Original Article

Critical Reevaluation of Previously Diagnosed Normal Tension Glaucoma Patients- A Three Year Study

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Purpose: The objective of this study was to reevaluate the previously diagnosed patients of normal tension glaucoma, visiting Eye Department of Military Hospital Rawalpindi, to confirm whether they really had normal tension glaucoma or not.

Material and Methods: All diagnosed normal tension glaucoma patients with routine follow-ups were given a thorough ophthalmic evaluation including best corrected visual acuity, slit lamp examination, stereoscopic disc evaluation using a 90 dioptre lens, Humphrey 30-2 statistic threshold perimetry, central corneal thickness measurement using ultrasonic pachymetry, Goldmann applanation tonometry, and gonioscopy.

Visual field testing was carried out using the 30-2 Humphrey field analyser (HFA). Phasing of IOP was done and CT scan and MRI were arranged wherever neuro-ophthalmological lesions were suspected. After thorough evaluation of each patient and ruling out all other conditions mimicking NTG the actual frequency of normal tension glaucoma was determined.

Results: It was found that out of 30 patients evaluated only two patients qualified to be labeled as NTG.

Conclusion: If NTG is considered a diagnosis of exclusion chances of making diagnostic mistakes should be minimized.

Key Words: Normal tension glaucoma, Applanation tonometry, Central corneal thickness, Intraocular pressure.

Normal tension glaucoma (NTG) has been described as a condition in which there is typical pathological cupping of optic nerve head with corresponding field defects but with an intraocular pressure within the accepted statistically normal range.

NTG is an entity that has created a lot of confusion among ophthalmologists for many decades. Its diagnosis can be very challenging and it has served as a real brainteaser for many eye doctors.

We were motivated to carry out this study by a similar study conducted in Israel in 1993, wherein 90% of previously diagnosed NTG patients were found to have mimicking lesions of optic nerve highlighting the importance of neuro-imaging in such patients[1], so we decided to carry out a similar reevaluation of our own NTG patients.

MATERIAL AND METHODS

We carried out a hospital based descriptive study at Department of Ophthalmology, Military Hospital, Rawalpindi starting August 2001 till August 2004.

Thirty patients of diagnosed normal tension glaucoma who fulfilled the inclusion criteria were selected from the outpatient department on the basis of convenience sampling.

Data was analyzed using statistical package for social sciences (SPSS) software method. Chi square test was used for nominal data.

Inclusion Criteria

Patients who had been diagnosed as normal tension glaucoma by an ophthalmologist at any time were included in the study. This included patients diagnosed by consultants, registrars and residents in training.

Examination

Examination was carried out according to the proforma and it included both local and systemic examination and direct questions were asked regarding ocular and medical history, any history of anemia, blood loss, and Raynaud's phenomenon.

Ocular Examination

All patients were given a thorough ophthalmic evaluation including best corrected visual acuity, slit lamp examination, stereoscopic disc evaluation using a 90 dioptre lens, Humphrey 30-2 static threshold perimetry, central corneal thickness measurement using ultrasonic pachymetry, Goldmann applanation tonometry, and gonioscopy. Twenty four hour phasing of IOP was also done. Water drinking test was done when considered appropriate.

Visual field testing was carried out using the 30-2 Humphrey field analyser (HFA). Visual fields were repeated whenever the test results were unreliable or edge defects were present.

CT scan and MRI were arranged whenever neuro-ophthalmological lesions were suspected or water drinking test and phasing tests were negative.

Systemic Examination

The systemic examination of all the patients was carried out placing special emphasis on cardiovascular status and neurological evaluation.

RESULTS

Thirty patients were included in the study, out of which 26 (86.7%) were male and 4 (13.3%) were female in the ratio of (Table 1) (Fig. 1). The patients' age ranged from 22 to 73 years with a mean value of 42.6 years.

Our study showed that out of 30 patients diagnosed as NTG at some stage in their life by any ophthalmologist, we were only able to label two (6.7%) patients as NTG. In the remaining 28 patients (93.3%) we were able to demonstrate a mimicking lesion or no pathology at all (Table 2, Fig. 2).

Out of these 28 patients 7 (25%) were found to have no ocular or neurological pathology. While 21 (75%) out of these 28 patients were found to have various ocular and neurological lesions accounting for excavation of optic disc and visual field defects.

