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Oxidative Stress, Trace and Toxic Metal Levels in Alzheimer's Disease in Sub-Sahara Africa

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Abstract

Background: Alzheimer's Disease (AD), an age-related neurodegenerative disease characterized by loss of memory has been attributed to oxidative stress induced by accumulation of Amyloid Protein (Aβ) in the brain; environmental and genetic alterations have been implicated as the pathogenesis of the disease. This work investigated levels of selected trace (Iron, Zinc and Copper) and toxic (Cadmium and Lead) metals in AD patients.

Method: In this case-control study, a total of 38 participants (aged>60years) consisting of 18 clinically diagnosed AD subjects and 20 apparently healthy age-matched adults were recruited from the University College Hospital Ibadan Geriatric Centre. Semi-structured questionnaire was used to obtain demographic information, clinical history, lifestyle and dietary patterns from participants. Blood levels of iron, copper, zinc, lead and cadmium were analyzed using Atomic Absorption Spectrophotometry (AAS); levels of Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), Hydrogen Peroxide (H_2O_2), and Total Plasma Peroxide (TPP) were determined spectrophotometrically, while Oxidative Stress Index (OSI) and copper to zinc ratio (Cu:Zn) were calculated.

Results: Mean plasma level of zinc was significantly lower in cases (86.04 ± 11.07 µg/dl) compared to controls (108.80 ± 12.47 µg/dl), while blood lead (13.85 ± 2.96 µg/dl, 8.32 ± 2.10µg/dl) and cadmium (1.34 ± 0.71 µg/L, 0.71 ± 0.14 µg/L) levels were significantly higher in cases than in controls respectively. Although Fe and Cu levels were similar in cases and controls, Cu:Zn ratio was significantly elevated in cases compared to controls (p=0.000). Though other OS markers were not significantly different in both groups, TPP was significantly higher in cases [64.96 ± 7.20 µmol/H_2O_2 *vs.* 55.41 ± 2.38 µmol/H_2O_2) while MDA correlated inversely with TAC in cases (r= -0.477, p=0.045).

Discussion: The low plasma Zn coupled with high blood Lead (Pb) and Cadmium (Cd) levels may precipitate the elevated TPP and Cu:Zn ratio in cases. The reduced metallothionine defense of the system as indicated by the elevated Cu:Zn ratio in cases may also exacerbate this problem.

Conclusion: The damaging effect of increasing toxic metal levels may be accentuating development of oxidative stress facilitating the progression of AD.

Keywords: Alzheimer's disease; Oxidative stress; Trace metals; Toxic metal

Introduction

Background

The prevalence of age-related health problems is becoming an important public health concern as proportions of older individuals in populations worldwide grow [1]. Alzheimer's Disease (AD) is one of the most common age-related neurodegenerative diseases characterized by accumulation of a type of protein and its interplay with both environmental and genetic influences on the brain. Recently in 2013, studies by the Institute For Health Metrics And Evaluation [2] showed that of all causes of death, AD was ranked fifth among most years of life lost in developed countries. A global study on neurodegenerative diseases estimated that Alzheimer's and other dementias were responsible for about 3% of all deaths in 2013. The largest relative increases were seen mainly in developing regions such as Sub-Saharan Africa (Niger, Eritrea etc.) where greater than 200% increases were recorded between 1990 and 2013 [2]. Owing to the complex and diffuse aetiology of the disease, considerable effort has been directed towards identification of an effective strategy to not only manage but also prevent these devastating brain pathologies. Although oxidative stress remains a major player in the pathogenesis of AD, diagnosis and management of the disease remain a medical challenge especially in terms of relating causes to effects.

Oxidative stress is essentially a result of imbalance in oxidant/antioxidant equation in the body, the high oxygen demand of the brain makes it vulnerable to oxidative damage by Reactive Oxygen Species (ROS) [3]. The role of oxidative stress in neurodegeneration is well documented. AD is characterized by abnormal protein deposition in the brain, and the typical hallmark in most neurodegenerative disorders such as AD and Parkinson's Disease (PD) is the interactions of these proteins with free radicals and metal ions leading to their increased aggregation and oxidative damage [4]. Besides abnormal protein deposition, the lipid bilayer of the membrane is rich in polyunsaturated fatty acids and oxygen; it is therefore highly susceptible to lipid peroxidation leading to the generation of unstable end products, including aldehydes, such as Malondialdehyde (MDA) [5]. MDA is not only a product of oxidative damage to membrane lipids, it also drives the generation of oxidative stress by interfering with the antioxidant defense system. Some toxic trace metals (including Pb, Cd) have been reported to either facilitate production of oxidants by their toxicity [6,7,8] while some essential metals (including Fe, Se and Cu) may also become prooxidants when present in excess amount in the body [9,10].

