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Evaluation of Some Haemostatic, Haematologic, ABO and Lewis Blood Group as Stroke Risk Factors in Ogoni Indigenes, Rivers State, Nigeria

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ABSTRACT

Objectives: The study evaluated haemostatic, haematologic, ABO and Lewis blood groups as stroke risk factors in Ogoni indigenes. **Method:** Full blood count was done using automation (SYSMEX). Activated partial thromboplastin time and prothrombin time was done using manual method. Factor VIII, von Willebrand factor, fibrinogen, D-dimer, tissue plasminogen activator was done using ELISA method. ABO, Lewis blood groups were analysed using standard tube methods. **Results:** Statistically significant increase was observed in white blood cell counts in blood group O ($p = 0.0222$), white blood cells higher in stroke group. For haemostatic parameters, statistically significant difference was observed in mean platelet volume (MPV) of blood group Le a ($p < 0.0001$), mean platelet volume lower in stroke group and activated partial thromboplastin time of blood group A versus stroke group ($p = 0.0447$). **Conclusion:** Based on odd ratios and likelihood ratios, the risk for stroke to occur due to blood group differences was in the order of: (B)>(Le-a)>(Le-b)>(A)>(O). Based on haemostatic values associated with selected blood groups which were not significant but relevant because of some marginally higher mean values of the stroke subjects against controls, they are not significantly associated as risk factors. However, based on odd ratios and likelihood ratios presence of blood group B, Le-a and Le-b antigens may be associated risk factors for stroke event.

Keywords: Haemostatic; Haematologic; ABO Blood Group; Lewis Blood Group; Stroke; Ogoni

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INTRODUCTION

Some blood group antigens have long been recognized as potential risk factor of venous thrombotic-embolism which could ultimately lead to stroke. Stroke is one of the abnormal health conditions common among the elderly and of recent, quite a number of young adults that are being affected have been documented [1].

Stroke is termed as a "neurologic calamity" which is more conveying in terms of clinical outcome, than other terms used to describe it such as "cerebral infarction" and "cerebral accident" [2]. The latter terms, fall short in capturing the sudden occurrence, apparent gravity and randomness of the disease [2]. Also, there is another term for stroke which is "brain attack" and it was introduced as a synonym for stroke since 1990 by the American Stroke Association [3]. Stroke can therefore be defined as a sudden or abrupt onset of a neurologic deficit attributed to a main or focal cause in the vasculature [4]. The prevalence rate of stroke in Nigeria is 1.31 % [5].

Stroke can be ischaemic or haemorrhagic. It is ischaemic when there is thrombus formation in the veins that supplies blood to the brain and it is haemorrhagic when there is bleeding that causes an aneurism [4]. It should be noted also that in haemorrhagic stroke, there are two important main causes: hypertensive intracerebral haemorrhage and aneurysmal subarachnoid haemorrhage [4, 6].

There are haemostatic derangements associated with stroke, which can be proven with strong evidence based on haemostatic and haematological laboratory outcomes as stated by Christian *et al.* and Buseri *et al.* [1, 7]. These findings have laid credence to medical proof that diabolical beliefs on stroke occurrence cannot be said to be true without having issues that have to do with the alterations of normal haemostatic balance.

Haemostasis is the process whereby clots are formed in the walls of blood vessels that are damaged and then preventing the loss of blood whilst maintaining blood in a fluid/liquid state within the vascular system [6]. Haemostasis involves a balance in coagulation and fibrinolysis. This physiological balance is very critical in the prevention of stroke.

The occurrence of some disease condition has been associated with the person's blood group based on the antigens or agglutinogens present in that particular blood type [8]. ABO antigens are fully expressed on red blood cells membranes and other blood group antigens are also expressed on red blood cells, it is therefore imperative to extend research on associating the occurrence of stroke as a result of differences in ABO and Lewis blood group antigens, how these antigens interact with the blood vessels that supplies blood to the brain, and if their interaction may likely support thrombotic activities.

The ABO blood types have long been recognized as a potential risk factor of venous thrombotic-embolism [9, 10]. The ABO blood group is a risk factor for venous thrombosis and embolism [11], and von Willebrand factor has been linked with venous thrombo-embolism, it mediates the aggregation and adhesion of platelets, and also help in stabilizing FVIII in plasma [11]. No direct evidence has associated ABO locus with the synthesis of von Willebrand factor [12], but the A, B, and H antigens are expressed in von Willebrand factor molecules and the location of these antigens on the von Willebrand molecule is close to the A2 domain which binds for ADAMTS 13

(A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [12, 13]. These A and B antigens are known to reduce the binding capacity of ADAMTS 13 and in the long run, it reduces cleavage [12, 13]. Therefore, there is a link between ABO blood group and the expression of the H antigen, and lower levels of von Willebrand factor, which is now well established [9].

The Lewis agglutinogens, are structures that are synthesized by the exocrine epithelial cells that are absorbed passively unto red blood corpuscular bi-layers and some group of Lewis agglutinogens function as counter ligands for selectins [14]. This has been observed to be consistent with the relationship of Lewis antigens in the occurrence or development of thrombosis [15].

Studies have associated stroke with individuals who are of ABO blood group [10, 15, 16], but there is dearth of data on similar work conducted in Nigeria and particularly in Ogoni ethnic group of Rivers State, hence the study.

MATERIALS AND METHODS

Study Design

This was a case-control study carried among indigenes of Ogoni whose first generational maternal and paternal origins are Ogoni. Subjects were divided into groups based on differences in blood group system.

Study Area

The Ogoni ethnic group is found in Rivers State. It comprises majorly of individuals from Khana, Gokana, Tai and Eleme Local Government Areas [17]. In 2006, according to the National Population Census, Ogoniland has a human population of about 832,000 [18]. Ogoni land is located in an area along the Niger Delta Eastern edge, and to the north-east of the Imo River and Port Harcourt city. Ogoni land covers about 1036 Sq Km and borders the Bay of Guinea. It is a land of aggressive oil exploration that has resulted to severe environmental pollution. Bori is the traditional headquarter of Ogoni, the administrative headquarter of Khana Local Government Area; and sample collection was done in Bori [17]. Bori is located on latitude: 4^0 40′ 34.64″ N and longitude: 7^0 21′ 54.68″ E. The people of Ogoni are predominantly Farmers and Fishermen but others that are educated finds themselves in the teaching profession and civil/public service [17].

