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ORIGINAL ARTICLE

A Cross-Sectional Study on Behavioral Manifestation in Alzheimer's Disease Patients and their Association with Cognitive Impairment

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ABSTRACT
Background and Aim: Dementia psychological and behavioral symptoms are significantly associated to Alzheimer's disease (AD). Clinical profile and characterization of Alzheimer's disease patients might assist in evolution, diagnosis, and better treatment of the disease. The present study aimed to evaluate the behavioral manifestation of Alzheimer's disease patients.
Methodology: This multi-centered cross-sectional study was carried out on 96 Alzheimer's disease patients in the department of Psychiatry Lahore General Hospital and Psychiatry unit, Khyber Teaching Hospital Peshawar, Pakistan for duration of six months from 1st July 2021 to 30th December 2021. Alzheimer's disease patients with lower and higher Behavioural and psychological symptoms of dementia (BPSD) scores (≤25 and 26-50 respectively) were enrolled. The patient's demographic details and clinical information were gathered. Mini-Mental State Examination (MMSE) was used for the evaluation of dementia severity whereas severity varies from mild 27-21 to severe ≤10. Demographic details, AD pharmacological treatments, psychotic breaks presence, AD diagnosis, treatment of concomitant diseases, and extrapyramidal symptoms such as hypokinesia, fluctuating cognition, tremors, etc. were secondary outcomes.
Results: Of the total 96 AD patients, 44 (45.8%) had higher and 52 (54.2%) had lower BPSD scores. About 62 (64.6%) were women and 34 (35.4%) were male patients. The overall mean age was 79.6±8.4 years. The majority of the patients had a BPSD score at inclusion and the incidence of psychotic out breaks was reported in 19 (19.8%) patients. The prevalence of symptoms such as depression, delusions, lack of concentration, lack of cooperation, and tremors was 41 (42.5%), 33 (34%), 52 (54.6%), 34 (35.9%), and 52 (54.6%) respectively. Psychotic symptoms such as hallucinations, delusions, and delirium were significantly prevalent in patients with high BPSD scores whereas Apathy and tearfulness-like emotional symptoms were predominated in lower BPSD patients. ADAS-non cognitive score and MMSE were adversely related (p=0.0314), signifying BPSD and cognitive impairment correlation. Appetite changes and lack of concentration were prominently associated with MMSE (p=0.035 and 0.052).
Conclusion: Our study found a higher prevalence of non-cognitive symptoms in Alzheimer's disease patients. Also, BPSD and cognitive impairment are significantly associated with AD. ADAS-non cognitive is a useful assessment tool.
Keywords: Behavioral Manifestation, Alzheimer's disease, Cognitive Impairment

INTRODUCTION
Dementias, especially Alzheimer's disease, are a major growing concern of public health with population growing age [1]. Psychosis, depression, and apathy are the core features of AD and faster cognitive decline, shorter survival, and loss of independence are predictors for AD symptoms severity [2]. It is unclear whether these symptoms are caused by the same pathogenic processes that cause cognitive decline or if they have separate etiologies unrelated to AD-related neuro-degeneration. Dementia is distinguished by functional, cognitive, and behavioural manifestations. Behavioral symptoms are among the first signs of dementia, appearing before cognitive changes [3], at some point during the illness [4], and varying according to dementia severity [5]. Behavioural and psychological symptoms of dementia (BPSD) are non-cognitive symptoms that are commonly associated with Alzheimer's disease. Early detection of BPSD is critical, as these symptoms not only cause visible disability in demented patients, but also increase caregiver stress [6].

In fact, BPSD worsens the patient's quality of life [7], increases daily living activities impairment [8], hastens cognitive decline [9] and worsens the patient's life quality [10]. Furthermore, behavioural disturbances are the primary cause of and contribute to early institutionalization of patient [11]. However, when these disorders are properly diagnosed, they can be effectively treated with drugs [12-14], in turn improving the quality of life of both patients and caregivers. Numerous studies has been carried out in order to evaluate the BPSD symptoms prevalence and varied from 61% to 92% depending on the type of population studied and the methods used to assess it [15]. The ADAS, and particularly its non-cognitive subscale (ADAS Noncog), is a precise diagnostic tool intended to perceive BPSD in Alzheimer's disease patients. This rating scale is also available in a Spanish version that has been adapted and validated [16]. The neuropsychiatric symptoms and behavioural abnormalities associated with Alzheimer's disease have a significant impact on patient QOL and are thought to be predictive of eventual (or more severe) dementia [17]. The present study was carried out to assess the behavioural manifestations in Alzheimer's disease patients and their association with cognitive impairments.

