ABSTRACT

Primary angle-closure glaucoma (PACG) frequently leads to severe vision loss. Prevalence among older Asian populations is high and given global demographics, the number of persons with PACG will increase dramatically in the coming decades. Improvements in imaging of the anterior segment will help us to identify more of those with angle closure, and important clinical trials that are currently underway will provide important evidence to support screening and treatment approaches for PACG. In this manuscript, we intend to review the existing evidences, to introduce some important on-going studies on PACG and to share the experience and viewpoints of the authors.

Key words: angle-closure glaucoma, clinical trial, epidemiology.

INTRODUCTION

A PubMed search (20 September 2011) on open angle glaucoma (OAG) and angle-closure glaucoma (ACG) identified 11219 and 2966 articles, respectively. ACG is far less well studied despite the fact that it is a more visually destructive form of glaucoma. Glaucoma is the commonest cause of medically and surgically irreversible blindness globally,1 with OAG being the most prevalent clinical variant of the disease, affecting an estimated 45 million people in 2010, increasing to around 59 million people by 2020. In contrast, ACG will have affected around 16 and 21 million people at the same time points. Among those with established glaucomatous optic neuropathy (both OAG and ACG), around 8.4 million people were blind in 2010. This figure is projected to rise to 11.1 million in 2020. While the ratio of prevalent glaucoma indicates a 3:1 excess of OAG, the ratio of rates of blindness appears to be 1:1.2 ACG therefore carries a three-fold excess risk of severe, bilateral visual impairment. While secondary forms of glaucoma (notably neovascular and uveitic) are familiar to those working in a hospital or clinic environment as carrying a bleak prognosis and complex surgical intervention(s), it is only in the last decade that we have come to realize just how harmful ACG is in those affected. Fortunately, new concepts in management of ACG offer the potential of dramatic improvements in outcomes for patients.3

Clear demographic risk factors for primary angle-closure (PAC) disease have been identified in research over the last 40 years. These have important clinical implications. For example, nearly a quarter of older Chinese women have angle closure. It is therefore reasonable for clinicians in general
ophthalmic practice to assume that any elderly Chinese female has angle-closure disease until proven otherwise. From research in the high-risk population of Singapore, female sex carries a 2.4-fold excess risk of PACG, and Chinese race (vs. Malay or Indian) a 2.8-fold increased risk. Furthermore, age of 60 and older (compared with those 30 to 59) increases the risk 9.1 times. Assuming these are additive, an old Chinese woman is theoretically at 14 times greater risk of acute angle-closure than a younger Indian or Malay man. Prevalence rates vary widely in Asia, with lower rates seen in some populations (such as the Japanese) and much higher rates in others (extremely high rates were recently reported from Myanmar).

Although the precise difference in relative risk of all forms of angle closure for Caucasians is not known, based on the difference in incidence rates of acute angle closure attacks (4.7/100 000/year in Europeans vs. 15.5/100 000/year in Chinese Singaporeans), one would expect around a three-fold greater risk. It is reasonable to infer that young men of European origin are at very low risk of angle-closure disease. However, even at this lower rate, about one in 200 white persons over the age of 40 has angle closure. Based on clinical experience in the UK, European-derived persons with ACG are identified either through routine optometric/ophthalmic screening, or as a consequence of directed examinations resulting from a family history of angle-closure disease. Once identified, especially if they are young, they should be thoroughly investigated to exclude systemic and genetic anomalies, foremost of which are connective tissue abnormalities and bestrophinopathies. In addition, exogenous agents (primarily therapeutic or recreational drugs) should be excluded.

There is wide variation in the prevalence estimates for ACG European people. Figures range from 0.09% to 0.6% for people aged 40 years and older. In interpreting these figures, two facts are important. First is that the prevalence of glaucoma varies widely according to the criteria used to define the disease. Second, while in Asian people most cases of angle-closure are asymptomatic, it is unclear if the same is true of Caucasians. Indirect evidence from the UK would suggest it is; rates of acute angle-closure are falling, while rates of laser iridotomy are rising.

There is a need for reliable estimates of prevalence of angle-closure disease in Caucasians.

The variation in estimated prevalence of glaucoma as a whole according to definition of disease and the scientific imprecision of the ‘traditional classification’ of ACG in particular, provided the impetus to develop a framework around which to build a sound evidence base. The currently accepted classification of glaucoma (agreed upon by the World Glaucoma Association) was based on a system intended to be primarily a tool for describing epidemiological research. It has evolved into a widely used system for describing the natural history of ACG, identifying three separate conceptual stages to the development of the disease; primary angle-closure suspects (PACS) with inability to visualize the pigmented trabecular meshwork in primary gaze but no other abnormality of intraocular pressure (IOP) or glaucomatous optic neuropathy; PAC with the same angle findings and either elevated intraocular pressure or peripheral anterior synechial scarring (PAS); PACG, where the posterior trabecular meshwork is not visible, combined with structural and functional damage to the optic nerve consistent with glaucoma.

