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- Objective** To review acute angle closure attacks induced by local and systemic medications.
- Data sources** PubMed literature searches up to August 2011.
- Study selection** The following key words were used for the search: "drug", "iatrogenic", "acute angle closure glaucoma".
- Data extraction** A total of 86 articles were retrieved using the key words. Only those concerning acute angle closure attack triggered by local or systemic drug administration were included. For articles on the same or related topics, those published at later or more recent dates were selected. As a result, 44 articles were included and formed the basis of this review.
- Data synthesis** An acute attack of angle closure can be triggered by dilatation of the pupil, by anatomical changes in the ciliary body and iris, or by movement of the iris-lens diaphragm. Local and systemic medications that cause these changes have the potential to precipitate an attack of acute angle closure. The risk is higher in subjects who are predisposed to the development of angle closure. Many pharmaceutical agents including ophthalmic eyedrops and systemic drugs prescribed by general practitioners and various specialists (in psychiatry, otorhinolaryngology, ophthalmology, medicine, and anaesthesia) can precipitate an acute angle closure attack. The medications include: anti-histamines, anti-epileptics, antiparkinsonian agents, antispasmodic drugs, mydriatic agents, sympathetic agents, and botulinum toxin.
- Conclusion** Since acute angle closure attack is a potentially blinding eye disease, it is extremely important to be vigilant and aware of ophthalmic and systemic medications that can lead to such attacks in predisposed subjects and to diagnose the condition when it occurs.

Introduction

Glaucoma is a potentially blinding disease caused by progressive and irreversible optic neuropathy. The number of persons worldwide estimated to become blind as a result of primary glaucoma is 4.5 million, which accounts for more than 12% of all global blindness.¹ The two major types of glaucoma based on the anatomy of the drainage angle in the eye are primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG). While POAG is an insidious disease, PACG can go through a highly symptomatic acute stage known as an acute angle closure attack which is also termed acute angle closure glaucoma. This article reviews several retrospective case series and case reports on acute PACG induced by local and systemic medications. Acute angle closure is caused mainly by the natural distortion of the anterior segment of the eyeball predisposing an individual to sudden occlusion of the drainage angle. An acute attack of angle closure can be triggered by dilatation of the pupil leading to blockage of the angle by the iris tissue. Local and systemic medications that possess mydriatic effect have the potential to precipitate such an attack acute. The risk is higher in subjects predisposed to the development of angle closure. These subjects may have a shorter eyeball, larger crystalline lens, shallower anterior chamber, and a narrower drainage angle than normal subjects. In which case acute angle closure is a potentially blinding side-effect of many local and systemic drugs, including antipsychotics, antidepressants, monoamine oxidase inhibitors, anti-histamines,

Key words

Acute disease; Anti-allergic agents;
Glaucoma, angle-closure; Mydriatics;
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藥物引致的急性閉角型青光眼

- 目的** 回顧因局部及全身性藥物引致急性閉角型青光眼的文獻。
- 資料來源** 在醫學資料庫PubMed中搜尋至2011年8月發表的文獻。
- 研究選取** 用以搜索文獻的關鍵詞為「藥物」(drug)、「醫原性的」(iatrogenic)及「急性閉角型青光眼」(acute angle closure glaucoma)。
- 資料選取** 利用關鍵詞共搜索到86篇文章。其中只揀選與局部及全身性藥物引致急性閉角型青光眼相關的文獻。遇上有類似課題的文獻，只會選擇近期發表的資料。最後揀選了44篇文章成為本文的基礎。
- 資料綜合** 急性閉角型青光眼可能是由於瞳孔放大而誘發、睫狀體和虹膜形狀有變、以及晶狀體—虹膜隔的移動所致。凡局部及全身性藥物能夠引致這些反應的都有機會導致急性閉角型青光眼。對於容易患有此症的人士來說，誘發的風險更高。很多藥物都可能促成急性閉角型青光眼，包括全科及各專科醫生（精神科、耳鼻喉科、眼科、內科及麻醉科）處方的滴眼液及全身性藥物。這些藥物包括抗組織胺、抗癲癇藥、抗震顫麻痺藥、抗痙攣藥、擴瞳劑、交感性眼藥及肉毒杆菌毒素。
- 結論** 急性閉角型青光眼有可能導致失明，所以醫生處理容易患有閉角型青光眼的人時，對於一些可能導致青光眼的眼部及全身性藥物要加倍小心謹慎。當有病徵時要盡早為病人診斷。

