The course of neuropsychiatric symptoms in dementia. Part II: relationships among behavioural sub-syndromes and the influence of clinical variables

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SUMMARY

Background Although several studies have mentioned associations between neuropsychiatric symptoms, there have been no prospective studies determining interrelations among behavioural sub-syndromes.

Objectives To investigate the influence of several clinical variables on the course of neuropsychiatric symptoms, and to determine interrelationships between the behavioural sub-syndromes.

Methods One hundred and ninety-nine patients with dementia were assessed every six months for two-years, using the Neuropsychiatric Inventory (NPI) to evaluate neuropsychiatric symptoms.

Results Age, sex, and socioeconomic status were not associated with a specific neuropsychiatric symptom. Greater cognitive impairment was related to more severe psychosis, and dementia stage influenced the course of total NPI problems. There were strong interrelations among most behavioural sub-syndromes. The sub-syndrome hyperactivity was of influence on the development of psychosis, but not vice versa. Neither was the sub-syndrome mood/apathy of influence on the course of psychosis.

Conclusions While different neuropsychiatric symptoms have their own specific correlates, there is a strong interrelationship between behavioural sub-syndromes. The data have implications for clinicians and the nosology of neuropsychiatric symptoms in dementia. Copyright © 2005 John Wiley & Sons, Ltd.

key words — behaviour; neuropsychiatric symptoms; sub-syndromes; dementia; Alzheimer

INTRODUCTION

Neuropsychiatric symptoms are a major problem in patients with dementia. They decrease the quality of life of both patients and caregivers, are associated with caregiver distress, and increase the likelihood of institutionalization (Fink et al., 1998; Chan et al., 2003). Authors have mentioned correlations between separate neuropsychiatric symptoms (Flynn et al., 1991; Lopez et al., 2003; Senanarong et al., 2004). Moreover, there is evidence for the presence of behavioural sub-syndromes in dementia (Hope et al., 1997; Frisoni et al., 1999; McShane, 2000; Fuh et al., 2001; Lyketsos et al., 2001a; Lyketsos et al., 2001b; Aalten et al., 2003). The presence of behavioural sub-syndromes in dementia is recognized in clinical practice, but it is unclear to what degree the sub-syndromes co-occur and influence each other. Lyketsos et al. (2001a) found a complex co-occurrence of neuropsychiatric symptoms in a population-based study including patients with Alzheimer’s disease, however, they did not mention temporal relationships between the different problems, and in particular behavioural sub-syndromes. More knowledge about the interrelations among behavioural sub-syndromes may help clinicians to make a better prediction of the clinical course, and to develop better treatment strategies. In addition, knowledge about the influence of clinical characteristics of

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patients on the development of the neuropsychiatric symptoms may help to define vulnerable patients. Previous studies have reported inconsistent results regarding the association of neuropsychiatric symptoms with clinical variables such as age, sex and severity of dementia (Levy, 1996; Devanand et al., 1997). These inconsistencies reflect differences in inclusion criteria, methodologies, and referral populations. Moreover, most studies were limited by a cross-sectional design.

In this article we report findings from a two-year longitudinal prospective study of the course and predictors of neuropsychiatric symptoms in nearly 200 subsequently referred dementia outpatients, with evaluations at six-month intervals. The aim of this study was to examine relationships among behavioural sub-syndromes, and to investigate whether clinical and demographic characteristics, in particular age, sex, severity of dementia, level of cognitive impairment, and socioeconomic status (SES) influence the course of neuropsychiatric symptoms.

METHODS

Patients

The present study was part of the MAAstricht Study of BEhaviour in Dementia (MAASBED), a study that focuses on the course and risk factors of neuropsychiatric symptoms in dementia. MAASBED is a two-year prospective study of 199 ambulatory patients with dementia, who are followed up at six-month intervals. Patients were enrolled from the Maastricht Memory Clinic of the University Hospital Maastricht, or the geriatric division of the Regional Institute for Community Mental Health Care (RIAGG), Maastricht. Both are psychiatric-based clinics. Most of the patients were referred by a local practitioner because of cognitive deficits, while in some cases the presence of neuropsychiatric symptoms was the reason for referral. The study patients were a representative sample of dementia patients living in the community.

Patients were included if they met the DSM-IV criteria for dementia (American Psychiatric Association, 1994) and if there was a reliable informant. Of these, 146 patients met the NINCDS-ADRDA (McKhann et al., 1984) (possible, probable) Alzheimer-type dementia, 32 patients met the NINCDS-AIREN criteria for vascular dementia (Roman et al., 1993), two patients met criteria for dementia with Lewy bodies (McKeith et al., 1996), and 19 patients met criteria for dementia due to multiple etiologies. Patients were excluded if they were living in a nursing home at the start of the study. Written consent was given by the caregiver, and, when possible, by the patient. The Medical Ethics Committee of the University Hospital Maastricht approved this study.

Neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), an informant-based rating scale developed to assess psychopathology in patients with dementia. The current version (Cummings, 1997) evaluates 12 neuropsychiatric symptoms commonly observed in dementia: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities. The severity and frequency of each symptom are scored on the basis of structured questions administered to the patient’s caregiver. The score for each symptom is obtained by multiplying severity (1–3) by frequency (1–4). The summed symptom scores give the total NPI score. The validity and reliability of the NPI (Cummings and McPherson, 2001), and of its Dutch version (Kat et al., 2002), have been established previously.

In addition, NPI items were clustered based on a previous principal component analysis study (Aalten et al., 2003). This resulted in three factors: (1) a ‘mood/apathy’ factor including depression, apathy, night-time behaviour disturbances and eating abnormalities (four items, Cronbach’s alpha = 0.63); (2) a ‘hyperactivity factor’, including the symptoms agitation, euphoria, irritability, disinhibition, and aberrant motor behaviour (five items, α = 0.73); and (3) a ‘psychosis factor’, including hallucinations and delusions (two items, α = 0.72). Anxiety was regarded as a separate symptom. The total score for each sub-syndrome was calculated by summing the NPI item scores for each factor.

In line with previous studies (Ballard et al., 2001; Lyketsos et al., 2002; Steinberg et al., 2003; Steinberg et al., 2004), a score greater than 3 was taken to indicate the presence of specific ‘clinically relevant’ NPI total score, and sub-syndromes.

Predictors

The Mini-Mental State Examination (Folstein et al., 1975) (MMSE) was administered as a measure of cognitive impairment. The severity of dementia was rated with the Global Deterioration Scale (GDS) (Reisberg et al., 1982). For the purpose of this study,
cognitive decline is expressed as mild (MMSE scores $> 20$), moderate (MMSE scores between 20 and 11), and severe (MMSE scores $\leq 10$); and severity of dementia as mild (GDS scores 3 and 4), and severe (GDS scores $\geq 5$). Patients were grouped by age as follows: youngest (53–65 years), middle (66–75 years), and oldest (76–96 years). Highest level of profession, ranging from untrained work to higher professions, determined the SES. We decided not to include the level of education, because elderly women, in particular, have not had the opportunity to receive higher education.

**Statistical analyses**

Statistical analyses were performed with the Statistical Package for Social Sciences, version 10. Analyses of variance (ANOVA) with repeated measures were performed to determine whether age, sex, SES, and severity of dementia (as assessed by the MMSE and GDS) at baseline were predictors of the development of the three sub-syndromes, and NPI-total score. In addition, the same analyses were performed to determine whether the presence of clinically relevant behavioural sub-syndromes at baseline was associated with the course of neuropsychiatric problems, after controlling for MMSE or duration of illness. All significance tests were performed at a two-tailed alpha level of 0.05.

**RESULTS**

**Patient characteristics**

Table 1 shows the demographic and clinical characteristics of the patients. At baseline, 83 men (41.7%) and 116 women (58.3%) were included in the study. The mean age was 76.4 ± 8.0 years (range 53–96 years). Most patients had a relatively low SES. Patients had an average MMSE score of 18.1 ± 4.7 at baseline, which declined at each subsequent follow-up, to reach 14.7 ± 5.8 after two years. The GDS scores increased during follow-up, indicating that the global severity of dementia increased with time.

A number of patients dropped out during the study (refusal, $n = 51$ (26%); death, $n = 49$ (24%)), so that complete two-year follow-up data were available for 99 patients (49.7%). At study entry, neuropsychiatric symptomatology (NPI total score and sub-syndromes), and major demographic characteristics of patients who fulfilled total follow-up were similar compared to those individuals who had died or were discontinued from the study. However, the 100 patients who did not complete the total study were more severely cognitively disturbed, with lower MMSE scores ($17.4 \pm 4.8$ vs $18.8 \pm 4.6; p = 0.04$) and higher GDS stage ($4.2 \pm 0.8$ vs $4.0 \pm 0.6; p = 0.02$), at baseline than were the subjects who completed the study. This indicates some selective attrition of patients with relatively severe dementia.

**Predictors of neuropsychiatric symptoms**

To determine whether age, sex, SES, and severity of dementia at baseline were of influence on the course of the neuropsychiatric symptoms, analyses of variance with repeated measures were performed including one-year follow-up data. Later follow-up assessments were not analyzed in this way because of the small sample (due to dropout).

Age, sex, and SES were not associated with the presence of any symptom during follow-up. Greater cognitive impairment, as determined with the MMSE, at baseline was related to higher level of psychosis at follow-up assessments ($F = 3.5(2,132), p = 0.034$). Post-hoc comparisons revealed a significant difference in psychosis between the groups at baseline ($F = 4.7(2,190), p = 0.010$), indicating patients with moderate MMSE scores to have higher levels of psychosis than patients with mild cognitive impairment. At six months ($F = 3.4(2,152), p = 0.035$), patients with severe dementia had higher scores for psychosis than did patients with mild dementia.

