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Psychiatric symptoms in patients with dementia predict the later development of behavioural abnormalities

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ABSTRACT

Background. Cross-sectional studies of non-cognitive symptoms in dementia show that patients with psychotic symptoms tend to have more disturbed behaviour. However, it is not known whether individuals who experience psychiatric symptoms early in dementia are more prone to develop behavioural problems later in the illness.

Method. The behaviour of 86 community-dwelling subjects with dementia was intensively studied for 4 years or until death, using an informant interview which was administered every 4 months on a median of eight occasions. The extent to which psychiatric symptoms, age, sex and cognitive function predicted clinically significant physical aggression or motor hyperactivity was assessed.

Results. Physical aggression was predicted by sad appearance and motor hyperactivity was predicted by persecutory ideas. These associations were robust, remaining significant over 2, 3 and 4 years of follow-up and were independent of cognitive function, age, sex and duration of illness.

Conclusions. There may be two distinct longitudinal syndromes of non-cognitive symptoms in dementia. This suggests that important aberrant behaviours in late dementia may share pathophysiological mechanisms with psychiatric symptoms in early dementia.

INTRODUCTION

Behavioural changes in patients with dementia place an enormous burden on those who look after them. They increase the likelihood that the sufferer will be admitted into institutional care (Hamel *et al*. 1990; Steele *et al*. 1990) and their severity is linearly related to depression in carers (Pruchno & Resch, 1989). Aberrant behaviours are also associated with risks to the patients themselves. For example, physically aggressive patients are at risk of being abused themselves (Ryden, 1988) and sometimes injure other vulnerable nursing home residents (Malone *et al*. 1993). Patients with motor hyperactivity are prone to falls (Buchner & Larson, 1987). Neuroleptics and restraints are sometimes needed in the management of behavioural problems, but both may hasten cognitive decline (McShane *et al*. 1997; Burton *et al*. 1992).

The non-cognitive symptoms of dementia include psychiatric symptoms as well as behavioural abnormalities (Weiner *et al*. 1996). Psychiatric symptoms are less clearly related to poor cognitive function than behavioural disturbances (Devanand *et al*. 1997). They are also less persistent (Devanand *et al*. 1997). Although it is recognized that both types of phenomena are best assessed by interviewing informants who know the subject well (Moye *et al*. 1993), the reported prevalence of non-cognitive symptoms in dementia has varied widely because of differences in the criteria used and the populations from which samples have been drawn (Bolger *et al*. 1994). Cross-sectional studies have found varying patterns of symptom clusters for similar reasons, but generally show that behavioural changes such as physical aggression

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and motor hyperactivity occur concurrently with psychiatric symptoms such as hallucinations and delusions (Patel & Hope, 1993; Bolger *et al.* 1994).

However, cross-sectional studies do not reveal relations between symptoms that are separated in time. It would be useful to be able to predict in advance which patients are more likely to develop problematical behaviours. The families of such patients might then be in a better position to plan for the future, and earlier intervention might be possible because of increased vigilance. Furthermore, if the evolution of symptoms tended to follow an identifiable pattern, this would be indirect evidence that the later symptoms shared a pathophysiological basis with the earlier symptoms. The possibility that early psychiatric symptoms might lead on to later behavioural disturbances has not been examined in longitudinal studies.

METHOD

The data reported here were collected as part of a study that was designed to examine the natural history of, and relations between, a wide variety of non-cognitive symptoms in dementia. One hundred and four subjects with dementia diagnosed using the criteria from DSM-III-R, and who were all living at home with carers who were able to give a good account of their symptoms, were recruited through general practitioners (70%), psychogeriatricians and community psychiatric nurses (Hope *et al.* 1997*a*). Subjects with DSM-III-R diagnoses other than Alzheimer's disease or multi-infarct dementia were excluded. Neuropathological diagnoses of AD were made according to CERAD criteria (Mirra *et al.* 1991). After complete description of the study to the carers and subjects, written informed consent was obtained from carers.

