POAG AND CAUSALITY

Case Report, Discussion and Literature Review
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ABSTRACT

A rather typical case of primary open angle glaucoma (POAG) is considered in some detail over the last 6 of the patient's 27years of treatment involving both medications and surgery. Some interesting events are considered in greater detail under the management section whilst their aetiology and broader significance are considered in the discussion/aetiology section. An attempt is made through an illustration and comment to give as broad as possible a picture of the factors that are believed to be involved in the pathogenesis of POAG. Discussion is devoted only to certain aspects of diagnosis and management. It is concluded that there is a need to promote formal discussion on the non-genetic causes of glaucoma with the view towards formulation of a list of recommended factors to be discussed by practitioners with their ocular hypertension (OHT) and POAG patients.

INTRODUCTION

POAG requires no introduction for eyecare professionals. It is the most common form of glaucoma and together with ocular hypertension (OHT), will increase three-fold over the next 20years as the population ages.[1] Given that about a third of these patients consider the diagnosis of glaucoma as a blow to their quality of life, [2, 3] we are likely to have an increasing population of discontented individuals, even in the unlikely event that they were all diagnosed appropriately. There is a definite need to consider the many environmental factors that are involved in the pathogenesis of glaucoma, as we know that factors other than genes are of greatest importance in most individuals.[4] These factors are so numerous and complex that one may be tempted to avoid thinking about them altogether.

Despite this complexity, patients are demanding to know more about what they can do to help their condition. As their trusted practitioners, we need to direct efforts, with an open mind, towards the causality of POAG. However, it is unlikely that we will ever find a singular cause of POAG and more likely that if we wish to prevent POAG, at least in some cases, we will have to look at improving aspects of the general health, and where possible, the environment. This may seem difficult at first; however, the rewards would justify the effort. The quality of life for these people would not only be prevented from worsening, it would improve overall as other related health problems would, as a consequence of investigating the causality of POAG, be detected/prevented. Four examples of this type of approach are given in the Discussion/Aetiology section.

CASE REPORT

Mrs EP was born in 1930. She was referred to the Royal Victorian Eye and Ear Hospital (RVE&EH) in August 1996 by her ophthalmologist for RE cataract extraction as a public patient. Mrs EP was first detected with elevated intra-ocular pressures (IOP) when she first needed reading glasses in 1975. She was then followed for some time before being placed on glaucoma medication. In 1983 she had a R) trabeculectomy. She had a gastrectomy in 1967 with secondary anaemia due to folate and B12 deficiency. Subsequent to the anaemia, she developed angina. Mrs EP stopped smoking in 1980. She also suffers from systemic hypertension and occasional shortness of breath.

Medication: Ferro-Gradument, Renitec, Tenormin, Aprinox, Nitrolingual Spray, Ogen, Provera

Mrs EP has nine other siblings. Remarkably, none are known to have glaucoma. She admitted to taking over five cups of coffee/tea per day even prior to the initial diagnosis of ocular hypertension. She also engaged in prolonged near work both at work and when at home. When questioned about whether she felt she was a stressful type of person, she admitted to having a similar (stressful) personality to one of her brothers. However, he did not suffer from glaucoma. Her brother did not engage in much close work, nor did he have a liking for caffeine beverages.

On 29th April 1996, Mrs EP was on Timpilo 2 (LE) and Atropine 1% (RE). IOP's were R: 12 L: 22mmHg. Unaided vision was R: 6/36 (PH6/24) L: 6/6(pt). The filtration bleb was described as cystic in appearance. Despite dilating drops, the pupil in the right eye was constricted due to posterior synechiae at the pupil margin and no fundus view was possible. The synechiae were probably due to the combination of ocular inflammation secondary to the trabeculectomy in 1983 and pupillary miosis due to chronic pilocarpine use.[5] The cataract operation was complicated by a capsule tear as synechiolysis was necessary and conversion to ECCE was required. The corneal incision was adjacent to the superior limbus. At 1-week post-cataract extraction, the IOP in the right eye was 22mmHg, being almost double the pre-operative pressure. One month later the pressures were R: 29 L: 28mmHg with Timoptol 0.5% in both eyes. The pressures dropped to 20mmHg (R&L) one month later using the same medication. Visual acuities with new glasses were R: 6/9 L: 6/6^{-}.