Study Population

The study was carried out among adults of Ogoni ethnic group. Sample size was obtained based on convenient sampling method. A total of one hundred and one (101) participants within the age of 30 – 60 years comprising of twenty-six (26) first-ever stroke subjects (9 females and 17 males), and seventy-five (75) apparently healthy control participants (40 females and 35 males) of age between 30 and 60 years were recruited for the study. The control participants were grouped into different groups based on differences in blood groups. The total control groups in the study were 5 which include: blood group A control group participants (15); blood group B control participants (13); blood group O control participants (39); Lewis A blood group control participants (11); and Lewis B blood group control participants (8).

Inclusion Criteria

Ogoni indigenes diagnosed of stroke by a Physician constituted the test subjects; individuals that are apparently healthy and not on medication/drug for the past two weeks; and are non-smokers and non-alcoholics were recruited as control subjects.

Exclusion Criteria

Individuals that are "Mixed Breed Ogonis" [either of their parents not from Ogoni], were excluded from the study; individuals that were diagnosed clinically with other disease conditions and individuals that declined consent were excluded.

Sample Collection and Processing

For prothrombin and activated partial thromboplastin time, 4 ml of venous blood was drawn from the antecubital fossa of the subject as described by Cheesebrough [19], into a vacutainer tube containing 0.5 ml of 32.0 g/L trisodium citrate solution, and properly mixed to prevent clot formation. For haematological parameters and blood groupings, 2.5 ml of venous blood was collected into a vacutainer containing 0.5 ml of 1.2 mg/mL dipotassium ethylene diamine tetra-acetic acid [EDTA]. For estimation of coagulation factor VIII, von Willebrand factor, fibrinogen, D-dimer and tissue plasminogen activator, 2.0 ml of venous blood was collected and introduced into a plain vacutainer. A total of 8.5 ml of blood was collected from each subject.

Blood collected in sodium citrate vacutainers were centrifuged at 2500 rpm for 5 minutes to obtain citrated plasma, Blood collected in dipotassium ethylene diamine tetra-acetic were analysed within 24 hours of collection for the estimation of complete blood count. Blood collected in plain non-anticoagulated vacutainer bottles were allowed to clot over time; and serum obtained by centrifugal separation for analysis.

Collected samples were transported under cold chain (ice packs/crushed ice in air tight and sealed thermo-container, from Bori (site of collection) to Port Harcourt (where analysis was carried out).

Sample Analysis

All samples for complete blood count were analysed using the automated machine (SYSMEX, manufactured by KOBE, Japan, Model No: KX-21N). All samples for activated partial thromboplastin time and prothrombin time were analysed using manual method as described by Quimica Clinica Applicada, SA, Spain, the manufacturers. All samples for coagulation factor VIII, von Willebrand factor, fibrinogen, D-dimer and tissue plasminogen activator were analysed using ELISA machine (STAT FAX-2100), Awareness Technology Inc, with reagents prepared by Bioassay Technology Laboratory, Shanghai Korain Biotech Co., Ltd, Shanghai, China, using standard methods as described by the manufacturers. ABO and Rhesus D blood grouping was carried out with reagents manufactured by Atlas Medical, Cambridge, using standard methods as described by the manufacturers; Lewis A and Lewis B groupings were carried out with reagents manufactured by Lorne Laboratories Ltd, United Kingdom, using standard tube methods as described in the kit leaflets.

Data Analysis

Data were analysed using Graph-Pad Prism 8.0.2.263 version statistical package to obtain mean and standard deviation of the study groups. Analysis of variance was used to determine the statistical significance between stroke groups and the control groups, and p-values of < 0.05 were considered to be statistically significant. Also, odd ratios, relative risk, positive predictive value, negative predictive value, and likelihood ratio were obtained using Graph-Pad prism. Results were presented as mean ± standard deviation [$\bar{x} \pm SD$] and in Tables.

RESULTS

Comparison of Haematological Parameters in the Study Population

Comparison was made on haematological parameters based on differences in blood groups of control subjects against those who had a stroke attack. The mean ± standard deviation ($\bar{x}$ ± SD) for each control group was compared with that of the stroke group. There was no statistically significant difference in the studied haematological parameters at $p < 0.05$, in stroke group versus blood group A, B, Le^a, and Le^b. Statistically significant increase was observed in white blood cell counts in blood group O [p = 0.0222] with the mean values of white blood cells higher in stroke group; no statistically significant difference was observed in other parameters in blood group O. Details are shown in Table I to Table V

Table I: Comparison of Mean ± Standard Deviation of Haematological Parameters in Stroke Group and Control Blood Group A

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group A (N = 15) $\bar{x}$ ± SD	p-value
WBC [$x10^9$]	8.20 ± 8.19	6.65 ± 2.39	0.6467 (NS)
RBC [$x10^{12}$]	4.74 ± 0.54	4.42 ± 0.50	0.4324 (NS)
HB [g/dL]	12.32 ± 1.47	11.74 ± 1.24	0.8148 (NS)
PCV [%]	38.70 ± 4.18	36.74 ± 3.43	0.5325 (NS)
MCV [fL]	81.80 ± 5.74	83.33 ± 4.16	0.9820 (NS)
MCH [pg]	26.08 ± 2.79	26.73 ± 2.18	0.9924 (NS)
MCHC [g/dL]	31.80 ± 1.55	32.06 ± 1.38	0.9994 (NS)

Key: SD = Standard Deviation; NS = Not Significant; HS = Highly Significant. Applicable to all Tables.

