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Imaging features associated with the susceptibility to brain fog: a major secondary complication observed in patients with ischemic stroke

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ABSTRACT

INTRODUCTION: Stroke is associated with an increased risk of brain fog with a variable impact on cognition. While some stroke survivors show a decline in cognitive functions, others have stable cognitions or revert to baseline cognitive functioning. Understanding the phenomenon of brain fog following stroke is necessary for prompt intervention and management as it is unclear whether Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) features of the brain in patients with ischemic stroke are associated with future risk of secondary complications, hence, the rationale for the study. The purpose was to assess the imaging features associated with susceptibility to brain fog.

METHODS: The study assessed anonymous images of 340 subjects aged 15 to 75 years with suspected stroke, referred for either brain CT or MRI in selected tertiary healthcare facilities/ radio-diagnostic centres in Nigeria. A retrospective descriptive research design was adopted. White matter changes, and regions of infarct, including lobar atrophy, were imaging features noted in patients confirmed with ischemic stroke. Analysis was done using the Statistical Package for Social Sciences (SPSS), Inc. Chicago, IL, USA, version 25.0.

RESULTS: White matter changes occurred most (39.06%), followed by cerebral ischemia (21.48%) and lobar atrophy (19.14%). Also, two-thirds (79.69%) of the patients presented with ischemic stroke may be vulnerable to developing secondary complications of the disease ($p < 0.05$).

CONCLUSION: The imaging features noted in the present study may contribute significantly to brain fog development, a major secondary complication observed in patients with ischemic stroke. These may help to investigate other brain pathology.

Keywords: Brain CT, Brain fog, Brain MRI, Imaging features, Ischemic stroke, Secondary complication.

INTRODUCTION

Globally, it is estimated that there are approximately 16 million new cases of stroke each year and over 62 million individuals living with the lasting consequences of a stroke, including severe secondary complications [1]. Stroke accounts for 9.7% of deaths and leads to five million

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disabilities annually, with incidence rates varying across different racial groups. If comprehensive, accessible healthcare interventions are not implemented, the number of new stroke cases is projected to increase to over 23 million by 2030, resulting in 7.8 million stroke-related deaths. Due to the high rate of disease morbidity, stroke has become the leading cause of global mortality [1–6]. The African population is worst hit and twice at risk of developing stroke compared to Caucasians and other races. This could be due to the nonchalant attitude of most Africans regarding health issues, lack of accessibility to healthcare, and low awareness, especially in developing and underdeveloped African countries. Individuals affected by stroke suffer a loss of cognitive/ neurological functions known as brain fog [7,8]. In Nigeria, stroke remains a major cause of cardiovascular admissions, with a high mortality rate of about 40-50% within the first three months of diagnosis. Also, about 39% of those who survived stroke after three months die within 12 months, while 11-12% develop severe secondary complications, including brain fog [8,9].

Brain fog, also known as cognitive dysfunction, is one of the major secondary complications of stroke. A stroke or cerebrovascular accident (CVA) occurs when blood flow to the brain is disrupted due to a blood clot or rupture in cerebral vessels, cutting off the supply of oxygen and nutrients contained in the blood, which results in damage to the brain tissues. Brain fog is the loss of intellectual functions of the brain because of the interruption of the cerebral blood flow [6,9–12]. Risk factors of brain fog include old age, recurrent CVA, transient ischemic attack, depressive illness, vascular co-morbidities, genetic variants, family history, and low educational status. Symptoms include poor reasoning of ample severity that obstructs daily functioning, thinking, and remembering. Usually, patients with brain fog have difficulty with verbal recall, basic arithmetic, and concentration. Various forms of brain fog are seen in stroke survivors [10–15] .

Brain fog was initially used to describe any dysfunction of the brain following stroke, irrespective of whether it involved vascular, neurodegenerative, or mixed processes. It was reported that 25-30% of ischemic stroke survivors developed immediate or delayed brain fog. In another study, about 48.3% of patients with stroke had vascular cognitive impairment [8–11]. Despite being common in different populations with a prevalence of between 20% and 80%, brain fog is often overlooked and ignored in the follow-up of CVA survivors [9–11]. However, brain fog entails a difficult cause with altering combinations of small and large vessel disease in addition to non-vascular neurodegenerative condition. Brain fog development depends on the stroke type, location, severity, level of related neuronal damage, and pre-existing brain fog [9–12].

