The relationships between neuropsychiatric symptoms, cognitive deficit and prescription of psychotropics in Alzheimer’s Disease: The LASER-AD study

Korelacje pomięǳy objawami neuropsychiatrycznymi, deficytami poznawczymi, a przepisaniem leków psychotropicznych u chorych z chorobą Alzheimera. Projekt badawczy LASER-AD

Georgina Train¹, Cornelius Katona², Gill Livingston¹

¹ Royal Free and University College Medical School, Department of Mental Health Sciences, University College London, London, England
² Kent Institute of Medicine and Health Sciences, University of Kent, Kent, England

Key words: dementia, anti-psychotic drugs, agitation, hallucinations, aberrant motor behaviour, depression

Słowa kluczowe: ośpienie, leki antypsychotyczne, pobudzenie, halucynacje, dziwaczne zachowanie ruchowe, depresja

Summary

Background: The relationship of neuropsychiatric symptoms to the severity of cognitive impairment in Alzheimer’s disease (AD) remains unclear. The purpose of our study was to determine the prevalence and severity of neuropsychiatric symptoms in patients with AD and mild, moderate and severe cognitive impairment, and the relationship of these symptoms to prescriptions of psychotropic drug.

Method: Neuropsychiatric symptom scores (NPI) were rated in 224 participants recruited as a representative sample. We also collected information on cognition and psychotropic drug use.

Results: 93.8% of the patients had neuropsychiatric symptoms at baseline. The total NPI score correlated significantly with greater cognitive impairment on the MMSE. Significant correlation with severity of cognitive impairment were found for agitation, hallucinations and aberrant motor behaviour. Hallucinations were worse in mild and severe dementia than in moderate dementia, while aberrant motor behaviour was worse in severe, but not moderate dementia. Antipsychotics were more likely to be prescribed with lower MMSE scores, while cholinesterase inhibitors were less likely. Total

Adres do korespondencji:
Gill Livingston MD
Royal Free and University College Medical School
Department of Mental Health Sciences University College London
Archway Campus, Holborn Union Building
Highgate Hill, London
N19 5NL Great Britain
tel. +(20) 756 14 218, fax +(20) 7288 3411
e-mail: g.livingston@ucl.ac.uk
NPI score and agitation correlated with severity of cognitive impairment. Depression and agitation were more common with more severe impairment, unless the patient was taking antidepressants. Increased apathy and depression scores both correlated with antipsychotic use.

**Conclusions.** A high overall NPI symptom score is associated with greater cognitive impairment, but this pattern is only evident for some individual symptom domains. Aberrant motor behaviour is mainly a feature of severe dementia, and hallucinations in mild and severe dementia. Psychotropic drugs may be an important mediator of this effect.

**Introduction**

Neuropsychiatric symptoms (NPS) in dementia are common and important to both the patient with dementia and the caregiver since they are associated with both carer distress and breakdown of care [1-6]. There are relatively few studies examining the community prevalence of these symptoms. Such studies as have been reported have found the symptoms are common, with prevalences ranging between 61%-88%. Higher rates are reported when informants as opposed to people with dementia are interviewed [7-10]. NPS have also been reported in as many as 80% of people with dementia living in 24-hour care settings [11].

The natural history of behaviour and psychiatric symptoms in Alzheimer’s disease shows great individual variation, but despite this some changes may show a recognisable sequence [12]. Overall, neuropsychiatric symptoms increase in Alzheimer’s Disease as the illness progresses [13-15]. Despite their importance for caregivers we are not currently able to give much information about which individual symptoms are more common at particular stages of AD. This may not however be the case for all individual symptoms. There is most evidence about the prevalence of psychotic symptoms at different stages of dementia but the pattern is still unclear. A cross-sectional study of a large inpatient population, found that psychotic symptoms (as well as aggression) worsened with every three point decrease in MMSE [16]. Other studies have reported that hallucinations were associated with greater degree of cognitive impairment but that delusions were not (eg [17]). In contrast, Jeste et al [18] found that delusions were more prevalent in people with more severe AD. Finally, psychotic symptoms are unrelated to severity of cognitive impairment in some studies [13-14, 19-20]. Lachs et al [19] reported that although there was no overall change in the frequency of delusions as impairment increased, there was a trend towards greater prevalence of delusions in dementia of moderate severity. Apathy has been found to increase with disease progression, both in those who were depressed and those who were not [21, 22]. Other studies have reported that mood changes (elation and depression) were not related to severity of cognitive impairment (eg [23]).

