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A 2-Year Follow-Up of Behavioural and Psychological Symptoms in Alzheimer's Disease

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Key Words

Alzheimer's disease · BPSD · Longitudinal evaluation · Correlates of persistence

Abstract

Background: The aim was to examine the longitudinal occurrence and persistence of behavioural and psychological symptoms of dementia (BPSD) in Alzheimer's disease (AD). ***Methods:*** Following 60 patients with mild to severe AD over a period of 2 years with annual evaluations, the prospective occurrence and persistence of BPSD in AD were determined by using the Behavioural Abnormalities in AD Rating scale (BEHAVE-AD). Clinical and demographic features of the AD patients were analysed for their association with course features of these symptoms. ***Results:*** All of the 60 AD patients experienced BPSD at some point during the 2-year period, particularly agitation was present in every patient within this period. 2-year persistence of BPSD in AD was frequently observed in patients with agitation and with depressiveness, with less frequency in patients with anxiety and aggressiveness, but not in patients with delusions or hallucinations. 2-year persistent aggressiveness was associated with older age and more functional impairment. More functional impairment was also related to 2-year non-persistent hallucinations. ***Conclusions:*** Counselling AD patients and their families and tailoring therapeutic strategies should take into account the different modi of BPSD in AD occurring and persisting longitudinally and interacting with functional disturbances.

Introduction

Non-cognitive symptoms are frequent features in the clinical syndrome of dementia [1]. Recently, they have been termed 'behavioural and psychological symptoms in dementia' (BPSD) [2]. The presence of these symptoms in Alzheimer's disease (AD) strongly contributes to premature institutionalization [3]. These symptoms, furthermore, reduce the individual well-being of the dementia sufferer and critically increase the burden of the caregiver in the management of the patient in daily living. Moreover, BPSD in AD are principally remediable by psychopharmacological and psychotherapeutic interventions [4, 5]. A considerable amount of literature has been accumulated pertaining to the cross-sectional prevalence of these

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symptoms, their symptom pattern and their association with severity and rate of progression of cognitive and functional impairment [1, 6]. It has been demonstrated that the prevalence of BPSD, particularly in AD, increases with disease progression and may herald a poor prognosis [7–9]. However, relatively little attention has been paid to the longitudinal occurrence of BPSD, especially their tendency to persist, fluctuate or remit during the course of the disease. The collection and analysis of such data are imperative, if useful criteria for their longitudinal identification are to be developed and optimal treatment duration for different types of BPSD can be determined. The identification of specific treatment durations for specific symptoms is important because the use of psychotropic medication is related to increasing side effects with advancing age [10].

In a 1-year prospective study of depression in patients with AD, vascular dementia and with Lewy body disease, depression tended to be persistent in vascular dementia over a period of more than 3–6 months, whereas most of the AD patients presented with depression of 1–5 months' duration [11]. Investigating the same sample over a period of 1 year, Ballard et al. [12] also reported that more than half of the demented patients with psychotic symptoms experienced resolution of their symptoms which lasted less than 3 months. Long-term persistence of psychotic symptoms in these patients was not related to the type of dementia [12]. In addition, prescription of neuroleptics did not significantly influence the course of psychotic symptoms. Devanand et al. [13] reported from their prospective study of AD patients over a period of up to 5 years with 6-month assessment intervals that behavioural disturbances, particularly agitation, were common and persistent almost over 2 years, whereas psychotic symptoms showed moderate persistence and a depressed mood was rather uncommon and rarely persisted. In another study [14] the longitudinal course of depression was investigated in AD over a period of up to 2 years with annual assessment intervals. The authors separated dysthymia from major depression in their AD patients, using DSM-III-R diagnoses, and reported that dysthymia in AD was a brief emotional disorder while the majority of AD patients with major depression (58%) experienced a longer-lasting mood change persistent over the mean follow-up of 16 months [14].

In order to determine the longitudinal occurrence and persistence of different types of BPSD in AD we followed 77 patients with initially mild to moderate probable AD with annual evaluations over a period of 2 years.