Stroke severity (volume), strategic site lesion (combination of infarct features), severity of white matter changes (extent and location), and lobar atrophy appear to be the most vital contributors to recurrent brain fog [16,17]. Some authors have observed that atrophy of the medial temporal lobe is related to shorter time brain fog in elderly stroke survivors. Another study demonstrated that pre-existing morphological changes may impact the incidence of brain fog after stroke [18,19].

In Africans, CVA impairs all health-related quality of life status, including physical, psycho-emotional, eco-social, and especially cognitive function [5–7]. The severity of impairment is directly proportional to the gravity of stroke, particularly in young people. The incidence of stroke and its secondary complications is higher in the younger African population compared to populations in high-resource countries, probably due to the increasing stress levels young Africans are exposed to, including lifestyle substance abuse [5]. Brain fog may temporarily increase during episodes of CVA but can be managed depending on the clinical findings and non-contrast CT in addition to either CT or MRI brain scan [15,16,20].

The risk of secondary complications from stroke has been on the increase, and so the development of brain fog following stroke still appears to be relatively common [5,17,20–23]. Despite these harmful consequences, there is still a lack of understanding of stroke predictors. Stroke, therefore, remains one of the most devastating of all neurological diseases, often causing death and or gross permanent physical disability [6,20–22].

It is unclear whether CT and or MRI scans in patients with stroke could provide features associated with future risk of significant complications. In addition, the question of whether secondary complications from stroke are related to other structures of the brain affected needs to be addressed. Neuroimaging has become very useful in the identification of brain lesions. For example,

in patients with suspected cerebrovascular disorders, such as ischemic stroke, early diagnosis can be achieved using non-contrast CT. However, non-contrast CT is limited in predicting secondary complications, especially for patients affected by stroke. Computed Tomography Angiography (CTA) or Magnetic Resonance Imaging (MRI) or a combination of both, has the potential to provide significant information and inform optimal management. In addition, in the presence of occlusion in the arterial tree, CTA and MRI enable the estimation of the extent of occlusion and are very useful for guiding the treatment of acute ischemic CVA. However, the role of CT and MRI in the prognosis of stroke is poorly understood. An understanding of the imaging features of the brain associated with impending CVA, affected regions of the brain, and patient outcomes is crucial in designing interventions to improve patient outcomes for people affected by stroke. The present study sought to address this.

METHOD

Research design

A retrospective descriptive (cohort) study of images of brain CT and MRI of patients with suspected stroke aged 15 to >75 years. The archived images were sourced from selected hospital/diagnostic centres with CT and MRI scanners. The patients scanned had a non-contrast CT before the CT protocol, while those for the MRI were scanned using the three-dimensional MRI time of flight sequence.

Study dataset

The dataset includes archived images of cranial scans of patients with suspected stroke referred for either brain CT or MRI scan with specifications of the different scanners (CT and MRI) listed in Tables 1 and 2.

Study population and sampling technique

The study population involved images of 340

Table 1: Specifications of CT scanners

S/N	Hospital/ centre	Name	Make	Country	Machine S/N	Date of	Output (Max.)	
							kVp	mAs
1.	A	Bright-Speed 4-Slice	GE	USA	16507017m4	2007	140	300
2.	B	Optima 64-Slice	GE	USA	369366HMO	2014	140	800
3.	C	Brivo 385 Series 16 slice	GE	India	96369B14	2014	140	200
4.	D	Brivo 385 16-Slice	GE	China	353806HM3	2013	140	180

S/N- Serial number, Max. mAs- Maximum milliampere-seconds, kVp- Kilovoltage peak, GE- General Electric, USA: United States of America

Table 2: Specifications of MRI scanners

S/N	Hospital/ centre	Name	Make	Country	Date of manufacture	Output
1.	U	Somatom	Siemens	Germany	2007	0.2 Tesla
2.	V	Multiva	Philips	Holland	2016	1.5 Tesla
3.	W	Signa Ovation	GE	USA	2014	0.35 Tesla
4.	X	Magnetom Concerto	Siemens	Germany	2014	0.2 Tesla
5.	Y	Brivo 235	GE	USA	2014	0.5 Tesla
6.	Z	Brivo 235	GE	India	2014	0.5 Tesla

S/N- Serial number, GE- General Electric, USA: United States of America

individuals (males and females) aged 15 to >75 years referred for either brain CTA or MRI scan indicative of a suspected cerebrovascular accident. A convenient non-probability sampling technique was used to select images of 340 patients referred for either brain CTA or MRI who met the inclusion criteria.

