>
<tr>
<td>Ferndale, Wales</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Framingham, USA</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>Baltimore, USA</td>
<td>194</td>
<td>59</td>
</tr>
<tr>
<td>Beaver Dam, USA</td>
<td>104</td>
<td>32</td>
</tr>
<tr>
<td>Roscommon, Ireland</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>Blue Mountains, Aus</td>
<td>108</td>
<td>75</td>
</tr>
</tbody>
</table>
Disc assessment sensitivity & specificity

- Stereophtotography* Sen~75% Spec~95%
- Imaging systems† Sen~87% Spec~84%
- C/D ratio ‡ Sen~64% Spec~57%
- Clinical exam ^ Sen~81% Spec~90%

NB – Figures are early examples from literature - comparison between different studies invalid

† Mikelberg et al, J Glaucoma 1995
* Schultz et al, J Glaucoma 1995
‡ O’Connor et al, Ophthalmology 1993
^ Harper & Reeves, Graefe’s Arch Clin Exp Ophthalmol 2001
VF sensitivity and specificity

- Henson 26pt test*  Sen~84%  Spec~100%
- OKP *  Sen~81%  Spec~96%
- FDT †  Sen~93%  Spec~100%

NB: Figures are early examples from the literature - comparison between different studies invalid

* Sponsel et al, AJO 1995
† Johnson & Samuels, IOVS 1997
Predictive power of tests

positive proportion of individuals with predictive a positive test result who have value disease

\[
\text{TP/(TP+FP)}
\]

negative proportion of individuals with predictive a negative test result who do value not have disease

\[
\text{TN/(TN+FP)}
\]

N.B. Depend on prevalence of disease
Predictive power + ve example 1

Assume Sensitivity/Specificity are 95%
Prevalence of undetected glaucoma is 1%

What happens if we screen 10,000 people?
~100 glaucoma, ~9,900 normals

Pick-up 95 glaucomas (True +) and falsely say
495 (5%) of normals are glaucoma (False +)

Predictive power positive is 95/(95+495) = 16%
Assume Sensitivity/Specificity are 95%
Prevalence of undetected glaucoma is 10%

What happens if we screen 10,000 people?
~1000 glaucoma, ~9,000 normals

Pick-up 950 glaucomas (True +) and falsely say 450 (5%) of normals are glaucoma (False +)

Predictive power positive is $\frac{950}{950+450} = 68\%$
What about screening for glaucoma?

• Key findings
  – Population screening is not cost-effective, although targeted screening of high risk groups may be
  – Detection can be improved by:
    • Encouraging increased attendance for eye examination
    • Improving the performance of current testing by refining practice or by adding in a technology based first assessment
  – Research needed:
    • Feasibility study of interventions to improve detection
    • Obtain further health economics data
    • RCT of interventions to improve uptake of screening

Review of clinical effectiveness and cost-effectiveness of screening (HTA 2007)
Referrals and glaucoma

- No screening – case finding by optometrists
- Use of 'screening' tests (visual fields in particular) is variable
- Referrals for glaucoma are initiated by optometrists (>90% cases)
- Quality of information in referrals is variable
- False positive referral rate is high (~40%)
What influences referral accuracy?

• Epidemiological issues:
  – Prevalence of undetected glaucoma
  – Diagnostic accuracy of ‘screening’ tests

• Case finding protocol
  – Test strategy, use of repeat testing etc

• Criteria for referral

• Optometrist’s ‘attitude’ towards referrals

• HES ‘gold-standard’ for defining true positive
Referral rate and outcome of GRR

Referral Rate:
- Referred: 59%
- Not Referred: 41%

Total Sample Size (N): 670
Acknowledgement

Thanks for your attention!

Dr Paul Spry
- Bristol Eye Hospital