Methods

Patients and Instruments

From a total of 265 consecutively admitted outpatients, 90 patients were selected for a longitudinal study. They met NINCDS-ADRDA diagnostic criteria for mild to moderate probable AD. Twelve months after the first evaluation 77 of these 90 patients could be investigated again. In these 77 AD patients data were collected with the Cambridge Mental Disorder of the Elderly Examination [CAMDEX; 15]. This examination is a lengthy diagnostic interview made up of a mental state examination, including the Cambridge Cognitive Examination (CAMCOG) and the Mini Mental State Examination [MMSE; 16], a medical and psychiatric history and a brief physical examination. It furthermore contains a semistructured interview with an informant, in this study caregiving relatives. This section of the CAMDEX also includes an abbreviated version of the Dementia Scale [DS; 17] which globally assesses impairment in tasks of daily living. Diagnostic procedures in the AD patients encompassed laboratory examinations, EEG and CCT. Clinical diagnosis of AD was concordant with the postmortem diagnosis in 25 (96%) of the 27 AD cases who died during follow-up and in whom autopsy was obtained. BPSD in AD were evaluated with the Behavioural Abnormalities in AD Rating Scale [BEHAVE-AD; 18], a scale specifically designed to assess the presence and rate the severity of these symptoms in AD patients. The BEHAVE-AD has demonstrated a good sensitivity to change of rated symptoms and has a high reliability and validity [19]. Each item is scaled from 0 (= not present) to 3 (= most severe). The scores of the items were summed over rated behaviours to yield subscale scores for delusions, hallucinations, agitation, aggressive behaviour, depressiveness and anxiety. Information was obtained through the rater's observations during the interview with the patient and through the information of caregivers about abnormalities in daily living.

Hallucinations were identified from caregiver reports of instances in which a patient spontaneously described a sensory perception in the absence of a concomitant external stimulus. Psychotic symptoms or agitation that occurred in the context of delirium were not included in the BEHAVE-AD score.

Psychopharmacological medication was documented throughout the study period and rated as present or absent. Neuroleptic medication was prescribed for 44% of the AD patients with psychotic symptoms and 42% with motor disturbances. Furthermore, 32% of the depressed AD patients were given antidepressant medication. None of the AD patients taking neuroleptics had to stay on medication for longer than 4 weeks and, likewise, none of the AD patients taking antidepressants needed a prescription for longer than 3 weeks.

Analysis Plan

First, we determined the prevalence of BPSD in AD, as measured by the BEHAVE-AD, at study onset and cumulatively within the 2-year observation period. A symptom was rated as present, if the item scored 1 or more points on the BEHAVE-AD scale. Second, we investigated the prospective occurrence of BPSD in AD by defining two groups at study onset: one group with a specific symptom present and the second group with a specific symptom absent. The influence of this group criterion was calculated for the presence of symptoms at the second and third assessment. Third, we determined groups of AD patients presenting with either persistent, non-persistent or completely absent BPSD within the study period. A symptom was 'persistent', if it was present at each of the three assessments, 'non-persis-

tent', if present at the first and third assessment, and 'absent', if it never occurred. Fourth, by means of stepwise discriminant analysis, we determined predictor variables potentially discriminating between these defined groups. These variables included age at onset, age at examination, gender, school years of education, initial severity of cognitive impairment, as measured by the CAMCOG and by the MMSE, and initial severity of functional impairment, as measured by the DS.

Furthermore, we established extreme group discriminant analysis to determine whether AD patients without specific BPSD over 2 years compared to AD patients with 2-year persistence of specific symptoms differed among demographic and severity-related measures, using the variables of the fourth step of the statistical analysis. Due to the relatively small sample size of AD patients completing the second follow-up, differences between mildly and moderately demented groups were not analysed.

The association of the presence of a specific symptom at study onset with the subsequent presence of this symptom was analysed by χ^2 tests. The relationship between the presence of a specific symptom at study onset and the subsequent severity of this symptom, as measured by the BEHAVE-AD subscale scores was calculated by t tests.

Results

Demographic and Clinical Features of the AD Patients

Of the 77 AD patients at study onset, 60 patients completed the 2-year study period. Table 1 lists the demographic and clincial features of these 60 AD patients. With a mean symptom duration of almost 5 years, some of the AD patients of this study were mildly, and the majority was moderately demented (see table 1). 48 AD patients were female, 12 were male. 32 of the 60 AD patients passed the secondary school examination and 19 AD patients the primary school examination. None of the 60 AD patients had a history of psychiatric disorders before the manifestation of dementia.

Initial and Cumulative Prevalence of BPSD in AD within 2-Year Observation Period

Table 2 presents the initial prevalence of BPSD of the AD patients. As can be seen, agitation was the most frequent symptom at study onset and, within a period of 2 subsequent years, all of the AD patients experienced agitation at some point during observation. Furthermore, depressiveness, anxiety and aggressiveness were quite frequent at initial assessment. During the subsequent evaluation, these symptoms were present in at least two thirds of the AD patients, depressiveness even in 78%. Hallucinations were less frequent throughout the 2 years of assessment.

Table 1. Demographic and clinical features of the AD patients who completed this study (n = 60)

Features	Mean	SD	Minimum	Maximum
Age at examination, years	73.4	7.7	57	88
Duration of symptoms, months	57.3	22.8	18	132
CAMCOG	38.8	25.2	1	88
MMSE	13.5	7.2	0	27
DS	15.7	6.7	5	32
GDS	5.4	0.7	4	7

GDS = Global Deterioration Scale.

