Relation between neuritic plaques and depressive state in Alzheimer’s disease
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Gerben Meynen, Heleen van Stralen, Jan Smit, Wouter Kamphorst, Dick Swaab, Witte Hoogendijk

Abstract

Objective: To investigate for the first time in a prospective study using a scale for depressive symptoms in dementia the relationship between depressive state and the neuropathological hallmarks of Alzheimer’s disease (AD), while controlling for clinical severity of dementia.

Method: Within the framework of a prospective longitudinal study of depression in AD, demented patients underwent a clinical evaluation every six months during the last years of their lives, using the Cornell scale for depression in dementia to assess depressive symptoms and using the Functional Assessment Staging scale to control for clinical severity of dementia. The brains of 43 Alzheimer patients were obtained. The last clinical evaluations prior to death together with post-mortem neuropathology measures were analysed.

Results: We found a significant correlation between the Cornell scores and the sum score for the density of neuritic plaques in the entire cortex ($p=.027$), and in particular in the temporal cortex ($p=.012$). The observed correlations were independent of sex, age of death, clinical dementia severity and duration of AD.

Conclusions: This study shows a positive relationship between depressive state at time of death and the presence of neuritic plaques in AD, which is independent of the clinical severity of dementia.

Introduction

Depression occurs in 20-50% of the Alzheimer’s disease (AD) patients during some time of the disease process (Lyketsos et al., 2002). Depression can also be one of the earliest symptoms of AD (Broe et al., 1990; Sultzer, 1996; Berger et
al., 1999; Chen et al., 1999). In addition, in a number of studies it was found that a history of depression is a risk factor for the future development of dementia (Reding et al., 1985; Kral et al., 1989; Devanand et al., 1996; Wilson et al., 2002; Green et al., 2003). It has been hypothesized that depression during AD could occur as a psychological reaction to the disease, but no association was found between the retention of insight into the dementia process and depression (Ott et al., 1992; Verhey et al., 1993).

The pathophysiology of depression in AD is unclear, while the pathogenesis of major depressive disorder (MDD) has been related to stress-regulating brain systems, such as the hypothalamo-pituitary-adrenal (HPA) axis and aminergic systems including the noradrenergic system (Antonijevic, 2006). However, the question whether depression in AD has the same pathophysiology is still open. In previous studies we did not find any difference between aminergic systems in depressed and non-depressed AD patients neither in the total number of norepinephrine producing locus coeruleus neurons (Hoogendijk et al., 1999b) nor in the concentration of norepinephrine, serotonin, dopamine or their metabolites in de cerebral cortex, hippocampus, amygdala and locus coeruleus (Hoogendijk et al., 1999a). Also, while in MDD an increased lumbar cerebrospinal fluid (CSF) cortisol level has been found (Gerner et al., 1983), in AD patients post-mortem CSF cortisol levels are not higher in depressed AD patients than in non-depressed AD patients (Hoogendijk et al., 2006).

Recently, Rapp et al. performed a post-mortem study to determine the relationship between a history of depression and the neuropathological hallmarks of AD (Rapp et al., 2006). Interestingly, they found that brains of AD patients with a lifetime history of depression, extracted from medical information, showed higher levels of both plaque and tangle formation within the hippocampus than brains of patients with AD without a life-time history of depression (Rapp et al., 2006). However, Wilson et al. found no correlation between plaques and tangle formation and depressive symptoms in AD patients (Wilson et al., 2003).

Diagnosing depressive disorder in AD patients is complex because, according to the DSM-IV criteria, a depressive disorder cannot be classified during the course of a neurodegenerative disease (American Psychiatric Association, 1994). Furthermore, there is a profound overlap of symptoms between depression and AD, e.g. loss of interest, decreased energy, difficulty in thinking or concentrating, and psychomotor agitation or retardation (Burke et al., 1988). To overcome these problems we used the Cornell scale, which is designed as a quantitative measure for depression symptoms in all stages of dementia (Alexopoulos et al., 1988). Our study aims to establish whether a relationship exists between depressive state at time of death as determined by the Cornell scale in a prospectively followed
cohort of AD patients and the post mortem neuropathological hallmarks of AD.

