A Comparison of Behavioral and Psychological Symptoms of Dementia (BPSD) and BPSD Sub-Syndromes in Early-Onset and Late-Onset Alzheimer’s Disease

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Abstract.

Background: Behavioral and psychological symptoms of dementia (BPSD) have a large impact on the quality of life of patients with Alzheimer’s disease (AD). Few studies have compared BPSD between early-onset (EOAD) and late-onset (LOAD) patients, finding conflicting results.

Objective: The aims of this study were to: 1) characterize the presence, overall prevalence, and time of occurrence of BPSD in EOAD versus LOAD; 2) estimate the prevalence over time and severity of each BPSD in EOAD versus LOAD in three stages: pre-T0 (before the onset of the disease), T0 (from onset to 5 years), and T1 (from 5 years onwards); 3) track the manifestation of BPSD sub-syndromes (i.e., hyperactivity, psychosis, affective, and apathy) in EOAD versus LOAD at T0 and T1.

Methods: The sample includes 1,538 LOAD and 387 EOAD diagnosed from 1996 to 2018. Comprehensive assessment batteries, including the Neuropsychiatric Inventory (NPI), were administered at the first medical assessment and at different follow-up period.

Results: The overall prevalence for the most of BPSD was significantly higher in EOAD compared to LOAD whereas most BPSD appeared significantly later in EOAD patients. Between the two groups, from pre-T0 to T1 we recorded a different pattern of BPSD prevalence over time as well as for BPSD sub-syndromes at T0 and T1. Results on severity of BPSD did not show significant differences.

Conclusion: EOAD and LOAD represent two different forms of a single entity not only from a neuropathological, cognitive, and functional level but also from a psychiatric point of view.

Keywords: Alzheimer’s disease, behavioral and psychological symptoms of dementia (BPSD), BPSD sub-syndromes, early-onset Alzheimer’s disease, late-onset Alzheimer’s disease, Neuropsychiatric Inventory, prevalence, prevalence over time, time of occurrence

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INTRODUCTION

Alzheimer’s disease (AD) is the most widespread neurodegenerative disorder affecting more than 24 million people worldwide [1–3]. Although it is considered mainly characterized by progressive memory loss and other cognitive function deficits [3, 4], an ever-increasing number of studies recognize neuropsychiatric or behavioral and psychological symptoms of dementia (BPSD) as core features of AD [5–7].

BPSD are a wide range of non-cognitive symptoms that can be classified in four different sub-syndromes: hyperactivity (agitation, disinhibition, irritability, aberrant motor behavior, and euphoria), psychosis (sleep and nighttime behavior disorders, delusion, hallucination), affective (depression and anxiety), and apathy (apathy and eating disorders) [5, 8].

Usually, all twelve BPSD as well as BPSD sub-syndromes are assessed by using the Neuropsychiatric Inventory (NPI) both in clinical practice and research contexts [9].

Several studies have reported that BPSD may have harmful consequences by reducing quality of life of AD patients and caregivers [10–12] and increasing caregiver’s distress and burden [13–15]. In addition, BPSD represent an important cause of early institutionalization [16–18] leading to considerable healthcare costs [19–20].

As far as we know, a comparison has never been made between EOAD and LOAD patients regarding time of occurrence, prevalence, and severity of BPSD from before the onset to the whole course of the disease. In addition, no studies compared the manifestation of BPSD sub-syndromes (i.e., hyperactivity, psychosis, affective, and apathy) between EOAD and LOAD patients in both before the onset and different stages of disease.

Thus, the aim of the current study was threefold. First, to better characterize the occurrence and overall prevalence of BPSD in a large cohort of EOAD versus LOAD patients. Second, to estimate prevalence over time, time of occurrence, and severity of each BPSD in EOAD versus LOAD patients by arbitrary analyzing three stages on the basis of mean duration of illness: pre-T0 (before the onset of the disease), T0 or Manifested Disease (from onset to 5 years), and T1 or Advanced (from 5 years onwards). Third, to compare the overall prevalence of BPSD sub-syndromes (i.e., hyperactivity, psychosis, affective, and apathy) in EOAD versus LOAD patients at T0 and T1.