Eligibility criteria

Patients referred for either brain CT or MRI whose indication was suspected stroke, an acute neurological deficit of not less than nine hours' duration, and unknown time of symptoms onset were used for the study.

Patients with fresh bleed such as intracerebral haemorrhage, subarachnoid haemorrhage, tumour, known contrast allergy, or previous renal failure at the time of admission and a history of brain surgery and or radiotherapy of the head and neck were excluded.

Features noted were region of lesion (cerebral ischemia), atrophy, and the presence or absence of white matter changes.

Data analysis

Data obtained were expressed using basic elements of descriptive statistics and analysed with the Statistical Package for Social Sciences (SPSS) version 25 and the Microsoft Excel computer programme. The level of significance was set at $p < 0.05$.

Ethical approval was obtained from the Federal Health Research Ethics Committee following the institutional guidelines and principles, as well as permission and clearance (Approval Number: FHREC/2019/01/51/13-05-19). In addition, permission was obtained from the selected hospitals/radio-diagnostic centres mentioned in the present study. All the patients' data were treated with a high level of confidentiality and privacy, following standards for conducting research. Data were collected and stored in a non-identifiable format.

RESULTS

Imaging features in 340 male and female patients with suspected stroke, aged 15 to >75 years (40.18 ±1.1 and 43.68 ± 1.18) have been assessed from either CT or MRI scans. Of the 340 angiograms for the CT and MRI evaluated, 256 (75.29%) patients had ischemic stroke, while 84 (24.71%) were patients without stroke (Figure 1). Figure 2 shows that more than two-thirds (79.69%) of the patients with stroke may be susceptible to developing

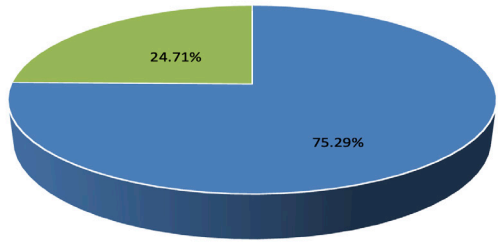

Figure 1: Percentage distribution of stroke and non-stroke patients

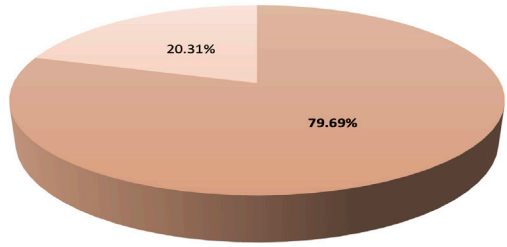

Figure 2: Susceptibility of patients with stroke to secondary complications of the disease

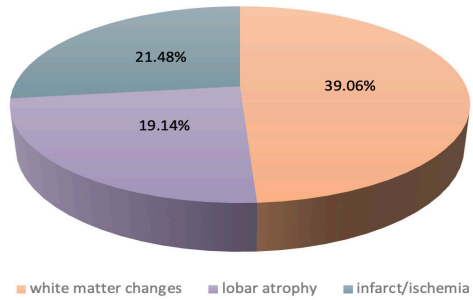

Figure 3: Pie chart of percentage distribution of imaging features in patients with stroke

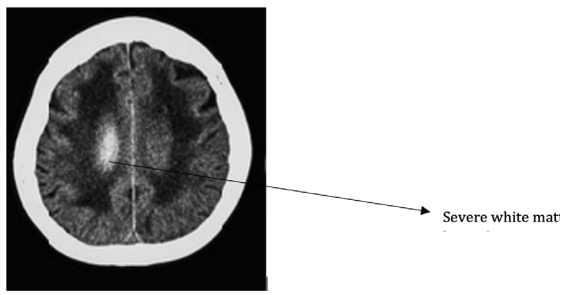

Figure 4: CT axial image shows hyperdense lesions of the white matter in patients with stroke observed in the present study.

