

Original Research Article

Risk factors, comorbidities, and social factors associated with alzheimer disease - An observational study from eastern India**Shankar Prasad Nandi^{1*}, Ratul Banerjee²**¹*Assistant Professor, Department of Neurology, Bankura Sammilani Medical College, West Bengal, India*²*Demonstrator, Department of Pharmacology, R G Kar Medical College, Kolkata, West Bengal, India***Received: 24-11-2021 / Revised: 16-12-2021 / Accepted: 07-01-2022****Abstract**

Alzheimer Disease (AD) is the most common type of dementia worldwide and is a progressive neurodegenerative disorder that results in diminished quality of life and caregiver stress. Although it is not possible to completely prevent the disease with current therapy, several associated comorbidities as well as social and risk factors can be addressed and managed if required. Our study attempts to clarify and delineate the comparative occurrence of these factors in patients presenting with AD and those presenting for other neurologic problems. The results show that diabetes, hyperlipidemia, cerebrovascular disease, and depression are strongly associated with dementia, suggesting etiologic factors and opportunities for timely intervention. Hypertension, dietary factors, occupational factors and marital status did not show a significant correlation. Limitations of the study include the overall elderly population with commonly occurring comorbidities and confounding factors. This study underlines the importance of treating modifiable risk factors with the hope of slowing down or preventing the development of dementia.

Keywords: dementia, Alzheimer Disease, hypertension, cognitive, diabetes, social, occupational factors, diet, ischemic stroke

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Introduction

Alzheimer Disease (AD) is the most common type of dementia and it usually begins with loss of recent episodic memory and progresses to involve other cognitive domains including visuospatial processing and language. Although significant advances have been made in recent times in the molecular biology and pathogenesis of AD, the preventive aspects of this disease have largely remained in the dark, owing to the paucity of epidemiological data about the modifiable and nonmodifiable environmental, social, dietary and occupational risk factors involved in the causation and progression of this dreaded disease. This becomes all the more important because of the limited treatment options available once this disease has begun its inexorable progression. It is intuitive to think that like some other chronic neurodegenerative diseases, the occurrence or at least the more distressing manifestations of AD might be influenced by such environmental factors.

In this study, we have made a cross-sectional and retrospective study of environmental, social, dietary and occupational factors in a cohort of patients with AD presenting to the Neurology OPD of a teaching hospital serving mainly semi-urban and rural patients.

AD is the most common type of dementia, accounting for an average of 70% of cases in most published studies[1]. This disease has a high impact on the quality of life of not only the patient, but also in the family and among caregivers. It begins with affection of memory and language, and progresses to involve visuospatial functions and ultimately leads to behavioral and psychotic manifestations that are very difficult to manage[2]. The gradual but inexorable progression of the disease in patients causes breakdown of the personality in the patient, causes financial loss to the family, and puts extreme degress of stress on caregivers[3]. Previously considered a near-incurable disease, recent advances have shed some hope for these patients[4]; however we should pay attention to environmental, social, occupational, nutritional and dietary factors since these may provide

us avenues to prevent the disease, or at the least give insights into the multiple modes of pathogenesis of this disease[5]. We have designed this observational, retrospective study such that the relative importance of these factors are highlighted based on the frequency of their occurrence in patients presenting with Alzheimer Disease in the Neurology OPD of a large teaching hospital in eastern India.

There have been several large studies that have explored education, occupation and cognitive reserve as risk factors in AD[6, 7]. We have investigated these variables in our patients as well as dietary and nutritional factors[8] (including vegetarianism), level of education, occupation, marital status, living alone versus with family, depression, sleep, and so on as described below. We also studied, although in brief, the impact of obesity, dyslipidemia, hypertension, and diabetes mellitus[9] in our study cohort.

Methodology

This study was carried out in a Bankura Sammilani Medical College situated in the state of West Bengal in eastern India, from June 2017 to July 2019. We evaluated 326 cases of Alzheimer Disease, which included 209 males and 117 females. The mean age of the men was 68 years and the women 76 years. Control populations were taken from the general mass of the public restricted to the age group of 60 years and above attending the Neurology OPD for any issue, and comparisons were drawn from these groups.

