Survey of Eye Patients' Haematology Parameters for Possible Biomarkers of Primary Open Angle Glaucoma in Gwagwalada, Nigeria

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ABSTRACT

Purpose: To determine and compare haematology parameters of primary open angle glaucoma (POAG) with non-glaucoma eye patients with a view towards identifying possible biomarkers for POAG.

Methods: Blood samples of 235 adult eye patients (96 POAG and 135 non-glaucoma) were collected and analysed. The mean values of the haematological indices (full blood count with differentials, ABO blood group and haemoglobin [Hb] phenotypes) for each of the groups were determined and compared using STATA 15.

Results: There were higher mean values in POAG group compared with the non-glaucoma eye patients (NGEP) for some blood differentials such as the monocytes percentage (POAG-11.29% versus NGEP-9.10%, p=0.012); monocytes number (POAG-0.50x10^3/µL versus NGEP-0.39x10^3/µL, p=0.034); red blood cell distribution width standard deviation (RDW-SD) (POAG-48.81fL versus NGEP46.27fL, p=0.033); haematocrit (POAG-43.66% versus NGEP-41.81%, p=0.014). Inversely, the mean corpuscular haemoglobin concentration (MCHC) in the POAG group was 29.81g/dL compared with 30.50g/dL in NGEP(p=0.012). There were no significant differences in the mean values of other differentials. The more common ABO blood groups were: O+ (50.21%), A+ (21.28%) and B+ (19.58%). There was no significant difference in the distribution of the blood groups among POAG patients compared with NGEP. The three identified Hb phenotypes were: AA (84.7%), AS (10.2%) and AC (5.1%). There was no significant difference in the distribution of Hb pheonotypes in both groups.

Conclusion: The monocyte values, RDW-SD, haematocrit and MCHC were associated with POAG. The blood group and haemoglobin phenotypes were not associated with POAG.
Keywords: Gwagwalada, haematology biomarkers, primary open angle glaucoma.

INTRODUCTION

Glaucoma remains a major cause of blindness across the globe especially in resource-limited climes.[1,2,3,4,5] Efforts at reducing glaucoma blindness span decades and continue with outstanding gains. The attention towards glaucoma is improving and more people are aware of glaucoma. Further, there are various automated central visual field analysers[6,7,8], optic nerve and retinal layer imaging devices[9,10] towards glaucoma

diagnosis and monitoring. There are improved and effective methods of glaucoma management.[11] Regardless, it is worrisome that many individuals with glaucoma (IWG) hardly benefit from these contemporary innovations that ensure better management of glaucoma and arrest glaucoma blindness.[12] These novelties are either unavailable to, inaccessible to or unaffordable by many IWG.[1,2,3,5,12,13]

The eye care practice in resource-limited settings is quite challenging: many IWG present late, and most eye care facilities cannot afford the expensive but necessary equipment for glaucoma detection or confirmation.[1,2,3] Moreover, when some eye facilities struggle to acquire such equipment, they hardly sustain their use for glaucoma care.[2] It is frustrating to often have many glaucoma patients presenting for the first time at an advanced stage. Of course, many IWG are unaware of their condition as a common type of glaucoma,primary open angle glaucoma (POAG), presents with visual impairment only at an advanced stage. The need for simple, effective, sustainable, affordable and accessible means of detecting glaucoma early towards appropriate management is underscored. Early diagnosis of glaucoma can prevent the magnitude of glaucoma blindness through appropriate intervention.

There are studies from different countries that investigated possible associations between glaucoma and blood groups.[14,15,16,17,18] A study among Pakistani[18] population showed a significant association between the B blood group and glaucoma ($P<0.05$, odds ratio [OR] 1.5, and x^2 15.8). Similarly, a report from Iran[19] indicated that in primary chronic glaucoma when compared with the control group, blood group B was more prevalent and blood group O was less prevalent. Glaucoma blindness is burdensome enough to warrant further research into these earlier reports on haematology parameters as possible biomarkers for glaucoma because of the inherent benefits. Meanwhile, those reports were not necessarily in climes where glaucoma has severe form of presentation such as Nigeria. Moreover, the inclusion of haematology indices aside blood group and haemoglobin phenotypes in this study has expanded the scope of blood parameters being investigated for glaucoma biomarkers. Discovery of biomarkers for glaucoma would make glaucoma diagnosis expeditious and less burdensome. This study analysedhaematology indices, specifically, blood group and haemoglobinphenotype, as possiblebiomarkers of POAG.

