One model of outflow damage

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SUMMARY The intraocular pressure, facilities of outflow, and Po/C ratios of 3 groups of eyes were compared. Group 1 consisted of 20 eyes at risk to the development of acute closed-angle glaucoma that had been treated with prophylactic pilocarpine for at least 8 years. Group 2 consisted of 20 eyes at risk that had received no treatment and had been followed up for at least 4 years. Group 3 comprised 20 eyes in which there was no evidence of glaucoma. There were highly significant differences between the 3 groups. The 60 eyes were then provoked with pilocarpine and phenylephrine; 90% of Group 1, 75% of Group 2, and none of Group 3 developed significant gonioscopic angle closure. These results suggest that asymptomatic partial angle closure was the cause of the observed changes and provide a naturally occurring model of one mechanism that can produce outflow damage without clinical symptoms.

There is no reason to suppose that acute, chronic, or intermittent closed-angle glaucoma is the only manifestation of angle closure in eyes at risk, and partial angle closure—without substantial changes in outflow or pressure—has been demonstrated in some (Mapstone, 1977a). There is therefore good reason to suppose that asymptomatic partial angle closure may occur spontaneously in some eyes, since the pressure increase can be small. It has also been shown that one episode of acute closed-angle glaucoma can leave an eye with a reduced facility of outflow, but the amount of damage is clinically insignificant, and the eye remains normotensive after an iridectomy (Mapstone, 1977b).

An eye at risk to the development of closed-angle glaucoma (because the fellow eye has had a spontaneous acute attack) is usually treated with a prophylactic peripheral iridectomy. There are other options. For example, it can be treated with miotics, or, if it does not develop a positive provocative test, may simply be observed. Since some of these eyes may develop spontaneous partial angle closure, it seems reasonable to suggest that they may, over the years, develop an increased pressure and outflow damage caused by a partial angle closing mechanism. This paper investigates that hypothesis.

Material and methods

The hospital records were searched for patients who had had acute closed-angle glaucoma in 1 eye

and the fellow eye treated with prophylactic pilocarpine drops. The criteria for selection were: (1) Closed-angle glaucoma in 1 eye treated by surgery, the fellow eye treated with pilocarpine drops; (2) a minimum period of treatment with pilocarpine of 8 years; (3) no evidence that the pilocarpine-treated eye had ever developed intermittent or acute closed-angle glaucoma; and (4) a gonioscopically open angle with no peripheral anterior synechiae.

Twenty-two patients were found and two rejected because of peripheral anterior synechiae, that is, 20 patients were left for study.

The 20 patients were instructed to continue their pilocarpine drops as was their habit, and on the morning of test, at zero hours, intraocular pressures were measured and facility of outflow recorded. Then a pilocarpine-phenylephrine provocative test was done.

Another group of 20 eyes from 20 patients were then randomly selected from a larger group of 32 patients by the following criteria: (1) Closed-angle glaucoma in 1 eye treated by surgery, the fellow eye *not* treated and its behaviour studied prospectively; (2) a minimum follow-up period of 4 years; (3) no evidence that the untreated eye had ever developed spontaneous intermittent or acute closed-angle glaucoma or a positive provocative test; (4) a gonioscopically open angle with no peripheral anterior synechiae.

The 20 eyes on no treatment were then investigated as described above.

Finally, 20 patients were randomly selected from a group of 89 who had no evidence of glaucoma but had had a pilocarpine-phenylephrine provocative

Fig. 1 Result of a provocative test in 3 groups of eyes. Solid line: 20 eyes that had received prophylactic miotics for at least 8 years. Interrupted line: 20 fellow eyes at risk, on no treatment, and followed up for at least 4 years. Dotted line: 20 eyes with no evidence of glaucoma. Mean and standard error recorded. P = pilocarpine. F = phenylephrine

test. The statistical test used was a Kruskal-Wallis one-way analysis of variance by ranks. Gonioscopy was done on every patient at the start and termination of the test.

Results

The mean intraocular pressure (Po), facility of outflow (C) and Po/C ratio for the 3 groups of eyes are shown in Table 1.

The first null hypothesis tested is that there is no significant difference in the mean intraocular pressure of the 3 samples. The calculated Kruskal-Wallis statistic was $H = 43.6$ and the probability of a value as large as this is < 0.001 . The null hypothesis is therefore rejected and the alternative hypothesis accepted—that is, the mean intraocular pressures of the 3 samples are so different that they cannot have been drawn from the same population.

