Cholinergic Supersensitivity of the Iris in Primary Open Angle Glaucoma. A Clinical Study

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Summary

Twenty patients with untreated primary open angle glaucoma (POAG) were tested for the presence of cholinergic supersensitivity of the iris using a 0.1% solution of pilocarpine. Nineteen patients had a significant miotic response compared to six of a group of twenty control subjects. We believe that an ocular parasympathetic neuropathy may be an important factor in promoting or perpetuating elevated intra ocular pressure in POAG. The mechanism of this is suggested and several possible areas of further study discussed.

In 1857 Von Graefe described the condition we know today as primary open angle glaucoma (POAG) as amaurosis with excavation of the optic nerve,¹ to which Donders in 1862 added increased ocular tension without congestion.² In 1938 Barkan with his improved gonioscopes separated primary glaucoma into two groups, the first with a deep anterior chamber and open angle, and the second with a shallow anterior chamber and a drainage angle closing to produce a rise in tension.³

Currently POAG may be defined as a chronic condition characterised by a typical pattern of visual loss, glaucomatous optic atrophy, and elevated intraocular pressure (IOP) in the presence of an open iridocorneal angle of normal appearance. The cause remains unknown. It is widely assumed that high IOP is an intrinsic part of the disease process despite the existence of low tension glaucoma and ocular hypertension. Furthermore it is generally accepted that this is due to inadequate aqueous egress through the outflow pathways.

Nesterov proposed canalicular blockage as the site of aqueous obstruction with collapse of the inner wall of Schlemm's canal against the outer wall.⁴ This seems to correlate with the frequent absence of blood in Schlemm's canal in eyes with POAG when viewed gonioscopically, even when the tension is normal.⁵ Furthermore, Grierson (Table I) in a study of outflow pathways documents similar histological features in aged and glaucomatous eyes, the exceptions being closure of Schlemm's canal and narrowing of collector channels found in POAG but not as a feature of ageing.⁶

The alkaloid pilocarpine in therapeutic concentration of 0.5% to 4% was the first line treatment for POAG for over one hundred years following its introduction by Weber in 1876.⁷ The most widely held explanation of its action is that it stimulates acetylcholine release at the neuromuscular junction of the parasympathetic short ciliary nerves and ciliary muscle, tautening the scleral spur and opening the trabecular meshwork and Schlemm's canal thus facilitating aqueous

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drainage. Curiously the neuromuscular substrate which pilocarpine alters has received scant investigation in the pathogenesis of elevated IOP in POAG. Additional evidence for disordered neuromuscular activity in POAG may be adduced from the frequent observation of early presbyopia in younger patients with POAG.⁸ Also examination of the pupil in early cases has revealed a bilateral reduction in the later phases of pupil constriction with more marked changes in all phases of constriction, and an increased latent period in more advanced cases which the authors, however, concluded was a fatigue phenomenon affecting hypothalamic sympathetic pathways.⁹

We hypothesised that increased IOP in POAG might be caused by an abnormality of the parasympathetic innervation of the longitudinal fibres of the ciliary muscle. To test this hypothesis we investigated cholinergic supersensitivity of the iris in untreated POAG versus a control group to a weak cholinergic agent 0.1% pilocarpine, since its innervation is similar and observation straightforward.

Patients and Methods

The study group was taken from non-diabetic new referrals to the department. Twenty consecutive glaucoma suspects later proven to have bilateral POAG were tested with 0.1%

pilocarpine eye drops. Patients already on topical treatment or who had undergone previous eye surgery were rejected and tonometry was delayed until after the test.

The control group was taken from a non glaucomatous population with normal IOP. Diabetics and those with a first degree family history of glaucoma were excluded. Subjects with dry eyes and corneal abnormalities were also excluded from both groups. Controls were selected by age and sex to match individuals of the experimental group. Age was matched within three years of date of birth. All subjects in both groups were Caucasian. The composition of each group is listed in Table II.