METHODS

This comparative cross-sectional study investigated haematology parameters of eye patients for biomarkers of POAG and was conducted at Department of Ophthalmology, University of Abuja Teaching Hospital (UATH), and Eye Clinic, Saint Mary's Catholic Hospital (SMCH), both in Gwagwalada, the Federal Capital Territory, Abuja. Whereas UATH is tertiary teaching public hospital with high eye patients load, SMCH is a catholic mission open to the public. The analyses of the blood samples were carried out at the Titan Research and Biochemical Laboratory Services, Gwagwalada, Abuja.

Study population

The participants were recruited among the eye patients attending UATH and SMCH, Gwagwalada, Abuja, Nigeria. Two groups of participants were recruited including primary open angle glaucoma (POAG) and non-glaucoma eye patients (NGEP).

The inclusion criteria comprised for all participants included written informed consent, adult age of at least 18 years, open anterior chamber angle (Van Herick's grade 3)[20]. An additional inclusion criterion for the POAG group was baseline Central Visual Field (CVF) difference of 2 dB with mean deviation (MD) of 6 dB or 1.5 dB in MD <6 dB in two CVF printouts done at a week interval using the automated perimeter with threshold strategy testing algorithm of 24 2 or 10 2 and target size III or V for VA of 6/60 at baseline, 3rd month, and 6th month considering accurate reliability indices of false positive <33%, false negative <33%, and fixation loss <20%.[20,21] Other criteria were vertical cup disc ratio of at least 0.5 and raised or normal intraocular pressure with or without medication. The additional inclusion criterion for non-glaucoma group was normal intraocular pressure (10 – 21mmHg).

The exclusion criteria were renal disease, liver disease, immunosuppression (HIV, chronic steroid therapy, radiotherapy), infective/

contagious conditions (epidemic kerato-conjunctivitis, COVID-19, Lassa fever, Ebola), other types of glaucoma apart from POAG, family history of high cup disc ratio (CDR) [familial high CDR], optic disc conditions (congenital/ traumatic atrophy, coloboma, drusen), use of lipid lowering medications, and lack of cooperation with the study processes.

Data collection

The details of eye patients who met the inclusion criteria during routine eye clinics were entered in the register and were informed about the research ahead of the study. Reminder phone calls were made to the patients to present on the selected day for the study. Written informed consent was sought and obtained from each participant. Thereafter, using aseptic procedures, four milliliters of fasting venous blood was withdrawn from ante-cubital vein of each participant and collected in the vacutainer ethylenediamin-etetraacetic acid (EDTA) bottle.

Laboratory analysis

The blood samples were transported in ice packed chamber same day to the laboratory for processing. The blood sample in EDTA bottles was analysed for full blood count (FBC) (white blood cell count (WBC), haemoglobin, haematocrit (PCV), platelet count using Automated Haematology analyzer (ESSE Model HA). The ABO and Rhesus blood groups were evaluated using tile method. The basic principles underlying blood grouping is the reaction between the red blood cell antigens and their corresponding antibodies. Monoclonal antisera (Anti-A, Anti-B, Anti-AB and Anti-D) reagents were used. In addition, the cellulose acetate electrophoresis (Helena machine Model: TITAN Plus and tank) was used to determine the participants' haemoglobin phenotypes (AA, AS, AC, SS, CC, and SC).

Ethical considerations

The approval to conduct the study was sought and obtained from University of Abuja Teaching Hospital (UATH), Health Research Ethics Committee (HREC). Written informed consent was obtained from each participant.