The following factors were considered and appropriate records kept: a) manual versus intellectual occupation b) rural versus urban c) cerebrovascular disease d) type 2 diabetes e) hypertension f) obesity g) dyslipidemia h) smoking i) vegetarianism j) marital status k) depression l) lack of adequate nocturnal sleep m) physical activity n) miscellaneous dietary factors o) vitamin D levels in the serum p) estrogen replacement therapy in women.

Some of the information was gleaned through the use of history taking and the physical and neurologic examination of the patient, whereas past medical records and necessary biochemical investigations were done where required.

Randomization of the study and control groups was done using the software Research Randomizer offered by the Social Psychology Network.

*Correspondence

Dr. Shankar Prasad Nandi

Assistant Professor, Department of Neurology, Bankura Sammilani Medical College, West Bengal, India

E-mail: drspnandi@gmail.com

Diagnosis of Alzheimer Disease

The NINCDS-ADRDA Criteria for the diagnosis of AD were used to identify patients in our study[10]. For the purposes of this study, it was considered too complex to categorize patients according to the cognitive domain most affected, so this part was left out. Presence of prominent behavioral manifestations was likewise ignored.

Factors under study

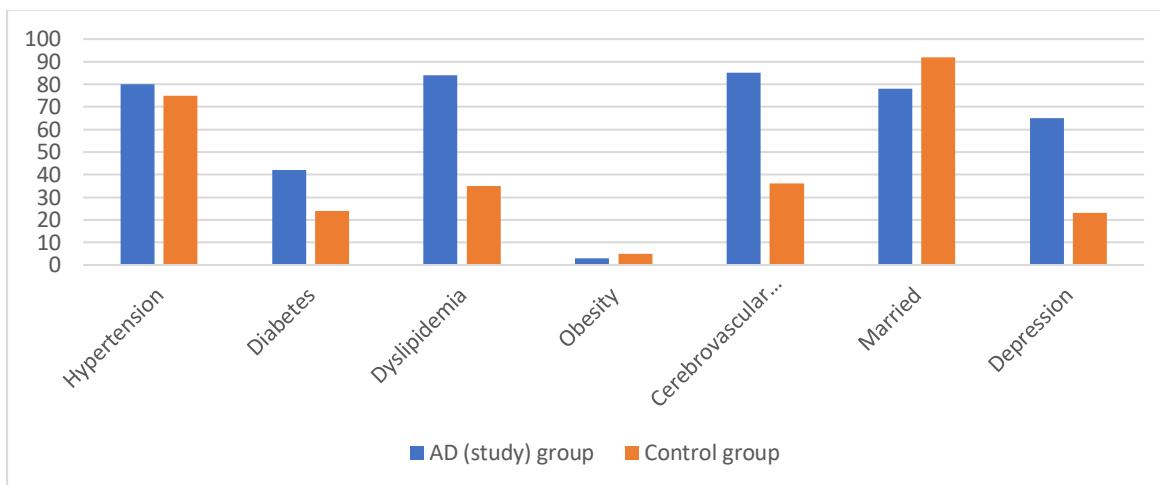
Rural residence was considered if the patient lived in a community mainly engaged in agriculture. Cerebrovascular disease was considered present if there was clinical or imaging evidence of an ischemic stroke in the past at any time. Nocturnal sleep adequacy was based on the patient's own subjective assessment. Similarly for physical activity, in which patients were classified as physically active or inactive based on their own perceptions and occupational and recreational physical activity. Miscellaneous dietary factors included intake of fruits and green leafy vegetables rich in antioxidants, assessed amount of protein in the diet, as well as fish and milk intake. Other parameters were defined in accordance with standard diagnostic and cut-off criteria.