One explanation of these apparently contradictory findings may be that the relationship between individual NPS and cognition may be more complex than a simple linear correlation. Some NPS may for example wax and wane throughout the illness. The present study aims to describe the prevalence of individual neuropsychiatric symptoms (as measured by NPI) as well as their overall severity in mild, moderate and severe AD (as measured by MMSE) and to examine whether pharmacotherapy may act as a confounder.

**Methods**

This study is part of a large longitudinal study in people with AD recruited from London and the South East region of England (LASER-AD study) for further details see [24-25]. CRs and their caregivers were contacted though local psychiatric services, the voluntary sector and managers of care homes.

The study aimed to recruit an epidemiologically representative sample of people with mild, moderate and severe AD and their carers. Mild impairment was defined by Mini Mental State Examination (MMSE; [26]) > 20, moderate as MMSE < 20 and > 10, and severe as MMSE < 10). In order to correspond to the epidemiological findings of Fratiglioni [27], the proportions recruited were: mild 30%, moderate 40%, and severe 30%.
The inclusion criteria were:

1. A standardised diagnosis of dementia [28]
2. Fulfilment of criteria for possible or probable AD [29]
3. Aged ≥ 55 years
4. Living in London and the Southeast region (LASER) of England - either North London (inner city and suburban areas) or Essex (semi-rural and new town).
5. Having a caregiver who spent a minimum of 4 hours a week caring for them.

Exclusion criteria included:

1. Having significant vascular symptoms as defined by a Hachinski Ischaemic Score (HIS; [30]) of > 3. The HIS is a brief assessment scale based on the patient’s past history of vascular disease and dementia, scored out of 10. The scores vary between 0 for absent and a possible 1 or 2 for present. Points would be scored for example for a history of hypertension (1 point), a history of stroke (2 points), or abrupt onset (2 points). Scores above 3 indicate higher likelihood of the dementia being of vascular origin.
2. Other significant neurological disease such as Parkinson’s disease, any enduring mental illness (including: psychotic episodes requiring hospitalisation or neuroleptic treatment for more than 2 weeks during the last 10 years not associated with AD), endocrine or metabolic disorders possibly causing dementia, or alcohol or drug abuse.
3. Being unable to comply with the study assessment, either due to another disease or inability to understand English to a degree that would interfere with their participation in the study.

A caregiver had to spend a minimum of 4 hours a week caring for the person with AD.

Procedure

The relevant Local Research Ethics Committees gave ethical approval for the study. Caregivers were contacted by letter and given an information sheet. People with AD were given the information sheet at the time of the interview and asked to give written informed consent if they could. Otherwise they gave verbal assent witnessed by a carer. The people with AD were seen at their place of residence. Interviews with carers took place at the participant’s home, the carer’s home or the carer’s place of work. Trained researchers from a range of disciplines (medicine, nursing and psychology) conducted all the interviews.

If possible a family caregiver was interviewed. If there was no such caregiver, a statutory carer was interviewed instead. All caregivers had to spend at least four hours a week with the care recipient.

The interview with the patient consisted of the following:

The patient’s cognition was assessed using MMSE and the Alzheimer’s disease assessment scale (ADAS-Cog; [31]).

The patient’s carer was also interviewed. They were asked about:

1. The patient’s sociodemographics,
2. Past medical history,
3. Current medication,
4. Psychiatric symptoms for the patient using the NeuroPsychiatric Inventory for dementia (NPI; [32]). This scale assesses 12 different psychiatric symptoms (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep disturbance and appetite disturbance) using caregiver report. Each symptom is rated by frequency (score 1-4) and severity (score of 1-3) or as absent (score 0). The frequency score is then multiplied by the severity score for each symptom and the sum of these then creates a global
The Neuropsychiatric Inventory (NPI) is a validated tool for looking at psychiatric symptoms in dementia [32]. It has been used to measure the prevalence and incidence of these symptoms in people with dementia [10, 33], and to classify them into three symptom clusters [34-35]. All of these classifications have a mood cluster and a psychosis cluster; the third cluster differs being respectively those with no or one neuropsychiatric symptom, hyperactivity and frontal signs. Using NPI, the profile of delusions and hallucinations have been shown to be different from schizophrenia supporting an AD-associated psychosis and a distinct syndrome with recently proposed diagnostic criteria [36-37].

Analysis

SPSS 11.5 was used to enter the data and for the statistical analysis. We tabulated the prevalence of each individual symptom. We used chi-squared to compare the pattern of each individual symptoms in mild, moderate and severe dementia. If there was a significant difference in the prevalence of symptoms between severity levels we then applied a post hoc ANOVA test to demonstrate where the difference occurred. All NPS had a non-parametric distribution. We used Spearman correlations and Mann-Whitney U-tests, as appropriate, to consider the relationship of each NPI symptom with cognition and possible confounders. We asked forward linear regression analysis to examine independent predictors of severity of individual neuropsychiatric symptoms and total score.

