The syndrome of closed-angle glaucoma

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Since Barkan (1938) first clearly distinguished between open- and closed-angle glaucoma (CAG), attention has been directed intermittently to precipitating angle closure (AC), by creating an experimental situation in which it can be predicted with a high degree of probability that a particular eye will develop CAG.

The methods used have mainly depended upon manipulating the autonomic nervous system:
1. Parasympathetic inhibition (dark room tests, parasympatholytic drugs)
2. Sympathetic stimulation (phenylephrine)
3. Parasympathetic stimulation (reading provocative tests, miotics)
4. Combined sympathetic and parasympathetic stimulation (pilocarpine and phenylephrine).

Such a varied group of precipitating events does not bespeak a unitary disease. The purpose of this paper is to define the main clinical syndromes, and explain apparent inconsistencies.

Material and methods

A method for provoking eyes which are at risk of developing CAG by using pilocarpine and phenylephrine simultaneously has been described previously (Mapstone, 1974c). Altogether 20 eyes of 20 patients who each reacted positively to pilocarpine and phenylephrine, were re-provoked with 0.5 per cent tropicamide. Drops were instilled three times initially at 1 min intervals, an anterior segment photograph taken, and the intraocular pressure (IOP) was measured. Thereafter, at approximately half-hourly intervals, the IOP was measured and a photograph of the anterior segment was taken. As soon as the IOP had risen significantly (more than 8 mmHg) with gonioscopic evidence of partial or complete AC, intravenous acetazolamide (Diamox) 500 mg, thymoxamine 0.5 per cent, and pilocarpine 2 per cent were given. If, after 2 h the IOP had not risen significantly, pilocarpine 2 per cent was instilled at half-hourly intervals. Subsequently, slides were projected and P/C* ratios calculated.

Another 41 eyes from 41 patients were provoked with pilocarpine and phenylephrine because the contralateral eye had had either an acute attack of CAG or a positive provocative test with pilocarpine and phenylephrine. These eyes form part of a larger series, details of which will be published separately; their inclusion in this paper depends upon the fact that the results of the provocative tests using pilocarpine and phenylephrine were negative. The 41 eyes were re-provoked with tropicamide 0.5 per cent using the methods described above.

Results

Of the 20 eyes which had a positive result when provoked with pilocarpine and phenylephrine simultaneously (P and P), eight developed CAG on re-provocation with tropicamide (T); 12 had negative results. For the purposes of this paper the significant measurement is the P/C ratio at which AC occurred or, if the result of the provocative test was negative, the maximum P/C ratio that was attained. This gives four P/C ratios:
1. The P/C ratio in P and P positive eyes at the time of AC; these eyes subsequently had a positive result with T (eight eyes, Table I)
2. The P/C ratio in P and P positive eyes at the time of AC; these eyes subsequently had a negative result with T (12 eyes, Table I)
3. The P/C ratio in P and P positive eyes which subsequently had a positive result with T—that is, the P/C ratio at which AC occurred with T (eight eyes, Table II)
4. The P/C ratio in P and P positive eyes which subsequently had a negative test with T—that is, the maximum P/C ratio attained on provocation with T (12 eyes, Table II).

Of the 41 eyes at risk of developing AC which had a negative provocative result with P and P, nine subsequently developed AC on re-provocation with T; 32 results were negative. This again gives four P/C ratios:
1. The maximum P/C ratio during provocative testing with P and P in eyes which subsequently developed a positive result with T (nine eyes, Table I)
2. The maximum P/C ratio during provocative testing with P and P in eyes which subsequently developed a negative result with T (32 eyes, Table I)
3. The P/C ratio in T positive eyes at the time of AC which had previously had a negative result with P and P (nine eyes, Table II)
4. The maximum P/C ratio in T negative eyes which had previously had a negative result with P and P (32 eyes, Table II).

*P and C = pupillary and corneal diameter in the horizontal meridian

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Discussion

In the interpretation of the results of provocative testing, it is assumed that equal pupillary states reflect equivalent autonomic drug delivery to the anterior segment as a whole—that is, if two groups of eyes are dosed with the same autonomic drug, and subsequently, there is no significant difference between their respective P/C ratios, it can be assumed that equivalent amounts of drug are present in the anterior segment. Any difference in subsequent behaviour is ascribed to differing autonomic response or to other nonautonomic factors.

