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Antioxidants and Biomarkers of Inflammation as Risk Factors of Vascular Cognitive Impairment in Adult Hypertensives

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Authors' contributions

This work was carried out in collaboration among all authors. Author OBA wrote the protocol, performed the laboratory, statistical analysis and wrote the first draft of the manuscript. Authors OBA, MACD and EOA managed the literature searches and the analysis of the study. Authors OBA and MOO enrolled the participants. All authors designed the study, revised and approved the final manuscript.

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ABSTRACT

Background: Impairment in cognition and attention involving memory loss characterize Vascular Cognitive Impairment (VCI), a complication of hypertension. The involvement of antioxidants and inflammatory biomarkers in the progression of hypertension to VCI is controversial and is investigated in this study.
Methods: A total of 216 normoglycaemic individuals (aged 40-75 years) were enrolled into this case control study by systematic sampling method. They consisted of 81 Newly Diagnosed Hypertensives (NDH) without cognitive impairment, 69 Newly Diagnosed Hypertensives with Cognitive Impairment (NDHCI) attending Medical Outpatient Clinic and 66 apparently healthy individuals without hypertension or cognitive impairment (Controls), who were members of staff of University College Hospital, Ibadan. Socio-demographic indices and lifestyle were obtained through a semi-structured questionnaire while Systolic and Diastolic tg6bn Blood Pressure (SBP and DBP, respectively) were obtained using standard methods. Neuropsychological assessment based on Cognitive Score (CS) was performed using Community Screening Instrument for

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Dementia. Antioxidants [Glutathione (GSH), Catalase (CAT) and Superoxide Dismutase (SOD)] and inflammatory biomarkers [Interleukin-6 (IL-6), High sensitivity C - reactive protein (hs-CRP)] in serum were estimated by ELISA. Data were analysed using Statistical Package for Social Sciences (SPSS) software 17.0 version. Analysis of variance (ANOVA) and Post Hoc test were used for comparison of variables while Chi square test was used to find associations between variables. Data analysed were significant at $p<0.05$.

Results: The inflammatory biomarkers hs-CRP (0.14±0.01; 0.12±0.01 versus 0.11±0.01 mg/L; $p<0.001$) and IL-6 (301.62±17.61; 115.60±16.01 versus 51.41±1.60 ng/mL; $p<0.001$) were significantly higher in NDHCI and NDH relative to control, respectively. Significant decreases in mean activities of catalase (81.71±1.01; 285.10±5.51 versus 403.00±17.31 ng/mL; $p<0.001$), SOD (5.04±0.97; 9.67±0.70 versus 12.02±0.53 ng/mL; $p<0.007$), GSH (7.02±0.89, 8.91±0.90; 20.5±1.31µg/mL; $p<0.001$) and cognitive scores (3.51±0.41; 18.81±0.50 against 28.71±0.20; $p<0.001$) were found in NDHCI compared with NDH and control, respectively.

Conclusion: Increased oxidative stress and inflammatory processes may underlie the progression of hypertension to cognitive impairment.

Keywords: Antioxidants; biomarkers; vascular cognitive impairment; hypertension.

1. INTRODUCTION

Dementia, characterized by significant irreversible decline in cognitive function that is sufficiently severe to impair independent social and occupational activities is a feared geriatric condition that has become a growing public health problem worldwide. The World Health Organization mental health gap (WHO mhGAP) considers dementia a priority mental health disorder earmarked for scaled-up action on account of its huge economic cost and social burden [1]. The prevalence of dementia increases with increasing age, doubling every 5-years after age 65 [2]. Impairment in cognition is one of the commonest precursors to the onset of dementia [3].

