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ASSOCIATION BETWEEN PLATELET AGGREGATION PARAMETERS AND PRIMARY OPEN ANGLE GLAUCOMA

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ABSTRACT Glaucoma is the leading cause of irreversible blindness in the world. Being a progressive optic neuropathy, understanding multiple mechanisms playing a part in its progression is of vital importance. Among them, vascular theory states that it occurs as a consequence of insufficient blood supply. To know if this insufficiency occurs due to thrombosis in the blood vessels, platelet aggregation parameters can be used as a guide.

Aims: To compare the association between platelet aggregation parameters in patients with and without primary open angle glaucoma and also to co-relate it with the severity of glaucoma.

Design: Randomized, Cross-sectional, hospital-based observational study.

Methods: A total 53 consecutive patients with POAG and 53 controls were recruited in the study.

The cases were grouped as mild, moderate and severe based on the clinical optic nerve head findings and mean deviation (MD) value of visual fields. In bilateral cases, the eye with worse MD was selected.

Complete blood count was done to assess Platelet count (PLT), Platelet distribution width (PDW), Plateletcrit (PCT), Mean platelet volume (MPV). These platelet aggregation parameters were compared between the two groups.

Results: In the POAG group, PDW (16.29±1.10 fL) and MPV (8.48±0.83 fL) values were significantly higher ($p < 0.05$) than those of the control group (PDW 15.85±0.74 fL, MPV 8.17±0.76 fL). In POAG patients, PLT counts were lower (276.1±43.5) compared to controls (291.2±53.0) though not statistically significant. MPV (8.80±0.55), PDW (16.65±1.25) was highest in the moderate group but no statistically significance found.

Conclusions: PDW and MPV values were found to be higher in POAG patients, suggesting the possibility of platelet activation and hence increased platelet aggregation leading to insufficient blood supply to the optic nerve head and hence development of POAG. Role of antiplatelet drugs in delaying the development of glaucoma can be considered based on the above evidence.

KEYWORDS : Platelet aggregation parameters, Primary open angle glaucoma, vascular theory of glaucoma.

INTRODUCTION:

Glaucoma is a progressive optic neuropathy characterized by structural changes in optic disc and retinal nerve fibre layer and functional changes in the form of visual field defects. Glaucoma is the leading cause of irreversible blindness. It is predicted to affect 112 million people worldwide by 2040[1].

The pathogenesis of glaucoma is multifactorial and IOP is the only modifiable risk factor. Two principal theories have been put forth:
Mechanical theory-states that stretching of laminar beams is due to raised IOP and also causes damage to the retinal ganglion cell axon.

Vascular theory- states that glaucomatous optic atrophy is a consequence of insufficient blood supply. [2] This vascular theory is based on the fact that abnormal perfusion and subsequent ischemia of optic nerve head play a major role in glaucomatous optic atrophy [3]

In other systemic diseases like ischemic heart disease and transient cerebral ischemia, platelet aggregation is implicated to be risk factor for the vascular damage.[4,5]

Since platelets contribute in blood coagulation and microcirculation, its activation and endothelial interactions play a major role in vascular theory [6].

Altered platelet aggregation in glaucoma has inverse relationship with the blood flow in the small branches of the short ciliary arteries supplying the optic disc compromising the blood supply.[7]

Many markers have been used for activation of coagulation like prothrombin fragment 1+2, thrombin-antithrombin complex (TAT) and for activation of platelets like β-thromboglobulin (β-TG) or soluble platelet P-selectin1. However, laboratory measurement of these indices is laborious and expensive.[11]

Platelet parameters like Platelet count (PLT), Mean platelet volume (MPV) are indicators of production rate and size of platelets.[8] Platelet distribution width (PDW), Plateletcrit indicate the variation in size and represent the fraction of platelet in blood respectively [9,10]

