RESEARCH ARTICLE

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Determining the Likelihood of Normotension Glaucoma (Ntg) Among the Patients with Increased Cup-To-Disc (C/D) Ratio

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ABSTRACT

Introduction: Glaucoma, a progressive eye disease associated with optic nerve damage and gradual vision loss, is primarily caused by elevated intraocular pressure. Increased pressure can lead to optic nerve compression and neuronal damage, resulting in visual impairment. Sometimes intraocular pressure is detected as being normal while optic nerve damage happens and cause increased C/D ration a variant called normotension glaucoma. This study aims to determine the frequency of Normotension Glaucoma (NTG) in patients with a high cup-to-disc ratio who were referred to the clinic.

Materials and Methods: This cross-sectional descriptive study includes 100 patients with a cup-to-disc ratio above 0.3 and normal eye pressure. According to the perimetry printouts and optic nerve head OCT imaging, these patients were categorized into those with a physiological large cup or normotension glaucoma. Then the frequency of NTG was determined among individuals with a high cup-to-disc ratio. Demographic data, including age and gender, were recorded in the data collection forms and analyzed.

Results: According to this study every person with increased C/D ratio and normal IOP have a 26% chance of glaucoma. The research findings also revealed a significant correlation between age, C/D ratio, Intraocular Pressure (IOP), and Retinal Nerve Fiber Layer (RNFL) thickness with NTG ($P < 0.05$). However, there was no significant association among gender and Central Corneal Thickness (CCT) with NTG.

Conclusion: Comprehensive evaluation and imaging is mandatory for every one with enlarged C/D ratio even with normal IOP to prevent sever irreversible visual loss.

Keywords: Frequency, normotension glaucoma, high cup-to-disc ratio.

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INTRODUCTION

Glaucoma, as the second leading cause of blindness, is an optic neuropathy characterized by progressive structural and functional changes of the optic nerve, leading to typical optic disc damage and visual field impairment if left untreated[1]. Glaucoma patients generally suffer from reduced quality of life dependent on vision and impose a significant burden on caregivers and communities[2]. Glaucoma often remains undiagnosed until advanced and irreversible stages, beyond the initial asymptomatic phase[3]. In the late stage of the disease, the effects of medical and surgical treatments may not be satisfactory, emphasizing the importance of early identification and management[4]. Since glaucoma can have an asymptomatic prodromal phase, lifelong management and monitoring are necessary to prevent further visual loss[4].

Glaucoma cause a progressive optic neuropathy due to increased IOP which characterized by increased C/D ratio and subsequent visual field loss[5,6]. Normal-Tension Glaucoma (NTG), also known as low-pressure or normal-pressure glaucoma, is defined as open-angle glaucoma with IOP within the normal range. Its pathogenesis is not yet fully understood, and there is debate whether it represents a subset of Primary Open-Angle Glaucoma (POAG) or represents heterogeneous diseases. The impact of NTG can range from non-progressive and asymptomatic disease to bilateral blindness. It can mimic other optic neuropathies, and thorough investigation of other causes is warranted if necessary[5, 6]. The visual impairment consequences of NTG can be significant and may lead to difficulties in Activities of Daily Living (ADL)[7].

Globally, there are over 64 million people affected by glaucoma, accounting for approximately 3.5% of the world's population. Among them, around 7.5 million individuals have vision impairment, and 1.3 million are blind[8]. Among various glaucoma subtypes, Primary Open-Angle Glaucoma (POAG) is the most prevalent type, accounting for more than two-thirds of glaucoma cases worldwide[9]. POAG is believed to be more prevalent in Africa geographically and has the lowest prevalence in Asia. However, due to the relatively large population size of Asia, more than half of the world's POAG cases reside in Asia[10].

Considering the direct association between glaucoma prevalence and aging and the increasing global population's age, it is expected that glaucoma will become an even greater public health concern in the coming decades[11]. As the IOP is normal in Normotension glaucoma, then the diagnosis of the disease and it's differentiation from pathological large cup may be challenging which can lead to severe visual impairment. Therefore, understanding the prevalence and distribution of different types of glaucoma in a community is of significant importance in raising awareness among clinicians and researchers, as well as guiding health policy-makers in allocating appropriate healthcare services. According to the working experience it seems that the increased C/D ratio in Ardabil province in Iran is more than reported rates. Thus, considering the lack of previous studies on the proposed subject in the Ardabil province region, we decided to conduct this current study to investigate the prevalence of physiological cupping and NTG in the Ardabil province, Iran[12].

METHODS

The present study was a cross-sectional descriptive study. The target population consisted of individuals referred to the ophthalmology clinic of Imam Reza Hospital in Ardabil province for increased C/D ration in the years 2022-2023. The sampling method was non-random sampling. All the patients with any history of retinal or ophthalmic disease affecting optic nerve head were excluded from the study.