Cognitive function plays a central role in determining the well being and quality of life of adults including their decisions to work, retire and spend or save their money as they pass from midlife to older ages [4,5]. Therefore, vascular cognitive impairment (VCI) is a spectrum of neurodegenerative disorders that is associated with cerebrovascular diseases [6]. It is linked to damages to the vascular system, especially abnormalities of the arteries and vessels supplying the head region, which lead to progressive decline in thinking abilities [6]. It is a concept that in its early stage creates an opportunity for preventive strategies for the onset of dementia [7]. VCI is characterized by a specific cognitive profile involving preserved memory with impairments in attention and executive functioning, which includes planning, task flexibility and problem solving. Daily activities are not necessarily impaired [7]. Impairment of cognition as a result of elevated blood pressure has been associated with memory loss and other cognitive deficits like dementia and Alzheimers disease [8].

Hypertension has devastating effects on the brain; it is the major cause of stroke and a leading cause of dementia [9]. It alters the structure of cerebral blood vessels and disrupts intricate vasoregulatory mechanism that assures an adequate blood supply to the brain. These alterations threaten the cerebral blood supply and increase the susceptibility of the brain to ischemic injury as well as reduced cognitive function [10,11,12]. Across all WHO regions, including the America, Africa has the highest prevalence of hypertension where 46% of the entire population, 25 years of age and older is estimated to be hypertensive compared to 35-40% elsewhere in the world [1]. Nigeria, the most populous country in the African continent, has an alarming record of hypertension with an overall prevalence of 30.7% (Men-29.5%, women-30.4%) [13]. Many hypertensive Africans are unaware of their status, and are rarely treated or poorly controlled, making them at high risk for stroke, cognitive dysfunction, heart and renal disease [13,14]. Charles-Davies et al, demonstrated significant hypertension among traders in Ibadan, who were unaware of the disease [15].

According to the global burden of diseases study (GBD) [16], hypertension is the most prominent non-communicable disease that has great impact on cardiovascular outcomes. Hypertension related diseases (specifically ischemic heart disease and cerebrovascular disease) are the

top two leading causes of disability adjusted life years (DALYs) and years of life lost (YLL) globally [15]. Hypertension may lead to cognitive impairment through several pathogenic factors; Gray matter loss as a result of micro vascular dysfunction induced by hypertension, loss of connectivity and network efficiency from white matter lesions, reduced perivascular clearance and neurovascular dysfunction (CONSTATIANO IADECOLA, 2019). All these anomalies may be linked to hypertension via large artery stiffening thereby increases pulsatility in microvessels, which has been proposed to alter perivascular spaces. The enlarged and distorted perivascular spaces cause an alteration that could inhibit the disposal of potentially toxic by-products of brain activity; amyloid-β, which may eventually instigate oxidative stress and inflammation [17,18]. The involvement of oxidative stress in hypertension leading to neurovascular dysfunction is further noticed when free radicals induce inflammation by activating redox-sensitive pro inflammatory transcription factors and endothelia dysfunction [19]. The endothelial dysfunction induced by oxidative stress can release vascular endothelial growth factors which may induce neurotoxic effect on cognition [20]. Vascular oxidative stress and inflammation impede the proliferation, migration and differentiation of oligodendrocyte progenitor cells, these processes may compromise repair of the damaged white matter [20].

The possible roles of inflammation and oxidative stress in the development of cognitive dysfunction among Nigerian hypertensive patients are unclear and are therefore investigated in this study.

2. MATERIALS AND METHODS

2.1 Study Population

Two hundred and sixty participants were enrolled into this study. Forty-four were excluded for the following pre-specified reasons: unwillingness to participate in the study (n = 10), dementia and Alzheimer disease (diagnosed by a neurologist; n = 4), Pre- hypertensive (SBP between 120 and 140 mmHg/ DBP between 80 and 90 mmHg, n =18), Type 2 diabetes mellitus patients (fasting plasma glucose>126 mg/dL on more than two occasions, n = 12). Two hundred and sixteen participants [81hypetensives without cognitive impairment (NDH), 69 hypertensives with cognitive impairment (NDHCI), and 66 relatively healthy participants (Controls), aged 40-75 years thus, constituted the study population.