Results

Demographics

We interviewed 224 people with AD. 160 (71.4%) were women. Their ages ranged from 55-98 (mean 81.0). MMSE scores ranged from 0 to 29. 66 (29.5%) of participants were classified as having mild dementia; 92 (41.1%) had moderate cognitive impairment and 66 (29.5%) were classified as severe. 51 (22.8%) of people lived alone, 73 (32.6%) lived in institutions. 89 (39.7%) were currently married. 122 (54.5%) had lost a partner. 12 (5.4%) were single. 176 (78.6%) were born in the UK. 178 (79.5%) were white British, 14 (6.3%) white Irish, 20 (8.9%) white other, 5 (2.2%) were black Caribbean, 1 (0.4%) black other, 1 Greek, 1 Indian, 1 Pakistani, and 3 others. The mean years of education were 9.41 (median 9.00, minimum 1, maximum 16).

Table 1. Mean score and standard deviation of individual neuropsychiatric symptoms on NPI.

<table>
<thead>
<tr>
<th>NPI Domain and NPI total symptom score</th>
<th>Mean</th>
<th>Median</th>
<th>Standard Deviation</th>
<th>Range (min-max)</th>
<th>% exhibiting symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>1.8</td>
<td>0</td>
<td>2.8</td>
<td>12 (0-12)</td>
<td>104 (46.4%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.7</td>
<td>0</td>
<td>2.8</td>
<td>12 (0-12)</td>
<td>108 (49.2%)</td>
</tr>
<tr>
<td>Apathy</td>
<td>3.1</td>
<td>0</td>
<td>4.1</td>
<td>12 (0-12)</td>
<td>106 (47.3%)</td>
</tr>
<tr>
<td>Appetite disturbance</td>
<td>1.2</td>
<td>0</td>
<td>2.7</td>
<td>12 (0-12)</td>
<td>48 (21.4%)</td>
</tr>
<tr>
<td>Delusion</td>
<td>1.3</td>
<td>0</td>
<td>2.6</td>
<td>12 (0-12)</td>
<td>73 (22.6%)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.4</td>
<td>0</td>
<td>2.5</td>
<td>12 (0-12)</td>
<td>92 (41.1%)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.7</td>
<td>0</td>
<td>1.9</td>
<td>12 (0-12)</td>
<td>48 (21.4%)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.3</td>
<td>0</td>
<td>1.3</td>
<td>12 (0-12)</td>
<td>20 (8.9%)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0.6</td>
<td>0</td>
<td>1.5</td>
<td>12 (0-12)</td>
<td>44 (19.6%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.7</td>
<td>0</td>
<td>2.8</td>
<td>12 (0-12)</td>
<td>89 (39.7%)</td>
</tr>
<tr>
<td>Motor Behaviour</td>
<td>2.5</td>
<td>0</td>
<td>3.5</td>
<td>12 (0-12)</td>
<td>100 (44.6%)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1.7</td>
<td>0</td>
<td>3.2</td>
<td>12 (0-12)</td>
<td>71 (31.7%)</td>
</tr>
<tr>
<td>Total NPI</td>
<td>17.6</td>
<td>14</td>
<td>15.5</td>
<td>79 (0-79)</td>
<td>209 (93.3%)</td>
</tr>
</tbody>
</table>
Individual neuropsychiatric symptoms

Table 1 shows the mean range and standard deviation for scores on each NPI domain of neuropsychiatric symptoms as well as the number and percentage of people with individual symptoms. The median score for all symptoms was 0. The least common individual symptom was euphoria (8.9%) and the most common was anxiety (49.2%). 209 (93.3%) had at least one neuropsychiatric symptom.

The relationship of MMSE to individual NPI Symptoms

Total NPI symptom score correlated significantly with greater severity of cognitive impairment as measured by the MMSE (Spearman’s rho = 0.17; p<0.05). Three individual symptoms also showed a significant correlation with severity of cognitive impairment: agitation (Spearman’s rho = 0.21; p<0.005), hallucinations (Spearman’s correlation = 0.16; p<0.05) and aberrant motor behaviour (Spearman’s rho= 0.19; p<0.005).

We repeated the analysis with cognitive severity classified into mild, moderate and severe. Two symptoms showed significant difference between groups: hallucinations and aberrant motor behaviour (chi squared = 23.65; p<0.05 and chi- squared =27.19; p<0.05 respectively.