Results

Sixty-four percent of patients had urban residence whereas in the general population of patients attending the OPD, 24 percent had urban residence. 94 percent of patients had current or former white-collar occupations, whereas the rest were engaged in occupations such as agriculture requiring mainly manual labour. In the control group, however, the percentage of manual and non-manual occupations was almost evenly divided. Type 2 diabetes was present in 42% of patients and 15% in the control group. Hypertension was present in 80% of AD patients and in 75% of the control group. Dyslipidemia was present in 84% of AD patients but only in 35% of the control

group. Obesity, defined as a Body Mass Index (BMI) above 30, was present in 3 percent of AD patients and 5 percent of the control group. Cerebrovascular disease, defined by a documented past ischemic stroke, was present in 85% of AD patients and 36% among the control population. Only 5% approximately of the AD cohort was vegetarian, mainly for religious and cultural reasons, whereas in the control group the percentage was 2%. Marital status was as follows: 78% of the study population was married, whereas the rest were either single or widowed, mostly the latter; in the control population, 92% was married. 65% of the study population had a current or previous diagnosis of depression as diagnosed by a psychiatrist, whereas it was 23% in the control group. Sixty-three percent of patients in the study group reported inadequate or fragmented nocturnal sleep whereas 32% of patients in the control group reported the same. Estrogen replacement therapy was difficult to assess due to inadequate comprehension and medical records so an average estimate was taken in the female patients and controls of course, which yielded a figure of 2% in both study and control groups. Dyslipidemia was taken on an arbitrary cut-off level of either LDL-C more than 120 mg/dL or triglycerides more than 180 mg/dL. It was found that 56% of the AD patients had dyslipidemia compared to 24% in the controls. Vitamin D deficiency was found in 88% of patients and 43% of controls. Physical activity assessment was done according to subjective assessment of the patients themselves. 14% of AD patients reported regular physical activity, compared to 68% of the control group. Miscellaneous dietary factors were assessed on an individual level, which included: 16% of the AD patients reporting dietary fads, inadequate protein intake, inadequate or absent green leafy vegetable and fruit intake, whereas none of the subjects in the control group gave any such report.

The important results are given in the following bar chart:



Discussion

We found, in general, that the following factors showed a large difference in occurrence between the study and control groups, indicating that these factors might have a bearing in either being part of the cause of AD or dementia in general in our patients or might be considered predisposing factors that enable the cognitive reserve of the patient to be affected to the extent that dementia becomes evident.

a. Patients in the AD group were found to have approximately twice the prevalence of diabetes mellitus type 2 compared to the control group. Several animal studies have shown how both insulin resistance and insulin deficiency stimulate β and γ -secretases, as well as reduce $A\beta$ clearance[11]. In the 1990s, the Rotterdam Study[12] found that type 2 diabetes almost doubled the chance of dementia and AD. Insulin resistance causes hyperphosphorylation of tau protein, leading to neurofibrillary

tangle (NFT) formation[13]. The Honolulu-Asia Aging Study also found that diabetes in old age was related to a higher risk of AD (relative risk 1.8) and AD pathology on autopsy, particularly in subjects with the APOE- $\epsilon 4$ allele[14]. There is some evidence that metabolic syndrome (abdominal obesity, hypertension, hypertriglyceridemia, and insulin resistance) might be more relevant to AD association rather diabetes alone[14]. Our study, however, did not consider the additive effect of the metabolic syndrome cluster but dealt with the individual factors separately. In addition, $A\beta$ peptide may undergo non-enzymatic glycation, making it an AGE more neurotoxic than its non-glycated form[15].

b. We did not find any major difference in the prevalence of hypertension among AD and control patients, which could be due to the high prevalence of hypertension in the age group

chosen for both study and control groups. The relation between hypertension and dementia is often counterintuitive. One the one hand, patients with dementia have lower blood pressure than controls[16], whereas longitudinal studies have shown that the presence of elevated blood pressure is associated with increased likelihood of developing dementia later in life. This phenomenon has been termed mid-life hypertension and late-life dementia.