Sample Size: After refinement (selecting cup-to-disc ratio above 0.3 and cup linear and vertical above 0.3 as high cup-to-disc) along with normal IOP reading on standard applanation Goldman tonometry, a total of 200 eyes (right and left) of 100 patients were included in the study.

Procedure: All patients with cup-to-disc ratio above 0.3 and normal intraocular pressure on examination referred for imaging with standard perimetry (SITA standard strategy 30-2) and optic nerve head OCT to determine optic nerve damage and discrimination among physiological cupping or NTG. Consequently, the frequency of normotensive glaucoma among individuals with a high cup-to-disc ratio was determined. This information, along with patients' demographic data (age and gender), was recorded in the data collection forms.

Data Analysis: After completing the sampling and data collection for all patients, the data were entered into a computer and analyzed using SPSS software version 25. Data analysis was performed using independent t-test, Analysis Of Variance (ANOVA), and Pearson correlation coefficient.

Ethical Considerations: All participants were ensured that their involvement in the study was purely for research purposes, and their identities would remain confidential. Informed consent was obtained from all participants, who willingly and satisfactorily answered the research questions. This study received ethical approval under the code IR.IAU.ARDABIL.REC.1402.063 from the Ethics Committee of Islamic Azad University, Ardabil branch.

RESULTS

A total of 200 eyes of 100 patients were included in the study, with 53% being male and 47% being female. The mean age of participants was 37.07±12.25 (15-61 years old).

To examine the prevalence of NTG among patients with increased C/D ratio, they were divided into two groups. The first group consisted of 26 patients with abnormal VF and OCT as NTG group and second group consisted of 74 patients with normal VF and OCT which considered as normal physiological cupping, so the likelihood of being diagnosed as glaucoma among the patients with detected high C/D ratio is 26%.

In Table 1, the mean and standard deviation of C/D ration on examination and OCT of optic nerve head (linear CD and vertical CD ratio), Intraocular Pressure (IOP), Central Corneal Thickness (CCT), and Retinal Nerve Fiber Layer (RNFL) were analyzed between the two study groups. The results showed that the mean examination C/D, linear cup-to-disc, vertical cup-to-disc, and IOP in the normotensive glaucoma group were higher than those in the physiological cupping group, while CCT and RNFL in the NTG group were lower than those in the physiological cupping group **(Table 1)**.

Chi-square test was used to examine the relationship between gender and NTG. The results indicated that gender does not have a significant effect on the presence of NTG (sig > 0.05) **(Table 2)**.

The average age for the NTG group was 40.5, while the average age for the physiological cup group was 35.864. An independent t-test revealed a significance between age and presence of NTG. Therefore, it can be claimed that the incidence of NTG increases with the age.

Based on the results presented in Table 3, there was a significant difference between CD ration on examination and OCT (linear CD, and vertical CD) between the NTG and physiological cupping group **(Table 3)**.

Reveals that all three dependent variables: (examination-based CD, linear CD, and vertical CD), exhibit significant differences between NTG and physiological cup groups (P< 0.05). In people with NTG, these three factors have higher values compared to individuals with physiological cup **(Table 4)**.

Table 1: Mean and Standard Deviation of CD ration on examination and OCT of the optic nerve head (Linear CD, Vertical CD), IOP, CCT, and RNFL in the NTG and Physiological Cupping Groups.

	Normotension glaucoma		Physiological cup	
Indicator	**Mean**	**SD**	**Mean**	**SD**
examination CD	0.746	0.075	0.61	0.086
CD Linear	0.763	0.071	0.625	0.089
vertical CD	0.767	0.071	0.623	0.092
IOP	16.846	1.258	15.358	1.335
CCT	506.173	26.741	512.695	41.309
RNFL	95.23	6.599	106.25	5.514

Table 2: Role of Gender in NTG Presence.

		Group			
Variable	**category**	**Normotension glaucoma**	**Physiological cup**	**Chi-square measure**	**P value**
Sex	Male	11	42	3.225	0.073
	Female	15	32		

Table 3: Multivariate Analysis of Variance Results for Comparison of Examination cd, Linear cd, and Vertical cd between NTG and Physiological Cup Groups.

Effect		**The amount of**	**F**	**The degree of freedom of the hypothesis**	**Error degree of freedom**	**P value**
Group	Pillai's effect	0.361	36.837	3	196	0
	Wilks Lambda	0.639	36.837	3	196	0
	Hotelling's effect	0.564	36.837	3	196	0
	The largest zinc root	0.564	36.837	3	196	0

Table 4: Intergroup Effects of Multivariate Analysis of Variance on Examination based CD, OCT based CD (Linear CD, and Vertical CD) between NTG and Physiological Cup Groups.