Using Tukey’s test to compare the mean value of psychiatric symptoms in mild, moderate or severe cognition, hallucinations (see figure 1) were significantly worse in severe dementia than in moderate dementia (F=6.127; p<0.005) but no worse in severe than in mild. Aberrant motor behaviour (see figure 2) was significantly worse in severe dementia than in mild dementia (F=3.093; p<0.05)

Psychotropic medication

67 (29.9%) of people were taking antidepressants, 55 (24.6%) were taking antipsychotics and 117 (52.2%) cholinesterase inhibitors. People with lower MMSE scores were more likely to be prescribed antipsychotics (p<0.0001) and less likely to be on cholinesterase inhibitors (p<0.0001). There was no relationship between MMSE scores and the prescription of antidepressants.

![Graph showing mean hallucination score by severity](image)

**Fig. 1.** One way ANOVA comparing mean NPI hallucinations score in mild, moderate and severe cognitive impairment.
We also examined whether psychotropic drugs were more likely to be prescribed for those with more severe neuropsychiatric symptoms. There was no relationship between the prescription of antipsychotics and the severity of any individual neuropsychiatric symptom. The only neuropsychiatric symptom in which severity was related to the prescription of antidepressants was depression (p<0.05). The prescription of cholinesterase inhibitors (ChEIs) was related to more impaired appetite (p<0.05).

Table 2 shows the relationship between neuropsychiatric symptoms, more impaired cognition and treatment with psychotropics. In those not taking antidepressants (but not those prescribed this class of medication) there were significant correlations between severity of cognitive impairment and NPI anxiety and depression scores. In contrast, hallucinations were more often present in those on antidepressants with higher MMSE scores. Aberrant motor behaviour was inversely correlated with MMSE score in people taking antidepressants but not in those who were not prescribed them. There was a significant correlation between severity of cognitive impairment and agitation, disinhibition, hallucinations and aberrant motor behaviour in those not taking antipsychotics but no such correlations in the group prescribed these drugs. Agitation, disinhibition and overall neuropsychiatric symptoms were significantly correlated with increased severity of cognitive impairment in those not taking ChEIs but these relationships were not apparent in those who were on ChEIs.

**Predictors of severity of neuropsychiatric symptoms**

We used forward linear regression analysis to examine whether MMSE score, gender, or the prescription of antidepressants, antipsychotics and cholinesterase inhibitors were independent predictors of severity of individual neuropsychiatric symptoms. Total NPI score was predicted by severity of cognitive impairment (p<0.01), as was the individual symptom of increased agitation (p<.05). Increased apathy and increased depression score were both predicted by taking antipsychotics (both p<0.05).
Our findings strongly suggest that, although there is an inverse correlation between overall NPI score and MMSE score, this is not equally the case for all individual neuropsychiatric symptoms. The strongest relationships with cognitive decline are with hallucinations and aberrant motor behaviour but this is not linear throughout the illness. Hallucinations are less common in moderate dementia and aberrant motor behaviour most common in severe dementia. We have also shown that prescription of psychotropic drugs may be an important mediator. Firstly, we have shown that MMSE score a predictor of psychotropic drug usage, with greater cognitive impairment being associated with more antipsychotic and less ChEI usage. Secondly the relationship between severity of cognitive impairment, hallucinations and

Table 2. Correlation between individual neuropsychiatric symptoms and severity of cognitive impairment in those prescribed/not prescribed antidepressants, antipsychotics or cholinesterase inhibitors.