On 5th August 1997 (4 months later) the IOP's were R: 27 L: 18mmHg. The C/D ratio in RE was 0.5 with a thinner superior rim. The C/D in LE was 0.2. Gonioscopy in RE revealed grade II angles except for grade III in the nasal sector. They were grade III in the LE. The visual fields performed on 19th August 1997 showed a marked superior arcuate scotoma and a less marked inferior arcuate defect in both eyes. Mrs EP was placed on adjunctive therapy of 2% pilocarpine bd for the right eye.

On 19th August 1997 it was noted that the filtration bleb was flat and scarred, compared to the cystic appearance prior to the cataract operation. The pressures were recorded at R: 22 L: 20mmHg. On 16th September 1997 they were R: 30 L: 21mmHg. Anterior chamber cells (2+) were noted, with a few KP's. Predsol 0.5% (q/d) was prescribed as a late response to possible persistent inflammation 2^{o} to the surgery causing elevated IOP. Tenopt OD, bd and Timpilo 2 OS, bd and Diamox 250mg bd were prescribed. On 30th September 1997 the IOP's were R: 25 L: 14mmHg, confirming a problem with the filtration bleb in the right eye. Tenopt was omitted and Timpilo 2 given BE bd.

Mrs EP presented to casualty two weeks later as she had a protruding suture which was removed. The coincidence of this event with the use of steroids may be significant. Steroids have been linked with various side effects on the cornea, including decreased wound strength.[6]

Timpilo 2 & 4 were both tried without success for the right eye. When Propine was added to TP4, the IOP in the right eye fell to 19mmHg. This finding confirms the compatibility of these two preparations. Unfortunately, as it seems, the patient discontinued using the Propine drops, and on 19th May 1998 the pressure rose to R: 28 L: 14mmHg on TP4 alone (BE). Xalatan was then added instead of reminding the patient to use Propine. On 18th June 1998 the IOP was R: 34 L: 22mmHg. This was then noted as a possible paradoxical response, and Xalatan was stopped. However, on 2nd July 1998 the IOP's were **R: 42 L: 32mmHg** while on TP4 for LE and Timolol 0.5% and Alphagan for RE. Alphagan has been shown to provide moderate additional reduction in pressure when added to timolol.[7] This marked increase in IOP on 2nd July 1998 affected both eyes and is most likely a reflection on other causes rather than the medication used. A week later the pressure in the left eye reduced to 24mmHg and three weeks later was 20mmHg while on the same medication (TP4). By this time, the Rx in RE was changed to TP4 qid, Trusopt bd and Alphagan bd. This yielded 24mmHg in RE when the LE recorded 20mmHg.

The pressures were well controlled for about 2 years on these medications. On 24th February 2002 Mrs EP again noticed pain in the right eye and presented once more with a protruding suture that was removed. The IOP's were then up in the mid-twenties (OU) until 13th June 2000 when they were found to be R: 34 L: 30mmHg. The fields result indicated little change since 1997.

Xalatan was again used in the RE in combination this time with Alphagan and Tenopt. The IOP had reduced only slightly to 31mmHg. It appears that this time there was no paradoxical response to Xalatan. When Trusopt was added to the RE, the IOP reduced to 25mmHg. On 5th September 2000 the LE was also placed on Alphagan and Tenopt in addition to TP4.

The IOP's were then well controlled for a while. On 27th February 2001 the IOP's were again elevated to R: 34 L: 32mmHg while on all four medication for the RE and three for the LE. Trusopt was added to LE as well and using all four medications the IOP's were R: 32 L: 22mmHg on 22nd May 2001. A repeat trabeculectomy was then arranged to be done with mitomycin C after the patient was explained the risks involved, i.e. hypotony, leaking, infection, bleeding, loss of vision and possible failure. Interestingly, at the pre-op assessment (3rd July 2001) one week prior to the repeat trabeculectomy, the IOP's were R: 22 L: 18mmHg.