Ratings and definitions

Non-cognitive symptoms of each subject were assessed every 4 months using the Present Behavioural Examination. This is a detailed, investigator-based, semi-structured interview that is administered to informants, takes between one and two hours to complete and has established inter-rater reliability (Hope & Fairburn, 1992). Each psychiatric symptom (hallucinations, persecutory ideas, anxiety, apparent sadness, verbal aggression) and physically aggressive behaviour was rated on a 7-point frequency scale which was anchored on the basis of the number of days in the previous 4 weeks on which the symptom occurred. These non-cognitive features were defined as 'severe' if they occurred on half the days or more. Hyperactivity was defined as 'severe' if the subject spent more than 3 h a day walking aimlessly, or walked distinctly more than normal for someone of similar age and normally sat for a median of less than 15 min before getting up again. The importance of identifying the persistence of non-cognitive features is increasingly being recognized (Devanand *et al.* 1997). Behaviours and psychiatric symptoms were therefore defined as 'clinically significant' if they were present on at least two consecutive interviews, at one or both of which the symptom was severe. 'Newly developing behaviours' were defined as having occurred if clinically significant behaviour had not occurred within the first three interviews (i.e. within the first year) but did occur subsequently. An important feature of the method was that cases in whom the target behaviour had already occurred in the first year were regarded as missing for the purposes of identifying possible precursor psychiatric symptoms. This permits a consideration of whether a psychiatric symptom predicts a behaviour (i.e. is associated with and precedes the behaviour) rather than merely occurs at the same time. The definitions of symptoms and behaviours used are further clarified in Appendix 1. Cognitive function was assessed at each interview with the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975).

Analyses

The relationships between different non-cognitive symptoms and between non-cognitive symptoms and cognitive function in the first year were assessed by testing the significance of the Pearson χ^2 or Student's t statistics, or Fisher's exact test as appropriate. A Cox regression model, derived using backwards stepwise deletion, was used to identify those features which best predicted the time to onset of physical aggression or hyperactivity. Sex, age, duration of dementia, and Mini-Mental State Examination score (MMSE) (Folstein *et al.* 1975) at study entry were entered as covariates as well as

Table 1. *Demographic characteristics of sample*

Study entry ($N = 86$)	
Age (median(interquartile range))	77 (8) years
Male : Female	43 : 43
Duration of dementia	4·5 (4) years
Mini-mental State Examination score	15 (12·25)

Table 2. *Diagnostic characteristics of sample*

Neuropathological diagnosis ($N = 52$)	N (%)
AD only	34 (65)
AD + LB	8 (15)
AD + VD	3 (6)
VD	4 (8)
Other*	3 (6)

AD, Alzheimer's disease; LB, Lewy body pathology; VD, vascular dementia.

* Two cases had marked degeneration of Sommer's sector of the hippocampus, one of which also had nigral cell loss with no Lewy body pathology. One case had unexplained laminar loss of neocortical neurones with no other pathology.

the five psychiatric symptoms (Table 1). *Post-hoc*, stepwise logistic regression analyses of newly developing physical aggression and hyperactivity were conducted to confirm the significance of variables identified as predictors in the Cox model. We initially restricted the period during which behaviours might be regarded as 'newly developing' to the 3 years after the first, symptom-defining year because a longer time frame would reduce the power to detect an association between predictor and outcome. However, in order to assess the robustness of the findings at 3 years, we then examined shorter time frames.

Analyses of the association of non-cognitive symptoms with neuroleptic use and institutionalization, were conducted *post-hoc* rather than including them as predictor variables in multivariate analyses, as these interventions were at least as likely to have occurred as a result of non-cognitive symptoms as to have been causal. The relationship of symptoms to neuropathological diagnosis was explored *post-hoc* but diagnosis was not included as a predictor variable because there were few cases which did not have neuropathological AD and the predictive value of clinical diagnostic criteria for identifying other neuropathological diagnoses in the presence of AD is relatively poor (Galasko *et al.* 1994; Gearing *et al.* 1995; Victoroff *et al.* 1995).

