ORIGINAL RESEARCH

Behavioral and Psychological Symptoms of Dementia in Alzheimer's Dementia: The Neuroimaging Correlates

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Abstract

Background: Behavioral and psychological symptoms of dementia (BPSD) is defined as "symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia." Behavioral and psychological symptoms of dementia is associated with significant caregiver burden, early institutionalization, and rapid cognitive decline. The worldwide prevalence of dementia is 5–7%; whereas in India, it is reported to be 0.8–4%. Alzheimer's dementia amounts to 60% of the total prevalence of dementia. We aim to study the neuroimaging correlates of BPSD in Alzheimer's dementia.

Objective: To study the correlation between BPSD with white matter changes on neuroimaging in Alzheimer's dementia.

Materials and methods: It is a cross-sectional study with a sample size of 30 patients. The magnetic resonance imaging (MRI) changes were seen using volumetric analysis and white matter hyperintensity change using Fazekas scale, global cortical atrophy (GCA) score, medial temporal atrophy (MTA) score, and KOEDAM scale.

Results: It was found that clinical dementia rating (CDR) scale has positive correlation with Fazekas, GCA, and KOEDAM. Addenbrooke's cognitive examination (ACE-3) has correlation with GCA. On neuropsychiatric inventory (NPI) questionnaire, depression followed by nighttime behavior were the most common BPSD symptoms. Sociodemographic factors such as age >65 years, middle socioeconomic status (SES) population, and urban population have higher mean neuropsychiatric inventory-frequency and severity (NPI-F*S) scores.

Conclusion: Our study here in concordance with other studies worldwide gives a clue about the role of neuroimaging biomarkers in understanding BPSD in terms of its neuroimaging correlates and builds the scope of future studies in this domain. The study sheds light on the common presentation of BPSD, which adds to our knowledge in clinical assessment of Alzheimer's disease (AD) patients. Finally, it also adds to our understanding of the role of sociodemographic factors in predicting the at risk population.

Keywords: Alzheimer's dementia, Behavioral and psychological symptoms of dementia, Neuroimaging.

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Introduction

According to the International Classification of Diseases, Tenth Revision (ICD-10), dementia is a syndrome caused by the disease of the brain. It is usually of a chronic or progressive nature, with disturbance in multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. The worldwide prevalence of dementia is 5–7% which contributes to 4.1% of all disabilities adjusted life years.[1] But in India it has been reported to vary from 0.8 to 4%. Of this, AD accounts for 60%, whereas vascular dementia accounts for ~30% of the prevalence.[2] It is estimated that the number of people living with dementia will almost double every 20 years, i.e., to 42.3 million in 2020 and 81.1 million in 2040. According to the International Psychogeriatric Association, behavioral and psychological symptoms of dementia (BPSD) is defined as "symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia". The pathogenesis of BPSD has not been clearly delineated, but it is probably the result of a complex interplay of psychological, social, and biological factors. There is still debt in our understanding of BPSD and its possible neuroimaging biomarkers; therefore, we have conducted a study to further understand BPSD with the help of neuroimaging correlates.

Aim

Primary Objective

To study the correlation between BPSD with white matter changes on neuroimaging in Alzheimer's dementia.

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Secondary Objective

To study the sociodemographic factors and BPSD in Alzheimer's dementia.

Materials and Methods

This is a cross-sectional study conducted in the outpatient facility of tertiary care private hospital at Hyderabad, India. Thirty subjects who fulfilled the inclusion criteria were enrolled for the study. Informed consent was obtained from each participant, and if some participant lacked capacity for consent, consent was obtained from the nominated representative/first-degree relative of the patient.

Inclusion Criteria

- Age of ≥50 years.
- According to ICD-10 diagnosed cases of AD with BPSD.

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- They will be right-handed as assessed by the modified Edinburgh handedness inventory.[3]

All subjects underwent routine investigations, neurocognitive assessment, and magnetic resonance imaging (MRI) brain dementia protocol and the required study parameters were obtained. The data were collected after approval from the ethics review committee board. The participants were compared on sociodemographic characteristics, performance on various neuropsychological tests, and neuroimaging scores. Statistically analysis was performed using the Statistical Package for the Social Sciences software version 16.0 (IBM Corp., Armonk, New York, USA). The data were analyzed using nonparametric correlation analysis. The data were screened for outliers. The correlation coefficient ranged from –1 to 1 and was tested for significance. If the *p* value is less than 0.05, correlation was considered as significant and two variables were said to be linearly correlated.