While several population studies have generated prevalence data, and short-term studies of acute angle-closure incidence have been conducted, data on the incidence and natural history of PACG are scarce. Velore in Southern India was the location of the first significant longitudinal study of angle-closure disease. In that setting, the 5-year incidence of PAC in persons with PACS was 22% (95% CI: 9.8 to 34.2), annually at 4.4%. A study of PACG incidence in PAC revealed a rate of 28.5% (95% CI: 12 to 45%) over 5 years, annually at 5.7%. In Mongolia, the incidence of PACS among high-risk individuals (anterior chamber depth < 2.53 mm) was 20.4% over 6 years (95% CI: 14.8 to 25.7), annually at 3.4%. Both of these studies report on relatively small numbers of events, and therefore, the estimates are not precise. The Mongolia data were derived from a randomized controlled trial of screening and laser prophylaxis of ACG. A total of 4725 people aged 50 years and older were enrolled, randomized to either screening (with or without prophylactic laser iridotomy) or observation. At 6 years after enrolment, 2047 people (54%) could be traced for re-examination. In an intention to treat analysis, PACG was diagnosed in 33 participants (1.61%, 95% CI 1.1% to 2.3%), indicating that among those who could be examined, rates of PACG development were fairly low. That said, 6 years is a short time, and the long-term incidence of PACG in this population remains uncertain. Whether prophylactic iridotomy among those who are screened is a successful strategy remains to be determined.

How should we diagnose angle closure now and in the coming decades?

The diagnosis of angle closure is made by gonioscopy which aids in identification of regions of apposition of the iris to the trabecular meshwork, and if this occurs for more than a certain extent of the angle...
(180 degrees or 270 degrees), the patient is said to have angle closure. With indentation, one is also able to identify the presence of PAS and distinguish synechial angle closure from appositional angle closure.\textsuperscript{18} The main limitation of gonioscopy is that it is observer dependent and subjective, with only moderate agreement reported among observers.\textsuperscript{19} Gonioscopic findings may also vary with the use of different gonioscopic lenses, and with changing ambient light conditions, from pressure on the gonioscopic lens or mechanical compression of the eye.\textsuperscript{20}

Several imaging methods have been developed that can be used to assess eyes for angle closure. These include:

1 Ultrasound biomicroscopy (UBM) which allows for the acquisition of real-time images of the angle, with resolution between 25 μm–50 μm.\textsuperscript{21} One is also able to visualize posteriorly located structures such as the ciliary body, lens zonule and anterior choroid. This makes it useful for imaging cases of plateau iris, iridociliary masses causing secondary angle closure or choroidal effusions. Although it is an objective method of angle imaging, UBM imaging requires a skilled operator and cooperation from patients, and the process can be time consuming and uncomfortable for patients. It is rarely used clinically.

2 Anterior segment optical coherence tomography (AS-OCT) is a non-contact imaging device that acquires high-resolution cross-sectional images of the anterior chamber, and allows for objective and quantitative angle evaluation. Comparison studies between AS-OCT and gonioscopy found a higher rate of diagnosis of closed angles with AS-OCT than gonioscopy, particularly in the superior and inferior quadrants.\textsuperscript{22,23} Several reasons have been suggested as to explain the differences between gonioscopy and AS-OCT such as inadvertent pressure on the globe and light entering the pupil during gonioscopy, leading to spurious widening of the angle.\textsuperscript{21} For both UBM and AS-OCT, imaging is limited to the cross-section(s) of the anterior chamber that is imaged, and the rest of the angle circumference is not assessed. At present, AS-OCT is not routinely used in clinical practice, but future improvements in imaging and analysis may lead to wider adoption of this technology.

3 Fourier or spectral domain OCT (SD-OCT) allows higher scanning speed and more images to be taken in a single pass, resulting in images of higher resolution.\textsuperscript{24} However, the shorter wavelength of the SD-OCT reduces the depth of penetration of the anterior segment making it less useful for imaging the iris and more posterior structures. With SD-OCT, one is able to identify angle landmarks such as the Schwalbe’s line, trabecular meshwork and Schlemm’s canal.\textsuperscript{25} However, the angle images obtained by SD-OCT have a limited field of view and depth penetration, and are also limited to the cross section that is imaged.