Table II: Comparison of Mean ± Standard Deviation of Haematological Parameters in Stroke Group and Control Blood Group B

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group B (N = 13) $\bar{x}$ ± SD	p-value
WBC [$x10^9$]	8.20 ± 8.19	7.14 ± 5.12	0.9457 (NS)
RBC [$x10^{12}$]	4.74 ± 0.54	4.78 ± 0.54	0.9997 (NS)
HB [g/dL]	12.32 ± 1.47	12.01 ± 1.02	0.9961 (NS)
PCV [%]	38.70 ± 4.18	38.33 ± 2.53	0.9996 (NS)
MCV [fL]	81.80 ± 5.74	80.90 ± 8.05	0.9993 (NS)
MCH [pg]	26.08 ± 2.79	25.48 ± 3.75	0.9964 (NS)
MCHC [g/dL]	31.80 ± 1.55	31.35 ± 2.12	0.9916 (NS)

Table III: Comparison of Mean ± Standard Deviation of Haematological Parameters in Stroke Group and Control Blood Group O

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group O (N = 39) $\bar{x}$ ± SD	p-value
WBC [$x10^9$]	8.20 ± 8.19	5.62 ± 1.64	0.0222 (S)
RBC [$x10^{12}$]	4.74 ± 0.54	4.64 ± 0.57	0.9927 (NS)
HB [g/dL]	12.32 ± 1.47	12.06 ± 1.72	0.9916 (NS)
PCV [%]	38.70 ± 4.18	38.08 ± 4.23	0.9936 (NS)
MCV [fL]	81.80 ± 5.74	82.21 ± 5.747	0.9996 (NS)
MCH [pg]	26.08 ± 2.79	26.01 ± 3.00	0.9999 (NS)
MCHC [g/dL]	31.80 ± 1.55	31.57 ± 2.11	0.9993 (NS)

Table IV: Comparison of Mean ± Standard Deviation of Haematological Parameters in Stroke Group and Control Blood Group Le[a]

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group Le[a] (N = 11) $\bar{x}$ ± SD	p-value
WBC [$x10^9$]	8.20 ± 8.19	5.36 ± 0.87	0.1192 (NS)
RBC [$x10^{12}$]	4.74 ± 0.54	4.41 ± 0.43	0.5183 (NS)
HB [g/dL]	12.32 ± 1.47	11.65 ± 0.95	0.7653 (NS)
PCV [%]	38.70 ± 4.18	36.41 ± 3.27	0.4658 (NS)
MCV [fL]	81.80 ± 5.74	82.64 ± 4.52	0.9994 (NS)
MCH [pg]	26.08 ± 2.79	26.47 ± 1.91	0.9995 (NS)
MCHC [g/dL]	31.80 ± 1.55	32.02 ± 1.11	0.9996 (NS)

Table V: Comparison of Mean ± Standard Deviation of Haematological Parameters in Stroke Group and Control Blood Group Le[b]

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group Le[b] (N = 8) $\bar{x}$ ± SD	p-value
WBC [$x10^9$]	8.20 ± 8.19	5.08 ± 1.14	0.1331 (NS)
RBC [$x10^{12}$]	4.74 ± 0.54	4.73 ± 0.95	>0.9999 (NS)
HB [g/dL]	12.32 ± 1.47	12.27 ± 1.33	0.9999 (NS)
PCV [%]	38.70 ± 4.18	38.19 ± 4.54	0.9995 (NS)
MCV [fL]	81.80 ± 5.74	81.78 ± 7.11	>0.9999 (NS)
MCH [pg]	26.08 ± 2.79	26.59 ±3.64	0. 9994 (NS)
MCHC [g/dL]	31.80 ± 1.55	32.40 ± 1.89	0.9824 (NS)

Comparison of Haemostatic Parameters in the Study Population

Comparison was made on haematological parameters based on differences in blood groups of control subjects against those who had a stroke attack. The mean ± standard deviation for each control group was compared with that of the stroke group. There was no statistically significant difference in the studied haemostatic parameters at $p < 0.05$, in stroke group versus blood group B, O, Le^b, and Le^a. Statistically significant increase in the stroke group was observed in APTT when compared with control blood group A subjects. No statistically significant difference was observed in other parameters in blood group A. Details are shown in Table VI to Table X.

Table VI: Comparison of Mean ± Standard Deviation of Haemostatic Parameters in Stroke Group and Control Blood Group A

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group A (N = 15) $\bar{x}$ ± SD	p-value
Platelets [$x10^9$]	188.9 ± 53.28	199.3 ± 56.89	0.9996 (NS)
PDW [fL]	13.99 ± 3.03	13.77 ± 2.64	>0.9999 (NS)
MPV [fL]	11.03 ± 1.25	11.01 ± 1.21	>0.9999 (NS)
P LCR [%]	32.48 ± 9.83	32.98 ± 10.0	0.9998 (NS)
PT [Sec]	14.35 ± 2.24	12.27 ± 1.62	0.0514 (NS)
APTT [Sec]	26.61 ± 2.82	24.20 ± 1.82	0.0447 (S)
VWF [ng/ml]	72.94 ± 40.67	54.44 ± 25.33	0.4299 (NS)
FVIII [ng/ml]	10.83 ± 16.42	9.44 ± 18.00	0.9996 (NS)
Fibrinogen [mg/ml]	1.90 ± 3.28	1.32 ± 2.00	0.9918 (NS)
D-dimer [pg/ml]	115.2 ± 222.2	129.3 ± 269.6	0.9996 (NS)
TPA [ng/ml]	18.31 ± 18.86	13.05 ± 11.63	0.9438 (NS)

Table VII: Comparison of Mean ± Standard Deviation of Haemostatic Parameters in Stroke Group and Control Blood Group B

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group B (N = 13) $\bar{x}$ ± SD	p-value
Platelets [$x10^9$]	188.9 ± 53.28	262.2 ± 263.1	0.3787 (NS)
PDW [fL]	13.99 ± 3.03	14.06 ± 3.56	>0.9999 (NS)
MPV [fL]	11.03 ± 1.25	10.59 ± 1.09	0.9997 (NS)
P LCR [%]	32.48 ± 9.83	29.97 ± 8.10	0.9795 (NS)
PT [Sec]	14.35 ± 2.24	15.00 ± 1.68	0.9768 (NS)
APTT [Sec]	26.61 ± 2.82	26.92 ± 2.13	0.9995 (NS)
VWF [ng/ml]	72.94 ± 40.67	75.15 ± 38.88	0.9997 (NS)
FVIII [ng/ml]	10.83 ± 16.42	4.70 ± 2.81	0.7611 (NS)
Fibrinogen [mg/ml]	1.90 ± 3.28	1.70 ± 3.05	0.9997 (NS)
D-dimer [pg/ml]	115.2 ± 222.2	82.43 ± 125.4	0.9963 (NS)
TPA [ng/ml]	18.31 ± 18.86	17.07 ± 17.35	0.9997 (NS)