2.2 Participants with Hypertension

81 newly diagnosed hypertensives with systolic blood pressure of ≥140 and diastolic blood pressure of ≥90mmHg were enrolled into this study. They were non-diabetics, without stroke, without lipid lowering drugs or antihypertensive drugs and had no family history of vascular cognitive impairment. The diagnosis of hypertension was based on the guidelines of the Joint National Committee on hypertension (JNC 7, 2012). Stage I hypertension was: - systolic blood pressure=140 – 159 mmHg and diastolic blood pressure 90-99 mmHg while Stage 2 hypertension was: - systolic blood pressure: ≥160mmHg and diastolic blood Pressure:-≥100 mmHg. Diagnosis was made by a consultant Nephrologists at the Medical Outpatients Department of the University College Hospital, Ibadan.

2.3 Participants with Hypertension and Cognitive Impairment

Diagnosis of hypertension with cognitive impairment was based on the guidelines of the 7th Joint National Committee on hypertension (JNC 7) and community screening instrument on dementia (CSI-D). The CSI-D was validated by the systematic mini mental state examination (SMMSE). The participants were non-diabetics, without stroke or family history of vascular cognitive impairment. Diagnosis was made by a Consultant Neurologist at the Medical Outpatient Department of the University College Hospital Ibadan.

2.4 Controls

They were apparently healthy, normotensive and non-diabetic participants with intact cognitive function as certified by the Neurologist. They were not on lipid lowering nor antihypertensive medications.

2.5 Sample Collection

Fasting venous blood (10 mL) sample was collected asceptically from the participants after an overnight fasting by venepuncture. This was done by applying a tourniquet 4-6 inches (10- 15 cm) above the puncture site to obstruct the return of venous blood back to the heart and to distend the vein. The site of the puncture, the media

cubital vein in the antecubital fossa was first cleansed with alcohol swab, blood was then collected with new disposable pyrogen free needles and syringes after the skin had dried.

2.6 Biochemical Parameters

Blood (6 mL) was dispensed into plain bottle and kept for 1hour to obtain serum for the analysis of biomarkers of inflammation [Interleukin-6 (ELABSCIENCE ASSAYPRO LLC. U.S.A), High sensitivity C-reactive protein (CALBIOTECH, U.S.A)] and the selected antioxidants [glutathione, superoxide dismutase and catalase (BIOCOMPARE ELISA KITS, SOUTH SAN FRANCISCO, CA94080, USA)] using enzyme linked immunosorbent assay method. 2 mL was put into lithium heparin tube for the albumin estimation by spectrophotometry while the remaining 2 mL was dispensed into fluoride oxalate tube for plasma glucose estimation within two weeks. All tubes were labeled appropriately and centrifuged at 500 g for five minutes after which serum and plasma were extracted and stored in small aliquots at -20^{0}C until analyses were done.

2.7 Demographic Indices

Semi structured pretest questionnaire was completed by each participant in order to obtain demographic data which include: - gender, age, smoking history, alcohol consumption, family history of hypertension, cognitive impairment, drug and dietary history, presence of undiagnosed diabetes, chronic kidney disease, educational status, marital status, occupation and life style.

2.8 Blood Pressure Measurements

Blood Pressure (BP) measurements were performed using a mercury sphygomanometer. Adequately sized cuffs (standard cuff of 23 × 12 cm / a large cuff of 34 × 15 cm) according to arm circumference were placed on the non-dominant arm. The first and fifth phases of Korotkoff sounds were taken as the systolic and diastolic BP, respectively. The measurements were taken after the patients had emptied their bladder and rested for 10 min in sitting position, rested their back, legs resting on the ground (not crossed). Two measurements were taken at 2-min intervals. The mean of the set of two measurements was calculated to give the systolic and diastolic BPs. Clinical hypertension was defined as a BP ≥140/90 mm Hg.