METHODOLOGY
This multi-centered cross-sectional study was carried out on 96 Alzheimer's disease patients in the department of Psychiatry Lahore General Hospital and Psychiatry unit, Khyber Teaching Hospital Peshawar, Pakistan for duration of six months from 1st July 2021 to 30th December 2021. Alzheimer's disease patients with lower and higher Behavioural and psychological symptoms of dementia (BPSD) scores (≤25 and 26-50 respectively) were enrolled. The patient's demographic details and clinical information were gathered. Mini-Mental State Examination (MMSE) was used for the evaluation of dementia severity whereas severity varies from mild 27-21 to severe ≤10. Demographic details, AD pharmacological treatments, psychotic breaks presence, AD diagnosis, treatment of concomitant diseases, and extrapyramidal symptoms such as hypokinesia, fluctuating cognition, tremors, etc. were secondary outcomes.

The ADAS-Non cognitive scores of first and second group had ≤25 and 26-50 respectively. Bahviour such as delusion, lack of concentration and cooperation, tremors, hallucinations, and appetite change and mood disorders like depression and tearfulness were assessed with ADAS-Non cognitive as a diagnostic tool. Each item was assessed on rating scale of 5 resulting variations from 0 to 50 indicated scores. Mood disorders were indicated with higher scores representing severe conditions.

Based on professional observations, information gathered, and patient's history, rating was assigned. The sample size was calculated using the dementia severity description. To obtain a precision dementia degree with a 95 percent confidence interval (95 percent CI), a minimum of patients per BPSD group were required, assuming a 10% patient loss.

RESULTS

Of the total 96 AD patients, 44 (45.8%) had higher and 52 (54.2%) had lower BPSD scores. About 62 (64.6%) were women and 34 (35.4%) were male patients. The overall mean age was 79.6±8.4 years. The majority of the patients had a BPSD score at inclusion and the incidence of psychotic out breaks was reported in 19 (19.8%) patients. The prevalence of symptoms such as depression, delusions, lack of concentration, lack of cooperation, and tremors was 41 (42.5%), 33 (34%), 52 (54.6%), 34 (35.9%), and 52 (54.6%) respectively. Psychotic symptoms such as hallucinations, delusions, and delirium were significantly prevalent in patients with high BPSD scores whereas Apathy and tearfulness-like emotional symptoms were predominated in lower BPSD patients. ADAS-non cognitive score and MMSE were adversely related (p=0.0314), signifying BPSD and cognitive impairment correlation. Appetite changes and lack of concentration were prominently associated with MMSE (p=0.035 and 0.052). Demographic details and most relevant clinical information are shown in Table-I. Table-II shows the Extrapyramidal symptoms among AD patients. Gender distribution is illustrated in Figure-1. Dementia severity was typically mild (38) to moderate (37) based on the MMSE score (48%) is shown in Figure-2. Only 14% of the patients had severe dementia as shown in Figure-3. Correlation between dementia severity (MMSE) and ADAS-Noncog score are shown in Tabele-III.

Table 1: Demographic details and clinical information of AD patients (Both lower and higher BPSD scores)

Parameters	AD patients with Positive BPSD	AD patients with Negative BPSD
Age (years)	79.6±7.4	78.8±7.1
Gender	35.6%	34.9%
AD symptoms duration (yrs)	3.9±2.2	4.1±3.2
AD diagnosis duration (yrs)	1.29±1.23	1.3±1.2
BPSD diagnosis	41.8%	38.9%
Behavioural Symptoms		
Depression	48.8%	50.9%
Concentration	58%	58.7%
Delusion	43.7%	38.2%
Cooperation	58%	58.7%
Hallucinations	33.5%	27.9%
Apathy	22.9%	23%
Apatite changed	28.9%	27.8%
Anxiety	26.9%	23.6%

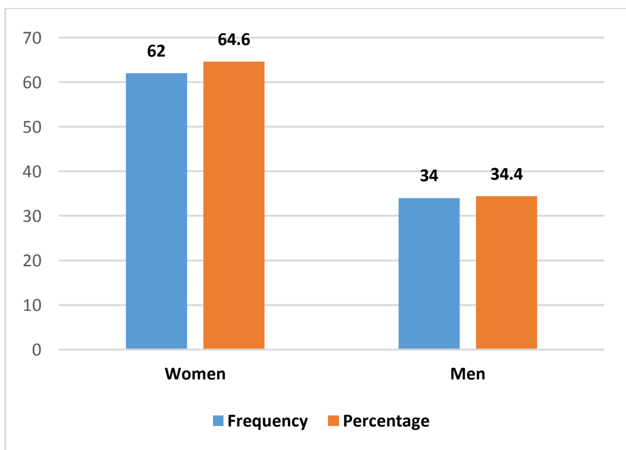

Figure 1: Gender distribution

Table 2: Prevalence of Extrapyramidal symptoms among AD patients.

