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Abnormal Changes in Some Haemostatic Parameters in First-ever Stroke Patients in Port Harcourt, Nigeria: A Preliminary Findings

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Authors' contributions

This work was carried out in collaboration among all authors. Author FIB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SGC and EME managed the analyses of the study. Author EME managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background and Purpose: Cellular component and clotting factors are involved in thrombotic events such as stroke, but the type and nature of alteration of those haemostatic parameters remain unclear. Our objective was to identify possible abnormal changes in some haemostatic parameters in established stroke patients.
Materials and Methods: This was a prospective case-control study conducted at Braithwaite Memorial Specialist Hospital, Port Harcourt, Nigeria. Standard operating procedures were adopted to assay fibrinogen, antithrombin, tissue plasminogen activator, prothrombin time and activated partial thromboplastin time as well as the determination of platelet count and platelet indices. The data were analyzed using Statistical Package for Social Science (SPSS) version 17.0 software.

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Results: A total of 108 individuals comprised of 54 stroke patients aged between 45 and 73 years (mean, 59± 13.04 years), 20 (37.04%) men and 34 (62.96%) women and another 54 age- and sex-matched healthy control subjects were studied. Significantly ($p<0.05$) higher mean values of mean platelet volume (MPPV), platelet distribution width (PDW), Platelet larger cell ratio (PLCR), antithrombin, tissue plasminogen activator and fibrinogen were observed in the stroke patients when compared to those of the control subjects. Whereas, significantly lower ($p<0.05$) mean values of platelet count, prothrombin time and activated partial thromboplastin time were observed in the stroke patients than in those of the control subjects.
Conclusion: Several haemostatic parameters were found to be altered in stroke patients and have the potential to be risk factors but have not been demonstrated as being causative. Further work is needed to establish where they begin to contribute to stroke prognosis.

Keywords: Stroke patients; haemostatic parameters; Port-Harcourt; Nigeria.

1. INTRODUCTION

Stroke, also known as cerebrovascular accident (CVA) or cerebrovascular insult (CVI) is the sudden loss of brain function due to lack of oxygen and nutrients in the brain tissue caused by interruption of blood supply to the brain. Brain tissue ceases to function if deprived of oxygen for more than 90 seconds, and after approximately three minutes will suffer irreversible injury possibly leading to the death of the tissue (infarction) [1]. Stroke was first recognized by Hippocrates, the father of medicine over 2,400 years ago. At that time stroke was called apoplexy, which means "struck down by violence" as the victims always develop sudden paralysis and change in well-being. The cause was unknown until the mid-sixteen century when Jacob Wepfer observed that patients who died of apoplexy had bleeding and blockages in their cerebral arteries or arterioles [2]. Now, stroke is commonly classified on the basis of its aetiology as either ischaemic or haemorrhagic [3] or cryptogenic, those of unknown or indefinite cause [4]. It can occur at any age including childhood but the risk increases with age and persons who are 60 years and above are more affected. A patient's risk of dying from stroke also increases with advancing age of 54 years.

The effect of stroke on an individual depends on how much of the brain is affected, which specific cells are damaged, and how fast blood flow is restored to the affected area. Thus, the effect can be mild to severe and may be acute or chronic. The commonly seen clinical features include numbness, hemiplegia/hemiparesis, failure to understand or formulate speech, difficulty in seeing due to visual impairment, dizziness, altered level of consciousness as well as the loss of balance and coordination [5]. Stroke is one of the major leading causes of morbidity and mortality worldwide affecting both male and female. It is the second leading cause of death worldwide [6,7] and the eighth in Nigeria [8]. The World Health Organization (WHO) estimated that fifteen million people worldwide suffer from stroke each year, of these, five million dies, another five million are disabled and the remaining 5 million recovered satisfactorily [7]. The burden of prolonged hospitalization required of stroke survivors, the aftermath of disability from the disease with the subsequent inability of many to return to work is a great burden on their family and the community. To the best of our knowledge, there is a paucity of reported studies on possible abnormal changes in haemostatic parameters in established stroke patients in Nigeria. The present study aims to identify possible abnormal changes in haemostatic parameters in established Nigerian stroke patients.

