

Comparison of Cognitive Symptoms in Subtypes of Alzheimer's disease (AD)-a study from South East Asia (Kashmir, India)

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Abstract

Background: The heralding of baby boomers and a subsequent surge in elderly population, has led to immense research in unravelling the mysteries in the geriatric age group with Alzheimer's disease (AD). Alzheimer's disease (AD) is a neurodegenerative disorder with varied cognitive dysfunctions. However no comprehensive study has been carried out in South East Asia (Kashmir, India) to investigate cognitive symptoms in subtypes of AD.

Objectives: To assess cognitive symptoms in subtypes of AD in Kashmiri (Indian) population.

Material and Methods: The study was conducted in Memory Clinic of Postgraduate Department of Psychiatry, Government medical college, Kashmir (India) from January 2012 to March 2014. The diagnosis of AD patients was done according to NINCDS-ADRDA criteria. A total of 80 patients of AD were screened (40 with age of onset less than 65 and 40 with age of onset greater than 64). Patients with age of onset less than 65 were called as Early Onset Alzheimer's disease (EAD) and patients with age onset greater than 65 were called as Late onset Alzheimer's disease (LOAD). MMSE (Mini Mental State Examination), CDR (Clinical Dementia Rating) and various other neuropsychological tests like verbal digit span, verbal fluency, the 15-item Mini-Boston Naming Test (Mini BNT), 10-item Auditory Verbal Learning Test, Constructions, calculations, and similarities from the Neurobehavioral Cognitive Status Examination were assessed in all the patients. The data was analysed using paired t test.

Results: The mean age of EAD and LOAD was 63.10 and 84.28 respectively. There was significant difference in MMSE of both of the groups and was found to be statistically significant ($P < 0.05$). Patients in the EAD group performed better than the LOAD group on all the tests of motor-execution ($P < 0.05$). LOAD group had lower mean score of verbal fluency compared to EAD group.

Conclusion: Wider dysfunctions in cognitive symptoms were present in LOAD compared to EAD.

Keywords: Late onset alzheimer's disease (LOAD); Early onset alzheimer's disease (EAD); National institute of neurological and communicative disorders and stroke-alzheimer's and related disorders association (NINCDS-ADRDA).

Introduction

Alzheimer's disease (AD) is the most frequent and prevalent form of dementia and is an international health problem, especially in a developing country like India [1-3]. AD is a neurodegenerative disorder that begins initially in the mesial temporal region and progresses to other brain regions subsequently. It is characterized by loss of memory and presence of cerebral atrophy, extracellular amyloid plaques, intraneuronal neurofibrillary tangles [3-6]. The condition affects 5% of the population age over 65 years and more than 20% of the population with age greater than 85 years. The most important risk factor for AD is increase age. The prevalence of AD doubles every 5 years (after age 65.2 years). Further the prevalence of AD in LOAD (in individuals over age 70.3) was found to be 2.3 million in 2002. The prevalence of AD in patients of age 65 or over was 4.5 million in 2000

in U.S. The prevalence was latter updated to 5.3 million in 2008. The prevalence of AD in the world is estimated to be around 35.6 million in 2010. The figures for the future are exceeding with estimated 65 million in 2030 affected with AD and 115 million in 2050 affected with AD. Thus making AD a global health concern for the world [2,5,6]. The prevalence of AD in our country has been difficult to estimate, although some studies estimate 37 lakh Indians affected by Alzheimer's disease presently [8]. Arbitrary two types of Alzheimer's diseases have been described i.e. early and late onset Alzheimer's disease. Early onset AD occurs before the age of 65 years and is considered to have a more aggressive course with relatively shorter survival time. Late onset AD occurs after the age of 65 [4]. It is not known whether early and late onset Alzheimer's are variants of the same disease or two distinct entities. Although neuropathological findings are the same in both the types, but phenotypic differences are present between them, considering age of onset as an important determinant of the diversity observed in the disease [1]. In both types of AD, functional, cognitive, and non-cognitive symptoms are present. Non-cognitive symptoms include behavioural and psychological symptoms of dementia (BPSD). Early detection of BPSD is extremely