Data entry and analysis

Data was entered into Excel®, cleaned, exported into STATA 15 and analysed. The analyses carried out include simple proportion, independent samples T test (Levene's test for equality of variances and t-test for equality of means) and Chi square test. The results of Chi square test were considered significant at $P<0.05$.

RESULTS

Two hundred and thirty-five participants including 96 POAG and 139 non-glaucoma were studied. The age range was 19 - 85 years. The mean age for the POAG group was 53.70±13.15 years and for non-glaucoma patients was 46.05±14.00 years. Overall, 114 (42.8%) were males.

Comparison of Haematological indices

The mean monocytes percentage for the POAG group was 11.29±7.25% compared with 9.10±5.32% for NGEP group (p=0.012). Also, the mean monocytes number for POAG group was 0.50±0.42 x10^3/µL compared with 0.39±0.29 x10^3/µL for the NGEP group (p=0.034). Further, the mean red blood cell distribution width standard deviation (RDW-SD) for the POAG group was 48.81±10.28 fL compared with 46.27±7.85 fL for the NGEP group (p=0.033). Similarly, the mean haematocrit for POAG group was 43.66±6.16% compared with 41.81±5.17% for the NGEP group (p=0.014). On the other hand, the mean corpuscular haemoglobin concentration (MCHC) for POAG group was 29.8±2.21g/dL compared with 30.50±1.88 g/dL for NGEP group (p=0.012). Regardless of the mean values of other haematological indices for POAG group compared with NGEP group, the differences were not significant (p>0.05) [Table 1].

Blood group distribution

The study found ABO Rhesus positives (91.06%) predominantly more than the ABO Rhesus negatives (6.38%). The most common being O (53.61%) followed by A (22.98%) then, B (20.85%), and the least being AB (2.55%). The distribution of ABO blood group based on the frequency of occurrence included O in POAG (54.17%) compared with NGEP(53.24%) followed