The IOP following R: trabeculectomy was 30mmHg and the bleb was noted as hardly formed. However, when the releasable suture was removed soon after, the IOP dropped to 12mmHg. The bleb was then seen to be elevated and diffuse after initially being moderately vascularised.

In recent months the IOP in the RE has been consistently around 11mmHg. However, the LE which was placed on maximal therapy since 13th June 2002, began to show unacceptable IOP's from December 2001 (22 –27mmHg).

On 28th March 2002, a writing error appears to have led to the belief that Mrs EP was taking the four medications in her RE instead of her LE. All drops were then stopped to get the baseline reading. The IOP's were then R: 14 L: 40mmHg. Singular additions were then tried although the IOP in the LE was still 38mmHg while on Xalatan, Timoptol and Alphagan. Trabeculectomy was being organized for the LE, at the time of writing.

DIAGNOSIS

Mrs EP was already diagnosed with POAG involving high intra-ocular pressures before attending the RVE&EH. The initial follow-up for her OHT would have involved regular visits to ascertain the presence of any visual field defect or changes in the optic disc if this was normal. Documented change in the optic disc appearance alone with normal findings on achromatic perimetry would necessitate more sensitive visual fields testing (e.g. SWAP). If a definite visual field loss is documented on achromatic perimetry after repeated testing, glaucoma therapy should be commenced. The magnitude of the field loss in this case would depend on the reliability of the result and other factors such as age. The ORBV guidelines suggest referral for treatment if the visual fields on automated perimetry shows three or more points with $\geq$15 dB loss. For any existing case, a definite defect (or progression) is considered one where 3 or more adjacent points show $\geq$ 10dB of change.

Glaucomatous optic neuropathy (GON) can also occur in the absence of high intra-ocular pressures. Studies differ in their estimates of the prevalence of normal tension glaucoma (NTG),[8] however, about a third of the cases of POAG are likely to have factors other than IOP as the principal cause. In these cases, as the IOP is normal, only careful analysis of the optic disc will alert the practitioner to perform visual fields testing.

Vingrys[9] describes the nerve-head changes in early stage glaucoma. He distinguishes between those disc appearances that can be present in both POAG and normals, and those that are highly indicative of glaucoma (risk factors vs. signs for glaucoma). For a variety of reasons, he argues that C/D ratios alone have poor sensitivity for glaucoma. He notes

that the presence of retinal nerve fiber layer defects or an absence of the ISNT sign give the greatest sensitivity for glaucoma when used as single signs. The presence of both signs is an even stronger indicator. If a third sign is present in the same eye (e.g. notching, blood vessel change, large C/D, peri-papillary atrophy) glaucomatous optic neuropathy is most likely present.

Some workers have tried to group glaucomatous optic discs into one or more of four different typical optic disc appearances.[10] This has been done in the hope of being able to predict other disease variables that may play a role in the pathogenesis of GON.

It must be stressed that whether or not one develops glaucoma cannot be assumed to be pre-determined. What may appear as a case of simple OHT, may progress to POAG. Conversely, changes in the causative factors may prevent progression in cases of OHT. (see examples in next section). Regular examinations are necessary to detect possible changes. Furthermore, the transition from normal to glaucomatous optic disc is continuous, as are the variables we use to define it.[11] No physical cut-offs exist that unequivocally define normal from glaucomatous findings.

Where the principle cause of glaucoma is known, the condition is then referred to as secondary glaucoma. In these cases the treatment may be different to that in POAG and thus it is important to be able to differentiate them. Chronic angle closure glaucoma may present in a similar way to POAG. A gonioscopic examination and Van Herrick estimate of the anterior chamber angle on all glaucoma suspects will help to differentiate those patients who may benefit from a laser iridotomy.