important, because these symptoms not only induce noticeable disability in demented patients, but also increase caregivers stress. In fact, BPSD increase impairment in daily living activities, accelerate cognitive decline and worsen patient's quality of life [5]. Cognitive decline in AD includes range of cognitive symptoms. Generally performance in one or multiple cognitive domains like memory, orientation, executive functions, and praxis is assessed to determine cognitive decline in AD. There are a lot of cognitive batteries used for assessing cognitive decline in AD. The most commonly used test is MMSE. Cognitive batteries that are use measures global cognitive function, verbal memory, visual memory, executive functions, attention ,IQ(Intelligence quotient) and reading ability .A review of the literature showed that some studies used only single measure like verbal memory test from the battery of tests to measure cognition dysfunctions in AD. However 40% of the studies used multiple neuropsychological tests to measure cognitive dysfunctions in AD [6].

General practitioners (GP) in primary care centres generally miss out diagnosing EAD, as they are reluctant in diagnosing AD in early stage. The recent trend is that diagnose of AD should be done in memory clinic and not in primary health care. However due to limited resources GP in primary health centres tend to diagnose AD patients [7].Large no of studies have been conducted on AD in western countries [1-5].However no comprehensive study about this common condition has been carried out in India. The few published studies are sporadic and generally focuses on only its epidemiology [8-11]. In view of the above, a comprehensive study to investigate cognitive dysfunctions in EAD and LOAD was carried out in memory clinic of Post Graduate Department of Psychiatry, Government medical College,Srinagar, India.

Methodology

Setting: The study was conducted in Memory Clinic of Postgraduate Department of Psychiatry, Government medical college, Srinagar; Kashmir (India). Government medical college and its associate hospital provide care to whole of Kashmir region, along with adjoining areas of Jammu and Ladakh region population of over 6 millions.

Subjects: A total of 80 patients of AD were screened from January 2012 to March 2014 (40 with age of onset less than 65 and 40 with age of onset greater than 64) .The two groups were divided by the conventional division line of the 65 years. Patients with age of onset less than 65 were called as Early Onset Alzheimer's disease (EAD) and patients with age onset greater than 65 were called as Late onset Alzheimer's disease (LOAD).. Each patient had a structured clinical interview, laboratory routine exams, physical and neurological examination and structural (CT or MRI)

Alzheimer's disease (AD) diagnoses: The diagnosed of AD was done according to NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's and Related Disorders Association) criteria [12] by two experienced psychiatrist.

Inclusion criteria were

- Diagnosis of probable AD according to the NINCDS-ADRDA criteria [12].
- Availability of a reliable caregiver, defined as someone able to ensure the patient's compliance with assessment procedures and

who contacted the patient at least twice weekly, with one contact being a personal visit.

- Classification in mild to moderate severity using the Mini-Mental State Examination (MMSE).

Exclusion criteria

Patients with MMSE score below 10, with past history of psychiatric illness and/or any neurological illness which could interfere with neuropsychological tests.

Instruments

The instruments used for neuropsychological evaluation was applied at the time of the diagnosis by two trained neuropsychologists. The instruments used in assessing the cognitive symptoms in subtypes of AD include

Mini Mental State Examination (MMSE)

It is a brief 30-point questionnaire test that is used to estimate the severity of cognitive impairment [13]. The instrument had to be culturally and linguistically acceptable to the local Kashmiri-speaking population. So, we used the Kashmiri version of MMSE,developed by Raina SK et al.In Kashmiri version of MMSE ,the selected items from the English version of the Mini Mental Status Examination (MMSE) have been translated into Kashmiri and then back-translated into English. It has good reliability and validity [11].The Clinical Dementia Rating or CDR is a scale with good reliability and validity used to assess and quantify the severity of symptoms of dementia (i.e. its 'stage') [14]. Other neuropsychological tests used in the study included the verbal digit span, verbal (animal and "F" word) fluency, the 15-item mini- Boston Naming Test, the 10-item Auditory Verbal Learning Test [15]. Constructions, calculations, and similarities from the Neurobehavioral Cognitive Status Examination [16]. Motor executive tests like Luria hand sequence test (LHS), the Go/No-Go test, and the alternating programs (AP) were also done to assess motor executive functions [17].

Consent and approval

The study was done after obtaining clearance from the ethical committee and no grant was funded by the committee. The patients gave their consent before being subjected to various tests.