antiparkinsonian agents, antispasmodics, anti-epileptic drugs, mydriatic agents, sympathomimetics, and botulinum toxin.

Methods

A PubMed search of literature up to August 2011 was conducted using the following key words: "acute angle closure glaucoma", "iatrogenic", and "drugs". A total of 86 articles were retrieved. Only those concerning acute angle closure attack triggered by local or systemic drug administration were included. During article selection, prospective studies had a higher ranking than retrospective studies, and case reports were also included. For articles on the same or related topics, those published at later or more recent dates were selected. In all, 44 articles were included and formed the basis of this review. These include 36 case reports, four review articles, three prospective non-controlled studies, and one prospective controlled trial. Other references were also cited for the background and related information of this review article. These included seven prospective non-controlled studies, one prospective controlled trial, three retrospective case series, and five review articles.

Highlights of literature review

Acute angle closure

Acute angle closure attack, formerly termed acute angle closure glaucoma, is sight-threatening and symptomatic, and is characterised by a sudden and marked rise in the intraocular pressure (IOP) due to obstruction of aqueous humour outflow. Symptoms during the acute attack include severe headache and ocular pain with nausea and vomiting and blurring of vision. The attacked eye is red and the pupil is semi-dilated. This is in contrast to the open angle glaucoma which runs an insidious and relatively asymptomatic course. A single episode of an acute angle closure attack can cause blindness, reduction in visual acuity, visual field loss, and glaucomatous optic neuropathy.²⁻⁴ It can also lead to corneal damage, cataracts, and iris atrophy.^{5,6} Acute angle closure attack is defined as: (1) eyes with IOP of above 21 mm Hg together with the presence of three or more of the following clinical signs: conjunctival injection, iris bombe, corneal epithelial oedema, mid-dilated unreactive pupil, and a shallow anterior chamber; (2) patients experience at least two of the following symptoms: ocular pain, nausea and/or vomiting, blurred vision, and seeing halos; (3) occluded angle in the attacked eye.⁷

Risks factors for the development of acute angle closure attack

Ethnic differences appear to be an important risk in the development of acute angle closure attacks; Asians are at higher risk than Caucasians. Among Asians, a Singapore study revealed that Chinese are at higher risk than the Malay and Indians.⁸ However, information on the inheritance of acute angle closure attack is limited. A study in Caucasians suggested that familial incidence of PACG was rare but it had a degree of genetic predisposition, and the disease was triggered by environmental factors.⁹ However, in a recent study on the heritability and sibling risk of narrow angles in Asians that consisted of mainly Chinese, it was found to be highly heritable. This was noted in 58.5% first-degree relatives of patients with PAC (primary angle closure with elevation of the IOP without evidence of glaucomatous optic nerve damage) and PACG (primary angle closure with elevation of the IOP and glaucomatous optic nerve damage). The recurrence risk of siblings having narrow angles was 49%. The relative risk of siblings having narrow angles was 6.57 times higher than the general population.¹⁰

Elderly women are at highest risk of developing acute angle closure attacks.^{8,11-13} Seasonal factors have also been found to be associated with acute angle closure attacks; the frequency was higher in autumn and winter than in spring and summer.¹¹