IOP measurements, in conjunction with optic disc assessment and fields testing, will help to some extent in sorting out those cases of POAG where the principle cause is not clearly IOP (i.e. NTG factors involved). For simplicity, glaucomatous changes that occur only when IOP's are > 30mmHg can be generalized as simply IOP-related and when they occur with IOP's of <15mmHg, are non-IOP related. (This is not to say that further reduction of IOP will not help reduce glaucomatous damage, but simply that something is

definitely at play that prevents the eye from behaving normally, with regards to its ability to withstand IOP). As many glaucomatous patients fall in between these IOP values, one can now only estimate (via disc and fields analysis) the relative importance of IOP versus NTG factors.

Occasionally, the IOP may rise momentarily for a very short period of time for a variety of reasons. A patient, who for whatever reason, squeezes their lid unusually hard during tonometery, will show higher IOP readings. Hard squeezing of the lids can increase the IOP to over 50mmHg.[12] Many factors can cause a transient change in IOP. Excessive fluid intake can induce a transient rise in IOP of 8mmHg or more.[13] Alcohol can reduce it by up to 6mmHg in normal and by up to 30mmHg in POAG.[13] If practitioners are actively aware of the many non-genetic factors that could possibly affect IOP, they would not only make a better diagnosis but also help at least a few of their patients to achieve a safe level of IOP without resort to life-long drug therapy.