Table VIII: Comparison of Mean ± Standard Deviation of Haemostatic Parameters in Stroke Group and Control Blood Group O

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group O (N = 39) $\bar{x}$ ± SD	p-value
Platelets [x10^9]	188.9 ± 53.28	194.2 ± 88.05	0.9997 (NS)
PDW [fL]	13.99 ± 3.03	16.36 ± 16.41	0.9635 (NS)
MPV [fL]	11.03 ± 1.25	10.92 ± 1.05	>0.9999 (NS)
P LCR [%]	32.48 ± 9.83	32.73 ± 8.32	0.9999 (NS)
PT [Sec]	14.35 ± 2.24	14.54 ± 2.33	0.9996 (NS)
APTT [Sec]	26.61 ± 2.82	26.51 ± 3.02	0.9998 (NS)
VWF [ng/ml]	72.94 ± 40.67	63.74 ± 31.76	0.8822 (NS)
FVIII [ng/ml]	10.83 ± 16.42	7.41 ± 11.12	0.9431 (NS)
Fibrinogen [mg/ml]	1.90 ± 3.28	1.35 ± 2.67	0.9755 (NS)
D-dimer [pg/ml]	115.2 ± 222.2	55.86 ± 73.05	0.6382 (NS)
TPA [ng/ml]	18.31 ± 18.86	15.34 ± 19.09	0.9923 (NS)

Table IX: Comparison of Mean ± Standard Deviation of Haemostatic Parameters in Stroke Group and Control Blood Group Le^a

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group Le^a (N = 11) $\bar{x}$ ± SD	p-value
Platelets [x10^9]	188.9 ± 53.28	161.4 ± 80.23	0.9933 (NS)
PDW [fL]	13.99 ± 3.03	15.35 ± 3.93	0.9999 (NS)
MPV [fL]	11.03 ± 1.25	11.60 ± 1.65	0.6727 (NS)
P LCR [%]	32.48 ± 9.83	36.36 ± 12.23	0.8151 (NS)
PT [Sec]	14.35 ± 2.24	14.00 ± 2.73	0.9994 (NS)
APTT [Sec]	26.61 ± 2.82	27.09 ± 2.73	0.9993 (NS)
VWF [ng/ml]	72.94 ± 40.67	51.15 ± 21.36	0.3553 (NS)
FVIII [ng/ml]	10.83 ± 16.42	17.05 ± 26.94	0.7956 (NS
Fibrinogen [mg/ml]	1.90 ± 3.28	1.01 ± 0.77	0.9443 (NS)
D-dimer [pg/ml]	115.2 ± 222.2	142.5 ± 142.5	0.9993 (NS)
TPA [ng/ml]	18.31 ± 18.86	15.56 ± 9.00	0.9993 (NS)

Table X: Comparison of Mean ± Standard Deviation of Haemostatic Parameters in Stroke Group and Control Blood Group Le^b

Parameters/Unit	Stroke (N = 23) $\bar{x}$ ± SD	Blood Group Le^b (N = 8) $\bar{x}$ ± SD	p-value
Platelets [x10^9]	188.9 ± 53.28	184.4 ± 37.16	0.9999 (NS)
PDW [fL]	13.99 ± 3.03	13.49 ± 1.74	0.9999 (NS)
MPV [fL]	11.03 ± 1.25	10.81 ± 0.80	>0.9999 (NS)
P LCR [%]	32.48 ± 9.83	31.26 ± 6.47	0.9995 (NS)
PT [Sec]	14.35 ± 2.24	14.25 ± 2.05	0.9999 (NS)
APTT [Sec]	26.61 ± 2.82	25.50 ± 2.20	0.9095 (NS)
VWF [ng/ml]	72.94 ± 40.67	48.99 ± 10.76	0.3765 (NS)
FVIII [ng/ml]	10.83 ± 16.42	7.28 ± 4.30	0.9960 (NS)
Fibrinogen [mg/ml]	1.90 ± 3.28	0.85 ± 0.97	0.9226 (NS)
D-dimer [pg/ml]	115.2 ± 222.2	66.60 ± 80.54	0.9861 (NS)
TPA [ng/ml]	18.31 ± 18.86	10.49 ± 7.12	0.8556 (NS)

Odd Ratios of the Blood Groups in Relation to Risk of having Stroke

The odd ratios for the various blood groups under study were calculated to determine the possibility of having stroke based on the presence of a particular blood group antigen. At 95% confidence interval, the odd ratios were 1.43, 1.69, 0.62, 1.65, 1.59, for blood group A, B, O, Le^a, and Le^b, respectively. This implies that blood group B, Le^a and Le^b antigens may be associated as risk factors for stroke. Details are shown in Table XI.

Table XI: Comparison of Odd Ratios, Relative Risk, Positive Predictive Value, Negative Predictive Value and Likelihood Ratio of the Blood Groups in Relation to Risk of having Stroke

Blood Groups	OR	RR	PPV	NPV	LR
A	1.434 CI:0.55- 4.07	1.302 CI:0.61- 2.57	0.3043 CI:0.16 -0.51	0.7662 CI:0.66- 0.85	1.313
B	1.694 CI:0.64-5.03	1.463 CI:0.68-2.86	0.3333 CI:0.17-0.55	0.7722 CI:0.67-0.85	1.500
O	0.6173 CI:0.25-1.45	0.6968 CI:0.35-1.36	0.2075 CI:0.12- 0.33	0.7021 CI:0.56- 0.81	0.786
Le^a	1.658 CI:0.52-4.71	1.439 CI:0.64- 2.86	0.3333 CI:0.16-0.56	0.7683 CI:0.67-0.85	1.500
Le^b	1.595 CI:0.49-5.35	1.397 CI:0.54-2.91	0.3333 CI:0.14-0.61	0.7614 CI:0.66-0.84	1.500