It is reasonable to suppose (Table I) that in each of the four separate groups there is no signifi-

The mean P/C ratios are shown in Tables I and II, and examples of results of provocative tests in Figs 1, 2, 3, and 4 for each of the four groups.

Application of Student's t test to the mean P/C ratios in all possible combinations taken two at a time shows no significant difference between any two means in either Table I or Table II. However, a highly significant difference was observed (at the 1 per cent level) between any mean from Table I and any mean from Table II.

Key to Figs 1, 2, 3, and 4: F = phenylephrine; IVA = intravenous acetazolamide; P = pilocarpine; T = thymoxamine; Tr = tropicamide.

FIG. 1 Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line) — both positive

FIG. 2 Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line) — P and P positive, T negative

FIG. 3 Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line) — P and P negative, T positive

FIG. 4 Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line) — both negative
Table I  P/C ratios on pilocarpine and phenylephrine testing

<table>
<thead>
<tr>
<th>Tropicamide (subsequent)</th>
<th>Pilocarpine and phenylephrine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>0·39 (8)</td>
<td>0·38 (9)</td>
</tr>
<tr>
<td>Negative</td>
<td>0·38 (12)</td>
<td>0·37 (32)</td>
</tr>
</tbody>
</table>

Table II  P/C ratios on tropicamide testing

<table>
<thead>
<tr>
<th>Pilocarpine and phenylephrine (previous)</th>
<th>Tropicamide</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>0·49 (8)</td>
<td>0·51 (12)</td>
</tr>
<tr>
<td>Negative</td>
<td>0·54 (9)</td>
<td>0·49 (32)</td>
</tr>
</tbody>
</table>

cant difference in the augmentation of sympathetic and parasympathetic activity. Similarly, parasympathetic activity of the separate groups is equally inhibited (Table II). There is, however, a highly significant difference between Tables I and II, largely because of the variations in parasympathetic activity—that is, angle closure occurs when the pupil diameter is significantly larger with tropicamide than with pilocarpine and phenylephrine. Four types of anterior segment therefore exist in eyes at risk of developing CAG:

1. Provocation with simultaneous P and P or T are both positive
2. P and P is positive but T negative
3. P and P is negative but T positive
4. Both P and P and T are negative. (This group will not be discussed in this paper.)

In a previous paper (Mapstone, 1974c) it was shown that sympathetic activity was not necessary for angle closure to occur, but that it might actively pull a sphincter to mid-dilatation and allow the results of parasympathetic activity to close the angle. It was also shown that, in the absence of parasympathetic activity, closed-angle glaucoma did not occur. The results show that angle closure occurs with both parasympathetic inhibition (tropicamide) and excitation (pilocarpine). It is therefore a necessary consequence that closed-angle glaucoma can result from the operation of more than one mechanism. How then can the experimental observations be related to the clinical situations in which it is known that closed-angle glaucoma can occur?

The problem essentially resolves itself into an explanation of how iris can become apposed to cornea. Theoretically and experimentally this can happen in two ways (Mapstone, 1974a, b, c), either a 'push' from behind, or a 'pull' from in front of the iris plane. Considering each mechanism separately:

1. A 'push' from behind

A plot of sphincter pupil block force against pupil size has the form shown in Fig. 5, and it can be seen that with a mid-dilated pupil—however obtained—pupil block force is at a maximum and iris stroma relaxed. Given a suitably predisposed anterior segment, some eyes will proceed inexorably to an acute attack if the pupil is placed in this position because of the increase in pressure in the posterior chamber. This mechanism depends upon pupil block alone, and it is unnecessary to invoke adjuvant parasympathetic or uveo-scleral effects.

2. A 'pull' from in front

This mechanism requires pupil block generated by a pupil in miosis or mid-dilatation, and a parasympathetically (ciliary body) induced increase in trabecular meshwork outflow. As a result a pressure deficit is produced between the anterior and posterior chambers, 'pulling' the iris on to the cornea (Mapstone, 1974c). Theoretically, uveo-scleral mechanisms may also be involved.