METHODS

Subjects

The dataset includes 1,925 patients (1,292 women and 633 men) diagnosed with AD and followed at the Regional Neurogenetic Centre (ASP CZ) from 1996 to 2018. Diagnosis was performed according to NINCDS-ADRDA criteria [30] and National Institute on Aging and Alzheimer’s Association Workgroup [31].

Mean age of the whole sample was 71.58 ± 9 years (57.7 ± 4.9 years for EOAD and 75 ± 5.7 years LOAD patients). Mean follow-up was 4 years, assessment was at every six months. Mean duration of illness was about 9-years. Most of the patients were from southern Italy. Data were retrospectively extracted from the respective medical records on the basis of completeness of clinical data. Inclusion criteria were: 1) Diagnosis of probable AD according to the NINCDS-ADRDA criteria; 2) Availability of a reliable caregiver; 3) Completeness of clinical data. Exclusion criteria were: 1) Patients with a past history of psychiatric illness and/or any neurological illness that could interfere with neuropsychological tests; 3) Unavailability of a reliable caregiver; 4) Incompleteness of clinical data; 5) Patients free from pharmacologic treatments for BPSD; 6) Known or suspected history of alcoholism or drug abuse.
The work was done according to Helsinki Declaration of 1975 and approved by the Ethical Committee of Calabria Region (Catanzaro, Italy).

Measures

All patients regularly performed at the first assessment and every six months the following examinations:

- Mini-Mental State Examination (MMSE) [32, 33];
- Clinical Dementia Rating Scale (CDR) [34, 35];
- Clinical Insight Rating Scale (CIRS) [36];
- Activities of Daily Living (ADL) [37] and Instrumental Activities of Daily Living (IADL) [38];
- Neuropsychiatric Inventory (NPI) to identify both individual BPSD [39, 40] and BPSD sub-syndromes [5, 8];
- Checklist encompassing the same BPSD of NPI referred to pre-T0 and extrapolated from the patient’s history collected in the medical records [41].

Statistical analysis

All analyses were performed with SPSS statistical software 21 (SPSS Inc., Chicago, IL, USA). To analyze occurrence and prevalence of BPSD, descriptive statistics, frequencies, contingency, coefficient test (cross tabs) were evaluated. For the analysis of dichotomous variable between two groups, a chi-square cross tabs test was performed. Statistical significance was given by a \( p < 0.05 \).

Frequencies were used to calculate the overall prevalence for each BPSD at a given time. The differences between EOAD and LOAD were analyzed with the chi-square test. To calculate the occurrence and prevalence over time, three periods in which symptoms appeared for the first time in our sample were analyzed. Time of occurrence of each BPSD was calculated as a mean of onset among EOAD and LOAD patients. To measure the general trend of the sub-syndromes, four clusters were created accordingly to Zhao et al. [5] and Aalten et al. [8] and their prevalence calculated through frequency analysis. Finally, to analyze BPSD severity we compared 1) NPI total score, 2) each individual BPSD, and 3) BPSD sub-syndromes at T0 and T1, between EOAD and LOAD by one-way ANOVA.