Tools used in the study:

- Sociodemographic data and clinical data sheet.
- Magnetic resonance imaging brain changes using volumetric analysis and white matter hyperintensity change using the Fazekas scale, global cortical atrophy (GCA) score, medial temporal atrophy (MTA) score, and KOEDAM scale.
- Psychiatric illnesses ruled out using MINI.
- The neuropsychiatric inventory (NPI) questionnaire[4] was used to measure BPSD.
- Severity of dementia was understood using the clinical dementia rating (CDR) scale.
- Addenbrooke's cognitive examination.
- Disability assessment for dementia.

Results

We found that among the total number of patients ($n = 30$), 18 patients were male with a mean NPI of 21.5 and 122 were female with an average NPI of 21 (Table 1).

Thirteen patients were less than 65 years of age and the rest (17) were more than 65 years of age (Table 2).

In all, 7 patients belonged to the upper class, 22 to middle class, and 1 to lower class, according to Kuppuswamy and Prasad socioeconomic scale (Table 3). Twenty-three patients were residents of urban areas and the rest living in rural areas (Table 4).

As shown in Table 5, only GCA score showed significant *p* value when compared with ACE-3. However, when compared with CDR scale, Fazekas, GCA, and KOEDAM score of posterior atrophy, all had significant *p* values, with the exception of the MTA score.

The percentage of various symptoms on NPI is mentioned in Table 6, with the highest number of patients having depression and only one patient showing elation. Hallucination was seen in 26% patients and only two patients showed disinhibition. The second most common symptom exhibited by the patients was irritability, with 20 patients showing the symptom.

The MRI of a 55-year male (Fig. 1) showed progressive cerebral atrophy over a period of 3–4 years. Patient had presented with BPSD which initially presented as depressive features progressing to apathy and unawareness during the course of follow-up of Alzheimer's dementia.

Table 1: Sex ratio with mean neuropsychiatric inventory

Gender	*Number of subjects*	*NPI-F*S (mean)*
Male	18	21.5
Female	12	21
Total	30	21.2

Table 2: Age ratio with mean neuropsychiatric inventory

Age (in years)	*Number of subjects*	*NPI-F*S (mean)*
<65	13	17.92
>65	17	23.7

Table 3: Socioeconomic correlation

Socioeconomic status	*Number of subjects*	*NPI-F*S (mean)*
Upper	7	13.14
Middle	22	24.46
Lower	1	1

Table 4: Residential demographics

Residence	*Number of subjects*	*NPI-F*S (mean)*
Urban	23	23.21
Rural	7	14.57

Table 5: Bivariate correlation between neurocognitive tests and neuroimaging scores

	Neuroimaging scores			
	p values			
Neurocognitive tests	*Fazekas*	*GCA*	*MTA*	*KOEDAM*
ACE-3	0.247	0.002	0.705	0.066
CDR	0.042	0.025	0.994	0.022
DAD	0.067	0.015	0.348	0.001
NPI-F*S	0.622	0.907	0.987	0.417
NPI-D	0.383	0.016	0.499	0.074