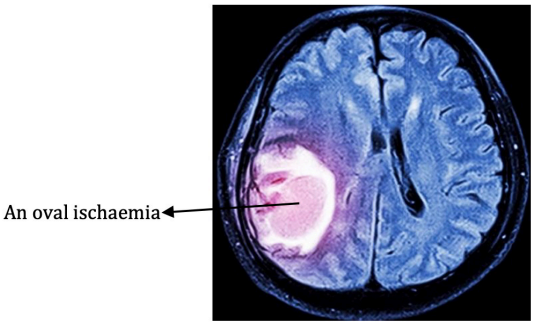

Figure 5: MRI axial image demonstrates oval hyperintense cerebral infarct in patients with stroke

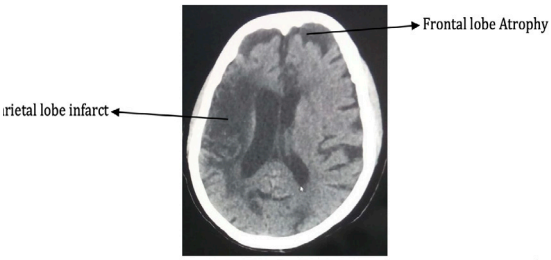

Figure 6: Axial CT image of the brain shows marked infarct and frontal lobe atrophy in patients with stroke

The susceptibility was based on the presence of imaging features (Figure 3), which include white matter changes Figure 4), cerebral infarct (Figure 5), and lobar atrophy (Figure 6).

DISCUSSION

Stroke is associated with an increased risk of brain fog with a variable impact on cognition. While some stroke survivors show a decline in cognitive functions, others have stable cognitions or revert to baseline cognitive functioning. Therefore, adequate knowledge and understanding of brain fog following CVA becomes crucial. In this study, white matter changes (39.06%) occurred most as the imaging features observed in patients with ischemic stroke. These white matter changes (Plate 1) consist of myelin rarefaction with shrunken oligodendrocytes and axonal abnormalities that may result from vascular insufficiency and the expression of hypoxia. Activated microglia, myelin breakdown, clasmatodendritic astrocytosis, axonal bulbs and degeneration, reactivation, and loss of oligodendroglia are features observed in the white matter as changes due to the loss of supply. For proper functioning of axons and oligodendrocytes, constant perfusion of the white matter by deep penetrating arterioles is, thus, essential. These white matter changes are associated with varying degrees of brain fog in CVA, depending on the duration and severity of the ischemic injury. Thus, patients with more severe white matter changes have an increased risk of recurrent cerebrovascular accidents and may be predictive of brain fog [23,24].

Cerebral ischemia/infarct (21.48%) and lobar atrophy (19.14%) were other imaging features noted in patients with ischemic stroke in the present study. Atrophy of the different lobes was more pronounced in the elderly, with advanced age being a risk factor (Plate 3), which may be due to reductions in blood flow because of the blockage/rupture of the affected vessel(s) supplying the different lobes, hence, the link between vascular pathology and lobar atrophy. These imaging features were more ($p < 0.05$) in male than female patients with CVA. The result of the present study is in tandem with works on CVA patients, which inferred that cerebral atrophy and infarction were related to white matter changes [25,26].

Ischemic white matter changes are most prominent in the frontal lobe and are linked with frontal subcortical disconnection. Atrophy of the different lobes is associated with brain fog after CVA. Studies have shown that in elderly stroke survivors, medial and temporal lobe atrophy were associated with shorter time to brain fog but more strongly associated with subsequent cognitive decline than were white matter changes [27,28]. This suggests a more significant role for other types of diseases, such as Alzheimer-type, than cerebrovascular lesions in the development of delayed brain fog after the onset of stroke. This was further supported by findings that reductions in blood flow, assessed by arterial spin labeling in the posterior artery territories and volumes of the hippocampal formation, were similar in brain fog after stroke [28].

On the susceptibility of stroke survivors to brain fog, about 79.69% of patients in this study with CVA may be vulnerable to having secondary complications of the disease ($p < 0.05$). The susceptibility to the development of brain fog was based upon the following determining factors (features), including lobar atrophy, white

matter lesions, and cerebral infarct, in addition to structural changes/morphological patterns in the circle of Willis (the major arterial supply to the brain) [29–33]. These imaging features suggest the link between patients with stroke and the vulnerability to having secondary complications, as constant perfusion of the white matter by deep penetrating arterioles is essential for the proper functioning of axons and oligodendrocytes. These results support studies that worked on the profile and determinants of vascular cognitive impairment in African stroke survivors but did not mention the vulnerability of stroke survivors to secondary complications [3]. This, the present study noted. In addition, our results support works that inferred patients with ischemic stroke, characterised by severe white matter change and lobar atrophy evident on CT and MRI, may have an increased risk of secondary complications [22,27,28,33,34]. Therefore, features of patients with stroke noted in the present study may form indices for stroke survivors to varying degrees of complications.