Eight patients (26.7%) were found to have pituitary tumor on CT scan giving rise to advanced cupping of disc bilaterally in the presence of normal IOP.

Four patients (13.3%) actually had primary open angle glaucoma and IOP was revealed more than 21 mm of Hg on diurnal phasing for 24 hours.

Three patients (10%) were found to be suffering from various neurological lesions which were discovered on CT/ MRI scan namely temporoparietal hemorrhage, astrocytoma of left parieto-occipital area and demyelination plaques.

Three patients (10%) had anterior ischemic optic neuropathy, which was revealed on Humphrey perimetry as altitudinal defects.

One patient (3.3%) suffered from papillitis, which was discovered on retrieval of the old notes.

One patient (3.3%) was found to have ethambutol toxicity giving rise to bitemporal hemianopia. This information was revealed when past history was explored. CT scan brain was normal.

One patient (3.3%) had high myopia with associated large discs and was falsely labeled as NTG while visual fields were grossly normal.

Table 1: Gender distribution of patients

Gender	No. of patients n (%)
Male	26 (86.7)
Female	04 (13.3)

Table 2: Prevalence of Normal tension glaucoma

No. of patients previously diagnosed as	No of patients with mimicking lesions n (%)	No of patients labeled as NTG n (%)

NTG		
30	28 (93.3)	02 (6.7)

Table 3: Frequency of neurological lesions in diagnosed patients of NTG

Type of lesion	No. of patients n (%)
NTG	02 (6.7)
Neurological lesions	11 (36.7)
Others	17 (56.7)

Seven patients (23.3%) had no pathology at all, as visual fields were perfectly normal. Initial edge defects were part of the learning curve on perimetry and disappeared on subsequent tests.

Analysis of Data

Data in this study was nominal so Chi square test was applied.

Majority of patients in the study initially diagnosed as NTG were not actually suffering from NTG but disc cupping was due to other causes which mimic NTG and for this group the value of test of significance (P value) is of the order of $P<0.05$.

Only two patients justified to be labeled as NTG and for this group the value of test of significance (P value) is of the order of $P<0.001$.

These all show that hypothesis in our study is an alternate hypothesis.

DISCUSSION

Normal tension glaucoma (NTG) is a subset of primary open angle glaucoma (POAG), with characteristic glaucomatous cupping and field loss, an open drainage angle, and an intraocular pressure (IOP) consistently within the normal range[2]. There are several factors that lead to estimation of artificially low IOP and resulting in ophthalmologist making a wrong diagnosis. It is recommended that before labeling a patient with NTG several other mimicking lesions must be ruled out.

Some of the patients actually suffering from primary open angle glaucoma go undiagnosed and land up in normal tension glaucoma group when we make diagnosis on single IOP reading and do not take into account diurnal variation in IOP.

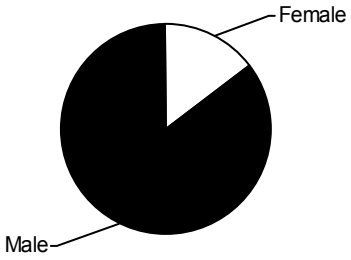


Fig. 1: Graphic distribution of patients according to gender

Study by Yamagami J, Araie M, Aihara M, Yamamoto S reported that mean of the IOPs recorded at the outpatient clinic in NTG patients had high correlation with the mean or peak of the IOPs recorded over a 24 hour period[3]. POAG is a significant mimicker of NTG as shown in our study where 4 patients actually had POAG that was revealed on diurnal phasing for 24 hours.