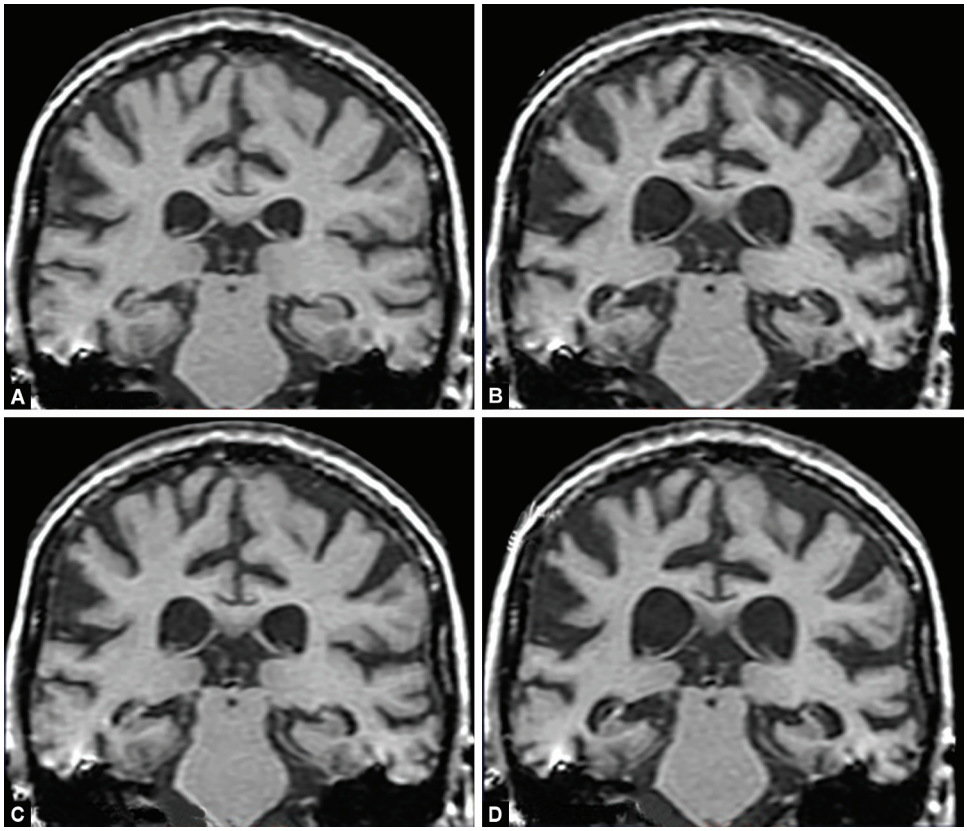
p value < 0.05 is significant

Table 6: Neuropsychiatric inventory parameters

NPI parameters	*Percentage*
Delusion	30
Hallucination	26
Agitation/aggression	40
Depression/dysphoria	73
Anxiety	56
Elation/euphoria	3
Apathy/indifference	53
Disinhibition	6
Irritability/liability	60
Motor disturbances	33
Nighttime behavior	66
Appetite/eating	36

Discussion

Behavioral and psychological symptoms of dementia are commonly seen in neurocognitive illness. It is the most studied and found to be widely associated with Alzheimer's dementia,[4] and its etiopathogenesis is still poorly understood. Various studies have been conducted to study the commonly occurring symptoms of BPSD, their prevalence, and severity at different stages of dementia.[1,2] However, not many studies have been conducted to assess the specific volumetric changes in brain and its association with frequency, severity, and pattern of BPSD.



Figs 1A to D: Magnetic resonance imaging showing progressive cerebral atrophy

In a study by Holthoff et al.,[5] based on MRI and fluorodeoxyglucose-positron emission tomography scan (FDG-PET), it was found that patients with apathy exhibited lower glucose metabolism in the left orbitofrontal cortex in comparison with other patients with no such symptoms [total study participants $n = 53$; apathy ($n = 17$), not apathy ($n = 17$), depressed ($n = 10$), not depressed ($n = 10$)]. Depressed group showed hypometabolism in the left prefrontal cortex and superior frontal cortex, when compared with subjects not depressed.

In another study, Bruen et al.[6] studied subjects ($n = 31$) with Alzheimer's dementia, on MRI 1.5 T. Apathetic Alzheimer's disease (DA) subjects presented gray matter (GM) atrophy in the right inferior frontal gyrus, orbitofrontal cortex, bilateral dorsolateral prefrontal cortex, putamen, and head of the left caudate nucleus.

Serra et al.,[7] [total study participants $n = 69$; AD ($n = 27$) mild cognitive impairment (MCI) ($n = 19$) controls ($n = 23$)] in a group of patients with MCI and control subjects with AD, found decreased GM volume in the bilateral cingulate, which correlated with the severity of disinhibition and delusions in AD on 3 T MRI voxel based morphometry (VBM). Similarly, Berlow et al.'s[8] study of AD patients ($n = 37$), the MRI findings showed that low volumes of white matter hyperintensity (WMH) were associated with disinhibition and high WMH volumes associated with anxiety.