Table 2. Initial and accumulated prevalence of behavioural and psychological symptoms in AD at study onset and over the 2-year observation period (n = 60)

Symptoms	Study onset		Within 2 years	
	n	%	n	%
Delusion	21	35	31	53
Hallucinations	11	18	21	35
Depressiveness	34	57	47	78
Anxiety	21	35	39	66
Agitation	52	87	60	100
Aggressiveness	28	47	44	74

Symptoms represent summed up subscale scores of the BEHAVE-AD scale.

Prospective Occurrence of BPSD in AD Patients Related to the Presence of Symptoms at Study Onset

As can be seen in table 3, the initial presence of delusions was not associated with its subsequent presence during the prospective observation. None of the AD patients with initial delusions showed delusional symptoms at second and at third assessment. Similarly, the initial presence of agitation was not associated with its subsequent presence during the observation. However, the number of cases without initial agitation was very small. AD patients with agitation at study onset continued to present with this symptom prospectively. Table 3 shows that 40 of the 52 initially agitated AD patients were rated as agitated at both follow-up assessments. With regard to hallucinations, depression, anxiety and aggressiveness, the initial presence of these symptoms was related to their prospec-

Table 3. Association of initial presence of specific symptoms with their subsequent presence in AD patients over a 2-year period

Symptom	Study onset	Present after 1 *or* 2 years	Present after 1 *and* 2 years	Absent at follow-up	χ^2	p
Delusion						
Present	21	9	–	12	1.02	0.3
Absent	37	11	–	26		
Hallucinations						
Present	11	8	–	3	12.7	0.002
Absent	48	9	1	38		
Depressiveness						
Present	34	9	20	5	10.5	0.005
Absent	26	7	7	13		
Anxiety						
Present	21	6	7	8	6.4	0.036
Absent	39	15	3	21		
Agitation						
Present	52	11	40	1	0.3	0.85
Absent	7	2	5	–		
Aggressiveness						
Present	28	8	13	7	6.1	0.04
Absent	32	10	6	16		

Table 4. Alzheimer patients with persistent, non-persistent and absent behavioural and psychological symptoms over the 2-year observation period

Symptom	Persistent		Non-persistent		Absent	
	n	%	n	%	n	%
Delusion	0	0	32	53	29	47
Hallucinations	0	0	21	34	39	65
Depressiveness	20	33	27	45	13	22
Anxiety	7	12	21	53	21	34
Agitation	40	67	20	33	0	0
Aggressiveness	13	22	21	52	16	26

tive occurrence. If one of these specific symptoms was present initially, this predicted its occurrence at the subsequent assessments. The effect was highly significant in AD patients with hallucinations and with depressiveness.

Furthermore, we analysed the relationship between the initial presence of BPSD of the AD patients and the subsequent severity of these symptoms after 1 year and 2 years. With respect to the 1-year observation, the initial presence of halluzinations (t value = 1.5; p = 0.15) and agitation (t value = 1.4; p = 0.16) was not related to a greater severity of these symptoms after 12 and 24 months. In contrast, AD patients presenting with either delusions (t value = 2.3; p = 0.02), depressiveness (t value = 2.1; p = 0.04), anxiety (t value = 2.2; p = 0.03) or aggressiveness (t value = 3.1; p = 0.003) at study onset experienced a greater severity of these symptoms after 1 year compared to AD patients without these initial abnormalities. However, after 2 years, depressiveness (t value = 3.3; p = 0.002) was the only feature of the AD patients which showed a relationship between its initial presence and its severity in the subsequent disease course.

Subgroups of AD Patients Presenting with either Persistent, Non-Persistent or Absent BPSD

As can be seen in table 4, AD patients with depressiveness, anxiety and aggressiveness were present in each of the three subgroups. These symptoms were either persistent, non-persistent or absent over 2 years of observation. AD patients suffering from delusions or hallucinations presented with non-persistent, and none with persistent abnormalities over the 2-year period, whereas a considerable number of patients never experienced these psychotic symptoms. Agitation, as already shown in table 2, was present in all AD patients within the 2 years. Table 4, in addition, demonstrates that at least 67% of the AD patients suffered from agitation at each of the three evaluations.

Predictor Variables Discriminating between the Defined Subgroups of AD Patients

We determined predictor variables which potentially discriminated between subgroups of AD patients with either persistent, non-persistent or absent BPSD. With respect to delusions, depressiveness, anxiety, agitation and aggressiveness, none of the examined variables discriminated between the three groups. However, the severity of impairment in tasks of daily living, as measured by the DS, was a significant predictor for discriminating the subgroup of AD patients with non-persistent hallucinations (DS mean score 12.7; SD 4.9) from the subgroup of AD patients without hallucinations (DS mean score 9.8; SD 4.3) over the 2 years of observation. AD patients without hallucinations were significantly less impaired in daily living (F value 5.1; $p = 0.02$).