Furthermore, there was a significant interaction between time and GDS score and the NPI total score ($F = 4.9(2,266), p = 0.008$). At baseline, patients with mild dementia (as determined with the GDS score) had significantly less neuropsychiatric symptoms than patients with severe dementia ($p = 0.009$). Then, while NPI total scores decreased on average during the one-year period in the patients with severe dementia, there was an increase in neuropsychiatric symptoms in patients with mild dementia. This effect

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Table 1. Demographic and clinical characteristics of 199 patients at study entry (mean ± SD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.4 ± 8.0</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>58.3</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>2.1 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>4.1 ± 0.7</td>
</tr>
<tr>
<td>MMSE</td>
<td>18.1 ± 4.7</td>
</tr>
<tr>
<td>Mood/apathy</td>
<td>9.7 ± 10.0</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>7.0 ± 10.2</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2.8 ± 5.3</td>
</tr>
<tr>
<td>Total NPI</td>
<td>21.6 ± 20.8</td>
</tr>
</tbody>
</table>

*Ranging from untrained work to higher profession.*
could largely be attributed to the sub-syndrome hyperactivity, where there was the same significant interaction between time and GDS ($F = 4.9_{(2,260)}$, $p = 0.008$).

**Relationship between presence of neuropsychiatric symptoms at baseline and follow-up**

The presence of the three sub-syndromes and a high NPI total score at baseline tended to be positively associated with their subsequent occurrence during the two-year follow-up (see Table 2). Most patients who had neuropsychiatric symptoms at baseline continued to have them, regardless of the type of problem. The presence of clinically relevant NPI-total score at baseline had a significant main effect on neuropsychiatric symptoms, independent of MMSE score or duration of illness. It most strongly predicted the subsequent development of the sub-syndrome mood/apathy ($F = 24.3_{(1,96)}$, $p < 0.001$). The sub-syndrome mood/apathy influenced the subsequent development of this sub-syndrome itself ($F = 14.2_{(1,96)}$, $p < 0.001$), NPI-total score ($F = 10.0_{(1,96)}$, $p = 0.002$), and hyperactivity ($F = 4.9_{(1,96)}$, $p = 0.03$), but not psychosis ($F = 2.7_{(1,96)}$, $p = 0.11$). However, psychosis was a predictor of the development of the sub-syndrome mood/apathy ($F = 9.0_{(1,96)}$, $p = 0.003$) at later assessments. Also of interest was that the sub-syndrome hyperactivity predicted the subsequent development of psychosis ($F = 4.1_{(1,96)}$, $p = 0.046$), whereas psychosis did not influence the development of hyperactivity ($F = 2.0_{(1,96)}$, $p = 0.16$).

**DISCUSSION**

This study examined the influence of several variables on the development of behavioral problems in patients with dementia, and interrelations among neuropsychiatric symptoms in a large longitudinal study. We did not find sex, and age at baseline to influence the course of neuropsychiatric symptoms, in contrast with the results of Levy et al. (1996). In line with their results, we found a relationship between neuropsychiatric symptoms and global severity of dementia. Patients with mild dementia at baseline showed more neuropsychiatric symptoms with time, whereas patients with severe dementia showed fewer neuropsychiatric symptoms. Greater cognitive impairment was related to higher levels of psychosis, which is in keeping with previous studies reporting psychosis to be associated with more rapid cognitive decline (Drevets and Rubin, 1989; Rosen and Zubenko, 1991; Levy et al., 1996). As in our study, Devanand et al. (1997) found no association between several clinical variables and the presence of any symptom, but greater cognitive impairment (i.e. low MMSE score) occurred in patients with delusions. The time to emergence of psychotic symptoms appears to be different in the various studies, but our finding that it is most common in moderate stages of dementia is consistent with the findings of Cummings et al. (1987).

We found that dementia patients, irrespective of which behavioral problems they initially had, were at very high risk of developing psychiatric problems later on. These findings confirm results from cross-sectional studies, which have found the close association among neuropsychiatric symptoms (Brodaty et al., 2001; Levy et al., 1996; Senanarong et al., 2004). Several authors have found correlations between psychosis and agitated behaviours, resembling our hyperactivity sub-syndrome (Rapoport et al., 2001; Lopez et al., 2003; Senanarong et al., 2004). Our data suggest that psychosis proceed from agitated behaviours, but not vice versa. Frontal-temporal dysfunction is found in patients with both psychosis and agitated behaviours (Lopez et al., 2001; Lopez et al., 2003), but even more, the present data support the hypothesis that frontal-temporal dysfunction results first in the appearance of behavioural disturbances, and later on in psychosis. In line with Lopez et al. (2003), we found no influence of affective disturbances on the development of psychosis.

The present data raise the question whether behavioural disorders in dementia should be regarded as specific symptoms, sub-syndromes, or even more as one disorder. This study, and a previous study from our group (Aalten et al., 2003), have stressed the importance of investigating behavioural sub-syndromes rather than separate symptoms. Lyketsos et al. (2001a) also mentions the superiority of the syndromic approach for many individuals with...
ACKNOWLEDGMENT

This study was funded by the Dutch Research Council (NWO: 940-33-039).

REFERENCES