RESULTS

With the exception of six dropouts, all subjects were followed for at least 4 years or until death. Twelve subjects died before the third interview. The remaining 86 form the sample for the analyses. The median number (interquartile range) of interviews among the 57 subjects who died between the first and fourth year was 8 (4). The other 29 were interviewed on at least 12 occasions. At the first interview, most of the informants were spouses (72% ($N = 62$)) or children (14% ($N = 12$)) of the subject. The remainder were siblings or other non-professional carers. The MMSE at the start of the study was less than 10 in 22 subjects, 10–20 in 39 and more than 20 in 25 subjects. Neuropathological diagnosis was available in 60% ($N = 52$) of cases (Table 2). Forty-five cases (86%) had AD either alone or in conjunction with other pathology.

The cognitive function of those with clinically significant behavioural problems during the year after study entry was worse than those without such behaviours. The MMSE (S.D.) of those with physical aggression ($8{\cdot}1 \pm 4{\cdot}8$, $N = 9$) was lower than those without ($15{\cdot}7 \pm 7{\cdot}4$, $N = 77$; $t = 3{\cdot}0$, df = 84, $P = 0{\cdot}003$) and the same was true of those with hyperactivity ($9{\cdot}2 \pm 6{\cdot}4$, $N = 14$ and $16{\cdot}0 \pm 7{\cdot}2$, $N = 72$ respectively; $t = 3{\cdot}3$, df = 84, $P = 0{\cdot}001$). None of the psychiatric symptoms was associated with significantly worse cognitive function. A cross-sectional examination of features present in the first year revealed that those who were physically aggressive (10·5%, $N = 9$) were more likely to be verbally aggressive (43·0%, $N = 37$; $P < 0{\cdot}001$, Fisher's exact test) or anxious (16·3%, $N = 14$; $P = 0{\cdot}005$, Fisher's exact test). Hyperactivity (16·3%, $N = 14$) and hallucinations (8·1%, $N = 7$) also tended to occur concurrently ($P = 0{\cdot}012$, Fisher's exact test). Subjects who were hyperactive at any stage (31·4%, $N = 27$) were more likely to be physically aggressive at some point (39·5%, $N = 34$; $\chi^2 = 6{\cdot}4$, df = 1, $P = 0{\cdot}01$). This association was not apparent when the time

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Table 3. *Relationship between psychiatric symptoms in first year and behaviours developing for first time in years 2 to 4*

			Newly developing behaviour					
			Physical aggression			Motor hyperactivity		
Symptom present in first year	*N*	%	*N*	%*	*P*†	*N*	%‡	*P*†
Apparent sadness	24	27·9	11	50·0	0·031	4	21·0	0·72
Anxiety	14	16·3	1	11·1	0·26	3	30·0	0·35
Persecutory ideas	10	11·6	3	37·5	0·70	4	57·1	0·012
Hallucinations	7	8·1	5	100	0·002	1	33·3	0·43
Verbal aggression	37	43·0	13	46·4	0·04	6	20·7	0·53

* Percentage of cases with psychiatric symptom going on to develop physical aggression, based on sample of 77 because 9 subjects with physical aggression in the first three interviews are excluded.

† Fisher's exact test.

‡ Percentage of cases with psychiatric symptom going on to develop hyperactivity, based on sample of 72 because 14 subjects with hyperactivity in the first three interviews are excluded.

frame was restricted to the first year and arose partly because of a trend for those who were hyperactive in the first year to become physically aggressive later (Fisher's exact test $P = 0{\cdot}09$).

In the Cox regression model, the time until the onset of physical aggression was significantly associated with the presence of apparent sadness ($B = 0{\cdot}94$, $df = 1$, $P = 0{\cdot}03$) and hallucinations ($B = 2{\cdot}16$, $df = 1$, $P = 0{\cdot}001$) in the first year, with trends for an effect of age ($B = 0{\cdot}064$, $df = 1$, $P = 0{\cdot}06$) and male sex ($B = 0{\cdot}83$, $df = 1$, $P = 0{\cdot}06$) but not cognitive function. The time until the onset of hyperactivity was significantly associated with the presence of persecutory ideas ($B = 1{\cdot}98$, $df = 1$, $P = 0{\cdot}002$) in the first year, with trends for an effect of cognitive function ($B = 0{\cdot}075$, $df = 1$, $P = 0{\cdot}07$). Logistic regression analysis, using binary variables representing the onset of behaviours within the subsequent 3 years, confirmed that apparent sadness in the first year predicted physical aggression ($B = 1{\cdot}17$, $df = 1$, $P = 0{\cdot}05$) and persecutory ideas predicted hyperactivity ($B = 2{\cdot}20$, $df = 1$, $P = 0{\cdot}008$). Furthermore, apparent sadness was a consistent predictor of the onset of physical aggression over the more restricted time frames of 1 and 2 years. Similarly, persecutory ideas were a consistent predictor of hyperactivity. Male sex was also an independent predictor of the onset of physical aggression over 1 and 2 years, but not over the 3 year time frame which we initially chose (data not shown). This was because men who were going to become aggressive tended to do so more rapidly than women.