Results of several researches have provided evidence that toxic metals can interact with DNA and proteins causing oxidative deterioration of biological macromolecules. Thus, the process of breakdown of metal-ion homeostasis has been reported in a plethora of diseases including neurological disorders [11-13].

Aside from generation of oxidants and ROS mediated by metal toxicity, the pathological hallmarks of AD include secretion/production of extracellular amyloid plaques and intracellular aggregates (neurofibrillary tangles). The major component of the amyloid plaques is the amyloid peptide Aβ, which results from the proteolysis of the Amyloid Precursor Protein (APP). APP is an ubiquitously expressed transmembrane protein exerting a critical role in neuronal growth and survival [14,15]. The crucial factor in Aβ toxicity in the pathogenesis of AD has been linked with the idea, that Aβ peptide can form free radicals through the generation of hydrogen peroxide [13]. This characteristic of Aβ is likely to derive mostly from its ability to bind metals and consequently, to mediate redox reactions [16,17]. In fact, Aβ1- 42 has been reported as a metallo-binding peptide with binding sites for Zn^{2+}, Cu^{2+} and Fe^{3+} [18]. The central tenet of Aβ toxicity is linked with the presence of redox metals, mainly copper and non-redox zinc [13,19]. Thus, the oxidative damage of Aβ is directly linked with the presence of redox metals, copper, and iron. Aβ has unusual high affinity for both transition metal ions copper and iron and has the capacity to reduce both metals and subsequently produce hydrogen peroxide and oxidized amyloid. This interplay between metals and oxidants in one hand with synthesis of Aβ protein is the ultimate focus of this work.

Materials and Methods

Recruitment of participants

A total of 38 participants consisting of 18 patients clinically diagnosed with AD were recruited as cases, while 20 age-matched adults without clinical manifestation of any neurological disorder were recruited as controls. Participants, aged ≥ 60years (cases and controls) were recruited from the University College Hospital Geriatric Centre, Ibadan. Diagnosis was made using the National Institute of Neurological and Communicative Diseases and Stroke based on Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) as diagnostic criteria for Alzheimer's dementia. Consenting adults above 60years of age without any history of AD, Parkinson's disease, amyotrophic lateral sclerosis, schizophrenia or bipolar disorder were recruited as control.

Collection of socio-demographic, anthropometric characteristics and clinical features of study participants

A structured questionnaire was used to obtain information on diet/lifestyle factors and other demographic and anthropometric indices like age, body weight, height, educational status, duration of AD, medical history, residential information and family history of participants.

Collection of blood samples for biochemical indices: Blood samples were collected from all participants for the determination of essential trace elements concentration (Cx) (plasma Fe, Se and Cu) and toxic (blood Cd and Pb) metals, as well as for the estimation of plasma levels of Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), Hydrogen Peroxide (H_2O_2), and Total Plasma Peroxide (TPP).

Laboratory methods and procedures

Determination of total antioxidant capacity: Total antioxidant capacity was estimated using the principle of Ferric Reducing Antioxidant Power (FRAP) as described by Benzie and Strain [20].

Determination of total plasma peroxide: Total plasma peroxide levels were determined using the ferrous oxidation (FOX2) method [21] with minor modifications [22].

Determination of malondialdehyde: Estimation of MDA was carried out using the method of Adam-Vizi and Sergi [23].

Determination of oxidative stress index: Oxidative stress index, an indicator of the degree of oxidative stress, was calculated from the above results as the percentage of Total Plasma Peroxide (TPP) to Total Antioxidant Capacity (TAC) values using the method of Harma et al., 2003 [24].

$$OSI\ (in\%) = [TPP\ (\mu mol\ H_2O_2)/TAC\ (\mu mol/L)] \times 100$$

Estimation of trace metals

Essential trace metals (Iron, Zinc and Copper) and toxic metals (Cadmium and Lead) were measured using Atomic Absorption Spectrophotometry (AAS) using Perkin Elmer Analytic Atomic Absorption Spectrophotometer. All the above laboratory procedures were performed following standard laboratory practices incorporating appropriate standards and controls.