MPV and PDW increase during the activation of platelets. This activation causes changes in the shape of platelet making it spherical. it also leads to formation of pseudopodia. These morphological changes make PDW the specific marker for platelet activation.[11] Large platelets are more adhesive and likely to aggregate than small ones suggesting MPV to be a useful indicator for activation.[8]

Significant elevation of these parameters was found in primary open angle glaucoma according to the study conducted by Yi Ma et al, with PDW being associated with disease severity. [12]

A group from Croatia determined circulating platelet aggregates in patients with advanced POAG and 20 healthy volunteers and detected an increased platelet aggregate ratio in the glaucoma group. [14] A study from the Netherlands compared platelet aggregation in 79 patients with POAG with that of 81 patients with OHT and detected a significantly higher incidence of spontaneous platelet aggregation in patients with POAG over 70 years of age[15].

Matsumoto reported that platelet aggregation which was defined by ADP or collagen was found to be increased in both NTG and POAG than controls[16]

There is abundant evidence that platelet aggregation is altered in POAG. Hence this study was planned to evaluate the association between platelet aggregation parameters in patients with and without primary open angle glaucoma to better understand the pathogenesis of POAG and additionally, to co-relate the platelet aggregation parameters with the severity of glaucoma.Subjects and Methods:

The sample size was estimated to be 106 subjects with 99% confidence level and a power of 90%. Hence, 106 consecutive patients attending the ophthalmology OPD in a tertiary care center (53 glaucoma patients and 53 healthy controls) who were willing to participate in the study with written informed consent were recruited for the study between March 2020 to Feb 2021.

Inclusion criteria for glaucoma patients were patients of either gender between the ages of 40-70 years, patients detected to have glaucoma based on IOP more than 21mmHg/ vertical cup:disc ratio above 0.7/ inter-eye asymmetry of above 0.2 with notching/ neuroretinal rim thinning/ retinal nerve fiber layer defect, visual field defect that

corresponds to presence of at least three contiguous nonedged test points within the same hemifield on the corrected probability plot at $p < 0.05$, with at least one point $p < 0.01$, excluding points directly above and below the blind spot [13] The cases were grouped as mild, moderate and severe POAG based on the clinical optic nerve head findings and mean deviation value of visual fields. In bilateral cases, the eye with worse mean deviation was selected.

For healthy controls, it was patients of either gender between the ages of 40-70 years, patients with IOP lesser than 21mmHg with normal optic disc and no clinical evidence of glaucoma.

Exclusion criteria for glaucoma patients and healthy controls were patients on antiplatelet or anticoagulant medication in the past 6months such as aspirin, clopidogrel, warfarin, patients with hematological disorders such as aplastic anemia and primary thrombocytosis, patients with abnormal coagulation functions, patients with severe cardiovascular, renal or hepatic disorders, patients with acute infections, autoimmune diseases, cancers or thyroid dysfunction, patients not willing to participate in the study.

Procedure: All the enrolled patients underwent a comprehensive ophthalmological examination by a glaucoma specialist which included visual acuity assessment and refractive error testing, slit lamp examination, IOP measurement with Goldmann's applanation tonometer, gonioscopy using Sussman 4 mirror gonioscope, optic nerve head examination by slit lamp fundus biomicroscopy using +90D lens, Visual field analysis using Humphrey field analyzer program 24-2 full threshold in both eyes. Mean deviation was noted.

Complete blood count (CBC) analysis for the study of platelet aggregation parameters were done using an automated hematology analyzer MINDTREE 6000(3part). The blood sample of 1.5ml for the same was withdrawn via venepuncture from the veins of the anti-cubital fossae (anterior elbow veins) and collected into tubes containing EDTA. The parameters tested were Platelet count (PLT), Platelet distribution width (PDW), Plateletcrit and Mean platelet volume (MPW).

Statistical analysis: Results are presented as Mean ± SD and range values for continuous data and frequencies as number and percentages. Unpaired t test was used to compare between the two groups. Categorical data was analyzed by Chi square test. A P value of 0.05 or less was considered as statistically significant. SPSS (version 17) software was used for all the analysis.