Table 3 shows how individual symptoms which were present in the first year were associated with the development of behaviours over the subsequent 3 years. Forty-six per cent of those with newly developing aggression ($N = 24$) had previously experienced clinically significant apparent sadness and a third of those with newly developing hyperactivity ($N = 12$) had had clinically significant episodes of persecutory ideas. However, the positive predictive values of apparent sadness as a prognostic indicator of later physical aggression (0·50) and of persecutory ideas as a prognostic indicator of later hyperactivity (0·57) were only moderate.

We addressed the possibility that institutionalization, medication or diagnosis might have been confounding variables. Nearly half the sample ($N = 42$) were admitted for at least 4 months to hospital, nursing or residential care facilities. Half of these ($N = 21$) were also physically aggressive at some point, but the aggression was no more likely to start after admission than before, and those with apparent sadness were no more likely to be admitted than those without. Those noted as having taken neuroleptics for 4 months or more were slightly more likely to have severe, persistent persecutory ideas (Fisher's exact text $P = 0{\cdot}059$) or verbal aggression ($\chi^2 = 3{\cdot}9$, $df = 1$, $P = 0{\cdot}05$) at some point. However, the start of neuroleptics use did not precede the onset of persecutory ideas in any case. It followed the onset of persecutory ideas and preceded that of hyperactivity in only one case.

Those with Lewy body pathology were more

likely to have had clinically significant hallucinations at some point ($P = 0{\cdot}007$, Fisher's exact test), but there were no other associations of diagnosis with non-cognitive symptoms. The neuropathological diagnoses of those who showed apparent sadness and went on to be physically aggressive, or who had persecutory ideas and went on to be hyperactive, were no more likely to include vascular or Lewy body pathology or Alzheimer's disease than those without these patterns of non-cognitive features.

DISCUSSION

In this prospective, community based study two patterns of evolution of non-cognitive symptoms were identified. First, apparent sadness predicted physical aggression. Secondly, persecutory ideas predicted motor hyperactivity. The positive predictive values of the psychiatric symptoms were insufficiently high to suggest that severe, persistent apparent sadness and persecutory ideas could be used in isolation as reliable predictors of aberrant behaviours. However, the occurrence of these two patterns may indicate that depression is an early, and aggression a late manifestation of the same pathophysiological process. Similarly, persecutory ideas and motor hyperactivity may have a shared underlying aetiology.

This study had several important strengths. It was prospective with frequent, regular, assessment of psychiatric and behavioural symptoms using a reliable instrument with specific, time-based anchor points. There was complete ascertainment of almost all recruited cases, in the majority of whom neuropathological diagnosis was available. We used multiple assessments for ensuring that only symptoms which are prospectively identified as persistent are defined as present. This is important because non-cognitive features, and particularly psychotic and affective symptoms are often relatively evanescent (Wagner *et al*. 1995; Levy *et al*. 1996; Devanand *et al*. 1997) but persistent symptoms are more likely to be indicators of relevant neuropathological changes (McShane *et al*. 1995). Finally, cases who already had the target behaviours in the first year of the study were excluded from the analysis of predictor symptoms. This prevents the possibility that the behaviours were caused by concurrent psychiatric symptoms.