Results

The study sample consisted of 80 patients: 40 with EAD and 40 with LOAD. Both Groups were matched for education, MMSE, CDR, disease duration and onset. The mean age of presentation of EOAD and LOAD was 63.10 and 84.28 respectively and the difference between the two was found to be statistically significant ($P < 0.05$) (Table1).There was significant difference in MMSE of both of the groups and was found to be statistically significant ($P < 0.05$) (Table1).The comparison of cognitive scores obtained by neuropsychological assessment in EAD and LOAD are presented in Table 2. The two groups (EAD and LOAD group) differed on several tests. Patients in the LOAD group had lower mean score of verbal fluency (Table 2). Patients in the EAD group also performed better than the LAD group on all the tests of motor-execution ($P < 0.05$) table 2

	EAD	LOD	T	p-value	95 % CI
	Mean (S.D.)	Mean (S.D.)			
Age at presentation	63.10 (1.128)	84.28 (2.172)	-54.723	≤.0001	-21.945 to -20.405
Age of onset	60.60 (1.150)	78.80 (1.951)	-50.83	≤.0001	-18.93 to-17.487
DOI	2.50 (0.506)	5.48 (1.062)	-15.994	≤.0001	-3.345 to-2.605
MMSE	19.98 (0.891)	18.15 (0.770)	9.802	≤.0001	1.454 to 2.196
Education	10.78 (0.920)	10.50 (0.847)	1.391	0.168	-0.119 to -0.669

Table 1: Showing age of onset, presentation and mean MMSE and Education in Early Onset Alzheimer's disease (EAD) versus Late Onset Alzheimer's disease (LOAD).

Tests	EAD	LOAD	T	p-value	95% CI
	Mean (S.D.)	Mean (S.D.)			
Verbal digit span	5.01(0.086)	5.22 (0.96)	-10.79	≤.0001	-0.26 to -0.17
Verbal fluency, animal"/min	10.75(0.84)	7.52(0.59)	19.77	≤.0001	2.90 to 3.54
Verbal fluency,F word/min	7.45(0.50)	3.97(0.83)	22.6	≤.0001	3.16 to 3.78
Mini-BNT(15 item)	10.70(0.56)	10.57(0.74)	0.84	0.401	-0.16 to - 0.41
AVLT delayed recall(10 item)	39.55(1.55)	38.40(1.59)	3.26	0.002	0.44 to - 1.85
AVLT Recognition	6.60(0.59)	5.37(0.49)	10.09	≤.0001	0.98 to - 1.46
Visual delayed recall (3 item)	0.72(.086)	0.81(0.10)	-5.25	≤.0001	-0.15 to -0.71
Constructions(4 items)	2.00(0.00)	1.42(0.50)	7.26	≤.0001	0.41 to 0.73
Calculations(3 items)	1.78(0.15)	1.89(0.09)	-3.91	≤.0001	-0.16 to -0.055
Similarity(3 items)	0.81 (0.051)	0.86(.062)	-3.65	≤.0001	-0.07 to -0.021
Luria hand sequence	2.00(0.00)	1.40(0.49)	7.64	≤.0001	0.44 to 0.75
Go/No-Go test	2.09 (0.25)	0.88 (0.08)	28.14	≤.0001	1.12 to 1.29
Alternating programs	2.10(0.10)	1.12(0.11)	38.6	≤.0001	0.92 to 1.02

Note: Group mean and standard deviation (SD) in years; t=T score.
C.I (Confidence interval); AVLT (Auditory Verbal Learning Test).

Table 2: Showing Neuropsychological performance in Early Onset Alzheimer's disease (EAD) versus Late Onset Alzheimer's disease (LOAD)

Discussion

Alzheimer's disease (AD) is the most common type of dementia and is an international health problem, especially in a developing countries like India [1-3].AD is characterized by loss of cognitive and non-cognitive functions in various domains .The loss of these functions causes significant disability in activities of daily life. The appearance of non-cognitive symptoms occurs occasionally before the onset of cognitive symptoms. The various non-cognitive symptoms in AD include behavioural and neurological symptoms and physical disorders including diabetes [4]. Despite the interactive link between cognition and function, these variables are occasionally only correlated in longitudinal studies. Studying the relationship between cognition and AD over the course of AD has beneficial implications. The

beneficial implications include in terms of choosing outcomes in clinical trials, clinical prognosis and treatment [18].

