Collaborative Normal Tension Glaucoma Study

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Purpose of review

Before this study was done, there was a difference of opinion concerning whether intraocular pressure (IOP) was involved in producing optic nerve damage when there was glaucomatous damage to the optic nerve and characteristic visual field loss, even though the IOP was in the statistically normal range. This article reviews the findings of a collaborative study aimed at finding the answer to this question.

Recent findings

The level of pressure influences the course of normal tension glaucoma, as evidenced by a slower rate of incident visual field loss in cases with 30% or more lowering of intraocular pressure. The rate of progression without treatment is highly variable, but often slow enough that half of the patients have no progression in 5 years. A faster rate occurs in women, in patients with migraine headaches, and in the presence of disc hemorrhages. Some patients may experience greater benefit from lowering of IOP than others, but further research is needed to be able to identify those most likely to benefit.

Summary

As a group, patients with normal tension glaucoma benefit from lowering of IOP. Variable rate of deterioration, as well as lack of progression in a substantial number in 5 years, suggest that treatment should be individualized according to the stage of disease and rate of progression. Traits that help predict risk and rate of progression and response to treatment are beginning to become known and, when fully known, will help guide management decisions.

Keywords

normal tension glaucoma, risk factors for glaucoma, natural course of untreated glaucoma

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Abbreviations

IOP	intraocular pressure
NTG	normal tension glaucoma

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Why was the study done?

In 1984, the Glaucoma Research Foundation of San Francisco sponsored the meeting of a group of clinicians and scientists to consider what was known about the puzzling entity of low tension glaucoma, now more often called *normal tension glaucoma* (NTG). These cases, perhaps heterogeneous, are people who have intraocular pressure (IOP) in the statistically normal range, but have optic nerve damage and visual loss characteristic of that seen in patients with chronic glaucoma related to an elevated IOP. Within just the decade before, there had been question of whether glaucoma could occur unless the IOP was at least sometimes above the statistical normal range. The conventional wisdom was that a normal IOP should not be harmful, and probably wasn't. Any pressure above the statistical normal range was potentially harmful and perhaps certain to be harmful eventually if left alone. It had, however, gradually been recognized that elevated IOP was not always harmful, at least for some people, often for quite a number of years.

If a patient had something that looked like glaucoma, but the IOP was never observed to be above the statistical limit of the normal range, the dilemma was to decide whether it was glaucoma or something that simply looked like glaucoma, but had no relation to the level of IOP. The practical question was whether it was of any help to lower the IOP from somewhere in the normal range to a place lower in the normal range. In view of this doubt, clinicians found themselves with the difficulty of deciding whether to undertake filtration surgery to achieve a lower IOP when the medications then available had produced in a given patient only a modest reduction of IOP. Because of the complications of filtering surgery, many simply placed such patients on the strongest medications then available, disappointed with both the pressure lowering achieved with surgery of that time and uncertain of the role of IOP in the disease, and therefore the effectiveness of halting the visual loss. It appeared that in general treatment of NTG was not optimal for halting visual loss, but it was not clear whether this was due to ineffective lowering of IOP or to the possibility that IOP plays no role in the pathogenesis of the disease. Clinical intuition was mixed: some thought that the condition of NTG was an optic neuropathy that looked like glaucoma but was unrelated to the level of IOP, while others thought that the reason for failure was that, lacking confidence in effectiveness of IOP lowering, most clinicians simply did not lower the IOP aggressively enough.

The following year (1985) a group met to design a clinical study, which then started in 1988, to determine which of two hypotheses might be true:

- The *first hypothesis* (that the disease is IOP-independent) seemed in keeping with the frustration of clinicians in halting the nerve damage and visual loss by conventional treatments aimed at lowering the IOP. If this is the case, this clinical entity consists of etiologic and pathogenic factors that produce optic nerve injury that looks like that caused by an elevation of IOP, but in fact the IOP neither causes nor influences the process.
- The *second hypothesis* (that IOP participates in producing the optic nerve damage in NTG) is that in both high pressure and normal pressure glaucoma, the impact of nerve-damaging factors is amplified by the level of IOP. Other etiologic and pathogenic factors are involved in the optic nerve damage, but the degree of insult or amount of harm depends on the level of the IOP.