CONCLUSION

White matter changes, cerebral infarction, and lobar atrophy contribute significantly to brain fog development, a major secondary complication in patients with stroke. Also, more than two-thirds (79.69%) of the patients with CVA may be susceptible to developing secondary complications of the disease. Given this, the imaging features provided may help investigate other brain pathology.

REFERENCES

1. World Health Organization Noncommunicable Diseases Country Profiles 2018; World Health Organization: Geneva, 2018; ISBN 978-92-4-151462-0.
2. Feigin, V.L.; Norrving, B.; George, M.G.; Foltz, J.L.; Roth, G.A.; Mensah, G.A. Prevention of Stroke: A Strategic Global Imperative. Nat Rev Neurol 2016, 12, 501–512, doi:10.1038/nrneurol.2016.107.
3. Adeloye, D. An Estimate of the Incidence and Prevalence of Stroke in Africa: A Systematic Review and Meta-Analysis. PLoS One 2014, 9, e100724, doi:10.1371/journal.pone.0100724.
4. Thrift, A.G.; Cadilhac, D.A.; Thayabaranathan, T.; Howard, G.; Howard, V.J.; Rothwell, P.M.; Donnan, G.A. Global Stroke Statistics. Int J Stroke 2014, 9, 6–18, doi:10.1111/ijs.12245.
5. Owolabi, L.F.; Akinyemi, R.O.; Owolabi, M.O.; Sani, M.U.; Ogunniyi, A. Profile of Stroke-Related Late Onset Epilepsy among Nigerians. Journal of Medicine in the Tropics 2013, 15, 29–32.
6. Go, A.S.; Mozaffarian, D.; Roger, V.L.; Benjamin, E.J.; Berry, J.D.; Blaha, M.J.; Dai, S.; Ford, E.S.; Fox, C.S.; Franco, S.; et al. Heart Disease and Stroke Statistics--2014 Update: A Report from the American Heart Association. Circulation 2014, 129, e28–e292, doi:10.1161/01.cir.0000441139.02102.80.
7. O'Donnell, M.J.; Xavier, D.; Liu, L.; Zhang, H.; Chin, S.L.; Rao-Melacini, P.; Rangarajan, S.; Islam, S.; Pais, P.; McQueen, M.J.; et al. Risk Factors for Ischaemic and Intracerebral Haemorrhagic Stroke in 22 Countries (the INTERSTROKE Study): A Case-Control Study. Lancet 2010, 376, 112–123, doi:10.1016/S0140-6736(10)60834-3.
8. Kalaria, R.N.; Akinyemi, R.; Ihara, M. Stroke Injury, Cognitive Impairment and Vascular Dementia. Biochim Biophys Acta 2016, 1862, 915–925, doi:10.1016/j.bbadis.2016.01.015.
9. Desalu, O.O.; Wahab, K.W.; Fawale, B.; Olarenwaju, T.O.; Busari, O.A.; Adekoya, A.O.; Afolayan, J.O. A Review of Stroke Admissions at a Tertiary Hospital in Rural Southwestern Nigeria. Ann Afr Med 2011, 10, 80–85, doi:10.4103/1596-3519.82061.
10. Akinyemi, R.O.; Ogah, O.S.; Ogundipe, R.F.; Oyesola, O.A.; Oyadoke, A.A.; Ogunlana, M.O.; Otubogun, F.M.; Odeyinka, T.F.; Alabi, B.S.; Akinyemi, J.O.; et al. Knowledge and Perception of Stroke amongst Hospital Workers in an African Community. Eur J Neurol 2009, 16, 998–1003, doi:10.1111/j.1468-1331.2009.02666.x.
11. Jacova C, Pearce LA, Costello R, McClure LA, Holliday SL, Hart RG. Cognitive Impairment in Lacunar Strokes: The SPS3 Trial. Annals of Neurology. 2012; 72: 351-362. - Google Search Available online: https://www.google.com/search?q=Jacova+C%2C+Pearce+LA%2C+Costello+R%2C+McClure+LA%2C+Holliday+SL%2C+Hart+RG.+Cognitive+impairment+in+lacunar+strokes%3A+the+SPS3+trial.+Annals+of+Neurology.+2012%3B+72%3A+351-362.&oq=Jacova+C%2C+Pearce+LA%2C+Costello+R%2C+McClure+LA%2C+Holliday+SL%2C+Hart+RG.+Cognitive+impairment+in+lacunar+strokes%3A+the+SPS3+trial.+Annals+of+Neurology.+2012%3B+72%3A+351-362.&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBBzQ2MWowajSoAgCwAgA&sourceid=chrome&ie=UTF-8 (accessed on 8 January