Table 1  
Baseline characteristics of the EOAD and LOAD groups

|                  | EOAD (n = 387) | LOAD (n = 1538) | p     |
|------------------|---------------|----------------|-------|
| Age, mean ± SD, y | 57.7 ± 4.9    | 75 ± 5.7       |       |
| Female, n (%)    | 238 (61.5)    | 1054 (68.5)    | 0.008 |
| Familiarity, n (%)| 195 (50.4)    | 793 (51.6)     | ns    |
| Education, n (%) |               |                |       |
| Low              | 194 (58.3)    | 1100 (76.5)    | 0.000 |
| High             | 139 (41.7)    | 338 (23.5)     |       |
| MMSE mean ± SD   | 15.8 ± 6.9    | 16.5 ± 5.9     | ns    |
| CIRS mean ± SD   | 1.4 ± 0.9     | 1.5 ± 0.9      |       |
| CDR, n (%)       |               |                |       |
| Mild (0.5/1)     | 90 (58.4)     | 492 (52.1)     | ns    |
| Moderate (2)     | 43 (27.9)     | 303 (32.1)     |       |
| Severe (3/4)     | 21 (13.6)     | 150 (15.9)     |       |
| ADL mean ± SD    | 4.8 ± 1.7     | 4.6 ± 1.7      | ns    |
| IADL mean ± SD   | 3.7 ± 2.6     | 3.3 ± 2.4      | 0.003 |
| NPI Total Score  | 12.46 ± 13    | 13.66 ± 13     | ns    |

Data are presented as N (%) or mean ± DS. *\( p < 0.05 \); **\( p < 0.001 \).

RESULTS

A total of 1,925 patients were included (387 EOAD and 1,538 LOAD). Table 1 shows demographic data for each group. The percentage of females was greater in LOAD compared to EOAD group (\( p = 0.008 \)), EOAD group was higher educated (\( p = 0.000 \)) and scored higher in the IADL (\( p = 0.003 \)). No significant differences different in terms of family history of dementia, MMSE, CIRS, CDR, NPI, and ADL score were found between the two groups.

Overall prevalence of BPSD

The pattern of overall prevalence of BPSD in the whole sample is presented in Supplementary Figure 1. Considering the whole sample, 90.8% of the patients manifested at least one BPSD. More than two thirds of patients showed Apathy (57.4%), followed by Irritability (50.5%), Agitation (42.3%), Depression (38.8%), Sleep and Nighttime Behavior Disorders (35.6%), Hallucinations (27.5%), Anxiety (26.8%), Disinhibition (26.3%), Delusions (24.8%), Eating Disorders (13.6%), Aberrant Motor Behavior (10.6%), and Euphoria (2.3%).

The pattern of overall prevalence of BPSD between the two groups is presented in Table 2. The prevalence was significantly higher in EOAD compared to LOAD patients for Apathy (\( p = 0.022 \)), Agitation (\( p = 0.001 \)), Depression (49.4 versus 36.25, \( p = 0.000 \)), Hallucination (\( p = 0.018 \)), Anxiety (\( p = 0.027 \)), Disinhibition (\( p = 0.004 \)), and Eating Disorders (\( p = 0.017 \)).
Table 2

| BPSD                        | EOAD | LOAD  | p     |
|-----------------------------|------|-------|-------|
| Apathy                      | 62.5 | 56.1  | 0.022 |
| Irritability                | 48.1 | 51.2  | ns    |
| Agitation                   | 49.6 | 40.5  | 0.001 |
| Depression                  | 49.4 | 36.2  | 0.000 |
| Sleep and Nighttime Behavior Disorders | 33.6 | 36.2  | ns    |
| Hallucinations              | 32.3 | 26.3  | 0.018 |
| Anxiety                     | 31.3 | 25.7  | 0.027 |
| Disinhibition               | 32   | 24.8  | 0.004 |
| Delusions                   | 26.1 | 24.5  | ns    |
| Eating Disorders            | 17.3 | 12.7  | 0.017 |
| Aberrant Motor Behavior     | 12.9 | 10    | ns    |
| Euphoria                    | 1.8  | 2.4   | ns    |

*p < 0.05; **p < 0.001.