Key: OR=Odd Ratio; RR=Relative Risk; PPV=Positive Predictive Value; NPV=Negative Predictive value; LR=Likelihood Ratio; CI=Confidence Interval @ 95%

DISCUSSION

A good knowledge of how stroke occurs and the haematological and haemostatic changes involved after a stroke attack is very important. There are haematologic and haemostatic interactions with blood group antigens found on red blood cells, which are components of blood flowing to the brain, supplying oxygen to it. If deprived of oxygen due to formation of clots, micro-clots, or an abnormal bleeding in the brain, it will lead to stroke, with the possibility of death, which is the end stage climaxing event. It is therefore necessary to understand how these antigens responsible for the differences in blood groups interact biologically and biochemically with these haematological and haemostatic parameters to cause or predispose an individual to suffer stroke.

This study was carried out on individuals who had stroke attack, and are recovering and being managed by a Specialist Physician; and also, on individuals who have not had a stroke and were apparently healthy. The study was carried out to determine their ABO blood group antigens, and the presence of Lewis blood group antigens, and how these antigens influence haemostatic and haematologic factors to become risk factors for the occurrence of stroke. Antigens of Lewis blood group, which were found in stroke subjects, were also found in apparently healthy subjects (control) of Ogoni ethnic nationality.

Haematological parameters were obtained from full blood count, which gives the blood picture of subjects in the stroke group and also those in the control groups. Oxygen must be transported without interruption to the brain cells through blood flow in order to prevent stroke. If the blood picture is such that the amount of red blood cells and the haemoglobin content is not enough to support oxygen delivery, this could lead to stroke or compound the severity of the stroke and for those who are recovering, it could lead to re-occurrence of stroke. Therefore, the evaluation of some haematological parameters is critical in stroke remediation, monitoring and prevention.

In this study, upon comparison of haematological parameters based on differences in blood groups of control subjects with persons who suffered stroke, the mean ± standard deviation for each control group was compared with that of the stroke group. There was no statistically significant difference in the studied haematological parameters at $p < 0.05$, in stroke group versus blood group A, B, Le^a, Le^b. Statistically significant increase in white blood cell counts in stroke group was observed over white blood cell counts in control groups of blood group O ($p = 0.0222$). No statistically significant difference was observed in other parameters in blood group O.

The white blood cell count in this study only showed statistical significant difference in two control groups, which is that of blood group O, in which there was an increase in white blood cell count in stroke group; and based on this finding, there was no agreement with the report of Christian *et al*. [1], where he and his co-authors recorded no statistical significant difference in their study groups which comprises of stroke group and one control group. The reason for this difference is not well understood but if studies on inflammatory cytokines are carried out, it may well give some explanations. Nevertheless, Christian and colleagues observed an increased in white blood cell counts in stroke group than in their control group. The finding of this study as regarding other blood groups as distinct controls apart from that of blood group O, agrees with the findings of Christian *et al.* [1], Orefice *et al.*

[20], and that of Fujii *et al.* [21]. It should be noted that despite the fact that there was a significant difference between the stroke group and control group of blood group O, the values were within the normal or reference range for white blood cell count ($4.8 – 10.8 \times 10^9$). There was no clinical sign or complaint of infection in persons in the study group and this account for the reason why the values obtained were within the reference range.

For red blood cell count, the outcome of the findings revealed no statistically significant differences in stroke group and all control groups. Red blood cell count was high in stroke group than the control groups, in exception of control males and control blood group B. Despite these, they were all within the normal range ($4.5 – 5.5 \times 10^{12}$). These normal values as obtained may be the reason why none of the stroke group individuals were anaemic or show clinical signs of anaemia; and may also be the reason why they were able to survive the initial stroke attack and are recovering, since the red blood cells enough and involved in oxygen delivery to the brain. The finding in this study concur with the finding of Christian *et al.* [1], the difference is that in the study carried out by Christian and colleagues, those in the control group had mean red blood cell count that was higher than the mean red blood cell count in stroke group, which is similar to the observations in the control group of blood group B and normal males versus stroke in this study. Orefice *et al*. [20], and Shah *et al*. [22], also reported findings that were in line with the findings of this study, though they adopted a single control group.

Haemoglobin is the oxygen carrying molecule found in the blood, and in this study, the concentration of haemoglobin in stroke group when compared with the concentrations from the control groups, were within close range, and there was statistically, no significant difference, which agrees with the findings of Christian *et al*. [1], Stanford *et al.* [23], and Fujii *et al.* [21]. Although the mean concentration in control group blood group B was higher than in stroke group. The finding in this study as regarding ABO blood groups pattern of haemoglobin concentration, indicated that individuals in control blood group O had a higher mean haemoglobin concentration than those in control blood group A, and control blood group B; this finding was not in agreement with that of Hajizadeh *et al*. [24], where they reported that non blood group O had higher mean haemoglobin concentration than blood group O individuals. The normal range values of haemoglobin concentration in the study groups, especially stroke group, supports oxygen delivery to the brain and is beneficial post-stroke to avoiding the recurrence of stroke.

Packed cell volume in this study showed high percentage in stroke group than all the control groups except that of control males (normal males do have high packed cell volume). There was no statistically significant difference upon comparison, and this agrees with the findings of Stanford *et al*. [23], and Christian *et al*. [1], where they also reported no statistically significant difference; with packed cell volume in stroke group higher than packed cell volume in control group. The subjects in stroke group were on medication and so their packed cell volume reflected the medications they may have been taking which include some blood boosting medication and haemoglobin syrup.

The outcome of red cell indices (mean cell volume - MCV, mean cell haemoglobin - MCH, mean cell haemoglobin concentration – MCHC) in this study showed no statistical significance upon comparison. This finding is partially in agreement with that of Christian *et al.* [1], as only the findings of mean cell volume and mean cell

haemoglobin concentration in the study carried out by Christian and colleagues showed no statistical significance. Mean cell haemoglobin however, showed a highly significant difference in their study, where the control group mean cell haemoglobin concentration was higher than that of stroke group. None of the subjects recruited showed any signs of anaemia and their values were all within the normal reference range.