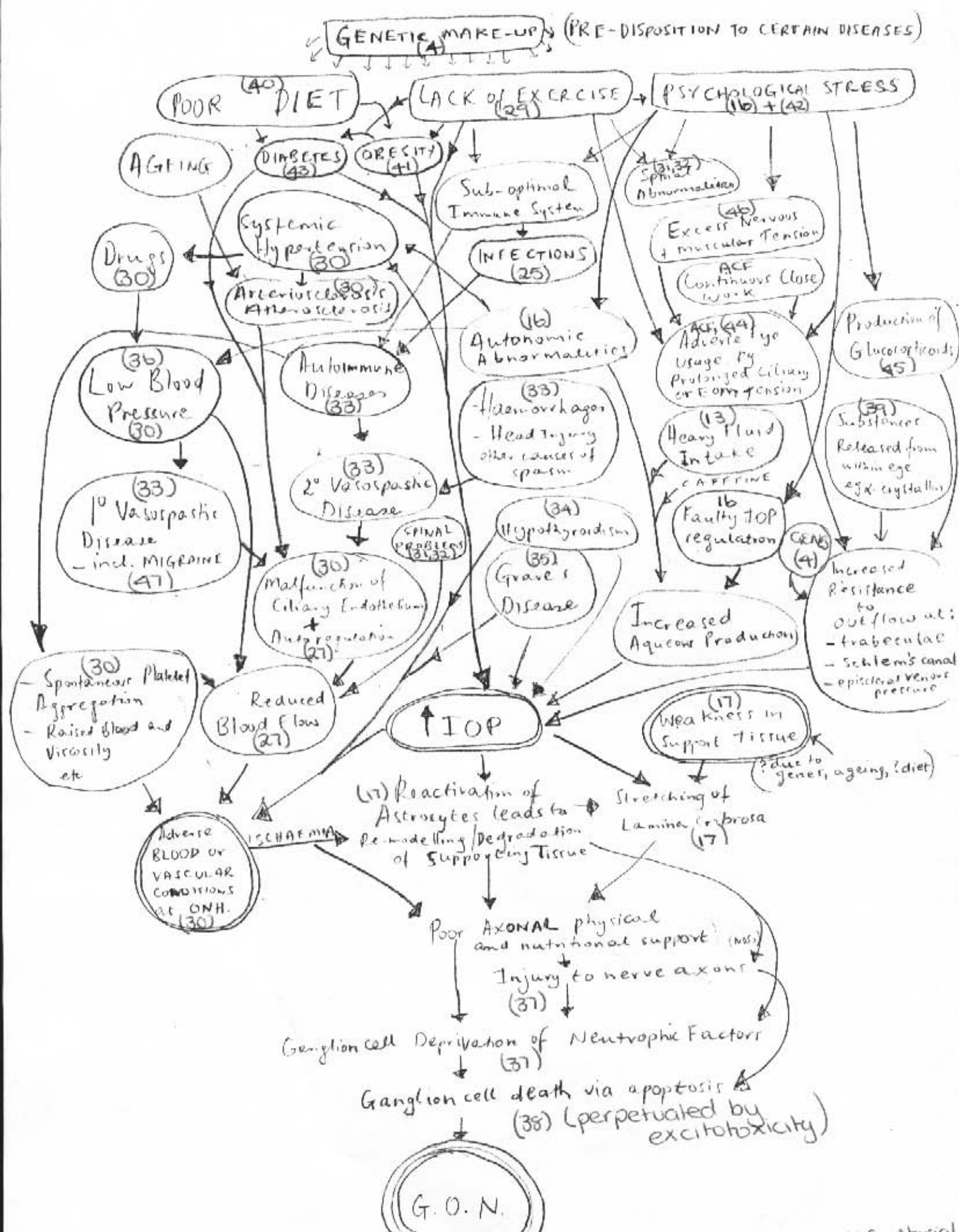
DISCUSSION/AETIOLOGY

POAG can be defined as glaucomatous optic neuropathy in the absence of obvious root causes, regardless as to whether or not raised IOP is considered to be the principal intermediary cause. The term normal tension glaucoma (NTG) is generally used to denote those cases of POAG where the average IOP is below 22mmHg(normal range).

A difficulty currently exists when one wishes to refer to those cases of POAG that cannot be considered as NTG. Often the term POAG is used for this purpose as well, however, this is inappropriate as POAG describes all cases of GON of primary cause. The general lack of consistency in how glaucoma is defined has been studied by Bathija et al,[14] who see a need for improvement.

The term primary high tension glaucoma (PHTG) could be considered to denote those cases of POAG that are atleast thought to be related *principally* to elevated IOP. The average IOP would generally need to be atleast 22mmHg. PHTG would be a helpful descriptor as it avoids lengthy descriptions such as 'those cases of POAG that do not include NTG' or the erroneous descriptor of 'POAG' on its own (assuming the need is to exclude NTG). There would be no necessity to include the abbreviation 'OA' (open angle) as that is implied by the term 'primary' (fundamental cause unknown). In essence, the term NTG only exists as we lack a good understanding of factors other than IOP that cause glaucoma. In order for the term NTG to exist, one is necessarily *implying* the existence of PHTG. Furthermore, the term allows for the coming of a time in the future, where such judgement of the relative importance of IOP may become more objective.

The diagram below attempts to give some understanding of the complexity and multifactorial nature of the pathogenesis of POAG. There are infinite interactions that can occur that converge and ultimately lead to GON. I refer to the causes higher up in the diagram as higher order causes and vice-versa. Generally, they represent order of occurrence in the disease process.



A proposed diagrammatic scheme illustrating the complex, multifactorial nature of POAG leading to glaucomatous optic neuropathy (GON)
ONH: optic nerve head. ACF: denotes authors own clinical findings.
numbers apply to references supporting the associated factors.

An individual's genes may lead to POAG in a more direct manner.[4] However, from the available evidence, a clear genetic trait could not be established in the majority of people examined in the Rotterdam Study.[15] The authors recommend that POAG be regarded as a heterogeneous, multifactorial disease. The rarity of definite glaucoma genes as such[4] suggests that genes may be involved in other ways than simply by acting directly on the outflow components. It may be that certain genes primarily affect other body functioning and then have an indirect contributory effect on the development of POAG.
For this reason, I have placed the genetic make-up high on the list as it affects all of our functions. However, it is furthest from GON, as cumulatively, environmental factors (including aging) must have a greater impact on most people with POAG.

Psychological stress, poor diet and lack of exercise are significant contributors to poor general health. There are numerous possible reasons for their existence and numerous ways in which they can impact on one's health. Thus finding the *exact* way by which these important factors cause ill health in a particular individual is a long way off from our present understanding. However, this should not discourage reasonable attempts at estimating their level of involvement in various diseases including POAG. In particular stress and lack of exercise have been implicated in several studies.[16] These fundamental causes of disease do not appear to be directly involved in POAG, however, they affect an infinite array of other functions and create diseased states that could contribute to POAG. Some of these are indicated in the diagram. These higher order causes essentially converge to one of three intermediary adverse conditions that affect the ONH.