2. MATERIALS AND METHODS

This was a prospective case-control study conducted among 54 clinically diagnosed stroke patients admitted at Braithwaite Memorial Specialist Hospital, Port Harcourt, Nigeria between November 2016 and October 2017 and another 54 age- and sex-matched apparently healthy control subjects without stroke. The control subjects were randomly recruited from spouse and relations of patients, hospital staff and the general populace.

Blood samples from both stroke patients and control subjects were obtained by clean venipuncture (without venous stasis) using commercial vacutainers containing 32mg/ml sodium citrate for the assay of the coagulation-fibrinolytic parameters and commercial EDTA vacutainers for the determination of Platelet count (PC) and platelet indices {mean platelet volume (MPV), plateletcrit (PLCR), and platelet distribution width, (PDW)} within 2 hours of

sample collection. All blood samples were properly mixed immediately after collection and the citrated samples were centrifuged at 2500 g for 15 minutes at room temperature (25ºC) to obtain clear platelet-poor plasma and stored frozen at -20ºC until assayed within 48 hours. All necessary aseptic precautions and standard operating procedures were applied.

Platelet count (PC) and calculation of platelet indices {mean platelet volume (MPV), plateletcrit (PLCR), and platelet distribution width, (PDW)} were determined using SYSMEX KX-21-N Haematology Auto-analyzer (KOBE, Japan). SYSMEX KX-21-N uses impendence flowcyto-metry for calculating different haematological parameters including platelet count and platelet indices.

Fibrinogen (FBG), antithrombin (AT) and tissue plasminogen activator (t-PA) assays were carried out using ELISA machine (STAT FAX-2100, Awareness Technology Inc) using Human Fibrinogen Elisa Kit, Elabscience Biotech Co., Ltd, China. Lot No AK0015OCT20019, Human Antithrombin Elisa Kit, Elabscience Biotech Co., Ltd, China; Lot No AK0015OCT20017 and Human Plasminogen Activator, Tissue Elisa Kit, Elabscience Biotech Co., Ltd, China. Lot No AK0015OCT20018, respectively. All the ELISA kits utilized sandwich-ELISA methodology. Determinations of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) tests were performed manually using QCA (Quimica Clinica Aplicada S.A Plasmascann Reagent Kit (Spain) Lot 130020. With each batch of coagulation screening tests and assays, a repeatability control was simultaneous processed.

2.1 Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0 (SPSS Inc. Chicago, IL, USA). Descriptive and frequency statistics were obtained for the variables of interest. Chi-square was used to test for statistical significance between categorical variables. A p value of <0.05 was considered statistically significant.

3. RESULTS

A total of 108 individuals comprised of 54 clinically diagnosed patients with stroke and another 54 apparently healthy subjects without stroke who served as the control group constituted the study population. The study population was recruited between November 2016 and October 2017. The stroke patients were aged between 45 and 73 years (mean ±SD, 59± 13.04 years) and the control subjects were aged between 41 and 69 years (mean 56.42± 11.58 years) (p>0.05). Thirty-four (62.96%) of the stroke patients were females and 20 (37.04%) were males, giving a female to male ratio of 1.7:1.0 (p<0.05). While 32 (59.26%) of the control subjects were females and 22 (40.74%) were males (p>0.05). The mean age and gender of the stroke patients as compared with those of the control subjects were not statistically significant (p>0.05). Table 1 shows the demographic profile of the study population.

Table 2 highlights the frequency distribution of stroke patients according to age groups. The majority (81.5%) of the stroke patients were between 57 and 73 years, while 10 (18.6%) were between 45 and 56 years. Thirty-two (59.3%) of the patients were between 63 and 73 years. There were only 3 patients (5.6%) that were between 45 and 50 years. The study did not encounter any stroke patient below 45 years. The frequency distribution shows an increasing incidence of stroke with advancing age.