Source	**The dependent variables**	**sum of squares**	**Degrees of freedom**	**average of squares**	**F**	**P value**
Group	CD on examination	0.705	1	0.705	100.266	0
	CD Linar	0.73	1	0.73	100.379	0
	vertical CD	0.801	1	0.801	104.484	0
Error	CD on examination	1.392	198	0.007		
	CD Linar	1.439	198	0.007		
	vertical CD	1.518	198	0.008		
Total	CD on examination	85.56	200			
	CD Linar	89.752	200			
	vertical CD	89.73	200			

The average IOP for the NTG group was 16.846 mmHg, while for the physiological cup group, it was 15.358mmHg. According to t-test individuals with NTG have higher IOP than physiological cupping group.

Regarding Central Corneal Thickness (CCT), the average CCT for the NTG group was 506.173 micrometer and for the physiological cupping group was 512.695 micrometer. The difference in CCT between these two groups was not considered significant.

According to OCT of the optic nerve head findings, the average RNFL thickness for the NTG group was 95.230 micrometer, while for the physiological cup group, it was 106.250 micrometer. An independent t-test yielded a significant difference. Individuals with NTG have lower RNFL thickness than other group.

DISCUSSION

Glaucoma is a progressive eye disease due to increased IOP that is characterized by optic nerve damage and gradual loss of visual acuity. It is primarily caused by increased intraocular pressure, which compresses and damages the optic nerve, resulting in the deterioration of neurons and reduced vision. The aim of this study was to determine the frequency of NTG among patients referred to the hospital clinic with a high cup-to-disc ratio.

According to this study every patient with high CD ratio and normal IOP have a 26 % chance to be diagnosed as NTG. The study results indicated that gender does not have a significant effect on the presence of NTG ($P > 0.05$). These findings align with previous studies conducted by Bonovas[13], Esporcatte & Tavares[14], Gao[15], and Suzuki[16] that also found no association between gender and NTG. In glaucoma there is generally no direct relationship between gender and NTG. However, some research suggests that gender may influence the occurrence of NTG in certain cases. Nonetheless, gender is just one potential influencing factor among many that can impact the disease. Although some studies have found variations in the gender-glaucoma ratio, more research is needed to establish a definitive conclusion. Existing studies have yet to demonstrate a direct and conclusive relationship between gender and NTG, highlighting the necessity for further research in this area[17].

The research findings indicate a significant difference in age between the NTG and physiological cup groups (sig < 0.05). It can be concluded that the incidence of glaucoma increases with age, which is in accordance with previous studies conducted by Nucci et al[18]. Glaucoma leads to permanent damage to the optic nerve, and neurotrophic factors which play a crucial role in maintaining neuronal health and function. Numerous scientific studies have demonstrated a relationship between age and glaucoma. Due to aging, the levels of neurotrophic factors in the body decrease that potentially resulting in damage to optic nerve and an increasing rate of NTG[19].

C/D ratio related variables (examination-based CD, linear CD, and vertical CD) showed significant differences between the NTG and physiological cup groups ($P < 0.05$). People with NTG exhibited higher values for all three factors compared to those with physiological cup, which is consistent with the studies conducted by Weinreb[20] and Ju et al.[21]. The increased values of these variables in NTG can be attributed to the main mechanism of the disease, which involves optic nerve damage, optic disc atrophy, and cup enlargement. Thus, the high ratio observed in NTG is a predictable outcome. While both normal tension glaucoma and physiological cup cases exhibit elevated C/D ratios, the level is generally higher in NTG[22].

There was also a significant difference between the groups of GNT and physiological cup in terms of intraocular pressure (IOP) (sig < 0.05), with higher IOP observed in individuals with GNT. These results are consistent with the studies conducted by Coleman[23] and Grierson[24], which also identified a significant difference in IOP between the two groups. Although both NTG and physiological cup cases exhibit IOP within the normal range, the amount of intraocular pressure tends to be higher in NTG patients. However, despite the statistically significant difference, the variation in IOP is not clinically significant and considered in normal clinical range[25].

The Central Corneal Thickness (CCT) had no significant difference between two groups ($P > 0.05$). This finding contradicts the studies conducted by Gupta et al.[26] but aligns with the study by Weinreb et al. As tonometry is influenced by CCT, the central thickness of the cornea (CCT) may be a determining factor, as thin CCT can potentially lead to falsely low eye pressure readings and contribute to misdiagnosis of the disease[27].

Based on the optic nerve head OCT readings, Retinal Nerve Fiber Layer Thickness (RNFL) was significantly thinner among NTG group (sig < 0.05. This finding is consistent with the study conducted by Mayro[28]. The thickness of the retinal nerve fiber layer serves as an important factor in diagnosis of functional disorders in the optic nerve head. Due to optic nerve damage in NTG, the thickness of this layer decreases, allowing for clear differentiation from the physiological cup. It is expected that RNFL thickness will be affected in any type of glaucoma-related optic nerve damage.

CONCLUSION

According to this study any kind of enlargement in CD ratio even in patients with normal IOP should be considered as an alarm sign for probable NTG which can progress to severe visual damage. So comprehensive evaluation and imaging is always necessary to identify real glaucoma cases before irreversible severe optic nerve damage.

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