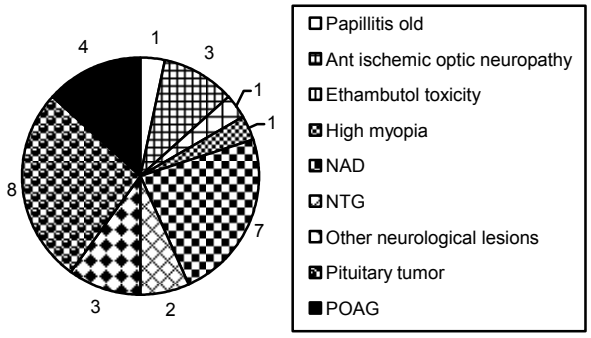
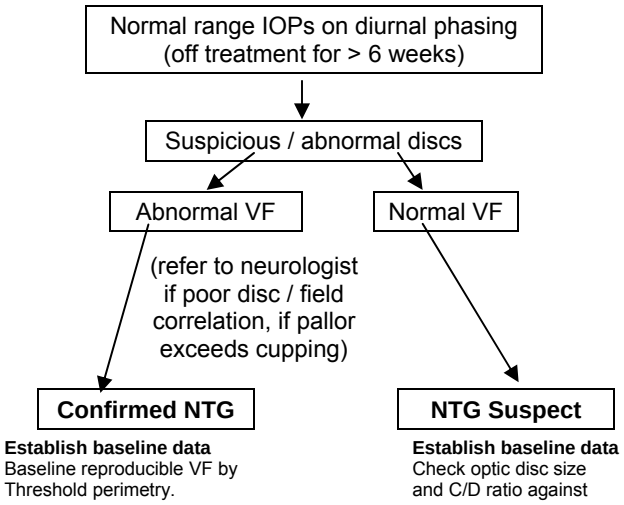
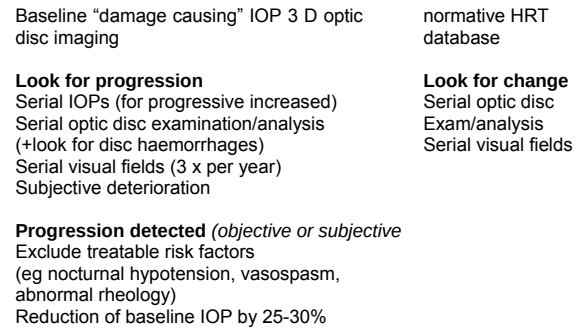


Fig. 2: Graphic distribution of patients according to final diagnosis





Alogrithm for the practical management of a patient with confirmed or suspected normal tension glaucoma. (Kamal D, Hitchings R. Normal tension glaucoma—a practical approach. *Br J Ophthalmol* 1998; 82: 835-40.

The progressive nature of glaucoma should always be borne in mind as this will help to distinguish true NTG from an isolated ischemic event, which may mimic it in terms of optic disc and visual field appearances[4]. Five cases of anterior ischemic optic neuropathy secondary to biopsy proven giant cell arteritis are presented in the study by Sebag J et al. In each case, cupping of the optic disc, which closely resembled glaucomatous cupping, was observed in the affected eye. These cases indicate that arteritic ischemic optic neuropathy can result in optic disc cupping, which closely resembles glaucomatous cupping. The similarities in the appearance of cupping of these discs with that seen in eyes with glaucoma suggest that the pathogenesis of cupping in glaucoma and in arteritic ischemic optic neuropathy may share some common mechanisms. Likewise Orgul S, Gass A and Flammer J. described a patient with arteritic anterior ischemic optic neuropathy who developed disc cupping within 4 months after an acute episode. This patient never had elevated intraocular pressure[5].

The end-stage optic disc appearance in arteritic AION secondary to giant cell arteritis is cupping, whereas segmental or diffuse pallor without cupping is the typical disc appearance after non arteritic AION[6-8]. A study was carried out in Japan which showed that angiographic picture of the optic disc in low tension glaucoma is clearly different from that in AION[9]. There should be little difficulty under most circumstances in making the clinical differentiation between a disc that has suffered ischemic optic neuropathy and a disc that has suffered pressure-induced damage, although occasional instances of ischemic optic neuropathy may be classified as low-tension glaucoma on the basis of field loss and cupping without elevated intraocular pressure[10]. Similarly in our study 3 out of 30 patients actually suffered from anterior ischemic optic neuropathy in the past.

When a person believed to have normal tension glaucoma continues to get worse despite treatment, it is likely that optic neuropathy is due to other causes. Of these other causes masses in the region of pituitary gland deserve special mention. These entities are not rare and can mimic disc and field changes in patients with glaucoma[11]. Baig MA et al[12] reported cases in which normal tension glaucoma was presented as multiple mimicking lesions. A case of NTG was reported in which visual deterioration continued despite anti glaucoma therapy so X-Ray pituitary fossa was ordered which showed ballooning of pituitary fossa due to pituitary tumor. Likewise another case is reported which was diagnosed as having unilateral normal tension glaucoma and was revealed to have aneurysm of the anterior cerebral artery compressing on the left optic nerve on MRI scan.