As depicted in Table 3 there was significantly (p<0.05) higher mean values of MPV (10.91± 1.56fl), AT (1029.00±414.50 ng/ml), t-PA (15.87 ± 15.50 ng/ml) and fibrinogen (543.10 ± 92.06 mg/ml) in the stroke patients as compared with those of the control subjects, 9.85 ± 1.23fl, 804.50±188.70 ng/ml, 6.86 ± 8.51 ng/ml, and 492.80 ± 136.60 mg/ml respectively. Whereas, significantly (p<0.05) lower mean values of platelet count (205.80 ± 58.30 x 10^9/L versus 257 ± 64.15 x 10^9/L), prothrombin time (11.70 ± 1.2 seconds versus 14.03 ± 1.8 seconds) and activated partial thromboplastin time (33.56 ± 2.17 seconds versus 36.61 ± 2.3 seconds) were observed in the stroke patients than in those of the control subjects. Platelet distribution width (PDW) and platelet crit (PLCR) of the stroke patients ranged from 11.57fl to 21.4fl and 25.0% to 45.3%, with mean values of 16.16±3.28 fl and 38.8±4.9%, respectively. While the platelet distribution width (PDW) and platelet crit (PLCR) of the control group ranged from 10.8fl to 20.6fl and 23.7% to 43.8%, with mean values of 13.57±2.82fl and 35.7±3.4% respectively. The mean platelet distribution width (PDW) and platelet crit (PLCR) were significantly higher in stroke patients than in those of the control group (P< 0.05). These platelet indices in either group were not influenced by age or gender. (10.91 ± 1.56 versus 9.75 ± 1.15).

Table 1. Demographic profile of participants in the study population

Demographic profile	Study population		P-values
	Stroke patients n=54)	Control subjects (n=54)	
Gender			
Females	34 (62.96%)	32 (59.26%)	p>0.05
Males	20 (37.04%)	22 (40.74%)	p>0.05
Age (years)			
Mean ±SD	59.36 ± 13.64	56.42 ± 11.58	p>0.05
Range	45-73	41-69	

Table 2. Frequency distribution of stroke patients according to age groups

Age group	Frequency (%)
45-50	3 (5.6)
51-56	7 (13.0)
57-62	12 (22.2)
63-68	15 (27.8)
69-74	17 (31.5)
Total	54 (100)

Table 4 shows the comparison of haemostatic parameters between male and female stroke. Using student t-test, there was statistically significant higher mean values of fibrinogen concentration and mean platelet volume respectively in males than in those of the females ($p<0.05$). On the other hand, there was a statistically significant higher mean value of tissue plasminogen activator ($p<0.05$) in females as compared to males. Values of other haemostatic parameters tested did not show statistically significant gender difference ($p>0.05$).

4. DISCUSSION

In this study, the majority (81.5%) of the patients with first-ever stroke was between 57 and 73 years of age (mean 59± 13.04 years). This suggests that the risk at the onset of stroke in many individuals in our environment is at their late fifties, while a small percentage can experience it at a younger age. This is in agreement with findings among Nigerian stroke patients [9] and in India [10] but not in agreement with findings among Caucasians where the majority of their patients are 75 years and above [11,12]. This disparity in age may be due to ignorance of potential risk factors or nonchalant attitude towards preventive measures or low perception of stroke early warning signs. The occurrence of stroke increases with advancing age of the patients in this study, which is in tandem with several published population-based studies [8,9,13,14]. Although the occurrence of stroke in patients below 45 years has been reported [9] our current study did not encounter any stroke patient younger than 45 years. The reason is not clear but can be attributed to environmental factors. Different environmental factors may determine different age at onset.

