

Original Article

FLAMMER SYNDROME-EYE BEYOND INTRAOCULAR PRESSURE

ARIJITA BANERJEE* , INDU KHURANA

*Dr. B. C. Roy Multi-Speciality Medical Research Centre, IIT Kharagpur, West Bengal 721302, India, Ex-Head Department of Physiology, PGIMS Rohtak, India
Email: b.arijita@gmail.com

Received: 07 Feb 2022, Revised and Accepted: 29 Mar 2022

ABSTRACT

Objective: Flammer syndrome or Vascular dysregulation has nowadays become an important topic of debate since it is said to pose a risk in development of glaucomatous optic neuropathy, besides raised intraocular pressure. Our study was implemented to determine the role of flammer syndrome, far less known and often neglected in pathogenesis of glaucomatous optic neuropathy.

Methods: The study group consisted of forty age and sex-matched diagnosed normal-tension glaucoma subjects and forty healthy controls. Each of them completed the Flammer syndrome questionnaire. T test was used for data analysis.

Results: Statistically significant differences in symptoms like increased sensitivity (cold, drugs, smell, pain), long sleep onset time and a reduced feeling of thirst were existed between cases and control groups ($p < 0.001$). They also demonstrated increased sensation to a few signs and symptoms like cold hands/feet, dizziness, migraines, headaches, and pain compared to controls but not significantly.

Conclusion: The study could explain the possible relationship between normal-tension glaucoma and Flammer syndrome. Further research to be done to confirm this link in order to prevent the onset of glaucomatous optic neuropathy.

Keywords: Normal-tension glaucoma, Optic neuropathy, Primary vascular degeneration, Autoregulation

© 2022 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>)
DOI: <https://dx.doi.org/10.22159/ijpps.2022v14i5.44348>. Journal homepage: <https://innovareacademics.in/journals/index.php/ijpps>.

INTRODUCTION

The classical triad of Glaucomatous optic neuropathy (GON) constitutes retinal ganglion cell loss, optic disc cupping and visual field defects. In normal-tension glaucoma (NTG) patients, where intraocular pressure is under normal range (10-21 mmHg), decreased blood flow at the ocular level may be due to a primary component or secondary to GON is the sole reason behind it. However, vascular dysregulation is not confined to the eye but can be seen in the capillaries of the nail bed, which indirectly supports the presence of the primary component [1, 2].

The patients with Flammer syndrome react to multiple stimuli, for example, cold, and stress which, when gets provoked could predispose to serious diseases. Studies of potential links between different health conditions and glaucoma led to much controversy in the literature because that authors used the term glaucoma sometimes for an IOP increase (a risk factor for GON). Rather all the risk factors for arteriosclerosis were also risk factors for an IOP increase. With growing knowledge, the terminology changed from vasospasm over vasospastic syndrome to primary vascular dysregulation and finally to Flammer syndrome. Although this syndrome is harmless, the present research has been conducted to emphasize the contribution of the same to the occurrence of glaucoma [3, 4].

MATERIALS AND METHODS

Methods

The study group consisted of forty age and sex-matched normal tension glaucoma patients and forty healthy controls. Informed written consent was taken from each subject prior to the test. Glaucoma patients were diagnosed by the ophthalmology department. The patients whoever on antihypertensive drugs or having any cardiovascular disease were excluded from the study.

The study was conducted after the approval of PGIMS Rohtak Institutional Ethical committee under the 'exempt category' due to the noninvasive nature of the study. Each individual was asked to fill the questionnaire following which blood pressure recording was

taken using aneroid sphygmomanometer and basal heart rate variability (HRV) using ECG lead II in Powerlab 26T Polyrite d system was taken for 5 min and different variables of time and frequency domain were analysed. The Flammer Syndrome Questionnaire (FSQ), prepared originally by the research team ocular blood flow of the department of ophthalmology at University Hospital Basel was used after taking approval from the above-mentioned concerned authority [5].

The 15-item scale consisted of 15 different signs and symptoms of Flammer syndrome. Responses to items along with HRV analysis were measured on a 4-point Likert scale ranging from 0 (I do not know) to 3 (often). The mean scores of all the cases and controls were analysed in the form of mean±SD, the higher the score, more is the vascular dysregulation. The mean score of each item between glaucoma cases and controls was compared by using a simple independent unpaired t test and regression analysis comparing the effect of questionnaire items on NTG patients to control subjects. $P < 0.05$ was considered statistically significant. SPSS 20.0 was used to analyse the data. The FSQ is depicted in fig. 1.

Name (Initials):

Date of birth:

Date:

Sex: female male

Fig. 1: Flammer syndrome-questionnaire

Q1. Do you suffer from cold hands or feet (possibly also in the summer) or have other people ever told you that your hands are cold?

often sometimes never I don't know

Q2. Do you feel cold when you sit down quietly for some time or when you are not moving?

often sometimes never I don't know

Q3. Do you have or have you ever had a low blood pressure?

yes sometimes no don't know

Q4. Do you ever feel dizzy when you suddenly stand up from a lying (or resting) position?

often sometimes never I don't know

Q5. Do you need a relatively long time to fall asleep (e.g. when you are cold)?

often sometimes never I don't know

Q6. How is your feeling of thirst?