2.9 Measurement of Cognitive Function

The CSID was used to assess cognitive function and results in a score of 30 (normal) to 0 (impaired). It provides a global score of cognitive ability that correlates with function in activities of daily living. The CSID measures various domains of cognitive function including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression construct a diagram, and follow a three-step verbal command. It provides opportunity for those that cannot read and write, provides a baseline score of cognitive function and pinpoints specific deficits that can aid in forming a diagnosis. The CSID was validated using SMMSE a reliable instrument that allows practitioners to accurately measure cognitive deficits and deterioration over time [16].

2.10 Statistical Analysis

Data from the study population were collected and analyzed using the Statistical Package for Social Sciences (SPSS) software 17.0 version (SPP Inc., Richmond, CA). Data analysed were considered significant at $p<0.05$.

2.10.1 For quantitative variables

Analysis of variance was used to test significance of variations and Post Hoc was used for comparison of multiple variables. Linear regression analysis was employed to determine relationship between variables.

2.10.2 For non quantitative-variables

Chi square analysis was used for determination of associations between variables.

3. RESULTS

Table 1 shows socio-demographic factors on cognitive function in (NDH), (NDHCI) and Control. Association was observed in the marital status, occupation, alcohol intake and type of symptoms among the groups ($p<0.05$).

Table 2 shows the comparisons of GSH, SOD, CAT and cognitive scores in NDH, NDHCI and Control. Significant decreases in the mean activities of Catalase, SOD, GSH and low cognitive scores were found in NDHCI compared with NDH and control respectively, $p<0.001$.

Table 3 shows the comparisons of albumin, interleukin-6, C-reactive protein and Cognitive score in NDH, NDHCI and Control. Interleukin-6 and CRP were significantly higher in NDHCI and NDH than in control (p<0.02). Conversely, albumin were lower in NDHCI and NDH than in control (p<0.01).

Table 4 shows the relationship of blood pressure, with markers of inflammation and Antioxidants in NDH, NDHCI and Control. In the NDH group, hs-CRP and SOD had a significantly positive relationship with SBP (β=225.22; β=0.843, respectively) while GSH had a significantly positive relationship with DBP (β=0.406; β=0.022, respectively). In control, hs-CRP, catalase and GSH had positive relationship with SBP (β=118.557; β=0.024; β=0.347, respectively).

Table 1. Socio-demographic factors in hypertensives, hypertensives with cognitive impairment and apparently healthy normotensive individuals with intact cognition