Furthermore, we examined potentially discriminating variables by opposing extreme groups of AD patients: one group with persistent symptoms and the other group without any symptoms. In this analysis, only three BEHAVE-AD subscale scores, representing depressiveness, anxiety and aggressiveness, could be included because they had allocated AD patients to both of these groups. Stepwise discriminant analysis revealed two predictors which discriminated between the group of AD patients with persistent aggressiveness and the group of AD patients without aggressiveness over 2 years of observation. AD patients with persistent aggressiveness were significantly more functionally impaired (DS mean score 12.9; SD 4.8) and significantly older (mean age 75.8; SD 6.4 years) compared to AD patients without aggressiveness over 2 years (DS mean score 8.5; SD 3.6; mean age 69.1 years; SD 6.8 years; DS: F value 6.4; $p = 0.005$; age: F value 7.9; $p = 0.009$). None of the predictors was able to distinguish between the groups with regard to persistence or absence of depressiveness and anxiety.

Discussion

In the present prospective study, the prevalence of specific types of BPSD in AD was consistent with findings from other studies of outpatients with AD [1, 20, 21], though rated higher than in some other investigations [22, 23]. Behavioural symptoms, particularly agitation, occurred in more than 4 out of 6 AD patients. Furthermore, psychological symptoms, such as depressiveness, were quite frequent at initial assessment in this study. Aggressiveness was a frequent behavioural abnormality. Its relatively high frequency may be explained with the fact that the BEHAVE-AD item aggressiveness includes physical violence as well as verbally aggressive behaviour.

The prospective longitudinal data are in part novel. They have important implications for clinicians and caregivers. Agitation in AD represents the most frequent behavioural disturbance during the course of the disease and affects every AD patient over a period of 2 years, as was demonstrated in the present study. Furthermore, in two thirds of the AD patients in this study agitated behaviour with persistence over 2 years could be observed. The mood disturbance depressiveness ranges among the most frequent symptoms in the 2-year disease course. In one third of the AD patients with initial depressiveness this psychological symptom persisted over a period of 2 years, while it was non-persistent in almost half of the AD patients. A 2-year persistence of symptoms was also demonstrated in AD patients with anxiety and aggressiveness at study onset, though this observation was less frequent. Furthermore, depressiveness, anxiety and aggressiveness at study onset were associated with their subsequent 2-year occurrence and with an increased severity of anxiety and aggressiveness at the 1-year assessment and of depressiveness at the 1- and 2-year evaluation.

These results suggest that agitation is both the most common and the most persistent symptom in AD patients, which is in accordance with another recent study [13]. Depressiveness, anxiety and aggressiveness are still quite frequent in AD and tend to persist over 1–2 years [14], while delusions and particularly hallucinations are less common and do not occur with long-term persistence [12]. The persistent nature of agitated behaviour as well as of depressiveness, anxiety and aggressiveness suggests that treatment strategies of these target symptoms may need to be prolonged in the clinical practice and individually tailored during long-term management. Delusions and hallucinations in AD do not present with longer duration and long-term maintenance therapy may not be appropriate. The results of this study, therefore, may offer suggestions for the optimal treatment duration for specific types of BPSD in AD. Empirical research designs should prove these suggestions.

Another interesting finding in this study was the association of functional impairment with the occurrence of hallucinations within the 2-year period. The presence of hallucinations seems to increase the likelihood of AD patients to be more impaired in instrumental and basic activities in their home environment, even if this behavioural symptom is non-persistent. This observation should take into account that AD patients with initial hallucinations showed an increased subsequent severity of

this behavioural symptom after 1 year compared to AD patients without initial hallucinations.

The between-group comparison further yielded an association of more functional impairment in AD patients with persistent aggressiveness compared to AD patients without this symptom within 2 years. Moreover, AD patients with persistent aggressiveness were significantly older. Persistent aggressiveness may significantly increase the inability of AD patients to cope with tasks of daily living [3, 24, 25]. Furthermore, it has been demonstrated that aggressiveness is associated with the presence of hallucinations in AD [6, 25]. Management of AD patients and counselling of their families, therefore, should include the assessment of these behavioural symptoms, in addition to an evaluation of activity disturbances in daily living and a thorough determination of their interaction [5, 26, 27]. Otherwise, the time span for AD patients remaining in their home environment may be significantly shortened. This risk may particularly apply to older AD patients. Prospective studies in the literature undoubtedly demonstrated that behavioural symptoms in AD, particularly aggressiveness, are strong predictors of premature nursing home placement and, therefore, should be treated rigorously to avoid institutionalization [3, 28]. Treatment interventions focussing on alleviating these symptoms in AD have already proved to be successful [29, 30].

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