Cognition is a combination of skills that include functions in attention, learning, memory, language, visuaspatial skills and executive functions. Cognitive function refers to an individual's perceptions, memory, thinking, reasoning and awareness. Neuropsychological testing is the only method used for evaluating cognitive symptoms in Alzheimer's disease and its subtypes [19]. Along with physical decline, decline in cognitive function is a hallmark of AD and is also predictive of its mortality. Further the decline of cognitive functions in AD is complex and not properly understood [20].In both types of AD, functional and cognitive symptoms are present. The mechanism by which cognitive symptoms that occurs in patients with Alzheimer's disease is not completely understood [4] Serotonin transporter

promoter gene, serotonin receptor 2a gene (5HT receptor 2a), dopamine receptors genes (DRD1 allele B1 and DRD3 allele) are all found to be associated with AD [3].

Earlier EAD and LOAD was considered distinct from each other. However the distinction vanished when similar neuropathology was found in both the subtypes [21]. Studies have found that EAD is distinguished from LOAD by increased parietal atrophy and lesser hippocampal atrophy [22]. Global cognitive functions as well as the severity of cognitive functions were assessed by MMSE [20]. The study showed that cognitive symptoms as measured by the MMSE were more deteriorated in LOAD compared to EAD. The difference between the two groups (LOAD and EAD) were found to be statistically significant ($p < 0.0001$). This finding of the study is interesting as most of the other studies report functional deterioration more in LOAD, although no significant difference exists in the MMSE values in both the groups [4]. The study also found significant differences in cognitive symptoms between patients of early and late onset AD. The LOAD patients had lower verbal fluency compared to EAD ($p < 0.0001$). There was also significant differences in language function, visuospatial deficits, recognition calculations and constructions. The finding of the study are in agreement with the study by Licht EA et al. who found greater impairment in verbal and language functions in LOAD patients [21]. However our finding is in contrast to Filley CM et al. who found greater impairment in verbal functions in EAD compared to LOAD [23]. Loring DW et al. also found greater deficits in verbal, visuospatial performance in EAD, compared to LOAD [24]. Wider Cognitive deterioration in LOAD, especially in verbal and language functions can be explained by normal age related changes that affects fronto-subcortical systems and sluggish information processing speed that can occur with increased age. However the decline of cognitive functions in AD and its subtypes are complex and not properly understood [4].

Language is a cognitive domain more useful in differentiating EAD from LOAD [1]. In language function, there was significant difference in naming, comprehension in LOAD, compared to EAD groups. However there was no difference in repetition scores in both the groups. Motor executive functions were more impaired in LOAD, compared to EAD. Memory is an important function used for assessing cognitive functions in AD and its subtypes. In the study we found that delayed recall was affected more in LOAD than EAD. It was assessed by AVLTs R (Auditory Verbal Learning Test Recognition) and AVLTs DR (Auditory Verbal Learning Test Delayed recall). Digit span was used in assessing immediate/working memory as well as attention. Most of the studies report working memory and attention impaired more in EAD. Our finding is in accordance with other studies [18]. In the study, construction abilities were more deteriorated in LOAD, compared to EAD. In a study by Smitts LL, early onset AD patients performed worse than LOAD on visuospatial functioning, executive functioning, and attention. However LOAD patients performed worse on memory, although not significantly [25]. These finding in the study can possibly be explained by normal age related changes that occur with increase age and also preferably by the fact that different areas of the brain are affected in subtypes of AD.

Limitations

There were few limitations in the study

The sample size was small and the study was conducted in one centre only. A comprehensive study with a much larger sample size is

required to gain more insights into the ubiquitous clinical psychiatric disorder. Another limitation in the study was possibility of selection bias, as the sample was obtained in one hospital only. The generalization of the results may be questioned, as the neuropsychological testing in patients of AD was difficult because of low MMSE (Floor affect). Floor affect occurs when neuropsychological instrument has a lower limit to the data values, it can reliably specify.

Conclusion

Although research on the subtypes of AD appears to be understudied and least explored in India. However our study was a maiden attempt to understand the symptoms of cognition in subtypes of AD. Wider dysfunctions in cognitive symptoms occurred in LOAD, compared to EAD.

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