1. Abnormally high IOP
2. Ischaemia at the ONH (that which is not due to high IOP)
3. Weakness in the supporting tissue of the ONH

In theory, these three states could independently lead to GON, however, in reality, there is most likely some overlap. If GON occurs only when the IOP is clearly too high (i.e. >30mmHg), it becomes easy to separate the principal intermediary cause. However, when the IOP is normal, the principal cause may be ischaemia (mainly from reduced blood

flow), although it may rest with the supporting tissue of the ONH.[17] As the variables are continuous, we can talk of the **sensitivity** of an individual to IOP increase with respect to GON development. This would depend to a large extent on the severity of adverse blood/vascular conditions at the ONH and composition of the tissue supporting it. (See diagram)

Comparatively more research is currently centered on the pathophysiology of NTG and on the mechanism of apoptosis. This will hopefully lead to medical treatment that will help to prevent progressive GON despite the use of ocular hypotensive drugs (see below for further discussion on optimal management strategy). However, the ultimate goal would be to intervene at the higher levels of causation if this were to effectively stop GON. Much work is needed to achieve that goal.

The assumption is made in the diagram that the pathology of GON occurs at the level of the ONH. However, elevated IOP and ischaemia may directly lead to apoptosis or even necrosis of ganglion cells. Osborne et all (1999)[18] discuss the various possible ways of ganglion cell death.

The diagram shows only those higher order causes that have been implicated in causing POAG through my own literature search. There may well be other documented causes and there will most likely be new factors revealed by further research.

The factors on the right of the diagram generally lead to higher IOP while those to the left generally lead to blood/vascular abnormalities. Several other factors could play a role in the development of both these intermediary states and some of these factors are shown closer to the middle of the diagram.

Those factors denoted ACF are based on my own clinical findings. I have noted that prolonged near work without changing of the focus is associated with slightly higher IOP's over time. I have especially found this to be the case in those presbyopes who are either uncorrected or under-corrected. The eye that is most used for near work (preferred

eye)[19] is the one that usually has the higher IOP by up to 2-3mmHg. If this finding is proven in large-scale studies, one has to interpret its importance in an absolute fashion and not just by the small inter-ocular IOP **difference**, as this is a reflection only of the effect of the difference in effort that is made *between* the two eyes, not of the total effect from the increased demand. The mechanism by which this occurs is most likely related to the role that the longitudinal muscle plays in pulling the scleral spur and creating a pumping action on the canal of Schlemm.[20]

Typical case examples of environmental factors playing a role in IOP are as follows:

Case 1: Mr BV, DOB: 1935, wide angles, mildly obese, IOP's fluctuated around 21mmHg for many years. Now he is treated for systemic hypertension. He had been drinking at least 5 cups of coffee per day for many years. On 29/05/01, the IOP was R: 27 L: 30mmHg. Mr BV was advised to stop drinking coffee. One week later the IOP's were 20mmHg (OU). A week later still, the IOP's were 27mmHG (R&L) after coffee intake. Similar readings were taken later and the minimum difference recorded (with and without coffee) was 4mmHg. No field defects have been noted. He has previously had an IOP response to Mydriacyl 1%. The IOP's then rose to R: 34 L: 27mmHg and 4hours later settled to R: 21 L: 20mmHg.

Case 2: Mrs CK, DOB: 1938, mildly obese, had been operated for thyroid problem prior to 1984. IOP's varied from 17-21mmHg until 12/11/97 when they rose to 24mmHg (OU) (7:00pm) and then 27mmHg (10:00am) a week later. Mrs CK had put on significantly more weight and developed joint problems and asthma. She was advised on regular exercise and made aware of other factors that could contribute to IOP increase. Hydrotherapy was taken up and within two years the weight was significantly reduced. The IOP's were measured twice since 1999 and were not more than 18mmHg on both occasions.