Extrapyramidal symptoms	Alzheimer's Disease +BPSD	Alzheimer's Disease -BPSD
Tremors	36.9%	37.6%
Hypokinesia	12.3%	10.2%
Fluctuating cognition	9.7%	8.3%
Postural instability	8.9%	7.4%

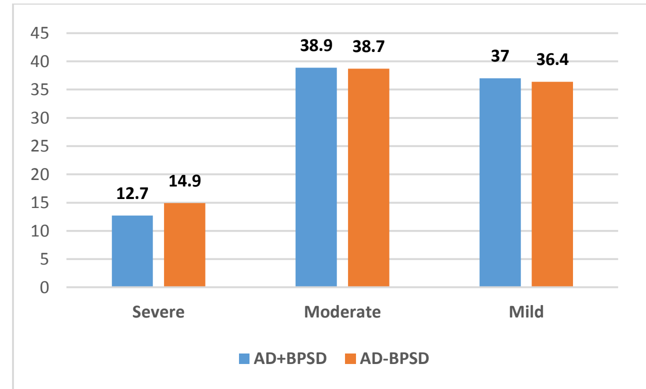

Figure 2: Dementia severity based on MMSE

Table 3: Correlation of dementia severity (MMSE) and ADAS-Noncog score with behavioural symptoms in AD patients

Behavioural Symptoms	Correlation Coefficient	P-value
Depression	0.01321	0.862
Concentration	-0.09638	0.0645
Delusion	-0.0123	0.837
Cooperation	-0.0902	0.528
Hallucinations	-0.0529	0.293
Apatite changed	-0.8976	0.0351

DISCUSSION

The present study found a higher prevalence of non-cognitive symptoms in Alzheimer's disease patients. Also, BPSD and cognitive impairment are significantly associated with AD. ADAS-non cognitive is a useful assessment tool Dementia psychological and behavioral symptoms are significantly related to Alzheimer's disease (AD). Clinical profile and portrayal of Alzheimer's disease patients might assist in evolution, diagnosis, and better treatment of the disease. ADAS-Non cognitive is a diagnostic tool that is particularly useful in outpatient clinics because of no special training required and can be used in a short spam. The current study's findings are consistent with other published studies that show that lack of concentration, tremors, depression, lack of cooperation, and psychotic symptoms are common in Alzheimer's disease patients [18, 19].

In our patient population, 89 percent had at least one BPSD in the previous year, and 90 percent had one at initial evaluation time. Likewise, alternative study [20] using the ADAS-Noncog scale found behavioural symptoms were seen in 95% patients during admission.

According to our findings, the most common BPSD was lack of concentration and tremors, which had a prevalence of around 54.6 percent. Marin and colleagues found similar results when researching non-cognitive impairments in Alzheimer's disease [21]. Concentration problems and a lack of attention appear very early in Alzheimer's disease patients [22], most likely as a result of the disease's associated bilateral temporoparietal degeneration [23]. Aside from its high prevalence, concentration loss is positively correlated with cognitive impairment, implying that this symptom should be considered a central deficit in Alzheimer's disease. Tremor, in its various manifestations, is common in the elderly population over the age of 65 [24. 25].

Depression is a common BPSD symptom in Alzheimer's disease patients, and it has a strong correlation with mood disorders. Actually, depression came in third place in our study,

with a 44 percent prevalence. These findings are consistent with previous studies results [26, 27]. Though, the prevalence of depression varies [28]. The association between dementia and depression is debatable whereas depression is an AD independent risk factor [29]. Depressive symptoms are common in Alzheimer's disease patients who do not have major depression [30]. Other studies, like ours, found no link between cognitive impairment and depression [31], indicating that depression can strike at any stage of the disease.