Patients with narrow irido-corneal angles are at high risk. Eyes with shallow anterior chamber depth, shorter axial length and a thicker lens as compared to normal eyes are at higher risk of developing acute angle closure attacks.^{9,14} With the advancement in technology, anterior segment optical coherence tomography has been used to visualise and capture high-resolution images of the anterior segment of the eye. Another group of investigators found that smaller anterior chamber angles, shorter anterior chamber opening distances, steeper iris root curvatures, and a larger number of quadrants with angle closure were all the risk factors for acute angle closure attacks.¹⁵ In most acute angle closure cases, the aetiology is unknown. However, it is believed that external pharmacological and environmental stimuli play an important role in triggering such attacks in high-risk patients.¹⁶ Topical mydriatics (sympathomimetic or anticholinergic drugs) can trigger acute angle closure due to bunching up of

the peripheral iris at the drainage angle (Figs 1 and 2) and also through the mechanism of pupillary block when aqueous humour flow is blocked at the pupil border. Such effects may also ensue due to systemic and other topical drug treatments that have sympathomimetic (eg nasal decongestants, cocaine, phenylpropanolamine) or anticholinergic (eg muscarinic antagonists, imipramine, fluvoxamine) actions. They may also occur as idiosyncratic reactions to anti-histamines, sulpha-based drugs, antidepressants, and topiramate. Drug-induced acute angle closure attacks may affect either or both eyes simultaneously.¹⁷⁻²⁰

Mechanisms of angle closure

Pupillary block

Pupillary block occurs when the iris border is in firm contact with the anterior lens surface. The contact area blocks the aqueous humour from flowing out

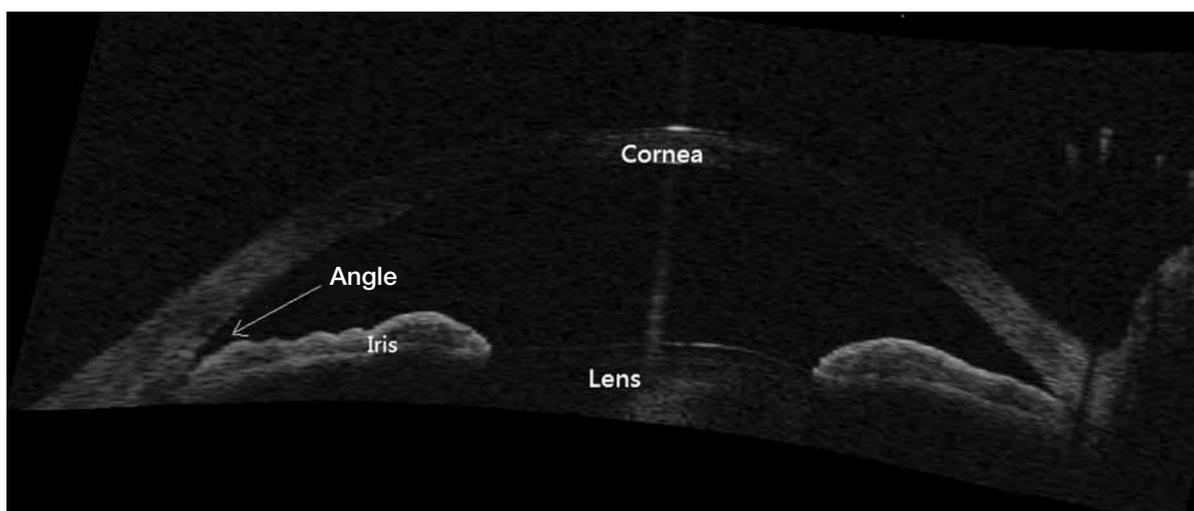


FIG 1. Anterior segment optical coherence tomographic image showing anterior segment structures under physiological conditions