Yamabayashi S, Yamamoto T, Sasaki T and Tsukahara S reported a case of low tension glaucoma with primary empty sella where a congenitally empty sella turcica allowed for the chiasm to herniate downward into the sella causing field defects and nerve pathologies[13]. Kamal and Hitchings do not recommend routine scanning of every NTG patient with CT and MRI as they found that the incidence of intracranial disease was not greater than that expected for the general population in NTG clinics[14]. Another study found two out of 53 patients to have intracranial lesions in a group referred for evaluation of probable NTG[15]. Stroman et al[16] examined MRI results of 20 NTG patients and compared them with those of patients undergoing imaging who had no ocular findings and found the prevalence of space occupying intracranial abnormalities was similar for both groups. However the presence of diffuse small vessel ischaemic changes was more common in the NTG group, a finding supported by a later study.[17] In our study we have found 11 patients to be suffering from various neurological lesions. Out of these 8 patients had pituitary tumors and the rest three had astrocytoma of parietal lobe, temporoparietal hemorrhage and demyelination plaques.

Although commonest cause of bitemporal hemianopia is pituitary tumor, however ethmbutol toxicity can also give rise to such field defects. In our study we also found one case of bitemporal hemianopia with ethambutol toxicity falsely labeled as normal tension glaucoma[18].

There are a host of masquerading conditions that present with field defects that are non-progressive. Baseline measurements should best rely on the second testing session, since mean deviation and mean sensitivity are somewhat poorer when subjects with no prior visual field experience are first tested on the frequency doubling technology instrument. This may be especially true for the purpose of following patients over time[19]. Earlier experience with computerised perimetry is important for test results. Sizeable minority of normal subjects do not produce a normal test result at the first test[20].

Sensitivity values are below normal in the mid periphery of field of inexperienced subjects while paracentral area is entirely normal. Mostly results of a subsequent test on another day will be normal. Most perimetric learning takes place between first and second sessions. If concentric contraction is encountered in the first test of patient with suspect glaucoma, one can always regard the result as an indication of normal field, which can most likely be confirmed on next visit[20]. Likewise in our study 7 patients showed edge defects that disappeared on subsequent testing repeated after 3 and 6 months.

Eyes with large discs are often falsely labeled as glaucomatous. In eyes with small discs, field defects are often present while optic disc topography is still normal.[21] In our study we also found that a case with large discs due to high myopia was falsely being treated as normal tension glaucoma while IOP and visual fields were normal.

If the ophthalmologist makes enough effort most cases of NTG can be properly ascribed to other diseases like burnt-out POAG, arteritic AION, diurnal variations in POAG, chronic angle closure glaucoma, compressive lesions, non-glaucomatous optic neuropathy, previously high IOP, optic nerve hypoplasia, tilted discs, optic pits and colobomas, large physiologic cup (megalopapillae), optic nerve drusen and secondary glaucomas (pigmentary glaucoma, glaucomatocyclitic crisis) [22].

CONCLUSION

We do not deny the existence of normal tension glaucoma however if normal tension glaucoma is considered a diagnosis of exclusion chances of making mistakes are minimized. If the ophthalmologist tries to rule out mimicking lesions first before labeling a patient as normal tension glaucoma and starting anti glaucoma therapy, most cases of "NTG" can be correctly ascribed to another disease. Stress should be placed on complete eye examination and history, measurement of diurnal pressure curve, general medical exam and neuro-evaluation, serial fields and fundus photographs. Emphasis should always be placed on the correlation between the pattern of cupping and the location of the field disturbance when "topographically" evaluating visual field defects. Although a number of entities should be considered when evaluating a patient with cupping associated with normal intraocular pressure, a careful history and ocular examination may help distinguish glaucomatous from non-glaucomatous mechanisms of optic nerve head injury. We also recommend from our study experience, performing neuroimaging i.e. MRI/ CT before ultimately labeling a patient with normal tension glaucoma.

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