A group of collaborators was assembled in 1986 to design the study, with patients first enrolled in 1988. As in the initial 1985 small group discussion meeting, the enlarged group was of mixed intuition with regard to the question of whether IOP was or was not involved in NTG, and therefore whether aggressive efforts to lower IOP in patients with this condition were warranted. It was clear that support for either hypothesis was only anecdotal. The main focus of the study was to understand the disease itself, that is, to determine whether IOP was or was not involved in the disease, and the approach was to compare the course of patients with their spontaneous levels of IOP and others who had successful lowering of the IOP. In that sense it was not a clinical trial, but had considerable implications for management of patients, as there would be no point in attempting to lower the IOP if it played no role.

Clinical import

Most clinicians were in practice inclined to make some effort to lower the IOP in cases of NTG, but hesitated to use aggressive measures with potential untoward effects because of the uncertain benefit. Evidence was needed to help decide whether to be aggressive in lowering the IOP in cases of NTG.

Methods: how was the study done?

Enrollment

Two hundred thirty patients were enrolled from 24 collaborating centers, each with Institutional Review Board approval. To be considered eligible, patients had unilateral or bilateral NTG evidenced by glaucomatous cupping of the disc and a defined type and severity of field loss with a median IOP of 20 mmHg or less in 10 baseline measurements.

Randomization

One eye of patients with NTG was randomized:

- to be followed without treatment until there was evidence of slight deterioration. The other eye could be treated at the discretion of the treating physician, except that systemic carbonic anhydrase inhibitors could not be used.
- to be placed on treatment with medication, laser trabeculoplasty, filtration surgery, or any combination, as required to lower the IOP by 30%.

In both arms, neither eye could receive beta-adrenergic blockers nor adrenergic agonists, because they might have systemic cardiovascular effects that could conceivably alter the course of the treated or untreated disease, confounding the analysis of data.

Some patients were randomized immediately, if the field defect threatened the point of fixation or there was previously documented progression of the disease.

Other patients were randomized later if there was visual field progression, progression of optic nerve head cupping, or a new disc hemorrhage.

By the end of the study, 145 eyes had been randomized: 66 to receive treatment and 79 eyes to serve as untreated controls. Of the 66 assigned to treatment, 5 withdrew before achieving the IOP-lowering goal.

Data collection

An important design consideration was the definition of progression. Some of the participating patients, who have a potentially blinding disease, would be followed without efforts to lower IOP—ethical in the face of very uncertain benefit, but worrisome. For that reason, an effort was made to define the absolutely minimal field alteration that would be reasonably certain to be genuine. Four types of change were defined: deepening of an existing defect, expansion of the size of an existing defect, a new defect in a previously normal region, and a new or expanded threat to fixation. Replicate testing was used to be sure the small changes were reproducible and genuine. The endpoint criteria used for the study were shown to be reasonably specific and sensitive in identifying a small increment of progressive field change.

The somewhat complex criteria for field progression, or change in the disc cupping confirmed by the reading committee, guided the conduct of the study: the patient was released from protocol constraints if progression was established by one of these methods. Those not receiving treatment could be treated, and drugs prohibited in the treated group during the study could be used.

Some analyses of results were based on the endpoint criteria used to determine when the patient was released from the protocol, but outcomes were also studied in terms of other variables as well. For reports released in October 1998, data had been collected through June 1996. Subsequent reports included additional data collected through September 1998.

Results

Reports and main conclusions resulting from the Collaborative Normal Tension Glaucoma Study

A detailed description of study design was published in a book on clinical trials [1], and the main elements of the study design and conduct included in the subsequent reports.

A 30% lowering of IOP can be achieved in patients with NTG with medical therapy and laser trabeculoplasty about half the time [2]. In view of the fact that cataracts developed in some of the treated patients, predominantly those that had glaucoma surgery, it is fortunate that lowering of IOP has become easier with medications not permitted in the NTG study protocol and with drugs that have more recently become available. The fact that 30% lowering of IOP could be achieved so often in this group without surgery was unexpected, and it is good news that nowadays probably a smaller percentage of patients will require surgery to receive an effective degree of IOP lowering.