Our current study observed that stroke was less frequent among men (37.04%) than in women (62.96%) with a male to female ratio of 1:1.7 ($P<0.05$). Desalu et al. [8] and Napoli et al. [15] also reported more first-ever stroke women than men but our male to female ratio is at variance with theirs. In contrast, some other population-based studies [9,10,13,14] reported a male preponderance (that men appear to be at a higher risk of stroke). The reason for female preponderance in this study is not clear and the notion that women on average live longer than men, and therefore suffer stroke more does not apply here. Both genders suffer a stroke and there is no report in the literature regarding particular gender predilection in occurrence.

The stroke patients had a significantly higher mean plasma fibrinogen concentration when compared to that of the control subjects (543.10 ± 92.06 mg/dl versus 492.80 ± 136.60 mg/dl, $P<0.0064$) respectively. Because fibrinogen is an acute phase protein, its high concentration in stroke patients may be due to upregulation of hepatic fibrinogen in response to cerebrovascular injury or to some unknown stimuli. The observed significant increase in fibrinogen levels in stroke patients as compared with control subjects is consistent with the findings of several previous

case-control studies [16-19]. Although causality cannot be inferred from our present finding, it is possible that raised fibrinogen concentration plays an important role in the development of stroke. Some earlier prospective studies have confirmed a strong and independent effect of raised plasma fibrinogen on both the onset and the progression of stroke [17,20]. These authors had also found that high levels of fibrinogen are strongly associated with stroke severity, which in turn is strongly associated with mortality and functional outcome after stroke in almost all studied populations. The Framingham study [21] also found a significant association between increasing fibrinogen concentration and risk of stroke in men but not in women. Increased fibrinogen levels have also been associated with early signs of atherosclerosis in asymptomatic individuals [22,23]. Definition of normal ranges for plasma fibrinogen distribution in populations and standardization of cutoff points where fibrinogen begins to contribute to stroke prognosis are areas which require urgent research. At the moment there are no well-defined and generally accepted stroke prognostic scores.

The stroke patients, contrary to having higher plasma fibrinogen levels, had shorter mean rate of fibrin formation as measured by prothrombin time (PT) (11.70 ± 1.2 seconds) and activated partial thromboplastin time (APTT) (33.56 ± 2.17 seconds) when compared to those of the control subjects 14.03 ± 1.8 seconds and 36.61 ± 2.3 seconds, respectively ($P<0.05$).These findings suggest a hypercoagulable state that may contribute to the pathogenesis of stroke. The hypercoagulability may precede the stroke and act as a risk factor to the pathogenesis of stroke. Consumption of platelets and subsequent compensational release of large platelets may also contribute to the shortened PT and APTT.

Table 3. Range and mean ± SD values of the haemostatic parameters of study population

Parameters/Units	Study Population		p-value
	Stroke patients (n=54)	Control subjects (n=54)	
Platelet count ($X10^9$)			
Mean ± SD	205.80 ± 58.30	250.50 ± 60.91	0.0109 (S)
Range	122.00 – 308.00	164.00 – 360.00	
PDW (fl)			
Mean ± SD	16.16 ± 3.28	13.57 ± 2.82	0.0043 (S)
Range	11.57 – 21.40	10.80 – 20.60	
Plateletcrit (%)			
Mean ± SD	38.8 ± 4.9	35.7 ± 3.4	0.0033 (S)
Range	25.0 – 45.3	23.7 – 43.8	
MPV (fl)			
Mean ± SD	10.91 ± 1.56	9.75 ± 1.15	0.0050 (S)
Range	8.10 – 13.20	8.20 – 11.60	
AT(ng/ml)			
Mean ± SD	1029.00 ± 414.50	804.50 ± 188.70	0.0206 (S)
Range	561.90 – 1972.80	492.80 – 1055.00	
t-PA (ng/ml)			
Mean ± SD	15.87 ± 15.50	6.86 ± 8.51	0.0165 (S)
Range	1.29 – 42.51	1.21 – 38.04	
PT (Seconds)			
Mean ± SD	11.70 ± 1.2	14.03 ± 1.8	0.0049 (S)
Range	9.00 – 15.00	12.00 – 14.00	
APTT (Seconds)			
Mean ± SD	33.56 ± 2.17	36.61 ± 2.3	0.0291 (S)
Range	32.00 – 39.00	33.00 – 38.00	
Fibrinogen(mg/ml)			
Mean ± SD	543.10 ± 92.06	492.80 ± 136.60	0.0064 (S)
Range	327.90 – 604.90	260.60 – 606.80	