Statistical analysis

Statistical Analysis was done using the Statistical Software Package for Social Sciences (SPSS) version 20. Data were subjected to shapiro wilk's test for normality prior to analysis. Quantitative variables were expressed as mean ± Standard Deviation (SD) and categorical variables as percentages. Independent samples t-test (two-tailed) was used to compare the means of the quantitative variables, while Chi-square test was used to test for association between categorical variables. Pearson's correlation was used to determine the degree of relationship between variables. Level of statistical significance was set at $p<0.05$.

Results and discussion

Levels of trace metals in cases and controls

Table 1 shows the comparison of mean levels of trace metals analyzed in cases and controls. The mean plasma levels of Copper (116.90 ± 19.67; 118.4116.72) and Iron (134.89 ± 22.69, 140.09 ± 23.22) were not significantly different between cases and controls (p=0.80, p=0.49) respectively. However, mean plasma Zinc level of 86.04 ± 11.07 µg/dL observed in cases was significantly lower than that of the controls, 108.80 ± 12.47 µg/dL (p=0.000). Mean blood lead (13.85 ± 2.96 µg/dL and 8.32 ± 2.10 µg/dL) and mean cadmium levels (1.34 ± 0.71 µg/L and 0.71 ± 0.14 µg/L) were significantly higher in cases than in controls (p=0.000, p=0.000) respectively.

To evaluate the metallothionine capability of the system, the copper to zinc ratio (Cu:Zn) was calculated; this was found to be significantly higher in cases than in controls (p=0.000) (Tables 1,2).

Table 1: Comparison of mean levels of trace metals in AD group and controls.

Variable	Cases	Controls	t-test value	p-value
Fe (µg/dL)	134.89 ± 22.69	140.09 ± 23.22	-0.697	0.49
Cu (µg/dL)	116.90 ± 19.67	118.41 ± 16.72	-0.255	0.8
Zn (µg/dL)	86.04 ± 11.07	108.80 ± 12.47	-5.924	0.000*
Pb (µg/dL)	13.85 ± 2.96	8.32 ± 2.10	6.696	0.000*
Cd (µg/L)	1.34 ± 0.71	0.71 ± 0.14	3.905	0.000*
Cu:Zn	1.36 ± 0.13	1.09 ± 0.16	5.52	0.000*

Note: *: p-values at least cases.

Table 2: Pearson's correlation matrix on oxidative stress parameters and trace metals in cases.

Variables	MDA (r)	TPP (r)	TAC (r)	OSI (r)	Fe (r)	Cu (r)	Zn (r)	Pb (r)	Cd (r)
MDA	1	-	-	-	-	-	-	-	-
TPP	-0.09 4	1	-	-	-	-	-	-	-
TAC	-.477*	0.222	1	-	-	-	-	-	-
OSI	0.434	0.062	-.933**	1	-	-	-	-	-
Fe	-0.25 2	0.059	0	0.039	1	-	-	-	-
Cu	-0.25 2	0.059	0	0.039	1.000**	1	-	-	-
Zn	-0.16 9	0.128	-0.10 3	0.132	.834**	.834**	1	-	-
Pb	-0.19 9	0.098	-0.09 4	0.157	0.196	0.196	0.414	1	-
Cd	-0.13 9	0.173	0.027	-0.02	0.112	0.112	0.021	-0.31 2	1

Note: *: Correlation is significant at the 0.05 level (2-tailed); **: Correlation is significant at the 0.01 level (2-tailed).

Table 2 shows the values of the various biochemical parameters were correlated using Pearson's method. OSI index value strongly correlated negatively with the TAC value, a strong indication of relevance of oxidative stress in AD.

Cu and Fe also correlated absolutely while strong correlations were also observed between Zn and Cu in one hand and Zn and Fe on the other. The relative importance of Zn for the various metabolic processes of Fe and Cu along with their interrelationship especially the production of metallothionein may be suggested by these findings.