4 The swept source OCT (SSOCT) is another novel anterior segment imaging device that employs a swept laser source at a wavelength of 1310 nm and a scan speed of 30 000 A-scans per second.\textsuperscript{26} The device has a wide scanning range of 16 mm, which allows an entire cross section of the anterior chamber to be captured simultaneously. Uniquely, the SSOCT has a three-dimensional angle analysis scan that simultaneously obtains multiple radial scans of the whole anterior chamber for the entire circumference of the angle.

The new methods of angle imaging that have been introduced offer advantages over gonioscopy of being more objective, reproducible and non-contact. Image acquisition is rapid, and angle images can undergo quantitative analysis as well as storage. While attempting to address the shortfalls of gonioscopy, these devices are not without their own limitations. None of these new devices can presently replace conventional gonioscopy, but their use will likely increase as newer imaging devices become better able to produce high resolution images of the angle that can rapidly and simultaneously scan the entire angle circumference in three dimensions. This will deliver an estimation of angle closure which is more analogous to that derived from gonioscopy.

**What are the trials telling us, and what will we learn in the coming years?**

Management of PACG differs considerably from that used in OAG cases because of the fundamentally different mechanisms of the two diseases. The pathogenesis of PACG starts with anatomical abnormalities of the anterior segment (narrowing of the drainage angle), followed by structural and functional damage of the trabecular meshwork by PAS or perhaps other mechanisms related to contact with the iris tissue,\textsuperscript{27} an intermittent or sustained rise in IOP, and subsequently glaucomatous optic neuropathy (GON). This ‘end organ damage’ is the final pathway for all forms of glaucoma.

Management of PACS and PAC is aimed at modifying the anterior segment configuration, hopefully
before irreversible trabecular damage and GON develop. When GON has developed the aim of treatment is to lower the IOP in order to prevent worsening of GON and visual field loss; in these cases, treatment aimed at altering the anterior configuration alone does not appear to be as effective as when the disease is at early phase.\(^{28,29}\)

Laser peripheral iridotomy (LPI) and iridoplasty both are used to widen a narrow angle. Surgical iridectomy and lens extraction are surgical procedures that have been used for a similar purpose. Pilocarpine also opens the drainage angle in many cases.\(^{30}\) LPI remains the cornerstone of angle-closure management. LPI breaks relative pupil block and equalizes the pressures in the posterior and anterior chambers. The efficacy of LPI for disease control is dependent both on the underlying mechanism causing closure and the stage of the disease. In PACS cases, laser LPI is commonly used as a prophylactic treatment, but evidence is lacking as to its efficacy in preventing PACG (it is known to prevent acute angle closure).\(^{31}\) In the Liwan Eye Study, a population-based study conducted in Guangzhou, China, we found that, among those identified as having PACS, LPI resulted in a significant increase in the angle width, but about one fifth of eyes had residual angle closure based on gonioscopy 2 weeks after the LPI. In this study, angle closure was defined based on the pigmented iris root.\(^{37}\) Recent work from Singapore showing that lens vault is a major risk factor for angle closure confirms this.\(^{32}\) Phacoemulsification cataract extraction (phaco/IOL) has been shown to result in better IOP outcomes in acute angle-closure eyes in a randomized controlled trial in Hong Kong.\(^{39}\) Early phaco/IOL (1 month after the control of the acute attack) was more effective in preventing IOP rise than laser PI, especially among those who presented with very high initial IOP. However, lens extraction alone was not able to achieve satisfactory IOP controls in all attack eyes. The success likely depends on the extent, duration and intensity of the angle closure. Those with long-standing PAS will probably have a worse prognosis.

Argon laser peripheral iridoplasty (ALPI) is another treatment to open the drainage angle by applying contraction burns (low power, large spot size, long duration) to the peripheral iris and creating space between the anterior iris surface and the trabecular meshwork. Given the wide use of ALPI in Asia, it is surprising how limited the evidence is for its use and in fact a recent Cochrane report found that there was insufficient evidence supporting its use.\(^{1}\) In a recent randomized control trial conducted in Chinese eyes with PAC or PACG, LPI alone (77 eyes) and LPI combined with ALPI (81 eyes) provided equivalent IOP reduction in 1 year.\(^{44}\) For patients undergoing acute attacks of angle closure, ALPI has been used as initial treatment to open the drainage angle prior to laser iridotomy. In an initial case series, Lam \textit{et al.} reported the rapid efficacy of immediate ALPI in a case series of 10 acute PAC patients in Hong Kong\(^ {35}\) and subsequently showed in a randomized controlled trial that ALPI lowers IOP more rapidly than conventional medical treatment in persons suffering an acute attack.\(^ {36}\)