Considering the role blood group plays in altering or causing changes in haematological parameters upon comparison with stroke subjects, there is no linkage of blood group with changes in haematological parameters as there were no statistically significant difference based on blood group that can play a role as risk factor for stroke.

Haemostatic markers are critical in evaluating changes in haemostasis and to identify imbalance in coagulation and fibrinolysis. These haemostatic markers are useful in the management of stroke and also the constant monitoring of these haemostatic markers can help in preventing the occurrence or re-occurrence of stroke, and at the same time use in predicting stroke.

Platelet count and platelet indices though part of the full blood count outcome was included as part of the haemostatic tests. The role of platelets in haemostasis is very critical from the point of primary haemostasis (formation of initial platelet plug) to that of secondary haemostasis (fibrin formation) which involves the biochemical interactions and sequential activation of several coagulation factors and co-factors. In this study, platelet counts in stroke group compared with the control groups revealed no statistical significant difference [$p > 0.05$], with the stroke group having mean platelet count that is lower than the control groups except in Le^a and Le^b control groups, where their mean platelet counts were lower than in stroke group. The finding in this study is not in line with the findings of Buseri *et al.* [7], where they observed a statistically significant difference between stroke group and a single control group. Despite the differences in statistical significance, both studies upon comparison revealed a decreased platelet count in stroke group. The decrease in platelets in this study can be linked to the consumption of platelets which may have occurred during the stroke attack. The findings of this study is in tandem with that of Stanford *et al.* [23], and Fujii *et al.* [21], where these authors also observed no significant difference. Therefore, blood group differences have no significant role in causing a change in platelet count.

Mean platelet volume (MPV) in this study was not statistically significant. The finding in this study on mean platelet volume is not in accord with the finding of Tohgi *et al.* [25], and also not in tandem with the findings of Buseri *et al.* [7], where they reported a significant difference ($p < 0.05$) with MPV increased in stroke patients. Blood group difference did not also play any significant difference as their mean values were within close range. A study has associated higher mean platelet volume with the extent of the largeness of the infarct, and the higher risk of death post-stroke [26]. This might also be the reason why the mean value of mean platelet volume was high in stroke group albeit not significant compared to controls, based on the fact that the stroke subjects recruited in this study were not in critical health conditions.

Platelet distribution width is a true reflection of the status of platelet activities in haemostasis, and it also represents the heterogenic nature of platelet size [27]. In this study, there was no statistically significant difference in platelet distribution width ($p > 0.05$). A lower platelet distribution width has been associated with a good outcome for thrombolysis as platelets activation may have

been reduced. This may be the reason why the subjects in stroke group are gradually responding to management therapy administered to them after the stroke event. The finding on platelet distribution width in this study oppose the findings of Buseri *et al.* [7], where they observed a significant difference ($p > 0.05$), with the mean value of platelet distribution width higher than in control group. It is also in opposition to that of Shah *et al.* [22]; but in concordance with the findings of Fujii *et al.* [21], and Stanford *et al.* [23].

No significant difference was observed in plateletcrit (PLCR) in this study. Considering the blood groups and other control groups, blood group A, O, Le^a had mean values that were higher than that of the stroke group, although with no statistically significant difference. The other control groups recorded a lower plateletcrit than in stroke group. The findings of this study are similar to the findings of Fujii *et al.* [21], and Stanford *et al.* [23], but dissimilar with that of Buseri *et al.* [7], and Shah *et al.* [22]. Plateletcrit has been associated with a poor functional outcome in respect to stroke and can be used as a prognostic tool for stroke [28]. Based on the fact that mean value of plateletcrit in stroke is within the reference range, it may be the reason behind the non-coagulation of their blood due to normal platelet aggregation pattern that has enabled individuals in the stroke group to recover, and improve in the disability that accompanied the first stroke attack.

Prothrombin time in stroke group and in control groups indicated no statistical significance upon comparison. Prothrombin time which measures the extrinsic and common pathway, critically measures the activities of FV, FVII, FX, prothrombin and fibrin, which are all important in the formation of clot albeit from an external stimulus. Mean prothrombin time in seconds was insignificantly high in stroke group than in control groups of blood group B and O. In the other control groups, mean prothrombin time were insignificantly low. This finding suggests that the blood coagulation which was hitherto implicated in the pathogenesis of stroke may have been reverted or normalize post stroke as a result of the blood thinning medication that was administered to the stroke subjects. The findings in this study as regarding prothrombin time test is in contrast with the findings of Buseri *et al.* [7], and Anthovic *et al.* [29], where these authors reported a significant difference reduction in mean prothrombin time in stroke group than in their control group; but in accord with the findings of Fujii *et al.* [21], and Stanford *et al.* [23]. Comparing mean prothrombin time in ABO blood groups, Ohira *et al.* [30], reported no significance in mean prothrombin time in blood group A, B, and O. The finding of Ohira and associates is inversely in tandem with the findings of this study, in that blood group B and O indicated increased mean prothrombin time, but decreased mean prothrombin time in blood group A, as opposed to decreased mean time in blood group O and B and an increase mean time in blood group A by Ohira and associates.

The activated partial thromboplastin time in this study showed statistically significant increase in stroke group when compared with that of control blood group A ($p = 0.0447$). There was no statistically significance observed in other control groups but the mean time for activated partial thromboplastin time was high in stroke group upon comparison with other control groups, except that of control groups of Le^a blood group and blood group B. In regards to blood group A control group and stroke group, the finding disagrees with the finding of Buseri *et al.* [7], and Stanford *et al.* [23], where they reported decrease in activated partial thromboplastin

time in stroke group when compared to the increase in activated partial thromboplastin time in stroke group in this study. Anthovic *et al.* [29], and Fujii *et al.* [21], reported a similar finding with this work; with mean activated partial thromboplastin time higher in stroke group, as observed in this study, but with no statistical significance as observed in other control groups except that of Le^a and B blood groups. Since activated partial thromboplastin time measures the intrinsic and common pathways, based on the findings in this study, in vivo hyper-coagulation may have normalized in stroke patients, as activated partial thromboplastin time was within the normal range.