This study had a number of potential weaknesses. First, the sample was not an epidemiologically selected sample of subjects with a neuropathological diagnosis of Alzheimer's disease, although the proportion of cases with confirmed AD similar to other series (Galasko *et al*. 1994). The number of cases with neuropathological diagnoses was insufficient to justify inclusion of a diagnosis variable in the regression analysis. The *post-hoc* finding of a lack of association with diagnosis of either of the two patterns of non-cognitive symptoms needs to be interpreted with caution. In particular, the inclusion in our study of subjects with vascular changes may have weakened the potentially confounding link between behavioural change and cognitive function (Kurita *et al*. 1993). Secondly, we did not assess extrapyramidal symptoms that may similarly moderate correlations between cognitive function and psychosis or hyperactivity (Gilley *et al*. 1991). Thirdly, the numbers on which the significant findings are based are relatively small, especially those relating to the association between persecutory ideas and hyperactivity.

Although there have been numerous studies linking different non-cognitive features, particularly psychosis and aggression (Morriss *et al*. 1990; Deutsch *et al*. 1991), these have been cross-sectional. We confirmed the findings of the only other prospective study which has presented data concerning the prediction of aberrant behaviours (Swearer *et al*. 1996): disease severity does not predict the subsequent onset of aggression or hyperactivity. The prevalence of 'severe and disruptive' hyperactivity (9%) and severe physical aggression (15%) that were reported by Swearer and colleagues (Swearer *et al*. 1996) are close to those found in the first year of the present study.

Discussion of the longitudinal development of symptoms in AD has tended to revolve around whether there are stages through which patients typically pass as suggested by Reisberg and colleagues (Reisberg *et al*. 1989), or whether the pattern of development of non-cognitive symptoms is so variable as to preclude staging (Cohen Mansfield *et al*. 1989*a*, *b*). It has also been suggested that some symptoms (wandering, agitation and incontinence) are 'typical' whereas others (hallucinations, irrational suspicions and restlessness) are idiosyn-

cratic (Teri *et al*. 1988). Other studies have also revealed associations between clinical features which are separated in time. For example, it has been shown that the differences between the behaviour of patients with early and late onset AD are most striking in late dementia (Gilley *et al*. 1991; Jost & Grossberg, 1996), whereas the differences between the behaviour of those with and without extrapyramidal symptoms are most striking in the early stages (Gilley *et al*. 1991). Our data suggest that there may also be two patterns in the development of non-cognitive symptoms. However, the patterns which we identified were not clearly related to severity of cognitive decline, in contrast to the patterns of behaviours seen in those with and without extrapyramidal symptoms.

Several groups, including our own, have used factor analytical techniques which have included both behavioural and psychiatric symptoms to identify cross-sectional syndromes of non-cognitive features within dementia (Cummings & Victoroff, 1990; Devanand *et al*. 1992*a*, *b*; Sultzer *et al*. 1992; Tariot *et al*. 1995; Ott *et al*. 1996; Hope *et al*. 1997*b*). The status of hyperactivity and physical aggression as distinct constructs is well supported by the work of some of these studies (Cohen-Mansfield *et al*. 1989*a*, *b*; Ott *et al*. 1996; Hope *et al*. 1997*b*), but is less clear in others (Sultzer *et al*. 1992; Tariot *et al*. 1995). Cohen Mansfield has provided evidence of the validity of these constructs by showing that non-aggressive agitation, which includes pacing and restlessness, has different medical and psychosocial associations from those of physically aggressive agitation (Cohen Mansfield *et al*. 1992). Our longitudinal results also lead us to favour a 'splitting' approach to the assessment of 'agitation'. Physical and verbal aggression, hyperactivity and anxiety should not be subsumed into a single concept such as agitation. Similarly persecutory ideas and hallucinations should not be considered as part of a unitary phenomenon such as psychosis.