The lens clearly plays an important role in the pathogenesis of angle closure, and lens removal offers yet another approach to treating angle closure. Lowe described a theoretical model for pupil block in which block is increased when the point of iris-lens contact is situated anterior to the iris root.\(^ {37}\) Recent work from Singapore showing that lens vault is a major risk factor for angle closure confirms this.\(^ {32}\) Phacoemulsification cataract extraction (phaco/IOL) has been shown to result in better IOP outcomes in acute angle-closure eyes in a randomized controlled trial in Hong Kong.\(^ {39}\) Early phaco/IOL (1 month after the control of the acute attack) was more effective in preventing IOP rise than laser PI, especially among those who presented with very high initial IOP. However, lens extraction alone was not able to achieve satisfactory IOP controls in all attack eyes. The success likely depends on the extent, duration and intensity of the angle closure. Those with long-standing PAS will probably have a worse prognosis.

Given the prominent role of the lens in the pathogenesis of angle closure, a large, multinational randomized controlled trial has been underway for several years to assess the effectiveness of early lens extraction with intraocular lens implantation for the treatment of PACG (the EAGLE Trial).\(^ {3}\) This study is evaluating whether early lens extraction improves patient-reported and clinical outcomes and will assess the cost effectiveness in comparison with standard care.\(^ {3}\) In this trial that involves 22 centres in UK and eight centres in East Asia, over 400 patients with either PACG or PAC with elevated IOP have been enrolled. Of note, the
degree of lens opacity is not considered as a criterion for enrolment in this study, and therefore some with clear lenses will undergo this treatment. This seminal study will provide strong evidence to either support or reject early lens extraction in these patients.

Final thoughts on current treatment approaches, and what we are likely to see in the future

Angle closure is a potentially devastating condition that results in substantial visual disability. Acute attacks lead to glaucoma-related blindness in about 10% of cases, and more chronic forms of angle closure also have high rates of severe vision loss. We currently do a poor job of detecting angle closure. Recent reports show that only half of those with diagnosed glaucoma in the United States had gonioscopy documented in the chart. Neither doctors nor patients enjoy the process of gonioscopy, but all with glaucoma must undergo this procedure if we are to manage patients appropriately. Is there a good alternative that can be used today? At present, imaging devices are good but not great for detecting gonioscopically proven angle closure, but moving ahead it is likely that most if not all cases will someday be detectable in this fashion. This could lead to a major shift in clinical practice as patients are routinely imaged for angle closure, and physicians are alerted to the findings. It also holds promise for better population-based screening. However, efforts to promote screening for angle closure should wait for the results of two seminal trials in this field, the ZAP Trial and the EAGLE Trial described above. It makes sense to wait until we know the best approach for treating the many with PACS who will be identified in any screening process. Evidence from natural history studies of untreated eyes will also enable us to define better which persons are at greatest risk and therefore should have prophylactic treatment.

The current algorithm for treating angle closure is likely to change in the coming decade as further insights are made based on ongoing clinical trials. At present, there is widespread agreement based on an abundant literature that LPI prevents acute attacks in the fellow eye of those with monocular acute attacks. While there is general consensus that nearly all with PAC should have LPI, there is less agreement on who should have LPI in an attempt to prevent PACG among those who are PACS. While many routinely perform LPI for those patients, others do not, and at present the literature to support LPI is lacking. What drives this decision making is almost certainly the fear of an acute attack, and our inability to determine which patients are at real risk of this occurrence. Better characterization of the baseline factors that predispose to worse outcomes is certainly to be available based on the data currently being collected in the clinical trials underway.

ALPI remains unproven, and we strongly recommend more high-quality studies to assess its efficacy in the clinical entities other than an acute attack (where it lowers IOP more rapidly than medicines but does not improve outcomes at one year). A lack of literature on ALPI does not necessarily mean that it should not be used. Rather, it points to an area of clinical uncertainty, one that would be greatly improved were a more systematic approach to evaluation to be used.

While PACG can be treated similarly to POAG with medicines and surgical interventions, the anatomic basis of angle closure and the strong role of the lens in causing angle closure have led to more widespread use of cataract extraction as a treatment for PACG. There is clear evidence that in some PACG patients, IOP is dramatically lowered after phaco/IOL, but average IOP lowering in one large series of patients from Hong Kong (all of whom had substantial amounts of PAS) was on the order of 1.5 mmHg at one year. This is not a huge mean response, and future research will need to identify which persons are most likely to benefit from phaco/IOL and which are not. At present, many of us are removing cataracts alone rather than performing other glaucoma procedures as one treatment for PACG.

The global demographics are staggering. PACG is an age-related illness and without better treatments and some form of prevention, we are likely to see a dramatic surge in the numbers with angle closure disease. Ongoing work in this area is needed.

References


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