2024).
12. Chaudhari, T.S.; Verma, R.; Garg, R.K.; Singh, M.K.; Malhotra, H.S.; Sharma, P.K. Clinico-Radiological Predictors of Vascular Cognitive Impairment (VCI) in Patients with Stroke: A Prospective Observational Study. J Neurol Sci 2014, 340, 150–158, doi:10.1016/j.jns.2014.03.018.
13. Yang, J.; Wong, A.; Wang, Z.; Liu, W.; Au, L.; Xiong, Y.; Chu, W.W.C.; Leung, E.Y.L.; Chen, S.; Lau, C.; et al. Risk Factors for Incident Dementia after Stroke and Transient Ischemic Attack. Alzheimers Dement 2015, 11, 16–23, doi:10.1016/j.jalz.2014.01.003.
14. Brodaty, H.; Liu, Z.; Withall, A.; Sachdev, P.S. The Longitudinal Course of Post-Stroke Apathy over Five Years. J Neuropsychiatry Clin Neurosci 2013, 25, 283–291, doi:10.1176/appi.neuropsych.12040080.
15. Park, J.H.; Kim, B.J.; Bae, H.-J.; Lee, J.; Lee, J.; Han, M.-K.; O, K.Y.; Park, S.H.; Kang, Y.; Yu, K.-H.; et al. Impact of Post-Stroke Cognitive Impairment with No Dementia on Health-Related Quality of Life. J Stroke 2013, 15, 49–56, doi:10.5853/jos.2013.15.1.49.
16. Ihle-Hansen, H.; Thommessen, B.; Wyller, T.B.; Engedal, K.; Øksengård, A.R.; Stenset, V.; Løken, K.; Aaberg, M.; Fure, B. Incidence and Subtypes of MCI and Dementia 1 Year after First-Ever Stroke in Patients without Pre-Existing Cognitive Impairment. Dement Geriatr Cogn Disord 2011, 32, 401–407, doi:10.1159/000335361.
17. Leys, D.; Hénon, H.; Mackowiak-Cordoliani, M.-A.; Pasquier, F. Poststroke Dementia. Lancet Neurol 2005, 4, 752–759, doi:10.1016/S1474-4422(05)70221-0.
18. Firbank, M.J.; Allan, L.M.; Burton, E.J.; Barber, R.; O'Brien, J.T.; Kalaria, R.N. Neuroimaging Predictors of Death and Dementia in a Cohort of Older Stroke Survivors. J Neurol Neurosurg Psychiatry 2012, 83, 263–267, doi:10.1136/jnnp-2011-300873.
19. Kalaria, R.N.; Ihara, M. Dementia: Vascular and Neurodegenerative Pathways-Will They Meet? Nat Rev Neurol 2013, 9, 487–488, doi:10.1038/nrneurol.2013.164.
20. Ojagbemi, A.; Owolabi, M.; Atalabi, M.; Baiyewu, O. Stroke Lesions and Post-Stroke Depression among Survivors in Ibadan, Nigeria. Afr J Med Med Sci 2013, 42, 245–251.
21. Donkor, E.S.; Owolabi, M.O.; Bampoh, P.; Aspelund, T.; Gudnason, V. Community Awareness of Stroke in Accra, Ghana. BMC Public Health 2014, 14, 196, doi:10.1186/1471-2458-14-196.
22. Liu, L.; Wang, D.; Wong, K.S.L.; Wang, Y. Stroke and Stroke Care in China: Huge Burden, Significant Workload, and a National Priority. Stroke 2011, 42, 3651–3654, doi:10.1161/STROKEAHA.111.635755.
23. Grieb, P. Neuroprotective Properties of Citicoline: Facts, Doubts and Unresolved Issues. CNS Drugs 2014, 28, 185–193, doi:10.1007/s40263-014-0144-8.
24. Komolafe, M.A.; Ogunlade, O.; Komolafe, E.O. Stroke Mortality in a Teaching Hospital in South Western Nigeria. Trop Doct 2007, 37, 186–188, doi:10.1258/004947507781524557.
25. Li, W.-Z.; Wu, W.-Y.; Huang, H.; Wu, Y.-Y.; Yin, Y.-Y. Protective Effect of Bilobalide on Learning and Memory Impairment in Rats with Vascular Dementia. Mol Med Rep 2013, 8, 935–941, doi:10.3892/mmr.2013.1573.
26. Aikawa, J.; Yamashita, T.; Nishiyama, M.; Horinouchi, S.; Beppu, T. Effects of Glycosylation on the Secretion and Enzyme Activity of Mucor Rennin, an Aspartic Proteinase of Mucor Pusillus, Produced by Recombinant Yeast. J Biol Chem 1990, 265, 13955–13959.
27. Román, G.C.; Salloway, S.; Black, S.E.; Royall, D.R.; Decarli, C.; Weiner, M.W.; Moline, M.; Kumar, D.; Schindler, R.; Posner, H. Randomized, Placebo-Controlled, Clinical Trial of Donepezil in Vascular Dementia: Differential Effects by Hippocampal Size. Stroke 2010, 41, 1213–1221, doi:10.1161/STROKEAHA.109.570077.
28. Black, S.; Román, G.C.; Geldmacher, D.S.; Salloway, S.; Hecker, J.; Burns, A.; Perdomo, C.; Kumar, D.; Pratt, R.; Donepezil 307 Vascular Dementia Study Group Efficacy and Tolerability of Donepezil in Vascular Dementia: Positive Results of a 24-Week, Multicenter, International, Randomized, Placebo-Controlled Clinical Trial. Stroke 2003, 34, 2323–2330, doi:10.1161/01.STR.0000091396.95360.E1.
29. Paulinus, S.O.; Igiri, A.O.; Egbe, N.O.; Ani, C.C.; Udo-Affah, G.U. Evaluation of Anatomical Variants of the Circle of Willis in a Nigerian Population Using Contrast Enhanced Computed Tomography (CECT) Scan. International Journal of Scientific and Engineering Research 2017, 2129-2135.
30. Paulinus, S.O.; Udoh, B.E.; Efanga, S.A.; Udo-Affah, G.U.; Eru, E.M.; Ani, C.C.; Okoro, U.U.; Egbe, N.O. Anatomic Imaging Study of Luminal Diameter of the Circle of Willis in Patients with Ischemic