Criteria for the diagnosis of POAG

Eyes were diagnosed as suffering from POAG on the triple basis of optic disc cupping, visual field defect of nerve fibre bundle distribution, and an IOP above 22mm of mercury. Discs were considered cupped if the vertical cup:disc ratio exceeded 0.6. Visual fields were measured with the appropriate near correction on a Friedmann Mark II analyser. IOP was measured by Goldmann applanation tonometry.

Observations

Observations were made by the authors in the windowless outpatient clinic. The illumi-

Table 1 Features associated with ageing, primary open angle glaucoma (POAG) and secondary open angle glaucoma (SOAG).

Feature	Aging	POAG	SOAG
Narrowing of collector channels	No	Yes	?
Closure of Schlemm's canal	No	Yes	Yes
Loss of giant vacuoles	Yes	Yes	Yes
Accumulation of extracellular materials in the endothelial meshwork	Yes	Yes	Yes
Thickening of trabeculae	Yes	Yes	Yes
Accumulation of wide spacing collagen	Yes	Yes	Yes
Fusion of trabeculae	Yes	Yes	Yes
Increased phagocytosis	Yes	Yes	Yes
Thickened scleral spur	Yes	Yes	Yes
Hyperplasia at anterior border of the meshwork	Yes	Yes	Yes
Cellular activation	?	Yes	Yes
Loss of meshwork cells	Yes	Yes	Yes

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Table II *Composition of Sample Groups*

	<i>POAG subjects</i>	<i>Control subjects</i>
Average Age	66.25 years	66.0 years
Age Range	47 - 81 years	47 - 80 years
Standard deviation age	9.6 years	9.5 years
Male/Female ratio	1:2	1:2
Total Number	20	20
IOP	Range 23-38mm Hg Mean 26.6mm Hg	Range 12-21mm Hg Mean 16.7mm Hg
Initial pupil diameter	Range 2-6mm Mean 4.0mm	Range 2-6.5mm Mean 3.9mm

nation was dim enough to allow passive pupil dilatation but sufficient to allow adequate pupil observation. The illumination was not measured but performed under the same conditions for all patients.

Each assessment required a separate controller who knew the patients medical record and an observer who did not. The controller selected the patient's and chose an eye by chance (coin toss). He invited the observer to assess the eye for pupil diameter, isocoria and reaction to light. He then instilled 0.1% pilocarpine solution using one drop from a glass dropper instilled into the lower conjunctival fornix. The observer read the test after a 30 minute interval and he recorded pupil equality or anisocoria against a hand held horizontal transparent millimetre scale under the same lighting conditions with the subject fixing a target at 6 meters. Although this method of quantitative assessment is not as accurate as infrared or flash photographic pupillometry, we had previously found good interobserver agreement on pupil measurements to within 0.5mm; an identical method has previously been employed by other workers in denervation supersensitivity studies.¹⁰

Results

Pupil responses to weak pilocarpine showed overlapping distributions in the experimental and control groups (Fig. 1).

Responses were divided into two groups with a pupil response of 1mm or less being counted as a negative response and above 1mm as a positive response.

The POAG group gave 1 false negative and 19 true positives; the controls showed 14

Fig. 1. *Induced anisocoria in POAG group and control group after 0.1% pilocarpine*

true negatives and 6 false positives. The difference in response between the two groups is statistically significant (Fisher's exact probability test $p < 0.0001$). As a screening test the sensitivity in POAG is high 0.95 (0.78 - 0.99 with a 95% confidence interval). Its specificity is lower at 0.70 (0.47 - 0.86 with a 95% confidence interval). If POAG is taken to have a prevalence of 1% the predictive value of using this test as a general screening method is low at 3.1%.

Discussion

It is incident to physicians, I am afraid, beyond all other men, to mistake subsequence for consequence. Samuel Johnson 1734.