Occurrence and prevalence over time of BPSD

The occurrence and prevalence over time of each BPSD in the whole sample is presented in Supplementary Figure 2. At pre-T0 (Supplementary Figure 2a), Depression, Anxiety, Apathy, and Sleep and Nighttime Behavior Disorders were the symptoms most represented whereas at T0 (Supplementary Figure 2b) and T1 (Supplementary Figure 2c) all BPSD were strongly showed except Euphoria. The occurrence and prevalence over time of each BPSD between EOAD and LOAD is presented in Table 3. At pre-T0, the prevalence of Sleep and Nighttime Behavior Disorders was higher in EOAD (p = 0.022). At T0, Irritability (p = 0.000), Agitation (p = 0.001), and Sleep and Nighttime Behavior Disorders (p = 0.000) were more frequently in LOAD, whereas Depression was more prevalent in EOAD (p = 0.018). At T1 Apathy (p = 0.000), Irritability (p = 0.000), Agitation (p = 0.000), Depression (p = 0.000), Sleep and Nighttime Behavior Disorders (p = 0.000), Hallucinations (p = 0.001), Anxiety (p = 0.000), Disinhibition (p = 0.006), Delusions (p = 0.000), Eating Disorders (p = 0.000), Aberrant Motor Behavior (p = 0.000), were more prevalent in EOAD compared to LOAD patients.

Time of occurrence of BPSD

The time of occurrence is presented in Fig. 1. Most BPSD were distributed between the fourth and fifth year after the onset of the disease in all groups. However, Apathy (p = 0.000), Irritability (p = 0.000), Agitation (p = 0.001), Sleep and Nighttime Behavior Disorders (p = 0.04), Hallucinations (p = 0.001), Disinhibition (p = 0.002), Delusions (p = 0.000), Eating Disorders (p = 0.000), and Aberrant Motor Behavior (p = 0.04) appeared significantly later in EOAD compared to LOAD patients.

BPSD sub-syndromes prevalence

The prevalence of BPSD sub-syndromes is presented in Fig. 2. At T0, Apathy (p = 0.000), Psychosis (p = 0.000) and Hyperactivity (p = 0.000) were more prevalent in LOAD group. At T1 all the four sub-syndromes, namely, Affective (p = 0.000), Apathy (p = 0.000), Psychosis (p = 0.013), and Hyperactivity (p = 0.000) were more prevalent in EOAD group.

Severity of BPSD

Finally, severity was investigated for Total NPI score, for each individual BPSD and for the BPSD sub-syndromes at T0 and T1. Results did not show significant differences (data not shown).

Table 3

| BPSD                        | Pre-T0 | T0       |
|-----------------------------|--------|----------|
|                             | EOAD   | LOAD     | p     | EOAD   | LOAD     | p     |
| Apathy                      | 1.8    | 2.7      | ns    | 43.2   | 46.3     | 0.000 |
| Irritability                | 1.3    | 0.5      | ns    | 26.1   | 40.2     | 0.000 |
| Agitation                   | 0.3    | 0.5      | ns    | 19.1   | 27.5     | 0.001 |
| Depression                  | 4.4    | 4.2      | ns    | 34.6   | 28.5     | 0.018 |
| Sleep and Nighttime Behavior Disorders | 2.3   | 0.9      | 0.022 | 13.4   | 25.1     | 0.000 |
| Hallucinations              | 0      | 0.3      | ns    | 15.2   | 18.2     | 0.001 |
| Anxiety                     | 2.8    | 2        | ns    | 21.2   | 19.1     | 0.000 |
| Disinhibition               | 0      | 0.2      | ns    | 28.2   | 23.4     | 0.006 |
| Delusions                   | 0.3    | 0.4      | ns    | 14.2   | 18.1     | 0.000 |
| Eating Disorders            | 0      | 0.1      | ns    | 7.5    | 9.1      | 0.011 |
| Aberrant Motor Behavior     | 4.1    | 5.9      | ns    | 8.8    | 4.4      | 0.000 |
| Euphoria                    | 0.8    | 1.5      | ns    | 1      | 1.1      | ns    |

*p < 0.05; **p < 0.001.
DISCUSSION

The main aim of this study was to characterize occurrence, time of occurrence, prevalence, and severity of BPSD and prevalence of BPSD subsyndromes in a large cohort of EOAD versus LOAD. Patients were observed at three stages: pre-T0 (before the onset of the disease), T0 or Manifested Disease (from onset to 5 years) and T1 or Advanced (from 5 years onwards).

