

Selenium Levels in Alzheimer's Disease: A Study from Kerala

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Abstract: *Oxidative stress resulting from free radicals released during metabolism is among the major pathophysiological processes responsible for Alzheimer's disease (AD). As a component of the antioxidant defence system, selenium plays a significant role in combating oxidative damage. Alterations of selenium concentrations in plasma and brain are hypothesized to affect the neurodegenerative process and dietary supplementation has been proposed as adjunctive treatment. Studies of plasma selenium concentrations the world over, have yielded conflicting and inconsistent results. Our aim was to analyse plasma selenium levels among AD patients in this region. Using a prospective case-control design, plasma selenium level of 30 patients and 30 controls was estimated using Inductively Coupled Plasma-Mass Spectrometry. Selenium levels were found to be elevated in patients compared to controls but did not reach statistical significance. Selenium supplementation is unlikely to benefit AD patients from Central Kerala.*

Keywords: selenium, Alzheimer's disease, oxidative stress

1. Introduction

Dementia affects 50 million people worldwide, the majority in middle and low-income countries. This number is projected by the WHO to reach 82 million in 2030 and 152 million by 2050.[1] In 2015 it was estimated that 4.1 million people in India had dementia; this was expected to double by 2030 and treble by 2050. [2, 3] In Kerala, a community survey of 2466 individuals found the age-adjusted prevalence of dementia to be 4.86% in people over 55 years and 6.44% in over 65-year-olds. [4] After 8 years follow-up, incidence of Alzheimer's dementia (AD), was reported to be 11.67 per 1000 person-years for those over 55 years and 15.54 for those ≥ 65 years. [5] Thus dementia, already a major public health problem, will worsen dramatically in coming decades.

The preponderance of dementia patients have AD or vascular dementia. Often Alzheimer and vascular pathology occur in combination.[6] Genetics, lifestyle, diet and exercise, all contribute to the etiopathogenesis of AD but oxidative stress plays a major role. Free radicals including reactive oxygen species (ROS) and nitrogen species (NOS) released during metabolism react with lipids, proteins, nucleic acids, and other molecules to damage tissue.[7] Antioxidant molecules and enzymes prevent or repair oxidative damage but increase in free radicals or depleted cell -defence mechanisms can exacerbate oxidative stress. The brain is particularly vulnerable since its antioxidant system is relatively deficient. [8]

Selenium (Se), an essential micronutrient, is vital to the antioxidant network. As selenocysteine, Se is a component of the enzymes glutathione peroxidase (GPx) and thioredoxin reductase which are powerful free radical scavengers responsible for reducing and detoxifying hydrogen peroxide. Selenoprotein P (SeIP), a selenium transport protein, functions as an antioxidant in extracellular

space. High concentrations of SeIP in the brain suggest an important physiological role. In post-mortem tissue from Alzheimer patients, SeIP immunoreactivity has been shown to co-localize with amyloid- β plaques and neurofibrillary tangles that are the histopathological hallmarks of the disease.[9] Variations in selenium level in blood and brain have been postulated to affect the antioxidant defence mechanisms, thereby influencing the pathogenesis and progression of AD. Studies of plasma selenium concentration in AD patients are few, especially from India, and have yielded conflicting results. This study aimed to evaluate levels of plasma Se in AD patients from central Kerala.

2. Methods and Materials

This Case-Control study was approved by the Institutional Ethics Committee.

Inclusion Criteria

Patients in the age group 40-90 years diagnosed with AD in the Neurology Department of the hospital and healthy individuals in the same age group to serve as controls, were recruited after obtaining voluntary, written, informed consent.

Exclusion Criteria

Subjects suffering from any major illness and those on selenium-containing supplements were excluded.

Methods

The sampling procedure used was purposive sampling. Demographic and clinical data were entered into a structured proforma. For selenium estimation, 2ml of blood, drawn using sterile techniques in EDTA tubes, was centrifuged at 3000 rpm for 15 minutes. The plasma collected in microvials was refrigerated at -40°C . Selenium concentration was

estimated using Inductively Coupled Plasma – Mass Spectrometry.

Statistical Analysis

Data were analysed using Statistical Package for Social Sciences (SPSS20.0). Comparison of means between the cases and controls was done using the Independent sample T- test.

3. Results

The 60 subjects included 30 (17 males and 13 females) diagnosed with AD and 30 controls (18 males and 12 females) between 40-90 years. The Table shows the comparison of mean plasma Selenium Concentration among AD patients and controls.