Von Willebrand factor plays a very critical role in platelet adhesion and is a carrier of coagulation factor VIII. Higher than normal levels of von Willebrand factor accentuates clot formation. In this study, von Willebrand factor concentration was higher in stroke group than in control groups except control blood group B that was higher than the mean concentration recorded in stroke group. There was no statistical significance ($p > 0.05$) upon comparison. Based on increased in concentration of von Willebrand factor in conditions that have to do with thrombosis, there was an accord with Ohira *et al.* [30], but disagreement based on statistical significance, as Ohira and colleagues observed a highly significant difference ($p < 0.0001$), whereas, there was no significance in this study. Bongers *et al.* [31], also reported similar finding ($p = 0.002$, with high concentration in stroke group) with Ohira and colleagues [30], and so differ with the outcome of this study. The elevated concentration of von Willebrand factor may have contributed to the pathogenesis of the stroke that hitherto occurred in the subjects.

For concentration of von Willebrand factor based on differences in blood types, non-blood group O subjects recorded high mean von Willebrand factor concentration compared to blood group O subjects according to Ohira *et al.* [30]. This was not the exact outcome in this study in comparison to Ohira and colleagues, as only blood group B subjects recorded concentration higher than that of blood group O. The findings of this study based on ABO blood group differences partially agrees with that of Gills *et al.* [32], and Moeller *et al.* [33], where they observed increase in blood group A and B than in blood group O. The elevated level of von Willebrand factor also play roles in stimulating platelets to fast-track coagulative processes via high adhesive mechanisms which may climaxes into hyper-coagulation, a risk factor in the pathogenesis of stroke.

In this study, factor VIII concentration was higher in stroke group than in control groups except in control blood group Le^b that was higher. There was no statistical significance ($p > 0.05$) upon comparison. Levels of factor VIII is dependent on the level of von Willebrand factor and also low alterations in von Willebrand factor will automatically affect levels of factor VIII. The level of factor VIII in stroke group from this study is an important indicator that may have been responsible for the pathogenesis of the disease. Based on increased in concentration of factor VIII in thrombotic conditions, there was an agreement with Ohira *et al.* [30], with disagreement based on statistical significance as Ohira and colleagues [30], observed a highly significant difference ($p < 0.0001$), whereas, there was no significance in this study. Bongers *et al.* [31], also reported similar findings ($p = 0.003$, with high concentration in stroke group) with Ohira and colleagues [30], and so differ with the findings of this study.

The level of factor VIII in terms of ABO blood group is in the order of A > O > B as against the findings of Moeller *et al.* [33], which was B > A > O. Moeller and associates

reported stroke risk at the detriment of non-blood group O [33]. This study indicates that blood group B individuals recorded low mean factor VIII levels than blood group O individuals. The implication of the findings of this study is that individuals who have low level of factor VIII and von Willebrand factor are at a risk of bleeding while those who have high level of these two coagulation factors, are at risk of having stroke.

The concentration of fibrinogen is critical for the resultant formation of fibrin and in this study, the mean concentration of fibrinogen in stroke group, was higher than the mean values of fibrinogen concentration in all the control groups. There was no statistical significance upon comparison. The finding in this study concur with the finding of Ohira *et al.* [30], in terms of no statistical significance but not in terms of having a higher fibrinogen level in stroke group as observed in this study, although the difference in concentration value of Ohira and associates is very low [33]. Stroke group in this study, and stroke group in the study carried out by Buseri *et al.* [7], recorded high concentration of fibrinogen than in the respective control groups, but statistical significance varies in that Buseri and associates reported a statistical significance ($p = 0.0303$) [7]. The finding of this study was not consistent with the findings of Anthovic *et al.* [29], and Stanford *et al.* [23], where these authors reported an increase of fibrinogen concentration in stroke when compared with the controls ($p < 0.001$). There was similarity and agreement in the finding of this study with that of Kario *et al.* [34], where they observed a statistically significant difference ($p = 0.059$). Ohira *et al.* [30], reported a non-significant difference ($p = 0.84$), but their findings disagree with the outcome of this study, in that their control group recorded a higher mean fibrinogen concentration than individual with thrombo-embolism. The high level of fibrinogen after the occurrence of stroke is still a reflection of what may have played out during the thrombotic events that led to the stroke, and probably the continuous response by the liver in stimulating the production of more fibrinogen and also as an acute phase reactant in stroke.

Considering fibrinogen levels based on blood group differences, it was discovered from the study that blood group B control subjects recorded mean fibrinogen level that was higher than that of blood group O control, and blood group A control in the order of B > O > A. This was not exactly the same with the findings of Ohira *et al.* [30], where they reported that blood group B subjects recorded high concentration of fibrinogen than blood group A and blood group O in the order of B > A > O.

Tissue plasminogen activator (TPA) is responsible for the generation or activation of plasmin which enables the breakdown of fibrin. Tissue plasminogen activator ensures that blood is maintained in a normal fluid form, enabling the supply of blood, nutrients and oxygen to the brain, which in turn prevent the formation of clots. The study revealed high mean concentration of tissue plasminogen activator in stroke group when compared with all the control groups. This finding is advantageous to individuals in the stroke group in that it will prevent the formation of thrombus, but in as much as it is advantageous, it could also be detrimental because it could support abnormal bleeding tendencies if the level is higher than normal. Also, the high level of tissue plasminogen activator may be as a result of the thrombotic tendencies of those in stroke group and as such, tissue plasminogen activator is increased in the process of inhibiting likely thrombotic events. Reference range for tissue plasminogen activator has not been established in our setting. This may pose some challenges in managing stroke patients

as they may be prone to bleeding if they are given recombinant drugs geared towards reducing thrombotic tendencies. The finding of this study disagrees with the findings of Buseri *et al.* [7], reason being that this study was carried out on subjects recovering from stroke, while the stroke group subjects recruited by Buseri and colleagues, had just suffered from stroke.