Cholinergic supersensitivity in autonomically denervated irides has been recognised for over fifty years¹¹ and led Cannon and Rosenbluth¹² to propose the principle of

denervation supersensitivity. This has been widely used clinically to detect parasympathetic denervation of the iris in Adie's pupil,^{13,14} familial dysautonomia,^{15,16} and diabetes mellitus¹⁰ using weak cholinergic agents such as 2.5% methacholine or 0.1% pilocarpine. Pupil constriction to these dilute agents is usually accepted as representing parasympathetic denervation. However, pupil size reflects an interaction between the sympathetic dilator and the parasympathetic sphincter. It is a hallmark of an acute and marked rise of IOP that the sphincter fails and the pupil tends to dilate. If any direct effect on the sphincter muscle itself was operative at the moderately elevated IOP in the POAG group (mean POAG IOP 26.6mm Hg, controls mean IOP 16.7mm Hg) then a larger initial pupil diameter would be expected, but the mean starting pupil diameters were similar (POAG group 4.0mm, control group 3.9mm). No correlation was found between the magnitudes of the initial pupil diameters and IOP in the POAG group, or in the amount of induced anisocoria and IOP alone.

Other suggested mechanisms for an exaggerated response to weak cholinergic agents include dry eyes, corneal abnormalities and corneal anaesthesia which were excluded at the outset.

We believe, therefore, that this study demonstrates a true and very high incidence of ocular parasympathetic neuropathy in Caucasian patients with untreated POAG and we propose that this may be significant in the pathogenesis of POAG. It can be argued that an ocular parasympathetic neuropathy is a result and not a cause of POAG as the parasympathetic fibres may be damaged in a similar fashion to the optic nerve head by elevated IOP. In this context it would be of interest to assess the response of subjects with ocular hypertension, and POAG with normalised IOP after trabeculectomy.

Whether or not an ocular parasympathetic neuropathy is a primary or secondary factor in the development of elevated IOP and POAG we suggest it plays an important part in a vicious and self perpetuating cycle (Fig. 2). This may in part explain a higher incidence of POAG in diabetics who have been

shown to have a high (81%) incidence of ocular parasympathetic denervation,¹⁰ compared with 8 - 14% of a non-diabetic control population.^{10,17}

Several further areas for study are suggested. Firstly the test appears highly sensitive in POAG but only moderately specific, thus rendering it a poor screening test for the general population.

It may be more valuable in screening certain groups of potential POAG patients e.g. those with a first degree relative with POAG. It may be possible to retain the sensitivity but

Ocular parasympathetic neuropathy

Fig. 2. Proposed mechanism of elevated IOP in POAG. Broken line indicated positive feedback loop.

reduce the false positives by lowering the concentration of the pilocarpine. Secondly, it would be of great interest to examine the effect of weak cholinergic agents on the ciliary muscle, outflow structures and dynamics directly. Thirdly, microscopy of the ciliary muscle and its innervation in POAG might be undertaken, particularly if specimens could be obtained from globes which had not been subjected to surgical or prolonged topical treatment. It would be worth while performing denervation supersensitivity studies in patients with pseudoexfoliative and pigmentary glaucoma which are generally assumed to be caused by a clogging of the trabecular meshwork and not due to canalicular blockage.

Evidence of systemic autonomic dysfunction in 58% of patients presenting with primary closed angle glaucoma (PCAG) has been found by Clark and Mapstone,¹⁸ more than could be accounted for by the number with abnormal glucose metabolism, in itself more frequently encountered in PCAG¹⁹ and for that matter POAG.²⁰ If widespread autonomic dysfunction was to be demonstrated commonly in patients with POAG it would suggest that an underlying abnormality in both primary open and closed angle glaucoma was an autonomic lesion which could produce a chronic elevation of IOP in the former and an acute close angle attack in the anatomically predisposed latter, a concept which perhaps would have amused Otto Barkan.

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