Variables	Response	Control n=66 (%)	NDHn=81(%)	NDHCI n=69(%)	X^2	p
Sex	Male	34(48.5)	35(43.2)	30(43.48)	1.7	0.426
	Female	34(51.5)	46(56.8)	39(56.52)		
Education	Yes	48(72.2)	55(67.9)	46(69.7)	0.4	0.816
	No	18(27.3)	26(32.1)	20(30.3)		
Education	Nil	18 (27.3)	26(32.1)	20(30.3		
	Primary	6 (9.1)	13(19.7)	09(13.6)	5.3	0.508
	Secondary	22 (33.3)	21(25.9)	13(19.7)		
	Tertiary	20 (30.3)	21(25.9)	24(36.4)		
Marital status	Married	45 (68.2)	58(71.6)	58(87.9)	13.7	0.008*
	Divorce	10 (15.2)	4(4.9)	3(4.5)		
	Widow	11(16.7)	19(23.5)	5(7.6)		
Occupation	Civil servant	26(39.4)	27(33.3)	22(33.3)	30.5	0.001*
	Trader	39(59.1)	32(39.5)	38(57.6)		
	Hair dresser	0(0.0)	5(6.2)	0(0.0)		
	Fashion	0(0.0)	6(7.4)	0(0.0)		
	designer	0(0.0)	10(12.3)	6(9.1)		
	Retiree	1(1.5)	1(1.2)	0(0.0)		
	Farmer					
Tobacco smoking	Yes	18(27.3)	14(17.3)	22(33.3)	5.1	0.077
	No	48(72.7)	67(82.7)	44(66.7)		
Alcohol Intake	Yes	18(24.2)	14(17.3)	31(47.0)	16.6	<0.001*
	No	50(75.8)	67(82.7)	35(53.0)		
Family History	Yes	25(37.9)	29(35.8)	34(51.5)	4.2	0.124
	No	41(62.1)	52(64.2)	32(48.5)		
Knowledge about HTN	Yes	43(65.2)	51(63.0)	47(71.2)	0.2	0.562
	No	23(3.8)	30(37.0)	19(28.8)		
Type of HTN Symptoms	Nil	11(16.7)	20(24.7)	8(12.1)	26.1	<0.001*
	HA	52(78.8)	51(63.0)	46(69.7)		
	HBP	1(1.5)	3(3.7)	12(18.2)		
	BV	2(3.0)	7(8.6)	0(0.0)		
Tribe	Togo	0(0.0)	0(0.0)	3(4.3)	7.154	0.307
	Hausa	4(6.1)	4(4.9)	5(7.2)		
	Igbo	8(12.1)	11(13.6)	7(10.1)		
	Yoruba	54(81.8)	66(81.5)	54(78.3)		

X^2=chi square value, p= probability value, H=hypertensives, HC=hypertensive's with cognitive impairment, C=controls, HTN= Hypertension

Table 2. Antioxidants and cognitive score assessments in hypertensives, hypertensives with cognitive impairment and apparently healthy normotensive individuals with intact cognition

Index	C (n=66)	NDH (n=81)	NDHCI (n=69)	P1	P2	P3	P4
Antioxidants							
GSH(µg/mL)	20.52±1.33	8.90±0.94	7± 0.89	<0.001*	<0.001*	≤0.001	0.438
SOD(ng/mL)	12.02± 0.53	9.67±0.70	5.04±0.97	<0.001*	0.028	≤0.001	0.007*
CAT(ng/mL)	402.99±17.2	285±5.49	81.70± 0.99	<0.001*	0.001*	0.001*	0.001*
Cognitive Score							
0-30	28.67±0.16	18.77±0.50	3.48±0.38	<0.001*	0.001*	0.001*	0.001*

*n=number of subjects, *=significant at p<0.05, P1=values obtained from ANOVA, P2= values compared between hypertensives and controls, P3= values compared between hypertensiveswith cognitive impairment and controls, P4=values compared hypertensives and hypertensives with cognitive impairment, , GSH=Glutathione, CAT=Catalase, SOD=Superoxide dismutase, 0=impaired and 30=unimpaired (cognitive score)*

Table 3. Inflammatory markers and cognitive score in hypertensives, hypertensives with cognitive impairment and apparently healthy normotensive individuals with intact cognition

Inflammatory Markers	C (n=66)	NDH(n=81)	NDHCI (n=69)	P1	P2	P3	P4
HS-CRP (mg/L)	0.11±0.00	0.12±0.01	0.14±0.00	<0.001*	0.149	<0.001*	0.001*
IL-6 (ng/mL)	51.41 ± 1.60	115.61 ±15.97	301.55 ±17.58	<0.001*	0.002*	<0.001*	<0.001*
ALB (g/dL)	4.91 ± 0.60	4.20 ± 0.40	4.10±0.52	<0.001*	0.001*	0.001*	0.919
Cognitive Score							
0-30	28.67±0.16	18.77± 0.50	3.48±0.38	<0.001*	0.001*	0.001*	0.001*