Table 1: Comparison of the blood differentials of the participants

Parameters	Group	N	Mean	SD	SE	P value
White Blood Cell	POAG	96	4.5678	1.81175	0.18491	0.277
(*4.0-11.0 x 10^9/L)	non-glaucoma	139	4.3327	1.48800	0.12621	
Neutrophils (%)	POAG	96	29.4479	12.83242	1.30970	0.886
(*40–75%)	non-glaucoma	139	29.2001	13.23020	1.12217	
Lymphocytes (%)	POAG	96	54.1667	14.54406	1.48440	0.225
(*20 - 45%)	non-glaucoma	139	56.5860	15.26125	1.29444	
Monocytes (%)	POAG	96	11.2917	7.25029	0.73998	#0.012
(*2 - 12%)	non-glaucoma	139	9.0993	5.31757	0.45103	
Eosinophil (%)	POAG	96	4.8198	7.08785	0.72340	0.283
(*1 - 4%)	non-glaucoma	139	4.0521	3.77305	0.32003	
Basophil (%)	POAG	96	1.2493	0.52479	0.05356	0.818
(*0.5 - 1%)	non-glaucoma	139	1.2319	0.59285	0.05029	
Neutrophil (number)	POAG	96	1.3324	0.98892	0.10093	0.748
(*1.8 - 7.7 x 10^3/µL)	non-glaucoma	139	1.2916	0.93557	0.07935	
Lymphocyte(number)	POAG	96	2.1363	0.76292	0.07786	0.713
(*1.0 - 4.8 x 10^3/µL)	non-glaucoma	139	2.1729	0.74009	0.06277	
Monocytes (number)	POAG	96	0.4955	0.41968	0.04283	#0.034
(*0.2 - 0.8 x 10^3/µL)	non-glaucoma	139	0.3899	0.28831	0.02445	
Eosinophil (number)	POAG	96	0.1765	0.20693	0.02112	0.217
(*0.0 - 0.6 x 10^3/µL)	non-glaucoma	139	0.2105	0.20730	0.01758	
Basophil (number)	POAG	96	0.1029	0.07580	0.00774	0.205
(*0.0 - 0.2 x 10^3/µL)	non-glaucoma	139	0.0906	0.07130	0.00605	
Red Blood Count	POAG	96	4.7400	0.83105	0.08482	0.931
(*4.2 -6.1 x 10^6/µL)	non-glaucoma	139	4.7483	0.64428	0.05465	
Haemoglobin	POAG	96	13.0740	1.85150	0.18897	0.190
(*12.1 -17.2 g/dL)	non-glaucoma	139	12.7801	1.55832	0.13218	
Mean Corpuscular Volume	POAG	96	91.9917	9.29373	0.94854	0.828
(*80 - 100 fL)	non-glaucoma	139	93.4009	62.86079	5.33178	
Mean Corpuscular	POAG	96	27.4521	2.57808	0.26312	0.097
Haemoglobin (*27 - 31 pg/cell)	non-glaucoma	139	26.8885	2.53264	0.21482	
MCHC (*33 - 36 g/dL)	POAG	96	29.8135	2.20662	0.22521	#0.012
	non-glaucoma	139	30.4947	1.87564	0.15909	
RDW CV	POAG	96	15.8125	12.91670	1.31831	0.271
(*11.5% - 14.5%)	non-glaucoma	139	14.5695	2.63054	0.22312	
RDW-SD (*39 - 46 fL)	POAG	96	48.8125	10.28265	1.04947	#0.033
	non-glaucoma	139	46.2701	7.85144	0.66595	
Haematocrit (*36.1 -50.3%)	POAG	96	43.6563	6.15729	0.62843	#0.014
	non-glaucoma	139	41.8135	5.16911	0.43844	
Platelet (150 - 450 x 10^3/µL)	POAG	96	206.2604	123.9206	12.6476	0.303
	non-glaucoma	139	191.7309	72.59275	6.15724	
Mean Platelet Volume	POAG	96	10.9615	1.22692	0.12522	0.696
(*7.5 - 11.5 fL)	non-glaucoma	139	11.2361	6.80067	0.57683	
Platelet Distribution Width	POAG	96	14.7250	2.71789	0.27739	0.936
(*9.6 - 15.5 fL)	non-glaucoma	139	14.6615	7.39680	0.62739	
Plateletcrit (*0.19 - 0.39%)	POAG	96	0.1868	0.06447	0.00658	0.612
	non-glaucoma	139	0.1821	0.07286	0.00618	

*MCHC, Mean Corpuscular Hemoglobin Concentration; RDW-CV, Red Blood Cell Distribution Width Coefficient of Variation; RDW-SD, Red Blood Cell Distribution Width Standard Deviation. #Statistically significant. *Laboratory reference value range in Système International d'Unités (SI units)*

Table 2: The blood group distribution among the participants

Blood group	POAG (%)	Non-glaucoma (%)	Total (%)	P
A-	2 (2.08)	2 (1.44)	4 (1.70)	0.303
A+	26 (27.08)	24 (17.27)	50 (21.28)	
AB	3 (3.13)	3 (2.16)	6 (2.55)	
B-	1 (1.04)	2 (1.44)	3 (1.28)	
B+	12 (12.50)	34 (24.46)	46 (19.58)	
O-	3 (3.13)	5 (3.60)	8 (3.40)	
O+	49 (51.04)	69 (49.64)	118 (50.21)	
Total	**96 (100.00)**	**139 (100.00)**	**235 (100.00)**	

Table 3: The haemoglobin phenotype distribution among the participants

Haemoglobin phenotype	POAG (%)	Non POAG (%)	Total (%)	P value
AA	78 (81.25)	121 (87.05)	199 (84.68)	0.170
AC	4 (4.7)	8 (5.76)	12 (5.11)	
AS	14 (14.58)	10 (7.19)	24 (10.21)	
Total	**96 (100.00)**	**139 (100.00)**	**235 (100.00)**	

by A in POAG (29.16%) compared with NGEP (18.71%) then, B+ in POAG (13.54%) compared with NGEP(25.90%). The AB blood group in POAG (3.13%) compared with NGEP (2.16%), p=0.303, [Table 2].