The second null hypothesis tested is that there is no significant difference in the mean outflow facilities of the 3 samples. This again is rejected ($H = 37.2$, $P < 0.001$), and the alternative hypothesis, that there is a difference, accepted.

Finally, the same result applies to Po/C ratios ($H = 42.5$, $P < 0.001$).

The result of a provocative test in the 20 eyes on miotics is shown in Fig. 1. The first dose of pilocarpine and phenylephrine decreased pressure from a mean of 20.1 to 18.9 mmHg and decreased outflow from 0.2 to 0.19 $\mu\text{l/mmHg/mm}$. The second dose

increased pressure from a mean of 18.9 to 20.5 mmHg, and outflow changed from 0.18 to 0.19. Two patients developed acute closed-angle glaucoma and 16 gonioscopic closure of part of the angle during the test.

In the 20 contralateral eyes at risk on no treatment the result of a provocative test is shown in Fig. 1. The first dose of pilocarpine and phenylephrine decreased pressure from a mean of 16.4 to 15.7 mmHg, and outflow increased from 0.19 to 0.20. After the second dose pressure decreased from 15.7 to 15.0 mmHg, and outflow increased from 0.20 to 0.24. No eye developed a positive test, and in 15 gonioscopic closure of part of the angle occurred during the test.

Finally, in 20 normal eyes (Fig. 1) the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 14.5 to 13.7 mmHg, and outflow increased from a mean of 0.26 to 0.34. After the second dose pressure increased to 13.9 mmHg, and outflow to 0.38. No eye developed gonioscopic closure of any degree.

Discussion

At the start of the experiments all angles were open and free of peripheral anterior synechiae. There is no reason to suppose, nor evidence to suggest, that the outflow system in eyes at risk to the development of closed-angle glaucoma is abnormal. There is, therefore, every reason to suppose that—in the absence of angle closure—mean intraocular pressure and outflow facility in a sample of eyes at risk would not differ significantly from values obtained in a group of eyes in whom there was no evidence of glaucoma. The results show, however, that this null hypothesis must be rejected for pressure, outflow and Po/C ratios. What, then, is the explanation?

Firstly, it is possible that pilocarpine in some way damages the outflow system. The possibility must be

Table 1 Mean intraocular pressure (Po), facility of outflow (C), and ratio Po/C for 3 groups of eyes

	Miotics	No treatment	Normals
Po	20.1	16.4	14.6
C	0.198	0.187	0.259
Po/C	138.4	102.6	63.3

allowed but is improbable, since in 20 eyes at risk that had received no miotics outflow at the start of the test was also reduced. Secondly, it could be argued that during tonography, in some narrow-angle eyes, the tonometer produces segmental iridocorneal contact and therefore low C readings. This may, of course, happen, but its significance is not immediately apparent. It would not, however, produce a significant pressure change.

The final possibility is that a raised pressure and outflow damage are a consequence of intermittent partial angle closure. There are two possibilities. (1) The mere apposition of iris to trabecular meshwork in some way damages the outflow system. This in turn produces a raised pressure. A priori this is an improbable explanation. (2) Intermittent partial angle closure produces an intermittently raised pressure which over the years is *the* cause of outflow damage. A potential vicious circle is generated which, once operating, no longer needs partial angle closure to sustain it.

The 20 eyes on long-term miotics all had narrow angles, and it is interesting that 80% developed partial angle closure but only 2 a positive provocative test with complete closure (normally 60 to 70% of eyes at risk develop a positive provocative test (Mapstone, 1976)). In the 20 fellow eyes on no treatment 75% developed partial angle closure and none a positive test.

The fact that in neither group had angle closure of any degree been seen—apart from during a provocative test—does not invalidate the argument. For if each angle is gonioscoped once a year and examined for 5 minutes that represents approximately 1 one-hundred-thousandth part of the year. It should occasion no surprise that partial angle closure had not been seen before a provocative test was done.

It is suggested, therefore, that the reduced outflow facilities in the eyes at risk are a consequence of intermittent partial angle closure, which, because it is partial, does not produce overt symptoms.

These observations have clinical implications, for they provide an explanation of one mechanism at work in some eyes with 'primary' ocular hypertension and open-angle glaucoma (Mapstone, 1978).

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References

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