D-dimer is indicative of the level of fibrin breakdown which by implication is reflective of the level or extent of thrombus formation. D-dimers are formed as a result of the action of plasmin on fibrin or cross-linked fibrin. Stroke patients with high level of D-dimer is suggestive of high level of ongoing fibrinolytic processes. In this study, the concentration of D-dimer was high in stroke individuals compared to the control groups except that of blood group A control group, but there was no statistical significance in the study. The high concentration of D-dimer noticed in stroke group may be as a result of the stroke that occurred, and it depicts the degradation of the formed thrombus. It may also be one of the reasons for their survival after the cerebrovascular accident. The finding of this study is in similarity to the findings of Anthovic *et al.* [29], and Fujii *et al.* [21], in terms of increase in D-dimer in stroke but varies in terms of statistical significance as both Anthovic and associates [29], Fujii and associates, reported statistical significance ($p < 0.05$) [21].

Odd ratios find its usefulness in comparing the relative odds for the occurrence of the possible outcome of a disorder or disease (in this case, stroke), based on the presence of a blood group antigen. The odd ratio in this study determines the risk factor associated with the presence of a blood group antigen in relation to stroke. An odd ratio of 1 (OR = 1), implies that the presence of that antigen will not affect the outcome, which is stroke. An odd ratio that is greater than 1 (OR > 1), implies that the presence of such blood group antigen is associated with a higher risk of having stroke. An odd ratio of less than 1 (OR < 1), implies that the presence of such blood group antigen is associated with a lower risk of having stroke. The likelihood ratio gives the usefulness of the blood group outcomes in ascertaining which blood group is more likely prone to having stroke. So, combination of odd ratios and likelihood ratios will give a better picture of stroke risk. Comparing the distribution of the ABO blood groups in stroke subjects in relation to percentage distribution of blood groups in the general study populations, and based on simple ratio, the study revealed that blood group A and blood group B individuals suffer stroke more than subjects who are blood group O (for the subjects with stroke: 7 were blood group A; 7 were blood group B; while 11 were blood group O). This shows that non-blood group O are affected with stroke more than blood group O individuals. This finding is in agreement with that of Zakai *et al*. [35], where he and his colleagues hypothesized that those that are non-blood group O are associated with the risk of having stroke; and also in agreement with Franchini and Mannucci [16], where they also said that non-blood group O individuals do have a two-fold increase risk of venous thrombosis. Moreso, Vasan *et al*. [36], corroborated with the fact that non blood-group O individuals are at a higher risk of having venous-thrombo-embolism. The reason behind this may be as a result of the lower incidence of venous thrombo-embolism in H antigen rich genotype than H antigen poor genotype, making ABO a risk factor [37, 38], which mechanism is not well understood. It should be noted that blood group O individuals are richer in H antigen than blood group A and blood group B individuals.

The Lewis antigens were present in persons with stroke and also in apparently healthy

persons that made up the control subjects. The study revealed that Le^a blood group showed a frequency occurrence of 6 subjects having the antigen in the stroke group and 12 subjects having the antigen in the control group. For Lewis B (Le^b) blood group, the study revealed a frequency occurrence of 4 subjects having the antigen in the stroke group and a frequency occurrence of 8 subjects having the antigen in the control group.

From the study, the odd ratios (OD) for the blood groups under consideration in relation to associating them as risk factor of stroke and the likelihood ratio (LR) for stroke to occur are as follows: Blood group A: OD = 1.43, LR = 1.31; Blood group B: OR = 1.69, LR = 1.50; Blood group O: OR = 0.62, LR = 0.78; Le^a blood group: OR = 1.65, LR = 1.50; Le^b blood group: OR = 1.59, LR = 1.50; Based on the findings above, the likelihood for stroke to occur amongst the blood groups under study, was in the order of: (blood group B) > (blood group Le^a) > (blood group Le^b) > (blood group A) > (blood group O).

For ABO blood group system, the study has revealed that non blood group O individuals are at risk than blood group O individuals. This finding is in agreement with the findings of Schleef *et al.* [37]; Buil *et al.* [38], Vasan *et al.* [36], Franchini and Mannucci [16], and Zakai *et al.* [35]. Wiggins *et al.* [39], reported an odd ratio of 1.59 in blood group B individuals which was higher than that of blood group O, the same applies to the finding in this study where blood group B odd ratio was higher than that of blood group O which implies that blood group B individuals are more at a risk to suffer stroke than blood group O individuals. Clark *et al.* [15], also reported similar findings.

For Lewis blood groups in this study, Le^a and Le^b blood groups had odd ratios of 1.658 and I.595 respectively. Clark *et al.* [15], also reported that odd ratio for Le^a and Le^b were 1.17 and 0.98 respectively. The findings of this study on Le^a blood group was in tandem with that of Clark and associates, while the findings of this study on Le^b differs from that of Clark and colleagues [15]. Individuals that possess the Lewis antigen are at a risk of having stroke and this could be linked to the fact that the Lewis antigens are present on the surface of platelets. Some group of Lewis agglutinogens function as counter ligands for selectins [14], and this has been observed to be consistent with the role Lewis agglutinogens plays in the occurrence or development of thrombosis [15].

CONCLUSION

Haematological parameters indicated no significant differences between the stroke group and control groups, except in white blood cell count, and specifically in the control groups of blood group O and Le^a. The study revealed no changes in haematological parameters based on blood group differences that could be linked as part of the risk factors for stroke. Therefore, blood group differences do not play a role in altering haematologic variables that can be associated with stroke.

The haemostatic picture in stroke group is indicative of the fact that the outcomes of these parameters were critical in the pathogenesis of stroke prior to when stroke patients were managed. However, there are no association with haemostatic derangement in the causation of stroke based on blood group differences or presence of a particular blood group antigen.

Based on the odd ratios and likelihood ratios obtained for the blood groups under study in relation to associating them as risk factor for stroke, the likelihood for stroke to occur comparing the outcomes from the blood groups under study, was in the order of: (blood group B) > (blood group Le^a) > (blood group Le^b) > (blood group A) > (blood group

O); it implies that blood group B, blood group Le^a and blood group Le^b antigens may be associated as risk factors for stroke.

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