With repeated, frequent visual field examinations in search of very subtle changes or a slow rate of progression, in NTG or likely in any other chronic glaucoma, there is a risk of judging falsely that progression has occurred [3]. In clinical practice, certainly progression must be evident on at least one subsequent field or be confirmed by consistency with other clinical findings to be sure it is genuine.

Once pressure has been successfully lowered 30% from the baseline, the rate of progressive visual field loss is slower than in a group that did not receive treatment. [4] However, cataracts, which occur more frequently in treated patients who underwent filtration surgery, also produce visual changes. [5] In a clinical trial format with a selected degree of visual field change at a specified number of locations in the visual field as the sole outcome measure, correction for cataract effect on the visual field uncovers the benefit of lowering the IOP. Some aspects of the study reported in these two papers were discussed and implications amplified in letters to the editor [6,7].

The rate of visual field progression in cases of untreated normal tension glaucoma is highly variable [8•]. Some cases showed progression in a few months, but half of the enrolled subjects who did not receive treatment showed no progression within their visual fields within five years. It is important in making clinical decisions to realize that cases that are recognized in a clinical practice, excluding those who are already very seriously affected when NTG is diagnosed, vary widely in their outcomes without treatment, and a large proportion do surprisingly well [9,10].

Risk factors involved in the pathogenesis or that can act as prognostic indicators for the untreated disease are migraine, female sex, a disc hemorrhage at diagnosis, and perhaps racial or genetic heritage [11•]. The presence or absence of these risk factors, along with other considerations, like the severity of the disease, may help in making decisions about therapy. To be determined is whether genetic, vascular, or other factors affect the degree to which lowering of IOP is helpful, and individually tailored therapeutic decisions will be easier when this becomes known. Further analysis suggests that individuals with certain traits are more likely to benefit from lowering of IOP than others, so that therapy may be guided both by individual traits that signify risk of progression and by traits that indicate the potential benefit from lowering the IOP.

Implications of Normal Tension Glaucoma Study results

The natural course of NTG is quite variable, some cases slow enough that they may never need treatment, but others progressing rapidly to potential blindness.

Prediction of the untreated course in a particular individual is not yet possible except perhaps through observation of the course over time, but women, patients with migraine, and patients who present with disc hemorrhages are at higher risk of faster progression. Probably race and family history are important too.

It is clear that within the total group of those with NTG, progression is affected by lowering the IOP, but it is not known whether it may do so more in some cases than others. In principle, lowering of IOP is not necessary for those who are a low risk of progression in the first place, even without treatment. To be determined is whether there are subgroups in which lowering IOP is more effective in changing the course of the disease than in other individuals.

While a 30% lowering was used in this study, it is likely but not yet documented whether there is graded benefit, so that the degree of benefit (how much the rate of visual loss is slowed) varies according to how much the IOP is lowered. It is also not yet known whether some patients may respond adequately with less IOP lowering, while others require more IOP lowering.

This means that case selection for treatment, as well as the IOP target, may depend on a clinician's estimate of

the expected course without treatment based on clinical information available, including the identified risk factors for progression, but the goal of 30% lowering used in this study was arbitrary for the purpose of scientific documentation of an effect. Practical considerations may also enter in, affected by the responsiveness of the IOP to various treatment modalities available. For example, although filtration surgery achieved pressure lowering somewhat in excess of the 30% goal when it was used, and potentially had more benefit, it comes with the price of a higher incidence of cataract formation.

While following patients with NTG (or perhaps any glaucoma), with repeat testing of the visual field on many occasions, a field will someday be obtained by chance alone that seems worse than the baseline. Any field change needs to be confirmed before it can be judged genuine. Stability or instability of the case should correlate with other clinical findings, such as whether IOP goal has been obtained, changes in the optic disc, and, in advanced cases, the subjective sense of patient.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • Of special interest
- •• Of outstanding interest

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