Table 1: Comparison of mean plasma selenium between cases and controls

	Alzheimers Disease	Controls
Number (n)	30	30
Age in years (mean ± standard deviation)	71 ± 6	59 ± 8
Gender		
• Male	17	18
• Female	13	12
Plasma selenium level (µg /L)		
• Range	18-190	53-141
• Mean	110.83	100.07
• Standard Deviation	39.67	17.94
Independent T test , T Value	-1.354	
P Value	0.181	

Mean selenium levels were higher in Alzheimer's patients compared with controls but the difference in means did not attain statistically significance at $p < 0.05$.

4. Discussion

Studies of Se levels across the world have reported inconsistent and often conflicting results with significant variation among populations. [10,11] A Swedish paper showed high plasma levels of Se and other metals in AD [12] while Se levels were not significantly different from the normal population in studies from France and Coimbatore, India. [13,14] Cardoso et al., found low dietary levels of Se in AD patients from Brazil compared to controls; levels of plasma, erythrocyte and nail Se were correspondingly low. [15] These findings were not replicated in Australian patients who had adequate dietary Se intake, although erythrocyte Se levels were low in patients with AD. [16, 17] Plasma Se levels were low in a study from Turkey [18] as were Selenium and zinc levels in hair of AD patients in another Turkish cohort. [19] A later study from Brazil, found higher concentrations of copper and iron in AD but no significant difference in selenium level. [20] Plasma selenium concentrations in patients from AD have not previously been published from Kerala. As in the Swedish study [12] greater levels were found in our patients compared with controls despite the mean age being higher. Cordoso et al had reported that selenium levels declined with advancing age. [8]

Methodological issues may also confound interpretation. Vinceti et al have questioned the reliability of the case-control design in assessing the role of Selenium. In a case-control study, AD risk was inversely correlated with inorganic selenium and with the selenoprotein P-bound organic form but directly correlated with other organo-selenium species suggesting compensatory selenoprotein upregulation following oxidative stress. A previous cohort study including a partially overlapping participant population had suggested an increased AD risk associated with inorganic selenium but this was not replicated in the case-control study. [21] Statistical attempts to resolve the issue through meta-analysis have concluded that plasma, RBC, CSF and brain tissue selenium concentration is lower in AD patients as compared to controls and that this decrease in selenium had direct correlation with GPx levels. [22]

As with other neurodegenerative diseases, the genesis and progression of AD depends on multiple factors. Except in families where it has been linked to a single gene, dissection of the interlinked genetic and environmental factors in disease causation is complicated. Regardless of the initiating insult, the integral presence of selenium in the antioxidant defence mechanism of the body suggests that variations in plasma and tissue Selenium levels could affect the progression of AD.

Both selenium deficiency and toxicity have been reported to be linked to neurodegeneration. Decreased concentrations have been detected in AD brain homogenates compared to controls and the APOE ε4 allele correlated with lower total selenium levels in the temporal cortex and a higher concentration of soluble selenium [23]. On the other hand, selenium treatment has triggered apoptotic degeneration in a human neuronal cell line in-vitro, suggesting that excess exposure to Se may also represent a risk factor for neurodegenerative disease. [24] Working on the hypothesis that insufficient supply of selenium to antioxidant enzymes in the brain may contribute to AD, Cardoso et al found that supranutritional selenium supplementation was well tolerated and effective in increasing CSF selenium, distributed across selenoproteins and inorganic species.[25] However, dietary selenium supplementation in AD has also been the subject of mixed reviews. Aaseth et al suggest that selenium supplementation for patients with MCI may be useful in preventing progression to AD [26] while Loeff et al conclude that the evidence only allows 'speculation on a potential preventive relevance'. [27]

Geographical and racial differences have to be factored before considering selenium supplements in AD. Selenium levels are affected by dietary Se content which is influenced by the soil concentrations, geographical location, seasonal changes, protein content and food processing. [10] Normal concentrations can therefore vary in different populations. Seafoods and organ meats are rich sources of selenium which is also present in muscle meats, dairy products, cereals and grains.[28] Since these are staple foods of the local population, low dietary selenium levels would not be expected to be a risk factor for neurodegenerative diseases in Kerala. This was confirmed in our study and our results do not argue favourably for dietary Selenium supplementation

as a strategy for slowing progression of AD in patients from Central Kerala. A study with a larger patient sample is advisable before dismissing any role for Selenium in the pathogenesis and progression of Alzheimer Disease.

5. Conclusion

Selenium levels in the serum of the AD patients were found to be elevated in patients compared to controls but did not reach statistical significance. A study with a larger patient sample is advisable and the association between high serum levels and disease progression needs to be explored further.

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