*Values are in mean±SD, N=number of participants, *=significant at p<0.05, P1=values obtained from ANOVA, P2= values compared between hypertensives and controls, P3= values compared between hypertensives with cognitive impairment and controls, P4=values compared hypertensives and hypertensives with cognitive impairment, ALB=Albumin, IL-6=Interleukin 6, Hs-CRP=High sensitivity C-reactive protein*

Table 4. Relationship of blood pressure, with markers of inflammation and antioxidants in hypertensives, hypertensives with cognitive impairment and apparently healthy normotensive individuals with intact cognition

Groups	Dependent	Predictors	β	t	P
NDH	SBP	HS-CRP	225.22	3.801	0.001*
		SOD	0.843	0.205	0.043*
NDHCI	DBP	GSH	0.406	5002.570	0.013*
Controls	SBP	HS-CRP	118.557	3.261	0.002*
		Catalase	0.024	2.882	0.005*
		GSH	0.347	3.224	0.002*

*β=standard coefficient, SBP=systolic blood pressure, DBP=diastolic blood pressure, HS-CRP=High sensitive C-reactive protein, SOD=superoxide dismutase, GSH= glutathione, NDH= Newly diagnosed Hypertensives, NDHCI=Newly diagnosed Hypertensives with cognitive impairment, t=student t test, p= probability, *=significant*

4. DISCUSSION

4.1 Impact of Socio-demographic Factors on Cognitive Function in Hypertensives Patients

The associations of marital status, occupation, alcohol intake and type of symptoms of hypertension were significantly different among NDH, NDHCI and Control ($p<0.05$). Marriage was associated with hypertension and cognitive impairment in this study contrary to the report of Feng et al. [21] that being single or widowed was associated with higher odds of cognitive impairment compared with being married. This may be linked with unresolved marital issues, issues with children, spouse attitude, lack of mutual trust and understanding, infidelity, fear of uncertainties and the likes. Predominantly, manual occupation throughout life has increased risk of cognitive impairment compared with those with higher intellectual requirements. This is in consonance with the work of Rebled et al. [22]. Heavy alcohol intake adversely affects the brain through neurotoxic and pro-inflammatory effects as well as micronutrient deficiency [23,24].

4.2 Inflammation and Oxidative Stress in Hypertension and Cognitive Impairment

Interleukin 6 and hs-CRP levels increased while albumin and Cognitive score decreased significantly from hypertension to cognitive impairment state. This suggests progressive inflammatory processes from hypertension to cognitive decline [25,26]. Significant reduction in the antioxidant level from hypertension to cognitive impaired state noticed in this study may be attributed to excessive production of reactive oxygen species (ROS) and the inflammation of the vasculature which could alter neurovascular dysfunction [27]. Additionally, the production of free radical is thought to be higher in cerebral tissue, which is particularly vulnerable to free radicals damage. There may be high content of polyunsaturated fatty acids in neuronal membranes and high oxygen requirements for its metabolic processes as well as reduced activities of specific mitochondrial enzyme complexes such as cytochrome oxidase and the presence of redox- active metals such as Copper (Cu) and Iron (Fe) [28].

Free radicals induce inflammation by activating redox-sensitive pro inflammatory transcription factors and endothelial dysfunction. This is pivotal in the pathogenesis of prostanoids, which promote vascular leakage, protein extravasations and cytokine production [28] Inflammation in turn enhances oxidative stress by up-regulating the expression of reactive oxygen species–producing enzymes and down regulating antioxidant defenses [29]. Vascular oxidative stress and inflammation impede the proliferation, migration and differentiation of oligodendrocyte progenitor cells and compromise repair of the damaged white matter [27] and consequently, cognitive impairment.

5. CONCLUSION

Increase in inflammatory biomarkers with decrease in antioxidants may facilitate the progression of hypertension to cognitive impairment in Nigerian hypertensive adults.

CONSENT

Informed consent was obtained from all participants.

ETHICAL APPROVAL

The Joint Ethical Committee of UCH/UI approved the research in line with the University and

international standard. The written ethical approval was collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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