Whitehead et al.[9] found left medial orbitofrontal and superior temporal cortices were significantly thinner in those with paranoid delusions, i.e., $n = 113$ patients, of which $n = 90$ did not have delusions and $n = 23$ had paranoid delusion. Female participants with paranoid delusions showed reduced cortical thickness in left medial orbitofrontal and left superior temporal regions.

In a large study by Palmqvist et al.,[10] it was demonstrated that of all the AD patients studied [$n = 259$; 8 patients underwent MRI and all others computed tomography (CT)], the occurrence of lacunes in the left basal ganglia associated with increased risk of delusions and hallucinations and the presence of lacunes in the right basal ganglia associated with the risk of depressive symptoms. Increased global atrophy is associated with agitation.

In a study by Poulin et al.,[11] the level of motor aberrant behavior correlated with more severe amygdala atrophy in AD subjects ($n = 264$) [mild AD sample 1 ($n = 90$) sample 2 ($n = 174$)], which is based on MRI 1.5 T.

In another large-scale study, Trzepacz et al.[12] based on the MRI findings showed atrophy in frontolimbic regions, right posterior cingulate, and left hippocampus were related to greater severity of agitation and aggression [i.e., total study patients $n = 462$ which included AD ($n = 163$), MCI converters ($n = 122$) and MCI stable ($n = 177$)].

Based on structural and functional 3 T MRI, Balthazar et al.[13] ($n = 57$) [AD ($n = 37$) and controls ($n = 30$)] suggested altered intrinsic connectivity of the anterior SN predicted behavioral symptoms in AD patients, e.g., hyperkinetic behavior. Hyperconnectivity of the salient network was observed in the anterior cingulate cortex and right insula.

In our study, it was found that nearly all patients had some behavioral or psychological symptoms on NPI, of which depression was the most common, followed by nighttime behaviors and the least being elation/euphoria and disinhibition, respectively; however, most other studies found apathy and delusions as the most common symptoms in the early progressive course of AD.[14] Also the corresponding MRI findings corroborated to the brain regions involved in the occurrence of these symptoms.[15]

The noteworthy finding here was correlation of neurocognitive assessment such as ACE-3 and CDR with neuroimaging scores such as Fazekas, GCA, MTA, and KOEDAM. It was particularly found that CDR scale correlated positively with Fazekas, GCA, and KOEDAM, which means as the performance on CDR deteriorates, the severity of neuroimaging scores increases. Similarly, ACE-3 had a positive correlation (*p* value of less than 0.05) with GCA score. These findings can give us the scope for future investigation in terms of the role of neuroimaging scores in predicting the development of BPSD symptoms and planning early targeted intervention in AD and BPSD.

We also studied whether BPSD varies with sociodemographic profile, and it was found that those above 65 years of age had higher mean value of BPSD than those below 65 years of age. No significant difference was observed when compared with gender. It was found that middle SES participants had higher mean value of BPSD as opposed to the upper and lower SES subjects. Finally it was found that urban patients had more mean value of BPSD compared to the rural patients.

Conclusion

Our study here in concordance with other studies worldwide gives a clue about the role of neuroimaging biomarkers in understanding BPSD in terms of its neuroimaging correlates and builds the scope of future studies in this domain.[15] The study sheds light on common presentation of BPSD which adds to our knowledge in clinical assessment of AD patients. Finally, it also adds to our understanding of the role of sociodemographic factors in predicting the at risk population.

The BPSD in Alzheimer's dementia still has a lacunae in our understanding of its definite etiopathogenesis; and thus, there is a barrier to predicting its course in disease and planning definite intervention. A worldwide more comprehensive prospective large-scale studies of neurobiomarkers might be a breakthrough and in the future might help us in improving our understanding of the course of the disease progression.

Limitations of our study:

- The study was conducted on a small sample population.
- We could not study BPSD in other dementias such as frontotemporal dementia, vascular dementia, dementia of Lewy bodies, and Parkinson's dementia.
- Our study did not include other neurobiomarkers such as FDG-PET and single photon emission computed tomography (SPECT) scans and solely relied on MRI neuroimaging scores.
- We did not study BPSD in MCI, which is a gray area in course of development of dementia.

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