<table>
<thead>
<tr>
<th>NPI Domain and NPI total symptom score</th>
<th>Anti-depressants (number=67)</th>
<th>No anti-depressants (number=157)</th>
<th>Anti-psychotics (number=55)</th>
<th>No anti-psychotics (number=169)</th>
<th>Cholinesterase inhibitors (number=117)</th>
<th>No cholinesterase inhibitor (number=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>-.350*</td>
<td>-.177*</td>
<td>-.097</td>
<td>-.218***</td>
<td>-.174</td>
<td>-.254**</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-.100</td>
<td>.177*</td>
<td>.139</td>
<td>.201</td>
<td>-.010</td>
<td>.178</td>
</tr>
<tr>
<td>Apathy</td>
<td>-.040</td>
<td>-.143</td>
<td>-.049</td>
<td>-.135</td>
<td>-.162</td>
<td>-.171</td>
</tr>
<tr>
<td>Appetite</td>
<td>-.133</td>
<td>.090</td>
<td>.011</td>
<td>.039</td>
<td>-.046</td>
<td>.042</td>
</tr>
<tr>
<td>Delusion</td>
<td>-.124</td>
<td>-.058</td>
<td>.156</td>
<td>-.139</td>
<td>-.154</td>
<td>.006</td>
</tr>
<tr>
<td>Depression</td>
<td>-.241</td>
<td>.183*</td>
<td>.126</td>
<td>.128</td>
<td>.028</td>
<td>.148</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>-.155</td>
<td>-.102</td>
<td>.045</td>
<td>-.156*</td>
<td>-.071</td>
<td>-.196*</td>
</tr>
<tr>
<td>Euphoria</td>
<td>-.067</td>
<td>-.020</td>
<td>-.105</td>
<td>.182</td>
<td>-.099</td>
<td>-.003</td>
</tr>
<tr>
<td>Hallucination</td>
<td>-.113</td>
<td>-.167*</td>
<td>-.127</td>
<td>-.172*</td>
<td>-.093</td>
<td>-.138</td>
</tr>
<tr>
<td>Irritability</td>
<td>.044</td>
<td>-.185</td>
<td>-.115</td>
<td>.072</td>
<td>.123</td>
<td>-.161</td>
</tr>
<tr>
<td>Aberrant Motor Behaviour</td>
<td>-.485**</td>
<td>-.126</td>
<td>-.256</td>
<td>-.158*</td>
<td>-.218*</td>
<td>-.201*</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>-.194</td>
<td>-.056</td>
<td>-.161</td>
<td>-.019</td>
<td>-.087</td>
<td>-.033</td>
</tr>
<tr>
<td>Total NPI</td>
<td>-.283</td>
<td>-.132</td>
<td>-.140</td>
<td>-.145</td>
<td>-.173</td>
<td>-.210*</td>
</tr>
</tbody>
</table>

Significance: * = <0.05; ** = <0.01; *** = <0.005;  = <0.0001

Table 3. Linear regression analysis examining relationships between total NPI and individual neuropsychiatric symptom scores and MMSE, medication, and gender.

<table>
<thead>
<tr>
<th>Neuropsychiatric symptom</th>
<th>Predictor</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total NPI</td>
<td>MMSE</td>
<td>0.008</td>
</tr>
<tr>
<td>Agitation</td>
<td>MMSE</td>
<td>0.001</td>
</tr>
<tr>
<td>Apathy</td>
<td>MMSE</td>
<td>0.015</td>
</tr>
<tr>
<td>Delusions</td>
<td>MMSE</td>
<td>0.043</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>MMSE</td>
<td>0.000</td>
</tr>
<tr>
<td>Appetite</td>
<td>Cholinesterase inhibitors</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressants</td>
<td>0.000</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Antipsychotics</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Discussion

Our findings strongly suggest that, although there is a inverse correlation between overall NPI score and MMSE score, this is not equally the case for all individual neuropsychiatric symptoms. The strongest relationships with cognitive decline are with hallucinations and aberrant motor behaviour but this is not linear throughout the illness. Hallucinations are less common in moderate dementia and aberrant motor behaviour most common in severe dementia. We have also shown that prescription of psychotropic drugs may be an important mediator. Firstly, we have shown that MMSE score a predictor of psychotropic drug usage, with greater cognitive impairment being associated with more antipsychotic and less ChEI usage. Secondly the relationship between severity of cognitive impairment, hallucinations and
aberrant motor behaviour was only apparent in those not taking antipsychotics and quite distinct patterns of relationship were apparent in those on and not on antidepressants or ChEIs.

The strengths of this study are its relatively large sample size and the attempt made to recruit a cohort of people with AD who were representative of people with AD in the community in terms of severity of cognitive impairment. Its main weakness is that it has examined the relationships between neuropsychiatric symptoms, cognition and psychotropic drug use cross-sectionally rather than over time. A further limitation is the relatively large number of comparisons made, though this is offset by the use of linear regression analysis.

Conclusion

Neuropsychiatric symptoms are common in people with AD. People with AD are more likely to develop aberrant motor behaviour when dementia is severe, but hallucinations in the mild and severe stages. High overall NPI symptom score is associated with greater cognitive impairment but this pattern is only evident for some individual symptom domains. Psychotropic drugs may be an important mediator of this effect.

Acknowledgements

We would like to thank Lundbeck for funding the salaries of the researchers who collected the data. We would also like to thank all the people with AD and their families, friends and other carers who participated in the study together with all the consultant psychiatrists and community mental health teams, the staff of the nursing and residential homes and hospitals who provided us with support and help.

References


[28] American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. APA, 1994;Washington DC.