Haemoglobin phenotype distribution

The commonest haemoglobin phenotype was AA (84.68%) including POAG (81.25%) compared with NGEP (87.05%), p=0.170. None of the participants had SS haemoglobin genotype. [Table 3].

DISCUSSION

The study determined, analysed and compared the full blood indices, blood group and haemoglobin phenotypes of two hundred and thirty-five participants including 96 primary open angle glaucoma (POAG) patients and 139 NGEP. The age range was 19 - 85 years and the majority of the participants in each group were in the middle age range. The gender distribution was almost equal. The mean monocytes percentage for POAG was significantly higher compared with non-glaucoma (NGEP). Notably, both POAG and NGEP mean monocytes percentages were within the laboratory reference value range of 2.0 - 12.0%. Regardless, it could be inferred that POAG was associated with higher monocytes percentage especially more than 11.0% compared with non-glaucoma with value less than 10.0%. Monocytes percentage may likely be a biomarker for glaucoma and further research should be conducted on it. Diagnostic evaluation for POAG should be considered in an individual with monocytes percentage $\geq$11.0%.

Similarly, the mean monocytes number for POAG group was significantly higher compared with NGEP group. Both POAG and non-glaucoma mean monocytes number were within the laboratory reference value range of 0.2 - 0.8 x 10^9/L. Nonetheless, it could be inferred that POAG was associated with higher monocytes number especially more than 0.50 x 10^9/L compared with non-glaucoma with value less than 0.45 x 10^9/L. Monocytes number may likely be a biomarker for glaucoma and further research should be conducted on it. Diagnostic evaluation for POAG should be considered in an individual with monocytes number $\geq$0.50 x 10^9/L.