Case 3: Mrs SA, DOB: 1937, was a sewing machinist all her working life. IOP was 19 in her only useable eye (RE) in 1991. On 08/11/01, IOP was R: 33. The corneal diameter was 11mm. The thickness was judged as greater than normal on slit-lamp. HVF II showed normal fields. Mrs SA's brother had died several months earlier and she appeared particularly stressed. She also appeared slightly obese. She was then advised on regular exercise (walking) and to avoid continuous close work, caffeine intake etc. On 22/11/01 the IOP in RE was 27mmHg, 29/01/02: 23mmHg, 18/07/02: 22mmHg. Probably the greatest gain for Mrs SA was the dramatic change she made in her general health. She is now normal weight and feels much better overall. It may be that Mrs SA was particularly motivated to improve her general health, as the RE was her only useable eye.

Case 4: Mrs ET has PXF. Her IOP's were always around 15mmHg since 1985. IOP's on 04/03/02 were 22mmHg (OU 10:00am). Mrs ET had been knitting intensely during that time. She was advised to avoid prolonged close work and to change her focus regularly. One month later the IOP's were R: 13 L: 15mmHg (3:00pm). On 05/08/02 IOP's were 18mmHg (12:00 noon after caffeine intake).

Caffeine has been noted to produce effects that resemble those of β-adrenoceptor stimulation and it antagonizes the action of adenosine by acting on α_1 and α_2 receptors.[21] These may well be the mechanisms by which caffeine increases IOP i.e. by increased aqueous production.

It is worth noting that if the outflow facility were perfectly normal (it was affected in above patients for a variety of reasons), then caffeine, autonomic dysfunction[16] and other causes of increased aqueous production would not be seen to elevate IOP significantly. However, when there is a definite outflow problem, aqueous-stimulating factors will be most effective in elevating IOP. This may well explain why some studies[22, 23] have not found significant changes in normals (only 3-4mmHg).

However, even the fields testing process has been shown to elevate IOP in POAG patients by up to 10mmHg.[24] The IOP in glaucoma patients typically fluctuates by about 11mmHg.[23] Normal changes in aqueous-stimulating factors may well account for most of this change, given the outflow problem. However, in some cases of POAG, one would expect dysfunction in the aqueous-stimulating factors that would be contributing to the disease.

A recent study claims to have found an association between both POAG and PXF glaucoma with Helicobacter Pylori infection of gastric mucosa.[25] It may be that this association is indirect or incidental. The true association may well be nervous stress and other variables (e.g. caffeine) directly with both glaucoma and gastric mucosal anomalies.

MANAGEMENT

As mentioned in the introductory comments, the intention here is not to expand on the properties of available glaucoma drugs. For a general discussion on the efficacy, side effects etc of currently used drugs, refer to Rait[1] and Bartlett and Joanus.[26] Research on neuroprotective drugs working at various levels within the eye is currently being conducted.[18] Efforts are also being made to find effective and safe *local* agents that will increase blood flow at the ONH,[27] in order to avoid the adverse effects of systemic calcium channel blockers. Gene therapy may also provide solutions to both the outflow problems and those of ganglion cell death.[28]

Mrs EP's case is not atypical of POAG. The treatment is often life-long and may involve surgery and perhaps repeat surgery. Her case involves a few interesting findings. One of these is the finding that her cataract operation led to the failure of her initial trabeculectomy, even though it was apparently successful for at least 14 years previously. Another interesting event was the unexpected IOP result obtained when Xalatan was used in June 1998. The case also demonstrates the potential for large, apparently inexplicable changes of IOP in POAG.

It is clear from this case that not only can trabeculectomies fail when performed on a previously operated eye, but they can also fail when unrelated surgery is carried out after successful trabeculectomy. The surgical complications (synechiolysis and capsule tear, leading to ECCE) and the proximity of the corneal incision to the trabeculectomy, may have had important causative roles in Mrs EP's case. The repeat trabeculectomy was successful with the use of mitomycin C.