Key: NS = Non Significant, S = Significant

Table 4. Comparison of haemostatic parameters in stroke patients based on gender

Parameters/Units	Gender		p-value
	Females n = 34	Males n =20	
Platelets ($X10^9$)			
Mean ± SD	197.00 ± 73.44	215.80 ± 31.22	0.4374 (NS)
Range	122.00 – 308.00	175.00 – 253.00	
MPV (fl)			
Mean ± SD	10.34 ± 1.68	11.66 ± 1.12	0.0279 (S)
Range	8.10 – 12.80	9.90 – 13.20	
PDW (fl)			
Mean ± SD	14.36 ± 3.80	16.17 ± 2.25	0.1591 (NS)
Range	10.20 – 20.40	12.20 – 18.10	
Plateletcrit (%)			
Mean ± SD	37.4 ± 5.8	37.4 ± 5.8	0.1591 (NS)
Range	24.7 ±48.9	24.7 ±48.9	
APTT (Seconds)			
Mean ± SD	38.40 ± 5.08	41.08 ± 3.80	0.1415 (NS)
Range	32.00 – 49.00	35.00 – 48.00	
Fibrinogen (ng/ml)			
Mean ± SD	509.30 ± 112.90	585.2 ± 17.89	0.0303 (S)
Range	327.90 – 602.50	550.80 – 604.90	
PT			
Mean ± SD	13.51 ± 5.17	13.43 ± 6.11	0.1351 (NS)
Range	11.53 – 16.87	11.47 – 15.70	
Antithrombin(ng/ml)			
Mean ± SD	898.40 ± 321.00	1193.00 ± 471.60	0.0654 (NS)
Range	561.90 – 1883.00	657.80 – 1972.00	
tPA (ng/ml)			
Mean ± SD	21.48 ± 16.92	8.86 ± 10.32	0.0324 (S)
Range	3.12 – 42.51	1.29 – 32.91	

Key: NS = Non Significant; HS = Highly Significant; S = Significant

It is well documented that platelets contain coagulant proteins, such as fibrinogen, factors V, VIII, IX, and XIII [24] and it is probable that these coagulant proteins released into the circulation by the reactive large platelets may be responsible for the reduced PT and APTT. Stanford et al. [19] also observed a significant difference in activated partial thromboplastin time between stroke patients and the control subjects; whereas, Fujii et al. [6] and Anthony et al. [25] did not observe any significant difference between the two groups.

A significantly higher concentration of antithrombin (AT) in stroke patients than in those of the control group ($p<0.05$) was observed in this study. This is probably an adaptive physiological response to prevent or reduce thrombosis (increase intravascular coagulation). Previous studies have demonstrated a significant decrease in antithrombin (AT) concentration in ischaemic and haemorrhagic stroke patients when compared to those without stroke [25,26]. They attributed the decrease concentration to its consumption during fibrinolysis; while, Orefice et al. [27] observed no statistically significant difference between the two groups.