RESULTS:

Demography:

There were 106 patients recruited. 53 patients in POAG group and 53 patients in the control group. Out of 53 patients in POAG group, 34 were males and 19 were females. In the control group 27 were males and 26 were females.

In our study, the mean age of the patients was 59.9 ± 10.9 years in POAG group. It was 56.6 ±10 years in controls.

Comorbidities:

In the POAG group, 5 patients (9.4%) had only diabetes mellitus. 1 patient (1.9%) had only hypertension. 3 patients (5.7%) had both diabetes and hypertension. 44 patients (83%) had no comorbidities.

In the control group, 6 patients (11.3%) had only diabetes mellitus. 3 patient (5.7%) had only hypertension. 7 patients (13.2%) had both diabetes and hypertension. 37 patients (67.8%) had no comorbidities.

Table 1: Distribution Of Comorbidities Among Subjects

	Cases (53)	Controls (53)
DM	5 (9.4)	6 (11.3)
HTN	1 (1.9)	3.(5.7)
DM + HTN	3 (5.7)	7 (13.2)
None	44 (83.0)	37 (67.8)

Platelet Parameters:

In the POAG group, PDW (16.29±1.10 fL) and MPV (8.48±0.83 fL) values were significantly higher ($p < 0.05$) than those of the control group (PDW 15.85±0.74 fL, MPV 8.17±0.76 fL).

In POAG patients, PLT counts were lower (276.1±43.5) compared to controls (291.2±53.0) though not statistically significant.

The plateletcrit (PCT) was 0.20 ± 0.03 in POAG group and it was 0.21 ± 0.02 in the control group. No statistically significance was found

Table 2: Comparison Of Platelet And Ocular Parameters In Subjects With And Without POAG

Parameter	Cases	Controls	Cases v/s Controls	
	Mean ± SD	Mean ± SD	t value	P value
PLT COUNT	276.1±43.5	291.2±53.0	1.60	0.11
PCT	0.20±0.03	0.21±0.02	0.92	0.36
MPV	8.48±0.83	8.17±0.76	1.95	**0.05*,S**
PDW	16.29±1.10	15.85±0.74	2.45	**0.02*S**

*significant

Platelet Parameters And Severity Of Glaucoma

On the basis on clinical optic nerve head findings and mean deviation of visual fields, the subjects were divided. There were 21 cases with mild POAG, 10 cases with moderate POAG and 22 cases with severe POAG. Platelet count was highest in the severe group (279.6±42.11) and lowest in the moderate group (262.1±36.13).

Plateletcrit (PCT) was found to be similar in all the groups (0.20±0.02). MPV was highest in the moderate group (8.80±0.55) and lowest in the severe group ((8.33±0.86). PDW was highest in the moderate group (16.65±1.25) and lowest in the mild group (16.11±0.94)

Table 3: Comparison Of Platelet Parameters In Subjects With POAG, Stratified According To Severity.

Parameter	POAG severity		
	Mild (n=21)	Moderate (n=10)	Severe (n=22)
PLT COUNT	278.9±48.5	262.1±36.13	279.6±42.11
PCT	0.20±0.02	0.19±0.02	0.20±0.03
MPV	8.48±0.90	8.80±0.55	8.33±0.86
PDW	16.11±0.94	16.65±1.25	16.31±1.19

Linear Correlation

The linear correlation was calculated based on the mean deviation of the visual fields of the patients and their corresponding platelet parameters and no statistical significance was found. This implies that there was no statistical linear correlation of increased platelet parameters with increasing severity of POAG.