In any one eye these two mechanisms may act separately or in combination, and can result in three main types of primary closed-angle glaucoma—namely:

A. 'PUSH' CAG

Eyes exist in which the result of provocation with simultaneous pilocarpine and phenylephrine is negative, but that with a parasympatholytic such as tropicamide is positive. The main difference between the two is that angle closure occurs with tropicamide at a pupil diameter significantly larger than with pilocarpine and phenylephrine—that is, the iris—in the presence of too much parasympa-

![FIG. 5 Plot of sphincter pupil blocking force (pbf) against pupillary diameter during normal pupillary play of light reflex. It can be seen that pbf is at a maximum in mid-dilatation and at a minimum when the pupil is small or widely dilated](http://bjo.bmj.com/Br J Ophthalmol: first published as 10.1136/bjo.60.2.120 on 1 February 1976. Downloaded from http://bjojb.co.uk/)
thetis activity—is too taut to become sufficiently bome to produce AC. With tropicamide, however, the pupil dilates enough for pupil block alone to close the angle. Too much parasympathetic activity precludes AC and either sympathetic or parasympatholytic activity is necessary.

There are two conditions in which 'Push' CAG can occur:

1. Passive pupillary dilatation glaucoma (PPDG). Here parasympathetic activity is at a minimum and the experimental model is a positive dark room test or cycloplegic test. Experimentally 10 per cent of positive provocative results are in this category (Mapstone, 1976).

2. Active pupillary dilatation glaucoma (APDG). The experimental model is a positive provocative result using a sympathomimetic—for example, phenylephrine, with a mechanism similar to PPDG. The clinical counterpart is an acute attack precipitated by 'emotion', and there are many reports in the literature suggesting that this can happen. Such a proposition is difficult to substantiate, and for the moment must remain an interesting possibility.

B. 'Pull' CAG

There are eyes in which the result of provocation is positive with simultaneous pilocarpine and phenylephrine but consistently negative with tropicamide—that is, too little parasympathetic activity in the presence of pupil block is insufficient to produce CAG. Additional trabecular meshwork outflow is necessary to pull the iris on to the cornea, the two mechanisms acting synergistically.

Clinically there is a sharply demarcated group of patients in whom the history is characteristic, episodes of intermittent CAG being precipitated by parasympathetic anterior segment activity—for example, reading, knitting, and writing. The experimental model is a positive provocative reading test (Higgitt and Smith, 1955), and CAG precipitated by parasympathomimetic drugs (for example, phos- pholene iodide—Jones and Watson, 1967). At the termination of a reading provocative test the angle is open and the pupil mobile. It must be assumed, therefore, that during miosis sufficient of the angle is closed—temporally or spatially—for an outflow deficit to occur.

However, most patients in this category do not give such a history and it may be relevant that most intermittent and acute CAG episodes occur in the evening, after meals and at periods of quietude rather than bustle, that is, in parasympathetic man.

C. 'PUSH-PULL' CAG

Finally, eyes exist in which provocation with simultaneous pilocarpine and phenylephrine or with tropicamide both produce positive results—that is, either pupil block alone or in combination with trabecular meshwork outflow—will produce AC. Approximately 40 per cent of eyes are in this category. An example is shown in Fig. 1.

The consequences of the above findings for provocative testing and management of the contralateral eye are described in subsequent papers.

Summary

Closed-angle glaucoma is the result of two mechanisms acting either separately or in combination:

1. Pupil block creates a greater pressure in the posterior than in the anterior chamber, pushing the iris on to the cornea.

2. Increased trabecular meshwork outflow in the presence of pupil block creates a lower pressure in the anterior chamber than in the posterior, pulling the iris on to the cornea.

Three main groups of eyes manifest closed-angle glaucoma:

(i) Mechanism (1) is necessary and sufficient, but (2) precludes the development of angle closure.

(ii) Mechanism (1) is necessary but insufficient. Mechanism (2) must also be present.

(iii) Mechanism (1) is necessary and sufficient but (1) and (2) may combine to produce an acute attack.

I should like to thank colleagues for referring patients, Miss E. Grogan for secretarial help, and Mr R. McBride for preparing diagrams.

References

MAPSTONE, R. (1974a) Ibid., 58, 36
——— (1974b) Ibid., 58, 41
——— (1974c) Ibid., 58, 46
——— (1976) Ibid., 60, 115