- c. Patients with AD in our study were found to have more than twice the prevalence of dyslipidemia compared to controls. This is in accordance with other studies, one of which[17] found 10% higher cholesterol levels in AD patients than in healthy subjects. The main mechanism by which high blood cholesterol predisposes to the development of dementia is by compromising the integrity of the blood brain barrier. Dyslipidemia also causes increased A β peptide deposition, NFT formation, neuroinflammation [18], dysfunction of cholinergic pathways[19], and microhaemorrhages.
- d. We did not find any significant difference when obesity was considered. This was perhaps due to the low prevalence of obesity in the patients attending our OPD according to community characteristics. Studies about obesity in dementia have yielded rather heterogeneous findings. A major study conducted by Fitzpatrick et al[20]. showed that obesity in middle age is a risk factor (hazard ratio - HR: 1.39; 95% CI: 1.03–1.87) but in later life is associated with a lower risk of dementia (HR: 0.63; 95% CI: 0.44–0.91).
- e. Cerebrovascular disease showed a high degree of correlation with dementia in our study. This is also in line with previous studies that showed a high magnitude of amyloid angiopathy and small vessel arteriolosclerotic disease in postmortem analyses of the brains of AD patients. There is a so-called 'double-stroke' theory of AD, in which the 'first stroke' caused oligemia in brain tissue leading to neuronal damage by amyloidogenic and non-amyloidogenic pathways. In the amyloidogenic pathway, there is increased expression and processing of APP[21], resulting in accumulation of A β peptide. The damage to blood-brain barrier leads to decreased clearance of A β peptide.
- f. We found a small difference in the marital status between the study and control groups which is likely to be significant because the vast majority of population attending our OPD have a married status. Håkansson et al in 2009[22] showed that widowed or never-married individuals have a higher chance of developing dementia from all causes, especially in carriers of the APOE ϵ 4 allele. This has also been linked to the lower occurrence of depression in married individuals.
- g. We found a significantly higher incidence of depression in our dementia patients compared to the controls, more than twice as much. In previous studies[23] the question as to whether depression is a consequence, cause or coincidence as far as dementia is concerned, has been addressed without definitive answers.
- h. Insomnia, coupled with psychosis and behavioral agitation, were found to be common in our AD patients, although we did not accurately quantify the differences between cases and controls with regard to this variable, mainly due to the difficulty in objectively assessing these factors based on the history taking. Studies have shown increased risk of dementia in the presence of sleep disorders[24], especially REM sleep disturbances[25].
- i. Other factors that we studied, miscellaneous dietary factors like vegetarianism, intake of milk products, fruit and green leafy vegetable intake, and serum vitamin D levels, did not yield any significant difference beyond a few percentage points in our study between the study and control groups, and are thus not tabulated or described in further detail.

Limitations of the study

There were certain limitations of our study which could be diminishing factors in drawing conclusions about the role of the factors studied in their association with Alzheimer Disease. One, the population from which the study and control groups was drawn consisted of patients with sundry illnesses presenting to the OPD with various neurologic complaints not all of which were related to cognitive dysfunction. Second, the study and control group participants were all in the elderly group. Thirdly, since the general mass of patients in our OPD come mainly from the lower middle and lower socioeconomic groups, the perception of dementia in such persons is likely to have a higher threshold than in highly educated and affluent persons in whom family members or the patient himself/herself is able to detect the onset of cognitive impairment at an earlier stage.

Conclusions

The effect of modifiable or partially modifiable risk factors in cross-sectional Alzheimer Disease have been evaluated in many investigative and observational studies. The time preceding the development of cognitive deterioration, that is, late middle age, is of paramount importance because it is at this stage that the proper control of risk factors like hypertension, diabetes mellitus, hyperlipidemia, adequate treatment of depressive disorders, and a healthy balanced diet and active lifestyle can be modified. This study highlights the importance of using these opportunities to at least partially offset or delay the development of dementia in the future. Even beyond that, the proper control of conditions like hypertension and diabetes will go a long way in improving overall quality of life and life expectancy in these patients, irrespective of the development of dementia.

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