Furthermore, the mean Red Blood Cell Distribution Width Standard Deviation (RDW-SD) for POAG group was significantly higher compared with NGEP group. Of note, both POAG and non-glaucoma mean RDW-SD were within the laboratory reference value range of 39-46 x 10^-15L.
Notwithstanding, it could be inferred that POAG was associated with higher RDW-SD especially more than 48.0 x 10^-15L compared with NGEP with value less than 47.0 x 10^-15L. The Red Blood Cell Distribution Width Standard Deviation may likely be a biomarker for glaucoma and further research should be conducted on it. Diagnostic evaluation for POAG should be considered in an individual with RDW-SD $\geq$48.0 x 10^-15L.
Additionally, the mean haematocrit for POAG group was significantly higher compared with NGEP group. Notably, the mean haematocrit of either POAG group or NGEP group was within the laboratory reference value range of 37.0 - 54.0%. Regardless, it could be inferred that POAG group was associated with higher haematocrit especially more than 43.0% compared with NGEP group with value less than 42.0%. Haematocrit may likely be a biomarker for glaucoma and further research should be conducted on it. Diagnostic evaluation for POAG may be considered in an individual with haematocrit $\geq$43.0%.
It is important to state the possibility that the observed elevated mean blood differentials might have been caused by some underlying confounders among the participants such as tuberculosis, HIV, rheumatoid arthritis, inflammatory bowel disease, chronic myeloid leukemia, recovery phase of acute infection and chemotherapy for monocytes; iron deficiency anaemia, vitamin B12 or folate deficiency, anaemia of chronic disease and haemolysis or haemorrhage for RDW-SD; and polycythemia vera, chronic hypoxia as well as dehydration for elevated haematocrit. [22,23,24]
On the other hand, the mean Mean Corpuscular Hemoglobin Concentration (MCHC) for POAG group was lower compared with non-glaucoma group. Notably, the mean MCHC of either POAG or NGEP group was within the reference laboratory value (33-36 g/dL). Regardless, it could be inferred that POAG was associated with lower MCHC especially lower than 29.00g/dL compared with NGEP group with value higher than 30.0g/L. The MCHC may likely be a biomarker for glaucoma and further research should be conducted on it. Diagnostic evaluation for POAG should be considered in an individual with MCHC $\geq$29.0g/dL. The MCHC, however, could also be reduced in some other health conditions such as in hypochromic anemias (iron deficiency anaemia, thalassemia, sideroblastic anaemia), chronic disease and inflammation (anaemia of chronic disease, chronic kidney disease), and other conditions including lead poisoning and heredity spherocytosis.[25]
Meanwhile, regardless of the mean values of the remaining blood differentials including white blood cell count, neutrophils, lymphocytes, eosinophils, basophils, red blood count, haemoglobin, mean corpuscular volume, red blood cell distribution width coefficient of variation (RDW CV), platelet, mean platelet volume, platelet distribution width, and plateletcrit for POAG group compared with NGEP group, the differences were not significant, P>0.05. Therefore, these other blood differentials may not be considered as biomarkers for POAG.
Of note, the findings of this study should be interpreted with caution as the exclusion of possible confounders was based onthe verbal reports of the participants on their health status and clinical examination. It would have been impractical to screen (medical investigations) all the participants for all possible confounders. Furthermore, it is possible that the blood differentials were affected by the antiglaucoma drugs since many of the patients in the POAG group were already on fixed combination antiglaucoma molecules unlike their counterparts in the NGEP group.[26] This is also an important area for further research.
This study found ABO Rhesus positive to be predominantly more than the ABO Rhesus negative. The preponderant Rhesus positive found in this study was noted in a previous review of gene frequencies of ABO and Rh blood groups in Nigeria where Rh+ was 94.90%[27] and an Iranian study[19] (Rh+POAG 84% and control 88%). Also of note, this study revealed the most common ABO blood group being O followed by A then, B, and the least being AB. The observed ABO blood group frequencies in this study is similar to that reported in a previous Nigerian review[27] which showed prevalence of ABO blood group frequencies in the order O > A > B > AB (52.93%, 22.77%, 20.64% and 3.66%) of the total population studied. The review provides information on the distribution/

frequency of ABO/Rh(D) blood group and their corresponding allelic proportion in a large Nigerian study. Moreover, the prevalence of O blood group among POAG was similar compared to the prevalence among non-glaucoma group; likewise the prevalence for AB in POAG compared with non-glaucoma. On the other hand, the prevalence of A blood group among POAG was higher than in the NGEP while, the prevalence of B among POAG was lower than in the NGEP. Meanwhile, an Iranian study[19] showed the prevalence of blood groups in POAG versus control as O (45% versus 38%, P<0.001), A (27% compared with 30%), B (19% compared with 24%) and AB (9% compared with 8%). There is similar pattern of ABO blood groups prevalence with O > A > B > AB in this study, previous Nigerian[27,28,29] and the Iranian[19] studies.

The finding in this study suggests that ABO blood group may not be biomarker for POAG as there was no significant difference between POAG and non-glaucoma groups. The finding is not peculiar to this study as Iranian[19], Leske and coworkers (in Barbados Eye Study)[9], and Blikas and coworkers[17] did not find any association between POAG and blood groups (ABO and Rh). Regardless of the aforementioned, some studies[16,18] indicated association between ABO blood group and glaucoma however, it is doubtful whether ABO blood group could serve as a biomarker for glaucoma.

Furthermore, three different haemoglobin phenotypes AA, AC and AS were identified in the study. The observed haemoglobin phenotypes are unlikely to be biomarkers for POAG as there was no significant difference in the phenotype prevalence between POAG and non-glaucoma groups.

In conclusion, monocytes, red blood cell distribution width standard deviation, haematocrit and mean corpuscular haemoglobin concentration were associated with the POAG in view of significance difference in their mean values between POAG and non-glaucoma groups. The blood group and haemoglobin phenotypes had similar distributions across both the POAG and non-glaucoma groups and were not associated with the POAG.

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