Table 4: Correlation Between Platelet Parameters And Severity Of POAG

Parameter	Mean Deviation of visual fields	
	r value	P value
PLT COUNT	-0.129	0.37
PCT	0.027	0.85
MPV	0.019	0.89
PDW	0.07	0.62

r: Pearson's correlation coefficient. P >0.05, not significant

DISCUSSION:

Vascular theory of pathogenesis of glaucoma considers insufficient blood supply due to reduced ocular flow to be the cause for ischemia and subsequent retinal ganglion cell death leading to glaucomatous optic neuropathy. Platelets contribute in blood coagulation and microcirculation. Therefore, its activation helps in identifying its role the disease process. MPV and PDW increase during the activation of platelets.

In our study, patients with POAG had significantly higher PDW and MPV values when compared with age matched controls. The platelet counts were lower in POAG group though not statistically significant. This is comparable with the study conducted by Ma Y et al.[12]

Increased PDW and MPV implies platelets are larger and are more active. They tend to have higher prothrombotic potential and aggregate more rapidly.[18,19,20] This leads to reduced ocular blood flow. A reduced blood flow can lead to ischemia of optic nerve head along with retinal ganglionic cell death due to loss of nutrient supply.[3]

Back in the 70s, Begg et al found that small vessel disease with hypercoagulable state was related to glaucomatous optic neuropathy.[21] Later on, Drance et al showed that hypercoagulability should be considered in pathogenesis of low-tension glaucoma.[17]

Matsumoto et al[16] showed increased platelet aggregation in normal

tension glaucoma and POAG by proving that ADP/collagen-induced secondary aggregation is frequently seen invitro in these patients. Hoyng et al[15] found association between spontaneous platelet aggregation and POAG.

Since the mechanism of damage due to platelet aggregation in not clear, several theories have been postulated like endothelial cell damage, flow rate reduction, vasoconstriction, collagen exposure ultimately leading to ischemic injury of the optic nerve.[16,22]

Another factor responsible for platelet aggregation is low levels of pigment epithelium derived factor which possesses antithrombotic properties. This factor was identified in glaucomatous patients by Ogata et al.[23]

MM Moschos et al conducted a study on anti-platelet properties of anti-glaucoma drugs and found that platelet aggregation was delayed in patients using those drops. They studied the aggregation using platelet activating factor, adenosine diphosphate, thrombin receptor-activating peptide and arachidonic acid.[24]This raises the question if anti glaucoma drops have been slowing the progression of glaucoma with their anti-platelet potential.

The platelet aggregation parameters and severity of glaucoma did not show any linear co-relation with each other in our study. This was in contrast to the study conducted by Ma Y et al.[12] Numerous studies have shown that reduced blood flow to optic nerve head is directly related to the progression in glaucoma causing increase in the visual filed defects.[25]

We should keep in mind that the platelet aggregation theory could fall into the secondary cause of pathophysiology since the values are within the normal limit. To the best of our knowledge, this is the first paper to test this hypothesis in our part of the country and it could be a prospective topic to study involving a larger population. This could help in throwing light upon the use of antiplatelet drugs in delaying the progression of glaucoma.

CONCLUSIONS:

PDW and MPV values was found to be higher in POAG patients, suggesting the possibility of platelet activation being an important factor in the vascular theory of development of optic nerve head damage in POAG. A future multi-centre study with a bigger sample size may provide additional information. Additionally, a study to evaluate the association between platelet aggregation parameters and other glaucoma varieties such as in primary angle closure disease may provide supportive evidence to the pathogenesis of optic neuropathy. Role of antiplatelet drugs in delaying the development of glaucoma can be considered.

REFERENCES:

1. Tham Y, Li X, Wong T, Quigley H, Aung T, Cheng C. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040.Ophthalmology. 2014;121(11):2081-2090.
2. Flammer J, Orgül S, Costa V, Orzalesi N, Krieglstein G, Serra L et al. The impact of ocular blood flow in glaucoma. Progress in Retinal and Eye Research. 2002;21(4):359-393.
3. Cherecheanu A, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L. Ocular perfusion pressure and ocular blood flow in glaucoma. Current Opinion in Pharmacology. 2013;13(1):36-42.
4. McGill DA, Ardlie NG. Abnormal platelet reactivity in men with premature coronary heart disease. Coron Artery Dis. 1994;5(11):889-900.
5. Hoogendijk EM, Jenkins CS, van Wijk EM, Vos J, ten Cate JW. Spontaneous platelet aggregation in cerebrovascular disease II. Further characterisation of the platelet defect. Thromb Haemost. 1979 May 25;41(3):512-22.
6. Popel A, Johnson P. Microcirculation and hemorheology. Annual Review of Fluid Mechanics. 2005;37(1):43-69.
7. M. Pache and J. Flammer, "A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma," Survey of Ophthalmology, 2006;51(3): 179-212.
8. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets. 2002;13(5-6):301-306.
9. Tvedten H, Lilliehöök I, Hillström A, Häggström J. Plateletcrit is superior to platelet count for assessing platelet status in Cavalier King Charles Spaniels. Veterinary Clinical Pathology. 2008;37(3):266-271.
10. Jindal S, Gupta S, Gupta R, Kakkar A, Singh H, Gupta K et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology. 2011;16(2):86-89.
11. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia. 2010;14(1):28–32.
12. Ma Y, Han J, Li S, Zhang A, Cao W, Sun X. Association between Platelet Parameters and Glaucoma Severity in Primary Open-Angle Glaucoma. Journal of Ophthalmology. 2019;1-9.
13. Chen Y, Qiu C, Qian S, Chen J, Chen X, Wang L et al. Lack of Association of rs1192415 in TGFBR3-CDC7 With Visual Field Progression: A Cohort Study in Chinese Open Angle Glaucoma Patients. Frontiers in Genetics. 2018;9.
14. Bojic´ L, Skare-Librenjak L: Circulating platelet aggregates in glaucoma. Int Ophthalmol 1998;22:151-4.
15. Hoyng PF, Greve EL, Frederikse K, et al: Platelet aggregation and glaucoma. Doc Ophthalmol 1985; 61:167-73
16. Matsumoto M, Matsuhashi H, Nakazawa M. Normal Tension Glaucoma and Primary Open Angle Glaucoma Associated with Increased Platelet Aggregation. The Tohoku Journal of Experimental Medicine. 2001;193(4):293-299.
17. Drance SM, Sweeny VP, Morgan RW, Fedman F. Studies of factors involved in the production of low tension glaucoma. Arch Ophthalmol 1973; 89: 457–465.
18. S. Karpatkin, "Heterogeneity of human platelets," Journal of Clinical Investigation, 1969; 48(6):1083-7
19. S. Kamath, A. D. Blann, and G. Y. Lip, "Platelet activation: assessment and quantification," European Heart Journal, 2001; 22(17): 1561-71
20. H. Giles, R. E. A. Smith, and J. F. Martin, "Platelet glycoprotein IIb-IIIa and size are increased in acute myocardial infarction," European Journal of Clinical Investigation, 1994; 24(1):69-72
21. Begg IS, Drance SM, Sweeney VP. Ischaemic optic neuropathy in chronic simple glaucoma. Br J Ophthalmol. 1971;55(2):73–90.
22. Yau JW, Teoh H, Verma S. Endothelial cell control of thrombosis. BMC Cardiovasc Disord. 2015;15:130.
23. Ogata N, Matsuoka M, Imaizumi M, Arichi M, Matsumura M. Decreased levels of pigment epithelium-derived factor in eyes with neuroretinal dystrophic diseases. Am J Ophthalmol. 2004;137(6):1129–1130.
24. Moschos MM, Moustafa GA, Papakonstantinou VD, Tsatsos M, Laios K, Antonopoulou S. Anti-platelet effects of anti-glaucomatous eye drops: an in vitro study on human platelets. Drug Des Devel Ther. 2017;11:1267-1272.
25. Y. Yamazaki and S. M. Drance, "the relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma," American Journal of Ophthalmology, 1997; 124(3):287-95.