In this study, the mean tissue plasminogen activator (t-PA) concentration was significantly higher among the stroke patients than in those of the control group. Tissue plasminogen activator activates plasminogen to plasmin for the digestion of deposited fibrin clot. Finding the higher concentration of tissue plasminogen activator (t-PA) also confirms the hyper-coagulable state of persons with stroke and the elevated concentration was to promptly clear the clot formed to minimize the fatality of stroke due to ischaemia. This physiological process is often augmented by the therapeutic use of recombinant tissue plasminogen activator (r-tPA) in managing and/or treating stroke patients. Lower than normal levels of tissue plasminogen activator may accentuate the occurrence of stroke. The high concentration of antithrombin

and tissue plasminogen activator may be the reason patients with stroke are surviving as these two proteins are needed to maintain free flow of blood; however, this advantage of preventing interruption of free blood flow may predispose stroke patients to bleed because of possible accumulation of high level of fibrin degradation products (FDPs), which can act as anticoagulant. Therefore timely assessment of antithrombin (AT) and tissue plasminogen activator (t-PA) are advised in order not to expose stroke patients to undue haemorrhage. Some authors described increased t-PA as a risk factor of ischaemic stroke [28].

In this study, the mean platelet count and mean platelet volume (MPV) of the stroke patients were significantly ($p<0.05$) lower and higher respectively than in those of the control subjects. That is a statistically significant inverse relationship between platelet count and mean platelet volume was observed in the stroke patients as compared to the control subjects. The significantly ($p<0.05$) lower platelet count in the stroke patients can be attributed to enhanced *in vivo* consumption for thrombotic events (platelet-fibrin plug formation) as well as its involvement in the early thromboembolic phase of the stroke.

Finding higher mean platelet volume (MPV) in stroke patients may suggest a larger population of circulating large platelets produced in response to the consumed or destroyed platelets. Newly produced platelets are synonymous to large platelets, which are very active metabolically and respond rapidly to vascular injury to provide platelet plug. These more reactive large platelets can be a risk factor to stroke due to hyperaggregability. However, whether these more reactive platelets are a cause or consequence of stroke is not clear. But it has been reported that patients with certain risk factors for stroke have some degree of platelet activation preceding stroke [10]. This possibility is in tandem with the suggestion that MPV when high may predispose an individual to have a stroke [10,29,30]. Our findings of lower platelet count and higher mean platelet volume in stroke patients are in agreement with several published studies [10,29-32]. In contrast, Fuji et al. [6] and Stanford et al. [19] observed no significant difference in platelet count between stroke patients and control subjects; whereas, Tohgi et al. [33] found MPV to be significantly lower in the stroke patients than in control subjects.

Our present study observed statistically significant higher mean values of platelet distribution width (PDW) and platelet crit (PLCR) in the stroke patients than in those of the control subjects ($p<0.05$). These observations were in agreement with Shah et al. [10] and not in an accord with Fuji et al. [6] and Stanford et al. [19] who observed no statistically significant difference between the stroke patients and control subjects. These platelet indices in either group were not influenced by age or gender.

Comparison of the haemostatic parameters on the basis of gender revealed a statistically significant increase in the mean values of fibrinogen concentration and mean platelet volume (MPV) in males; while tissue plasminogen activator (t-PA) showed a statistically significant increase in females than in males. Mean values of other haemostatic parameters did not show any significant gender difference.

5. LIMITATIONS

One limitation of the study is non-classification of the stroke patients due to the absence of brain computed tomography (CT) or magnetic imaging resonance (MRI) at the centre. Since stroke is a heterogeneous condition in terms of aetiology and severity its classification may have been more useful in guiding therapeutic interventions. Secondly, there is an inadvertent presumption that the stroke patients were not with other underlying hypercoagulable states or co-morbidities as they were compared only with apparently healthy control subjects.

6. CONCLUSION

This preliminary research work has identified several haemostatic parameters to be altered in stroke patients and have the potential to be risk factors but have not been demonstrated as being causative. Further work is needed to confirm if the abnormal levels are a preceding cause or a consequent of stroke as well as to establish cut-off values to determine where they begin to contribute to stroke prognosis.

CONSENT AND ETHICAL APPROVAL

Ethical approval to conduct the research was granted by the Ethical and Medical Committee of Rivers State Hospital Management Board, Port Harcourt, Nigeria and written consent were obtained from each participant.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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