I am little thirsty. I am very thirsty and I drink a lot. I am little thirsty and I drink little both thirst and drinking behaviour are normal

Q8. How often do you have headaches?

often sometimes never I don't know

Q9. In case you suffer from migraines, do you have accompanying symptoms (e.g. visual disturbances, transient altered sensation (e.g. cribbling) in your arms or in your legs etc.)?

often sometimes never I don't know

Q10. If you have to take medications (other than pain killers), do you have the feeling that you react strongly to them and/or that you would feel better, if you would take a lower dosis than that which is normally prescribed?

often sometimes never I don't know

Q11. Do you suffer from any type of pain (for which you would have to take pain killers)?

often sometimes never I don't know

Q12. How well can you smell: Can you smell things that other people don't smell or that others smell to a lesser extent?

often sometimes never I don't know

Q13. Please mark one of the following: At 20-30 years of age, I was....

very slim slim average weight overweight

Q14. If you had to judge yourself (e.g. in your work), would you say that you are particularly reliable with a tendency towards perfectionism?

yes a little no I don't know

Q15. Have you had phases in your life in which you had ringing in your ears (tinnitus)?

often sometimes never I don't know

Q16. Have you noticed reversible blotches (white or red) on your skin when you were very excited or angry (e.g. in stress)?

often sometimes never I don't know

RESULTS

In this study each item was compared between NTG and healthy control subjects. As shown in table 1, statistically significant differences in symptoms like increased sensitivity (cold, drugs, smell, pain), long sleep onset time and a reduced feeling of thirst have existed between cases and control groups ($p < 0.001$). Table 2 shows that the glaucoma patients significantly exhibited classical signs of hypotension and increased skin temperature inhomogeneity which is usually noted as reversible skin blotches to emotional stress. The basal HRV was also altered significantly in the case of NTG subjects with respect to healthy controls.

Table 1: Classical symptoms of flammer syndrome compared between NTG patients and controls

FSQ items	NTG (mean±SD)	Controls(mean±SD)	P value
Increased sensitivity	2.24±0.76	1.24±0.34	<0.001
Long sleep onset time	1.68±0.62	1.36±0.54	0.004
Reduced feeling of thirst	1.38±0.47	1.16±0.38	0.005

$P < 0.05$ significant, $n=40$, values obtained in mean±SD

Table 2: Signs of flammer syndrome compared between NTG patients and controls

FSQ items	NTG (mean±SD)	Controls (mean±SD)	P value
Skin temperature distribution (cold extremities and warmer trunk)	2.06±0.42	1.72±0.56	<0.001
Hypotension	1.62±0.22	1.14±0.28	<0.001
Reversible skin blotches	1.38±0.46	1.26±0.38	0.005
Altered HRV (LF/HF)	2.16±1.24	1.06±0.48	<0.001

$P < 0.05$ significant, $n=40$, Values obtained in mean±SD

The glaucoma group also demonstrated increased sensation to few signs and symptoms like cold hands/feet, dizziness, migraines and headaches compared to controls but not significantly.

DISCUSSION

The observations in our study could confirm the previous findings in most cases. Still, certain things need to elucidate. In neurodegenerative conditions, smell perception is usually affected

initially, which our study also showed that smell perception was significantly affected in NTG patients than in controls [6].

Also, in past, there is little information regarding the increased drug sensitivity in NTG patients which was observed in our study. Yet, increased sensitivity to bradykinin due to differential expression of ATP transport proteins have been depicted earlier in a study [6, 7].

Tinnitus in NTG patients was significant, the relationship not been studied well earlier. A typical for FS, sleep onset time was prolonged

in the NTG patients which is in accordance with previous study which explained how melatonin responsible for circadian rhythm is also responsible for fine tuning of vascular tone [10, 11].

The phenomenon of skin blotching is classic example of vascular dysregulation which goes in accordance with our study, showing NTG patients more prone towards skin blotches [8, 9].

Increased sensitivity to cold was again observed in NTG patients, which is in accordance with previous study. Hypotension, is till date, the best-documented risk factor for glaucomatous optic neuropathy. Studies depicted that the lower the BP was, the longer the more blood flow cessation took place in the nail bed capillaries. Our study confirmed that subjects with NTG indeed had significantly less desire to drink. Reports earlier stated that endothelin which gets raised in vascular dysregulation, suppressed the feeling of thirst via upregulation of PGE2 [12-14].

Therefore, from the above discussion it is clear that there is a relationship between flammer syndrome and glaucomatous optic neuropathy. Besides intraocular pressure, disturbed vascular dysregulation plays an important role in the pathogenesis of glaucomatous optic neuropathy leading to increased oxidative stress, which reduces the transport of oxygen from the blood vessels to the neurons [14-17].

LIMITATIONS

The results of our study could not be compared in other types of glaucoma. Further quantification of the study could be done using gene expression techniques and analysis of endothelin 1 levels in the above subjects.