Alzheimer's Disease (AD) remains the leading cause of dementia in the older population, and stands as the fourth highest cause of disability and death in the elderly [25]. One of the major clinical features of AD is the chronic decline in cognitive function and overall poor daily living. Cognition, a major clinical feature of AD, has been linked with the delicate balance in the biochemical milleu of neurons, which is also related to neuronal oxidant/antioxidant balance [26]. This study investigated the relationship between oxidant/antioxidant levels and some environmental trace and toxic metals reported to impact on the maintenance of this oxidative balance; the possible contribution of trace and toxic metals in the pathogenesis of several neurodegenerative conditions including AD in this environment was therefore examined.

Zn is one of the essential trace metals that modulate oxidative damage activities in the body. In the brain, metallothionein, the active antioxide form of Zn, is expressed as MT-3, and is a key antioxidant in the blood-brain barrier capable of binding to and preventing brain exposure to cadmium, mercury, arsenic, copper and other toxic metals. There have been several reports on the contribution of trace metals in the generation and neutralization of ROS *in-vivo* [27].

In this study, plasma zinc levels in AD were significantly lower than that of controls; this corroborates the findings in different studies [28,29]. The brain has been reported to be second only to the beta cells of the pancreas to contain the highest concentration of zinc [30], where it performs diverse roles in key processes such as enzymatic activity, neurotransmitter release and modulation of gated ion channels for synaptic transmission [31]. However, different studies have reported the antagonistic role of Aβ protein, an established macromolecule known to facilitate the development of AD by accumulating zinc ions in different studies on AD making Zn unavailable to protect the neurons through the formation of metallothionein complex [32,33]. Hence, the low zinc levels in this study may therefore be attributed to the zinc binding ability of the Aβ protein abundant in AD subjects. In normal physiology, zinc is released from the neocortical glutamergic synapse which is readily exchangeable with plasma zinc pool [34]. Mechanistically, as Aβ in AD brains continue to trap and accumulate zinc in these synapses, it creates a gradient that favors movement of zinc into the synaptic pool which in turn depletes zinc from the plasma zinc pool. This is supported by the findings [35], where low plasma levels of zinc in AD patients returned to normal levels after treatment with zinc binding compound, Clioquinol, which also have Aβ disintegrating properties.

Also, zinc deficiency has been associated with increased levels of oxidative damage including increased lipid, protein and DNA oxidation [36]. Hence, as an antioxidant, zinc at physiologic

concentrations protects the body's sulfhydryl pool directly by antagonizing other redox active metals (e.g. copper) or indirectly by serving as a cofactor for key antioxidant enzymes such as Cu/Zn-SOD [36]. Although an equivocal relationship of Zn in the development of AD as reflected by its non-significant relationship with OS markers was seen in this study, this may be more in consonance with previous works that questioned the link between this micronutrient and the development of AD [30]. It may also be attributed to strict compensatory mechanisms of the body that always maintain serum concentrations of trace essential metals such as copper and zinc at a given physiological ratio often expressed as copper:zinc ratio (Cu:Zn) [37]. Hence, the expression of copper as a ratio to zinc towards establishing the interplay of the two micronutrients in OS pathogenesis of AD becomes important. Previous work showed evidence that an increase in Cu:Zn was associated with several chronic age-related diseases [38] and systemic OS [39]. Thus the observed significantly increased Cu:Zn in AD patients in comparison to controls in this study may be worthy of note. Elevated Cu:Zn has been associated with mortality in the elderly and reflects an inflammatory response [38]. Since Zn is an important element that maintains the level of metallothionein which has been severally established as a major antioxidant in the brain, a reduction in its level especially in the presence of an increase in levels of Cu and Fe may facilitate the oxidant tendencies of Cu and Fe. This may therefore largely explain the progression of AD especially with respect to increase in cognitive dysfunction. This may then be exacerbated by several other mechanisms during inflammatory conditions driving an increase in plasma concentration of copper at the expense of zinc as reported by others [40].

Discussions on the role of iron and copper in the pathogenesis of AD may be said to be interrelated. Studies on iron and copper in AD have shown that excess of both metals stimulates hydroxyl radical formation *via* the Fenton reaction, which may contribute to increased OS in AD [41]. Though in this study, plasma copper levels were not significantly different in both groups, reports on the role of copper in AD pathogenesis remain largely equivocal [42-44]. Also, the non-significant difference in plasma iron levels in cases and controls as seen in this study is similar to results of some meta-analysis which reported unchanged or reduced plasma iron levels in AD patients compared to controls [45,46]. Notwithstanding, the increase in Cu:Zn ratio observed may largely precipitate the toxicity of both Cu and Fe especially in advanced age as seen in participants in this study.