**Overall prevalence and prevalence over time of BPSD in the whole sample**

The analyses of overall prevalence of each BPSD in the whole sample showed that apathy was the most frequent symptom (Supplementary Material), in line with previously published data [5, 42, 43]. This finding was very important since there is often an overlap between apathy and depression in dementia [44, 45]. Because depression and apathy have different neurobiological basis it is essential to identify them as two distinct BPSD in order to guide treatment decisions [46]. In addition, our results showed that euphoria was the less common symptom according to a recent metanalysis that included 64 studies carried out between 1964 and 2014 [5]. Considering the prevalence over time we found that depression, anxiety, and apathy occur before the onset of AD (see the Supplementary Material) accordingly to previous data for AD [47, 48] and mild cognitive impairment (MCI). Thus anxiety, depression, and apathy could represent a wake-up call to which clinicians should pay attention for the early detection of AD before the cognitive decline as already suggested by Ma et al. [49]. This paper outlines that these three BPSD when present at the same time seems to predict both cognitive decline and progression from MCI to AD.
In addition, it has been suggested that depression could represent a risk factor for developing dementia, strengthening the importance to implement preventive strategies targeting especially this latter BPSD [50].

Overall prevalence of BPSD in EOAD versus LOAD patients

Although BPSD are common in both EOAD and LOAD patients, their prevalence and frequency vary across the few studies carried out so far. Our findings are in keeping with those that found a higher BPSD prevalence in EOAD compared to LOAD patients [26, 29]. We found in particular that apathy, agitation, depression, hallucinations, anxiety, disinhibition, and eating disorders were significantly higher in EOAD patients (Table 2). The cause for increased BPSD in EOAD is likely multifactorial and includes both social and biological factors. Receiving a diagnosis of AD is probably more emotionally difficult for EOAD than LOAD patients due to their younger age, more responsibilities within their families such as taking care of children and holding down a job [29]. In addition, the pathophysiology of AD spreads in a more rapid and aggressive manner in EOAD compared to LOAD [51] determining a worse prognosis [52].

Prevalence over time of BPSD in EOAD versus LOAD patients

Comparing BPSD prevalence over time in the two groups we showed that in the preT0 phase the prevalence of Sleep and Nighttime Behavior Disorders was higher in EOAD compared to LOAD patients. However, at T0 these symptoms were higher in LOAD associated also with Irritability, Agitation, and Depression. Successively, at T1 phase all BPSD were more represented in EOAD patients. These results were particularly relevant demonstrating that EOAD is more rapid and aggressive than LOAD not only at a neuropathological [51, 53, 54], cognitive [52, 55] and functional [52] level but also at a psychiatric dimension.

Time of occurrence of BPSD in EOAD versus LOAD patients

Most BPSD occurred between the fourth and fifth year of the disease in both groups. However, Apathy, Irritability, Agitation, Sleep and Nighttime Behavior Disorders, Hallucinations, Disinhibition, Delusions, Eating Disorders, and Aberrant Motor Behavior emerged significantly early in LOAD compared to EOAD patients. Anxiety, Depression, and Euphoria presented with the same trend of occurrence without significant difference. This distribution can reflect the fact that a high proportion of AD patients receive a delayed diagnosis as already pointed out [56] probably when cognitive symptoms become disabling and/or BPSD destroy the family context.

However, as we already mentioned, some BPSD were present before the onset of AD in line with the literature that conceptualized mild behavioral impairment (MBI) as a transitional state between normal aging and dementia present even before cognitive symptoms appear [57, 58]. Thus, it is of primary importance to instruct general practitioners to consider BPSD as possible precursors of dementia and to promote awareness campaigns in the general population reaching an early diagnosis and, therefore, providing care as soon as possible.