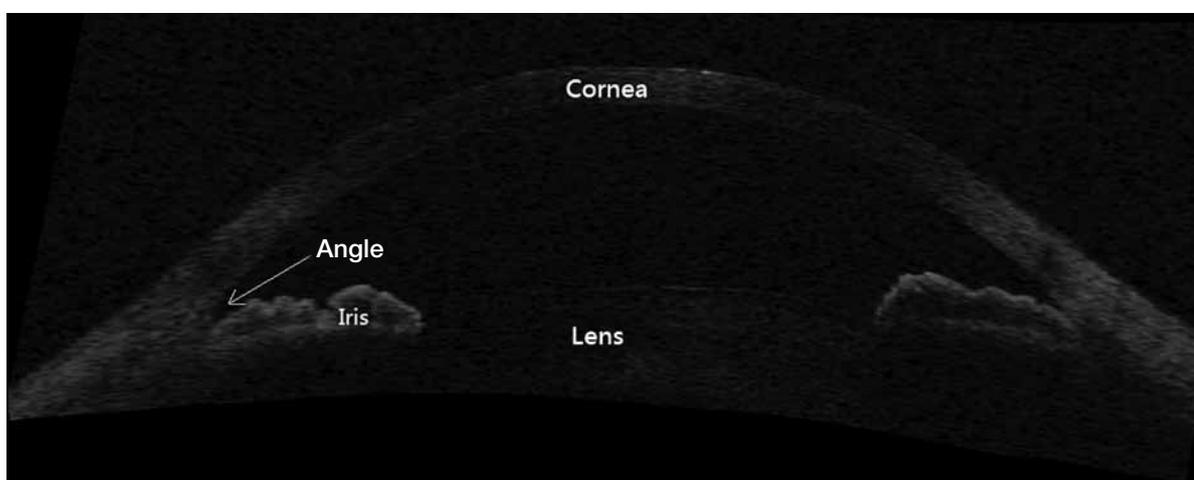


FIG 2. Anterior segment optical coherence tomographic image showing anterior segment structures after pupil dilatation. The iris bunched up at the angle causing narrowing of the angle

of the posterior chamber to the anterior chamber. The pressure that builds up in the posterior chamber pushes the iris root forward and eventually blocks the irido-corneal angle. Pupillary block usually occurs when the pupil is mid-dilated, as in this condition, the force of contact between the posterior iris and anterior lens is greatest.²¹ Interestingly, the iris volume increases in the narrow angle fellow eyes of patients who have a previous attack, but is decreased in open-angle eyes after pupil dilation. This increase in iris volume is associated with further narrowing of the angle.²² In other words, narrow angle eyes with an iris volume increase after dilatation are at higher risk of developing acute angle closure; the risk is highest when the pupil is mid-dilated.

Other angle closure mechanisms

Besides pupillary block, other mechanisms also exist that can close the drainage angle. The position of the ciliary body and the thickness of the lens play a contributory role in the development of angle closure.^{23,24} Subjects with an anterior position of the ciliary body (plateau iris configuration) or a thicker crystalline lens are prone to develop angle closure. There may be a combination of all the above factors in the development of angle closure. In some cases, uveal effusion can cause forward displacement of the iris-lens diaphragm resulting in angle closure. Uveal effusion refers to an abnormal collection of fluid in the suprachoroidal space, pushing the ocular tissues especially the iris and the lens to a more anterior position. Uveal effusion may occur in ocular inflammation, after ocular laser treatment or intraocular surgery.

Drugs causing acute angle closure

Most systemic drug profiles listing glaucoma as a contra-indication or an adverse effect are concerned with inducing acute angle closure. Several classes of drugs have potential to trigger an acute attack of angle closure.

Topical mydriatics

Topical mydriatics that dilate the pupils and cycloplegics that relax the ciliary muscle are mainly required for detailed fundus examination in out-patient clinics and during surgery, refraction and treatment for amblyopia. They are also used in the management of uveitis to prevent adhesion of the iris to the lens (posterior synechiae). Their cycloplegic effect can reduce the ocular pain and photophobia in ocular inflammatory diseases. Atropine, homatropine, cyclopentolate and tropicamide possess anticholinergic properties, while phenylephrine has sympathomimetic properties. The overall frequency of topical mydriatic-induced acute angle closure

attacks is around 0.03% (in white subjects aged >55 years).^{25,26} It is less than 1% even in subjects with shallow anterior chamber/occludable angles and is less than 0.1% in Asians.²⁷