When Xalatan was used for the right eye in June 1998, the result obtained was an *increase* of 6mmHg. This was then questionably regarded as a paradoxical response. However, two findings would suggest that no such response occurred. Firstly, the IOP's rose by 8mmHg in the left eye, yet only by 6mmHg in the right eye when the patient was reviewed. This effectively tells us that some other primary cause(s) were involved in raising the IOP in both eyes and that the net effect of Xalatan was to reduce the IOP by only 2mmHg (assuming the 1^{o} causes affected both eyes equally). Secondly, when Xalatan was again tried in June 2000 with Alphagan and Tenopt, the IOP reduced by a small margin. It is difficult to judge the effect of Xalatan on this latter occasion as the IOP was raised in the left eye as well, indicating a peak period. However, on 03/07/01, one week pre-operatively, the IOP's were R: 22 L: 18mmHg with the extra addition of Trusopt to both eyes. Xalatan most likely did not cause a paradoxical response in this patient, even though it did not help in reducing the IOP when it was used in combination with pilocarpine. Toris et al[48] found that latanoprost gives additional reduction in IOP when used in addition to pilocarpine but advise that it is not a preferred combination. They quote other studies that found optimal IOP results when pilocarpine is given one hour after latanoprost.

Mrs EP has had at least three periods of time within the last six years when her IOP's significantly rose and fell **bilaterally** that did not appear to be related to the effect of medications.

1) The IOP elevation occurred three weeks after Mrs EP's first post-cataract surgery IOP measurement, being 22 mmHg. This was double the pre-operative value. Such news, concerning an eye that had already undergone a trabeculectomy, must surely have affected such a stressful person as Mrs EP. The bilateral IOP rise occurring three weeks later, and the bilateral reduction of similar magnitude one month later, without any change of medication, cannot readily be attributed to any other factors, other than Mrs EP's reaction/stress.

2) The second time was in June 1998. Mrs EP somehow stopped using the Propine drops and the IOP increased to 28mmHg in the right eye on 19/05/98. However,

3) The third time that Mrs EP was recorded to have significant bilateral elevation in IOP's began in February 2001, when they were R: 34 L: 32mmHg. The IOP's consistently stayed up until one week prior to the repeat trabeculectomy, when they fell to R: 22 L: 18mmHg. (Medications were the same except for addition of Trusopt to LE)

These fluctuations in IOP certainly make it difficult to draw definite conclusions about the effect of particular drug combinations in POAG. It is important to keep in mind that there are environmental factors (e.g. stress) that interplay for varying lengths of time. One must thus judge the effect of drop combinations only when these 1^{o} causes have been given some consideration. Asking a few questions at the time of measuring IOP's, would lead to greater insight and assist the practitioner to make better judgements about the effect of IOP-lowering medications. A possible list that could be used is as follows:

1. Patient estimation of stress levels, and presence or change in frequency of migraines.
2. Time(s) of instillation of drops in last 24 hours.
3. Last caffeine intake (tea/coffee), or alcohol or excessive fluid intake
4. Frequency of exercise in last few months and last work-out/exercise
5. What is the systemic blood pressure at time of IOP measurement?
6. Is there a habit of close work and if so, last bout of close work exceeding ½ hour.

(In some people, short intervals of close work can have a temporary IOP-lowering effect, contrary to the tendency for a long-term elevating effect of excessive near work.)

It would also be in the patient's interest to be made aware that certain factors are *atleast* suspected of causing an increase in the IOP. Not only may this lead to reduction in IOP, but it may help improve the patient's general health. The fact that POAG is a complex disease with many causes, should not deter clinicians from discussing those that may be important for a particular individual.

For this reason, even cases of OHT should be assessed for the presence of direct or indirect factors that can adversely affect IOP. It may well be that a given individual may only have a *few* (controllable) causes for their IOP elevation and their consideration could lead to actions that may normalise the IOP's over a period of time. *In fact, OHT should be treated as a warning sign that tells us to begin looking at the patient's overall emotional and physical health.*

There is currently a need for discussion among the eyecare professionals to reach some form of agreement as to those higher-order factors that should be considered when assessing a patient with OHT or POAG. This could lead to a list of practical suggestions for use by the ordinary practitioner. Patients will thus not be told: "we do not know the cause of glaucoma", but that it is a condition with many causes and some of these can be looked at for their relevance in each individual's case.

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