Prevalence of BPSD sub-syndromes in EOAD versus LOAD patients

This study represents also the first attempt to compare and characterize the prevalence of BPSD sub-syndromes in EOAD versus LOAD patients. In agreement with the previous studies on BPSD subsyndromes, that considered AD patients without making a distinction between EOAD and LOAD, all the 4 sub-syndromes were manifested by AD patients [5, 8]. Interestingly, we found a different pattern of prevalence of BPSD sub-syndromes between EOAD and LOAD considering two different time points, namely, T0 and T1. At T0 the prevalence of the subsyndromes Apathy, Psychosis, and Hyperactivity was higher in LOAD patients whereas we found no difference in the prevalence of Affective subsyndrome between the two groups. Furthermore, at T1 the prevalence of all sub-syndromes was higher in EOAD compared to LOAD patients. This pattern of BPSD sub-syndromes strengthens the need to consider EOAD and LOAD as two different forms of a single entity [58] also from a psychiatric point of view.

BPSD severity in EOAD versus LOAD patients

The overall NPI total score was not significantly different between the two groups according to previous studies [26, 27] and also the severity of each BPSD and BPSD sub-syndromes, at T0 and T1, was similar. Overall, these findings demonstrated that it is
important to give equal attention to BPSD throughout the whole course of the illness in order to guide treatment choices and strategies for both EOAD and LOAD patients.

**Strengths and limitations of the study**

This study has some criticisms. These include the different distributions of gender, level of education, and IADL score between the two groups. However, it is well known that AD is higher prevalent in women than men, particularly at age of 70 years [60]. This might have unbalanced our sample. Concerning the different level of education, it has been shown that EOAD patients are typically more instructed compared to LOAD patients [52] probably due to the improvement in the education system. As mentioned above, the analyses performed showed that EOAD displays more apathy than LOAD patients. Accordingly to the previous literature, the lower IADL score of EOAD could be explained by persistent apathy that predict a more rapid instrumental functional decline [61]. In fact, the two groups were comparable for MMSE, CDR, CIRS, ADL, and NPI total score strengthening the validity of our analyses.

A strong point of this study was the sample size. Our research was performed on a very large number of patients unlike the previous studies. Second, patients were followed for a long time and their data collected with the same methodology and the same research team since 1996. Finally, as far as we know, this study represents the first attempt to compare the prevalence of BPSD sub-syndromes between EOAD and LOAD patients.

**Conclusion**

In conclusion, EOAD and LOAD represent two different forms of a single entity not only at a neuropathological, cognitive, and functional level but also from a psychiatric point of view. Indeed, BPSD manifest differently in occurrence, time of occurrence, overall prevalence, and prevalence over time between EOAD and LOAD patients along the whole course of the illness. In the same line also the prevalence of BPSD sub-syndromes follows a different pattern of manifestation over time. Our findings reinforce the clinical importance of not considering AD only as a “cognitive” disease emphasizing the urgency of characterizing the BPSD pattern of each patient to guide treatment choices and strategies. Interestingly, some signs of behavioral changes, such as apathy, depression, and anxiety, appear in both EOAD and LOAD patients before the onset of AD. The identification of these “wake-up call” signs of AD can be important and significant for the early detection of the disease. The different pattern of BPSD that we observed between EOAD and LOAD patients can be related to several genetic risk factors, brain’s pathophysiological changes, gender differences, and drug usage. Indeed, further studies are needed to correlate genetic risk factors with the manifestation of BPSD, as well as, to analyze the different pattern of BPSD and brain functional changes across the course of the disease in EOAD and LOAD, taking into account gender differences and drugs.

**DISCLOSURE STATEMENT**

Authors’ disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-5061r1).

**SUPPLEMENTARY MATERIAL**

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