Anticholinergic drugs

Anticholinergic agents block the neurotransmitter acetylcholine in the central and the peripheral nervous system. They inhibit the parasympathetic nerve transmission by blocking the acetylcholine receptors resulting in paralysis of smooth muscles present in the gastro-intestinal and urinary tracts, lungs, and elsewhere. Ipratropium bromide is used for the treatment of chronic obstructive pulmonary disease and acute asthma. It blocks the muscarinic acetylcholine receptors in the smooth muscles of these airways thus opening them up. Their anticholinergic effect also acts on the iris smooth muscle, resulting in pupil dilatation. Ipratropium bromide is often used in combination with β_2 adrenoceptor agonists. There have been numerous reports on the induction of acute angle closure attack following the use of nebulised ipratropium bromide in combination with β_2 agonists.²⁸⁻³⁶ Anticholinergic drugs are also used for the treatment of gastro-intestinal disorders, Parkinson's disease, and genitourinary disorders. Atropine belongs to this class of drugs and is used systemically to treat bradycardia in patients undergoing general anaesthesia. It is one of the most common systemically administered drugs that induces acute angle closure attacks, and has been reported to be the possible cause in patients undergoing orthopaedic, cardiac, and oral surgery under general anaesthesia.³⁷⁻³⁹

Adrenergic agents

These include drugs used topically such as phenylephrine eye drops, nasal ephedrine, nebulised salbutamol, and given systemically such as epinephrine in the treatment of anaphylactic shock. Bronchodilators administered in nebulised form have been reported to precipitate bilateral acute angle closure attack in a patient suffering from acute bronchitis who eventually went blind despite medical and surgical interventions.⁴⁰

Drugs for upper respiratory infections

Cough mixtures and anti-cold medications contain anticholinergic and epinephrine ingredients, both of which have pupillodilating effects. Lai et al¹² reported that 24% of patients suffering from acute angle closure attacks had upper respiratory infections, 36% of whom took anti-cough mixtures prior to the attack. Rudkin et al⁴¹ reported a patient with bilateral acute angle closure attack after taking an over-the-counter cold and flu medications that contained

active ingredients of atropa belladonna which was a herb with anticholinergic properties. The diagnosis of acute angle closure may be missed in these patients because symptoms like red eye, ocular pain, and headache may be mistaken as symptoms associated with upper respiratory tract infections. Onset of visual difficulty and the presence of a semi-dilated pupil may be clues to an attack of acute angle closure.

Anti-depressants

Tricyclic antidepressants (TCAs) like imipramine have been widely used in the past and are still used occasionally for the treatment of depressive illness. Their anticholinergic properties can precipitate acute angle closure attack in predisposed individuals.⁴²⁻⁴⁴ Although selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors have largely replaced TCAs, several of these agents like citalopram, paroxetine, and venlafaxine that increase the body serotonin levels may cause mydriasis. Acute angle closure has also been reported in patients receiving these classes of anti-depressants.^{19,45-48} The pathophysiological basis for acute angle closure in relation to SSRI antidepressant medications remains unclear. Citalopram may have a direct action on the iris or ciliary body muscles through serotonergic or anticholinergic mechanisms or both. Various reported cases highlight the importance of awareness of acute angle closure in psychiatric patients after the prescription of these classes of anti-depressants.

Anti-convulsants

Topiramate is a sulphamate-substituted monosaccharide used in the treatment of seizures, and in the prophylaxis of migraine. A few reports suggest an association between topiramate therapy and acute angle closure.⁴⁹⁻⁵² One report documented uveal effusion in both eyes causing bilateral acute angle closure in a 40-year-old woman after taking oral topiramate for 10 days, which resolved after discontinuation of the drug. Topiramate causes ciliary body oedema, uveal effusion and relaxation of the zonules, resulting in a forward shift of the iris-lens apparatus thus closing the angle abruptly. As the mechanism of topiramate-induced angle closure does not involve any pupillary block, standard treatments for acute angle closure (peripheral iridectomy and topical miotics) are not effective in this type of angle closure glaucoma. Fortunately, this type of drug-induced acute angle closure is rare.

