Angle-closure glaucoma: impact, etiology, diagnosis, and treatment

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Purpose of review

Recent studies underscore the importance of angle-closure glaucoma (ACG) as a cause of world blindness. A major contribution in assessing the true impact of this disease has been an article estimating the number of persons with occludable angles, angle closure, and blindness from ACG in China as 28.2 million, 9.1 million, and 1.7 million, respectively. Although these numbers are based on data from Singapore and Mongolia, which may be applied to China only with caution, they emphasize the blinding potential of ACG, which is three times as likely to be associated with blindness as open-angle glaucoma (OAG).

Recent findings

Recent reports in the Chinese literature on ACG prevalence suffer from definitional problems that would appear to lead to systematic overestimates of ACG prevalence and underestimates of OAG prevalence. Nonetheless, data from studies by Chinese investigators further emphasize the strong association between ACG and blindness, with fully 16% of subjects with ACG blind in one report—a far higher proportion than for OAG in China and elsewhere. The importance of topiramate as a cause of secondary angle closure has recently been understood, in part, because of a series of 19 such cases reported by investigators at the Food and Drug Administration.

Summary

Angle closure in this setting appears to be caused by uveal effusion and anterior rotation of the ciliary body with resultant closure of the angle. The condition is not always responsive to laser iridectomy, and elimination of the causative agent appears to be critical. Ultrasonic biomicroscopy is a potential new diagnostic modality for ACG, allowing the measurement of novel parameters, such as the angle opening distance (AOD) at 500 μm (AOD 500). The efficacy of such parameters in improving screening for ACG can only be established by prospective studies of potentially at-risk eyes. A number of novel treatments for AC and angle closure have recently been proposed, including cataract extraction, paracentesis, and argon laser iridoplasty. As with proposed new diagnostic modalities, the efficacy of these treatments remains to be demonstrated with prospective studies, ideally organized in a controlled, randomized fashion.

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Abbreviations

AAC	acute angle-closure
ACG	angle-closure glaucoma
ALPI	argon laser peripheral iridoplasty
AOD	angle-opening distance
DRPT	dark room provocative test
IOP	intraocular pressure
OAG	open-angle glaucoma
PACG	primary ACG
PEC	phacoemulsification cataract extraction with intraocular lens implantation
POAG	primary open ACG

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Angle-closure glaucoma: a leading cause of blindness

Recent literature on primary angle-closure glaucoma (PACG) has highlighted the importance of this disease as a worldwide cause of blindness. Foster and Johnson [1] estimate that the number of persons with "occludable" angles in China, based on previous population-based studies in Mongolia [2] and Singapore [3], is 28.2 million, whereas 9.1 million have significant angle closure. Even more importantly, among 1.7 million persons bilaterally blind from glaucoma in China, 91% are caused by PACG, although PACG comprised only 56% of primary glaucoma. This high proportion results from the fact that persons with PACG were three times as likely to be blind as those with primary open-angle glaucoma (POAG) in the models used by Foster *et al.*. The report concludes that PACG may be the leading cause of glaucoma blindness in the world today [1]. An accompanying editorial by Quigley *et al.* [4] emphasizes the need to develop screening tests that will both identify persons with occludable angles and also those who are likely to develop frank angle closure and angle-closure glaucoma (ACG). Tests that identify optic nerve and visual field damage of the kind seen in POAG will be appropriate for most of ACG, which manifests in the chronic rather than acute form. Clinical trials are needed to demonstrate the efficacy of treatments such as iridotomy in preventing the need for further treatment of angle closure, as well as clarifying the side effect profile of such treatment and the stages in the disease process at which benefits will still accrue. Finally, Quigley *et al.* [4] note that Foster and

Johnson's prevalence estimates are based on the assumption that rural Chinese have similar prevalence rates of PACG to Mongolians, whereas urban Chinese have rates similar to Singaporeans. This, indeed, may not be the case, and more research is needed to confirm the accuracy of these estimates.