Stroke. CJHS 2021, 5, 75–80, doi:10.25259/CJHS_50_2020.
31. Igiri, A.O.; Paulinus, S.O.; Egbe, N.O.; Ani, C.C. Classical Pattern of the Cerebral Arterial Circle of Willis in a Nigerian Population Using Contrast Enhanced Computed Tomography Scan. International Journal of Scientific and Engineering Research 2017, 1204-1207.
32. Udo-Affah, G.U.; Paulinus, S.O.; Eru, E.M.; Igiri, A.O.; Egbe, N.O. Anatomical Features of the Brain of Patients with Stroke (Cerebrovascular Accident) Relative to Types, Sites, and Shapes Using Computed Tomography Scan. CJHS 2021, 4, 79–83, doi:10.25259/CJHS_47_2020.
33. Cotroneo, A.M.; Castagna, A.; Putignano, S.; Lacava, R.; Fantò, F.; Monteleone, F.; Rocca, F.; Malara, A.; Gareri, P. Effectiveness and Safety of Citicoline in Mild Vascular Cognitive Impairment: The IDEALE Study. Clin Interv Aging 2013, 8, 131–137, doi:10.2147/CIA.S38420.
34. Baskys, A.; Cheng, J. Pharmacological Prevention and Treatment of Vascular Dementia: Approaches and Perspectives. Exp Gerontol 2012, 47, 887–891, doi:10.1016/j.exger.2012.07.002.