It is possible that the different patterns of non-cognitive symptoms which we observed were clinical manifestations of specific patterns of neurodegeneration of monoaminergic systems. Psychopharmacological investigations provide the best evidence of this possibility. Sultzer *et al*. (1997) compared the effects of trazodone and haloperidol on behavioural disturbance in dementia. Both drugs were equally effective. They also found that verbal aggression, opposition to assistance and repetitive sentences and mannerism responded preferentially to the antidepressant trazodone. In contrast, pacing, restlessness, trying to get out of the building and unwarranted accusations responded preferentially to haloperidol. Furthermore, Nyth and colleagues (Gottfries *et al*. 1992) found citalopram, a selective serotonin reuptake inhibitor, to be effective in reducing both depressed mood and irritability in dementia. A recent neuroendocrine study of patients with severe Alzheimer's disease was suggestive of upregulation of central serotonergic receptors in patients with impulsive aggression compared to those with other behavioural problems (Herrman *et al*. 1997). There is less evidence from post-mortem neurochemical studies to support our hypothesis, possibly because the assessment of behavioural features has generally been retrospective in such studies. In a subsample of 20 of the cases described in the present study, we found that orbito-frontal and temporal serotonin transporter sites were specifically reduced in patients with low mood (but not aggression) (Chen *et al*. 1996). Bierer and colleagues found that dopaminergic parameters were not associated with maximal severity of psychosis, depression or agitation (Bierer *et al*. 1993). Noradrenergic function has been implicated in depression, aggression and motor hyperactivity (Shankle *et al*. 1995), but there are no reports of any effect on delusions. Post-mortem work on larger, prospectively studied samples and functional imaging studies may support our hypothesis or give other clues about the aetiology of psychiatric symptoms and behavioural changes in dementia, and the links between the two types of phenomena.

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APPENDIX 1
NON-COGNITIVE SYMPTOMS IN PRESENT BEHAVIOURAL EXAMINATION (PBE)[1]

Hallucinations

During the development of the PBE it was found that it was not possible to distinguish reliably between different modalities of hallucinations (Hope & Fairburn, 1992). It can also be difficult to distinguish misperceptions from true hallucinations. Ratings were made conservatively: interviewers were careful to rate only those perceptual abnormalities clearly arising in the absence of an external stimulus.

Persecutory ideas

Delusional symptoms, of which persecutory ideas are the most common form (Burns *et al*. 1990; Deutsch *et al*. 1991; Ballard & Oyebode, 1995) are frequently transient and subjects often accept the truth if corrected (Devanand *et al*. 1992*a*, *b*). Persecutory ideas rather than 'delusions' were rated if the subject 'thought that people are trying to harm him/her, plot against him/her or damage or steal his/her property'.

Anxiety

In order to be rated as anxious, subjects were required to have appeared 'very anxious or frightened' and to have shown physical symptoms of autonomic arousal such as shaking, flushing or breathing rapidly.

Low mood

The core item 'apparent sadness' ('appeared particularly sad, miserable or depressed') was selected for use in these analyses for four reasons: it was the most sensitive of the PBE items relating to depression; similar questions are used in other instruments (Devanand *et al*. 1992*a*, *b*; Tariot *et al*. 1995) and fall squarely into a factor of 'depressive features'; vegetative symptoms of depression are often present in subjects with dementia who do not appear to have low mood (Teri & Wagner, 1992; Weiner *et al*. 1994); and single questions can be as accurate as scales in screening for depression in the elderly (Mahoney *et al*. 1994).

Verbal aggression

This was defined as 'speaking in an aggressive way, for example in a cross or angry tone, or with a voice raised in anger'.

[1] Copies of the PBE are available from Dr Tony Hope, Institute of Health Sciences, Old Road, Headington, Oxford, OX3 7LF.

Physical aggression

This was defined as hitting, kicking, scratching, pushing or spitting in an aggressive manner. The behaviour had to be perceived as hostile or threatening. Resisting help, unless accompanied by active aggression, such as pushing the carer away, was not included in this rating.

Hyperactivity

This item aimed to identify observable increases in motor activity. It was therefore a composite of 'aimless walking' and 'restlessness'. Aimless walking corresponds closely to what is commonly called 'pacing' and was rated on an anchored three-point scale (0 = aimless walking occurs, if at all, for less than 1 h in total on a typical day; 1 = aimless walking occurs for 1–3 h; 2 = aimless walking occurs for more than 3 h daily). 'Restlessness' was also rated on a three-point scale (0 = walks no more than normal for someone of similar age, 1 = time spent walking is distinctly more than normal, but normally sits for more than 15 min before getting up again, 2 = walks more than normal and normally sits for less than 15 min before getting up again). The 'hyperactivity' score was the score for aimless walking or restlessness, whichever was the greater.

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