More direct estimates of glaucoma prevalence in the People's Republic of China have also appeared recently, albeit in the Chinese literature. Zhao *et al.* [5] report on a population-based survey of 4880 individuals aged 50 years and above in Beijing Shunyi county. This study, which achieved an 87.9% response rate among the target population, reported a high preponderance of angle closure among subjects diagnosed with primary glaucoma: among the 1.95% of subjects with primary glaucoma, 85% or 1.66% were said to have PACG. Nonstandard definitions of glaucoma may have contributed to the high proportion diagnosed with PACG; a diagnosis of PACG required only that the subject have an "elevated pressure" (no cutoff is spelled out in the report) in the setting of a narrow angle without other primary cause. All subjects with a pressure rise (cutoff not specified) after dilation or dark prone testing (performed on those with suspicious angles) with partially or completely occluded angles on gonioscopy were also diagnosed as having PACG. Thus, persons who would be classified only as having angle-closure, or perhaps even occludable angles, according to the proposed international standard classification system for angle closure [6] are defined as ACG in this report. Furthermore, an intraocular pressure (IOP) of $\geq$ 24 mm Hg was required for the definition of POAG (although subjects with "classic" disc and field changes of glaucoma could receive the diagnosis at lower pressures). The application of visual field testing and gonioscopy are not clearly outlined in the report, but it appears that flashlight and Van Herrick testing, rather than gonioscopy, were used as initial screening tests on all subjects, and that visual field testing was not performed on all participants. This report likely represents both a significant overestimate of PACG and an underestimate of POAG and, as such, highlights the significant differences in definitions and study methods between investigations of angle closure by western researchers [2,3] and those in China [5,7]. Zhao does reiterate several important points concerning the epidemiology of glaucoma in China, which are in accord with the existing literature: IOP among Chinese persons (13.5 ± 2.2 mm Hg in this study) tends to be lower on a population basis than among Westerners [8,9] and tends to fall rather than rise [8,9] with increasing age. Moreover, as previously reported in other studies of Chinese populations [1], the proportion of persons bilaterally blind with angle-closure (nearly 16% in this study) tends to be higher than that reported for POAG in European-derived populations [8,9].

Mechanisms

Although the importance of ACG as a cause of blindness is increasingly clear, much remains to be learned about the mechanisms of this disease. Several recent reports on a newly recognized iatrogenic cause of angle closure may offer some insight in this area. Sankar *et al.* [10] reported in 2001 two cases of acute angle closure (AAC) associated with uveal effusion on therapy with topiramate. This report was joined a year later by a more extensive series of 19 patients reported to the Food and Drug Administration with AAC associated with topiramate use [11]. Common clinical findings in the cases included shallow anterior chamber, uveal effusion on ultrasound biomicroscopy, and several diopters of acquired myopia. Other notable features included young age (a mean of 36.5 years, with several pediatric cases reported), female gender (in 89% of cases), use of possible potentiating medications (*eg*, serotonin-specific reuptake inhibitors) in a number of cases, and relatively acute onset after instigation of topiramate (mean of 10 days). The authors report a broad range of indications for topiramate use, ranging from epilepsy and depression to migraine, neuropathic pain and weight loss. At least in these reported cases, the problem was usually recognized fairly rapidly and appropriate treatments, including cessation of the drug, topical and oral steroids, and cycloplegic agents, were successful in reversing the problem. Laser peripheral iridotomy was not always of benefit. The proposed mechanism of the secondary angle closure is an inflammatory response, perhaps to the sulfa-containing portion of topiramate, with uveal effusion and forward rotation of the ciliary body closing the angle. This mechanism has previously been reported for sulfa and nonsteroidal drugs [12], and stands in contradistinction to angle closure precipitated by dilation of the pupil with adrenergic sympathomimetics, anticholinergics, and other classes of medications, which are also reported regularly [13].

Diagnostic modalities

The recent interest in topiramate as a potential secondary cause of angle closure underscores the potential importance of structures (*eg*, the ciliary body) that lie near the anterior chamber angle and can greatly influence its configuration, and yet have not traditionally been assessed as biometric risk factors in the clinical evaluation or screening for angle closure. A modality that has the potential to expand our understanding of ocular biometry and angle-closure risk is ultrasound biomicroscopy, a topic of increasing interest in the recent literature on angle closure. In a case series reporting on 26 Korean patients with PACG, as compared with 21 controls with cataract only, Cho *et al.* [14] found significant differences in a number of parameters measured with ultrasound biomicroscopy. In addition to shallower anterior chamber depths and narrower angles among the patients with PACG, as has been reported previously by many investigators [15], Cho *et al.* also found significant differences

in two parameters that cannot be measured by more traditional means. These included a narrower angle opening distance (AOD) at 500 μm (AOD 500) and a shorter trabecular-ciliary process distance among patients with PACG as compared with normals. Whereas the AOD 500 offers a slightly different approach to characterization of the anterior chamber angle, the trabecular-ciliary process distance incorporates previously unavailable information regarding the position of the ciliary body with respect to angle conformation. A significant limitation of this study was the greater than 10-year age difference between cases and controls. Only prospective studies of eyes at risk for angle closure will demonstrate definitively whether this parameter is of genuine benefit in screening and clinical practice.

Ultrasound biomicroscopy has also recently been employed in a recent report by Canlas *et al.* [16] to demonstrate objectively the deepening of the anterior chamber angle after goniosynechialysis. Use of an imaging technique such as ultrasound biomicroscopy in a setting such as this may be of particular benefit in demonstrating the long-term efficacy of chamber-deepening procedures such as goniosynechialysis.

Treatment

Potentially, the most difficult remaining problems in the area of angle closure center on the treatment of the disease. Several publications have attempted to study the management of PACG as well as AAC. One study attempted to assess the benefit of brimonidine as prophylaxis for patients with PACG [17]. The authors reported that brimonidine suppressed the rise in IOP found with a dark room provocative test (DRPT). However, they do not define their diagnostic criteria for PACG, and they only enrolled subjects with large increases in IOP after DRPT for a second DRPT challenge. This design will tend to produce an apparent reduction in IOP on the second challenge because of regression to the mean.