Generally, Lack of cooperation is associated with increased motor behaviour, may be a result of the disease's natural course. According to our findings, a lack of cooperation has a low correlation with the degree of cognitive impairment (MMSE score). However, its prevalence in our sample (35.9%) highlights its importance among noncognitive symptoms. Psychotic symptoms of Alzheimer's disease, such as delusions and hallucinations, significantly contribute to characterising those patients in the higher BPSD group, most likely due to the increased severity of the disease. Although previous research has found a link between delusions and cognitive impairment [32], no such link was found in this study. Both of these symptoms are indicators of increased cognitive and functional decline. Furthermore, hallucinations have been linked to a higher rate of institutionalization and mortality [33].

Among behavioural symptoms, appetite change had a minor, but dementia severity is associated statistically significant, but negative correlation. Anorexia, hyperphagia, and dietary changes are some of the appetite disorders seen in Alzheimer's disease [34]. However, hypophagia is the most common gastrointestinal disturbance in these patients. A previous study [35] found that patients with Alzheimer's disease who lost weight had a higher frequency and severity of BSPD. Several hypotheses have been proposed to explain the hypophagia and weight loss observed in these patients, including medial temporal cortex atrophy [36].

BPSD are frequently a symptom of cognitive decline and are one of the leading causes of family burden and patient institutionalisation. As a result, proper management of these symptoms will improve their well-being and quality of life [37].

CONCLUSION

Our study found a higher prevalence of non-cognitive symptoms in Alzheimer's disease patients. Also, BPSD and cognitive impairment are significantly associated with AD. ADAS-non cognitive is a useful assessment tool. The current study found a high prevalence of BPSD in Alzheimer's disease, with nearly all patients (90%) exhibiting some mood or behavioural symptom at the time of exploration. Lack of concentration (54.6%) was the most common symptom, followed by depression, delusions, lack of concentration, lack of cooperation, and tremors was 41 (42.5%), 33 (34%), 52 (54.6%), 34 (35.9%), and 52 (54.6%) respectively.

REFERENCES

1. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Contributors. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018 Apr;14(4):535-562
2. Boyle PA, Yu L, Leurgans SE, Wilson RS, Brookmeyer R, Schneider JA, et al. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. Ann Neurol 2019 Jan;85(1):114-124.
3. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol 2017 Aug;134(2):171-186
4. James BD, Wilson RS, Capuano AW, Boyle PA, Shah RC, Lamar M, et al. Hospitalization, Alzheimer's disease and related neuropathologies, and cognitive decline. Ann Neurol 2019 Dec;86(6):844-852
5. Wallace LM, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. Lancet Neurol 2019 Feb;18(2):177-184.
6. Wallace LM, Theou O, Darvesh S, Bennett DA, Buchman AS, Andrew MK, et al. Neuropathologic burden and the degree of frailty in relation to global cognition and dementia. Neurology 2020 Dec 15;95(24):e3269-e3279
7. Fratiglioni L, Marseglia A, Dekhtyar S. Ageing without dementia: can stimulating psychosocial and lifestyle experiences make a difference? Lancet Neurol 2020 Jun;19(6):533-543.
8. Rockwood K, Howlett SE, Hoffman D, Schindler R, Mitnitski A. Clinical meaningfulness of Alzheimer's Disease Assessment Scale-Cognitive subscale change in relation to goal attainment in patients on cholinesterase inhibitors. Alzheimers Dement 2017 Oct;13(10):1098-1106.
9. Sabbagh MN, Hendrix S, Harrison JE. FDA position statement "early Alzheimer's disease: developing drugs for treatment, guidance for industry". Alzheimers Dement (N Y) 2019;5:13-19
10. Posner H, Curiel R, Edgar C, Hendrix S, Liu E, Loewenstein DA, et al. Outcomes assessment in clinical trials of Alzheimer's disease and its precursors: readying for short-term and long-term clinical trial needs. Innov Clin Neurosci 2017;14(1-2):22-29
11. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol 2021 Jun;20(6):484-496.
12. Morel T, Cano SJ. Measuring what matters to rare disease patients - reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. Orphanet J Rare Dis 2017 Nov 02;12(1):171
13. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2016 May;7(3):270-279
14. Rockwood K. An individualized approach to tracking and treating Alzheimer's disease. Clin Pharmacol Ther 2010 Oct;88(4):446-449. [CrossRef] [Medline]
15. Reeve E, Molin P, Hui A, Rockwood K. Exploration of verbal repetition in people with dementia using an online symptom-tracking tool. Int Psychogeriatr 2017 Jun;29(6):959-966
16. McGarrigle L, Howlett SE, Wong H, Stanley J, Rockwood K. Characterizing the symptom of misplacing objects in people with dementia: findings from an online tracking tool. Int Psychogeriatr 2019 Nov;31(11):1635-1641.
17. Rockwood K, Stanley J, Dunn T, Howlett S. PIH2 development and validation of a patient centered outcome measure for use in dementia drug trials. Value Health 2019 May;22:S183.
18. Shehzad A, Rockwood K, Stanley J, Dunn T, Howlett SE. Use of patient-reported symptoms from an online symptom tracking tool for dementia severity staging: development and validation of a machine learning approach. J Med Internet Res 2020 Nov 11;22(11):e20840
19. Hasegawa N, Hashimoto M, Koyama A, Ishikawa T, Yatabe Y, Honda K, et al. Patient-related factors associated with depressive state in caregivers of patients with dementia at home. J Am Med Dir Assoc 2014 May;15(5):371.e15-371.e18. [CrossRef] [Medline]
20. Vicini Chilovi B, Conti M, Zanetti M, Mazzù I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. Dement Geriatr Cogn Disord 2019;27(4):390-398.
21. Cook C, Fay S, Rockwood K. Decreased initiation of usual activities in people with mild-to-moderate Alzheimer's disease: a descriptive analysis from the VISTA clinical trial. Int Psychogeriatr 2018 Oct;20(5):952-963.
22. Bianchetti A, Perotta D, Cravello L, Ranieri P, Trabucchi M. Effectiveness of a specific nutritional supplement on cognitive, behavioral and functional symptoms in mild cognitive impairment and Alzheimer's dementia: caregivers judgments. Results of an observational survey. J Gerontol Geriatrics 2018;66(2):74
23. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol 2018 Nov;14(11):653-666.
24. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017 Dec 16;390(10113):2673-2734.
25. Shah RC, Kamphuis PJ, Leurgans S, Swinkels SH, Sadowsky CH, Bongers A, et al. The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. Alzheimers Res Ther 2013;5(6):59
26. Soininen H, Solomon A, Visser PJ, Hendrix SB, Blennow K, Kivipelto M, LipiDiDiet clinical study group. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. Lancet Neurol 2017 Dec;16(12):965-975
27. Soininen H, Solomon A, Visser PJ, Hendrix SB, Blennow K, Kivipelto M, LipiDiDiet clinical study group. 36-month LipiDiDiet multinutrient