Lead in biological systems is a neurotoxicant and a risk factor for neurodegenerative diseases [47]. The significantly elevated Blood Lead Levels (BLL) observed in AD patients in this study was consistent with findings of a similar study [48]. Environmental exposure to pollutants has been reported as veritable source of Lead contamination [49]; hence, the elevated BLL observed in AD patients in this study may be attributed to the higher proportion of AD patients living in low-income residential areas/slums (88.9%) and/or with houses closer to tarred roads (50%) than in the controls. Previous works also observed that exposure to leaded gasoline in persons living near major roads was associated with an increased incidence of dementia (also a known age related neurodegenerative disease) [50].

Leaded gasoline is one of the possible sources of environmental lead exposure. This is quite veritable in Nigeria with an average lead content of 0.66 g/L of gasoline in the country [49,51]. This, in conjunction with the high proportion of poorly maintained second hand vehicles common in Nigerian cities [49], may contribute significantly to environmental pollution *via* release of large quantities of incompletely combusted hydrocarbons in exhaust fumes, which release high percentage of lead into the atmosphere [52]. This is further supported by the evidence that distance from roadways has been found to be inversely correlated with soil lead concentrations and human BLL [53,54]. Vocational engagement has also been linked to the development of neurodegenerative diseases; a significant proportion of the AD patients (61.1%) were found to be engaged in unskilled labor, which has also been associated with an increased risk of exposure to toxic metals [55].

That elevated blood cadmium levels as observed in this study may predispose subjects to AD has also been previously reported [56]. This is further supported by a larger scale study conducted on a US-based population [57]. Since mode of exposure of cadmium in human is similar to that of Lead, engagement in unskilled labor and living in low-income, traffic prone areas may be the plausible link between elevated blood cadmium levels and AD in this study. Previous work also reported that road traffic associated emissions of metals such as cadmium from vehicle parts (such as tyres and brake linings) remain major sources of exposure to Cd in environmental pollution [58].

However, the level of blood cadmium in AD patients in this study was much higher than that observed (1.34 ± 0.71 ug/L *vs.*~0.6ug/L). Orisakwe, in a review [59], argued that Nigeria like most developing nations, is awash with heavy metals. This is backed by findings in environmental studies conducted in different parts of the country [49,60-62].

In this study engaging in unskilled labor, living in local residential areas/slums or closer to tarred roads were mostly associated with AD. A significant association between menial low skill occupations and AD dementia has been previously reported [63] while traffic-related air pollution has been reported to be associated with increased risk of developing AD dementia (Hazard Ratio=1.6) [64].

Though genetics is one of the major risk factors for developing many neurological diseases, AD was not associated with family history of the disease in this study. This may indicate that the development of AD in this environment is either sporadic or may have been previously overlooked by families of affected individuals as part of the normal ageing process. In conclusion, oxidative stress may be linked as the pathogenesis of AD in participants as seen from results of this study, this might have been precipitated by the residential and vocational dispositions. However, the progression of the disease may largely be due to an increase in the Cu:Zn ratio making the brain more vulnerable to the damaging effect of the antioxidants accumulating in the process.

Conclusion

AD has been known to be associated with accumulation of oxidants with its deleterious effect especially in the brain. However, progression of this disease is accentuated by an imbalance in levels of essential elements some of which may become pro-oxidants thus increasing the pool of oxidants and thereby accentuating progression of the disease. Environmental factors may also be playing significant role in the development of essential metal imbalance with its attendant problems. In this study, genetic manipulation may not be playing a significant role in AD development in spite of its prevalence while the low awareness of the disease may be due to the level of public health knowledge.

Declarations

Ethics approval and consent to participate

Approval was obtained from the University of Ibadan/University College Hospital joint ethics committee. (Approval No: UI/EC/18/0152)

Consent for publication

All authors agreed that the manuscript be published in BMC

Availability of data and materials

Materials and data in this manuscript can be made available to the public

Competing interests

There are no competing interests between authors and with any other party.

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Authors' contributions

Ishiaq olayinka omotosho supervised the work and wrote the manuscript; Michael roland ngwube carried out the laboratory analysis including statistical analysis of the results; Jibril omuya abdul malik out the clinical aspects of the work, recruited participants and reviewed the manuscript.

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