A second paper briefly discussed two small studies of latanaprost treatment in PACG [18]. The first study was a 2-week randomized trial comparing latanaprost use with timolol in Singaporean subjects with at least six clock hours of synechial closure, glaucomatous optic neuropathy with a visual field defect, and IOP > 21 mm Hg. Among 16 subjects in each group, the IOP reduction was 8.8 mm Hg in the latanaprost group and 5.7 mm Hg in the timolol group. With only 2 weeks of observation, however, the possibility cannot be excluded that the pressures observed in the two groups might have converged with longer follow-up. Again, a study design requiring a particular IOP as part of the definition of glaucoma is susceptible to regression to the mean. The second study evaluated latanaprost as an adjunct to other medical therapies for 26 Taiwanese patients with PACG with elevated IOP. Limited data were presented, but IOP was reduced at 1 year. This study, too, is highly susceptible to regression to the mean.

Hayashi *et al.* [19] in Japan assessed the impact of clear cornea phacoemulsification cataract extraction with intraocular lens implantation (PECE) on IOP control in individuals with elevated IOP (either measured or by patient report of symptoms) or PAS and narrow angles on gonioscopy. A total of 74 eyes met these criteria, 6 of which had pseudoexfoliation as well. IOP had decreased from 21.4 mm Hg preoperatively to 14.5 mm Hg at 2 years, with subjects requiring fewer medications as well. The same authors have also reported that the anterior chamber deepens significantly in patients with ACG having PECE, more so than in patients with open-angle glaucoma (OAG) [20]. Over 25 months of follow-up, six subjects (8%) were found to have IOP > 21 mm Hg or to require more medicines than had been used preoperatively. When compared with a group of patients with OAG having PECE, IOP-lowering was significantly greater throughout follow-up in the ACG group. Once again, however, as IOP was used in the definition of PACG but not POAG, follow-up pressure readings for PACG subjects would be subject to regression to the mean, which would artificially increase the apparent postoperative drop in pressure when compared with subjects with POAG.

Several papers have recently been published on the surgical management of patients with AAC [21–23]. Jacobi *et al.* [21] assessed the effectiveness of PECE for individuals who had suffered an AAC attack but still had elevated IOP. All subjects had a history of AAC treated medically, with a mean time between presentation and surgery of 2 days. Some patients had PECE, whereas others had a surgical iridectomy. The authors do not state how surgeons decided which procedure to perform. With an average follow-up of 10 months, the authors found that IOP control was better in the PECE group, and that anterior chamber depth had increased more in these subjects than in those having surgical iridectomy. Visual acuity also improved to a greater extent in the PECE group. Although these results indicate that PECE can be performed successfully in the early after attack state, the retrospective nature of the study precludes drawing firm conclusions about the relative effectiveness of cataract surgery when compared with surgical iridectomy.

Others have studied interventional management of AAC during the acute episode. Lam *et al.* [22,23] in Hong Kong reported two novel approaches to breaking acute attacks. One pilot study compared 10 eyes of 8 patients treated with pilocarpine, timolol, intravenous acetazolamide, intravenous mannitol, and paracentesis to those treated with medications alone and found that IOP was lowered more rapidly when a paracentesis was performed [23]. In the paracentesis group, IOP declined from a

mean of 67 mm Hg to 17 mm Hg after 15 minutes, with mean IOP remaining near 20 mm Hg throughout 2 hours of follow-up. Symptoms were relieved rapidly with paracentesis. The IOP declined more slowly in the medically treated group, but was similar to that of subjects having paracentesis after 2 hours. Although this study indicates that paracentesis can be effective in breaking an attack of AAC and can lead to more rapid resolution, caution is warranted in the widespread use of this technique. Although no significant complications are reported in this study, the possibility of damage to the lens and hyphema, and suprachoroidal infection or intraocular infection is certainly present. Whether long-term outcomes are improved by a slightly more rapid reduction in IOP is not addressed in this small pilot study.

Lam *et al.* [22] also reported the results of a randomized clinical trial to assess the benefit of argon laser peripheral iridoplasty (ALPI) in treating AAC Of 32 patients, 33 eyes received ALPI along with pilocarpine and timolol, whereas 40 eyes of 32 patients were treated with these medications and intravenous acetazolamide and mannitol. IOP was once again lower during the first hour after initiation of therapy in the ALPI group, but was similar between the groups after 2 hours. The most important complications of ALPI were iris burns, corneal changes, and increased anterior chamber reaction.

Conclusions

The safety and efficacy of all these proposed new treatments for ACG and angle closure remain to be established definitively with prospective, randomized, controlled trials. Although such studies are expensive, the weight of currently available data demonstrates that the scope of ACG as a blinding disease warrants this critical investment.

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