CONCLUSION

There is a clear evidence for an association between NTG and Flammer syndrome. It remains a challenge to explore if the diagnosis of Flammer syndrome could prevent the risk for NTG. Had the association been confirmed, this would be a revolutionary step towards preventive medicine.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

- Wang X, Jiang C, Ko T, Kong X, Yu X, Min W, Shi G, Sun X. Correlation between optic disc perfusion and glaucomatous severity in patients with open-angle glaucoma: an optical coherence tomography angiography study. *Graefes Arch Clin Exp Ophthalmol.* 2015;253(9):1557-64. doi: 10.1007/s00417-015-3095-y, PMID 26255817.
- Moore NA, Harris A, Wentz S, Verticchio Vercellin AC, Parekh P, Gross J, Hussain RM, Thieme C, Siesky B. Baseline retrobulbar blood flow is associated with both functional and structural glaucomatous progression after 4 y. *Br J Ophthalmol.* 2017 Mar;101(3):305-8. doi: 10.1136/bjophthalmol-2016-308460.
- Gasser P, Flammer J. Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. *Am J Ophthalmol.* 1991;111(5):585-8. doi: 10.1016/s0002-9394(14)73703-1, PMID 2021167.
- Flammer J, Konieczka K, Bruno RM, Viridis A, Flammer AJ, Taddei S. The eye and the heart. *Eur Heart J.* 2013;34(17):1270-8. doi: 10.1093/eurheartj/ehd023, PMID 23401492.
- Konieczka K, Ritch R, Traverso CE, Kim DM, Kook MS, Gallino A, Golubnitschaja O, Erb C, Reitsamer HA, Kida T, Kuryshva N, Yao K. Flammer syndrome. *EPMA J.* 2014;5(1):11. doi: 10.1186/1878-5085-5-11, PMID 25075228.
- Gasser P, Meienberg O. Finger microcirculation in classical migraine. A video-microscopic study of nailfold capillaries. *Eur Neurol.* 1991;31(3):168-71. doi: 10.1159/000116670, PMID 2044632.
- Palmer KT, Griffin MJ, Syddall HE, Pannett B, Cooper C, Coggon D. Raynaud's phenomenon, vibration-induced white finger, and difficulties in hearing. *Occup Environ Med.* 2002;59(9):640-2. doi: 10.1136/oem.59.9.640, PMID 12205240.
- Mozaffarieh M, Fontana Gasio P, Schötzau A, Orgul S, Flammer J, Krauchi K. Thermal discomfort with cold extremities in relation to age, gender, and body mass index in a random sample of a swiss urban population. *Popul Health Metr.* 2010;8:17. doi: 10.1186/1478-7954-8-17, PMID 20525354.
- Gasser P, Stumpf D, Schotzau A, Ackermann-Liebrich U, Flammer J. Body mass index in glaucoma. *J Glaucoma.* 1999;8(1):8-11. PMID 10084268.
- Krauchi K, Deboer T. The interrelationship between sleep regulation and thermoregulation. *Front Biosci (Landmark Ed).* 2010;15(2):604-25. doi: 10.2741/3636, PMID 20036836.
- Pache M, Krauchi K, Cajochen C, Wirz Justice A, Dubler B, Flammer J, Kaiser HJ. Cold feet and prolonged sleep-onset latency in vasospastic syndrome. *Lancet.* 2001;358(9276):125-6. doi: 10.1016/S0140-6736(01)05344-2, PMID 11463418.
- Flammer J, Guthauser U, Mahler F. Do ocular vasospasms help cause low tension glaucoma? *Doc Ophthalmol Proc S.* 1987;49:397-9. doi: 10.1007/978-94-009-3325-5_50.
- Kaiser HJ, Flammer J, Graf T, Stumpf D. Systemic blood pressure in glaucoma patients. *Graefes Arch Clin Exp Ophthalmol.* 1993;231(12):677-80. doi: 10.1007/BF00919280, PMID 8299973.
- Joe SG, Choi J, Sung KR, Park SB, Kook MS. Twenty-four-hour blood pressure pattern in patients with normal-tension glaucoma in the habitual position. *Korean J Ophthalmol.* 2009;23(1):32-9. doi: 10.3341/kjo.2009.23.1.32, PMID 19337477.
- Banerjee A, Khurana I. Altered autonomic balance in Normal-tension glaucoma. *Asian J Pharm Clin Res.* 2017;10(2):175-7. doi: 10.22159/ajpcr.2017.v10i2.15001.
- Banerjee A, Khurana I, Dhull C. Normal-tension glaucoma versus primary open-angle glaucoma- the autonomic perspective. *Natl J Physiol Pharm Pharmacol.* 2019;9(6):510-4. doi: 10.5455/njppp.2019.9.0307323032019.
- Banerjee A, Khurana I. Impact of glaucoma in cognitive decline. *Asian J Pharm Clin Res.* 2018;11(10):549-51. doi: 10.22159/ajpcr.2018.v11i10.27068.