Anti-histamines

Anti-histamines such as diphenhydramine, chlorpheniramine, and loratadine block the effects

of histamine released by the body in response to allergen exposure. Their mild anticholinergic pharmacological effect may induce mydriasis and precipitate acute angle closure in predisposed patients.⁵³

Drugs used during general anaesthesia

Acute angle closure is a rare complication of general anaesthesia. There have been case reports on unilateral or bilateral acute angle closure attacks following general anaesthesia.^{54,55} In one instance, there was bilateral acute angle closure after cervical spine surgery under general anaesthesia in a hypermetropic patient, for which the likely trigger was use of ephedrine, but nefopam administration and the prone position during surgery could also have been implicated.⁵⁶ As already discussed, anti-muscarinic agents, such as atropine and ipratropium bromide that are used as pre-anaesthetic medications, can cause pupil dilatation and precipitate an attack of acute angle closure. Moreover, salbutamol, a β_2 adrenoceptor agonist can compound the problem as it increases aqueous humour production and thus acts synergistically with anti-muscarinic agents to raise the IOP. It is important to note that iatrogenic acute angle closure attack under these circumstances can be masked by the general anaesthesia and timely treatment to prevent visual loss is critical.

Sulphamate derivative

Sulpha-based drugs like acetazolamide, hydrochlorothiazide, cotrimoxazole, and topiramate that have no pupillodilating effect can still induce acute angle closure by causing ciliary body oedema and forward movement of the iris-lens diaphragm.^{18,20} They induce 'non-pupillary block' angle closure as an idiosyncratic reaction in patients with narrow as well as open angles. There has been an interventional case report of a 76-year-old man who developed bilateral angle closure attacks with extensive choroidal detachment following administration of oral acetazolamide, immediately after routine cataract extraction and intraocular lens implantation.⁵⁷ Rapid clinical improvement occurred after cessation of acetazolamide use and high-dose intravenous steroid therapy. Although extremely rare, this adverse effect should be considered in patients who develop acute bilateral angle closure and choroidal effusion after cataract surgery. Ironically, acetazolamide, an IOP-lowering drug that is used for the treatment of all kinds of glaucoma, can itself induce acute angle closure through an idiosyncratic reaction.

Miscellaneous drugs

Botulinum toxin is widely used nowadays for medical and cosmetic treatment. Periocular injection of

botulinum toxin for the treatment of blepharospasm has been reported to precipitate an acute attack of angle closure. It was believed that the toxin diffused back from the site of injection to the ciliary ganglion inhibiting the pupillary sphincter, which resulted in pupil dilatation and caused an acute closure of the angle.⁵⁸

Cabergoline, an ergot derivative, is a potent dopamine receptor agonist. It is frequently used as a first-line agent in the management of prolactinomas. There has been a case report of bilateral acute angle closure attack after its oral use for the treatment of galactorrhoea.⁵⁹ Ophthalmic ultrasound demonstrated effusions in the vicinity of the ciliary body as well as an anterior rotation of the ciliary body as the possible causes of acute angle closure.

Sympathomimetic drugs such as phendimetrazine and ephedrine that are used as postoperative anorexiant may cause ciliochoroidal effusion, making shallow anterior chamber, resulting

in acute angle closure.⁶⁰

Conclusion

Acute angle closure is a blinding eye emergency. Visual loss is preventable if the condition is recognised early and managed properly. Many systemic drugs used in various specialties may precipitate acute angle closure attacks that can involve both eyes simultaneously. Unfortunately the ocular symptoms may be masked by symptoms of the underlying systemic disease or the patients may be under general anaesthesia. Female gender, a history of intermittent blurring of vision with or without ocular pain and headache, and a sensation of seeing halos should alert physicians that the patient may be at risk of developing acute angle closure. Clinicians should be aware and mindful of possible drug-induced acute angle closure and the symptoms during an attack. Whenever there is doubt, ophthalmological consultation is recommended.

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