clinical trial in prodromal Alzheimer's disease. Alzheimers Dement 2021 Jan;17(1):29-40

28. Rockwood K, MacKnight C. Assessing the clinical importance of statistically significant improvement in anti-dementia drug trials. Neuroepidemiology 2001 May;20(2):51-56. [CrossRef] [Medline]
29. Raghavan N, Samtani MN, Farnum M, Yang E, Novak G, Grundman M, Alzheimer's Disease Neuroimaging Initiative. The ADAS-Cog revisited: novel composite scales based on ADAS-Cog to improve efficiency in MCI and early AD trials. Alzheimers Dement 2013 Feb;9(1 Suppl):S21-S31
30. Jennings LA, Ramirez KD, Hays RD, Wenger NS, Reuben DB. Personalized goal attainment in dementia care: measuring what persons with dementia and their caregivers want. J Am Geriatr Soc 2018 Nov;66(11):2120-2127.
31. Jennings LA, Palimaru A, Corona MG, Cagigas XE, Ramirez KD, Zhao T, et al. Patient and caregiver goals for dementia care. Qual Life Res 2017 Mar;26(3):685-693
32. Rogalski EJ, Sridhar J, Martersteck A et al. Clinical and cortical decline in the aphasic variant of Alzheimer's disease. Alzheimers Dement 2019; 15: 543–552.
33. Dickerson BC, McGinnis SM, Xia C et al. Approach to atypical Alzheimer's disease and case studies of the major subtypes. CNS Spectr 2017; 22: 439–449.
34. Wolk DA. Amyloid imaging in atypical presentations of Alzheimer's disease. Curr Neurol Neurosci Rep 2013; 13: 412.
35. Oboudiyat C, Gefen T, Varelas E et al. Cerebrospinal fluid markers detect Alzheimer's disease in nonamnestic dementia. Alzheimers Dement 2017; 13: 598–601.
36. Marshall CR, Hardy CJD, Volkmer A et al. Primary progressive aphasia: a clinical approach. J Neurol 2018; 265: 1474–1490.
37. Mesulam MM, Lalehzari N, Rahmani F et al. Cortical cholinergic denervation in primary progressive aphasia with Alzheimer pathology. Neurology 2019; 92: e1580–e1588.