Method

Subjects
The sample and fieldwork are described in detail by Hoogendijk et al. (Hoogendijk et al., 1999a; Hoogendijk et al., 1999b). Demented patients were studied at six-month intervals in the framework of a prospective longitudinal study of depression in AD in eight nursing homes. Clinical evaluation and postmortem neuropathological data were available for 43 subjects (33 females, 10 males) with probable or possible AD. After complete description of the study, written informed consent for the interviews was provided by the patient’s next of kin along with the patient’s assent at the time of each interview. Written informed consent for brain autopsy and the use of the clinical information and brain tissue for research purposes was obtained before subjects entered the study, as part of the program of the Netherlands Brain Bank.

Clinical evaluation
The patient’s next of kin and the nursing-home physician were interviewed about previous medical history and the age at onset of AD symptoms. Possible and probable AD were diagnosed according to the NINCDS-ARDA (McKhann et al., 1984) and DSM-III-R criteria (American Psychiatric Association, 1987). The presence of depression was evaluated by the Cornell Scale for the Assessment of Depression in Dementia (Alexopoulos et al., 1988) at six-month intervals. The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was used at baseline as an indication for the severity of clinical dementia, but the scores were too low to be of discriminative value (bottom effect). At six-month intervals the Global Deterioration Scale (GDS) (Reisberg et al., 1988) and the Functional Assessment Staging (FAST) (Reisberg, 1988) were used as a measure for clinical dementia. The patient and the patient’s closest caretaker were interviewed.

Neuropathological assessment
The distribution of the AD changes was established according to the Braak stage for tangles (Braak et al., 1991). Moreover, a neuropathologist performed a differentiated semi-quantitative evaluation of the severity of the lesions (neuritic plaques (NP), neurofibrillary tangles (NFT) and disruption of the neuropil (DN) throughout the cortex), established in a Bodian silver staining of the medial frontal gyrus, temporal pole, parietal lobe and occipital pole (Hoogendijk et al., 1999b).
In each of these cortical areas AD changes were separately scored as 0 = absent, 1 = present but less than moderate, 2 = moderate (i.e. two to three neurofibrillary tangles, two to three neuritic plaques or 30-60% of the normal network replaced by neuropil threads per 0.4mm² area) and 3 = more than moderate. Neuritic plaques were defined as circumscribed rounded-off disturbances of the neuropil visible with the Bodian technique. A NP total score was obtained by adding the NP scores of all the four cortex areas, the same was done for the NFT and the DN. Furthermore, an AD total score was calculated by adding the three separately scored AD changes of all the four cortex areas (Hoogendijk et al., 1999a; Hoogendijk et al., 1999b; Liu et al., 2000).

Statistical analyses
The last clinical evaluations prior to death (on average 3 months before death) along with the post-mortem neuropathological data were used. Relationships between variables were assessed by two-tailed Pearson correlation coefficients when we analyzed the ratio data and Spearman’s rank correlation coefficients when we analyzed the ordinal data. Multivariate analyses with the neuropathology variables as dependent variables were performed to investigate the interrelationships between variables with general linear models (regressions). Statistical significance was set at p<0.05.

Results
The cohort consisted of 43 AD patients, 33 women (76.7%) and 10 men (23.3%) with a mean age at death of 82.8 years (SD;7.2, range;64-96) and a mean age at AD onset of 73.7 years (SD;8.1, range;54-87). The duration of AD was on average 9.1 years (SD;3.3, range;3-17). FAST scores ranged from 6a to 7f and GDS scores were 6 or 7 from baseline measures till death. The MMSE scores (M;8, SD;2.5, range;0-13) were too low to be of discriminative value. The mean score of the last Cornell measured before death was 10.9 (SD;5.5, range;2-26). Braak scores were on average 5.1 (SD;1.0, range;3-6) and the mean AD total score was 21.5 (SD;8.0, range;5-36).

The duration of AD correlated significantly positive with the NFT (r=0.42, p=0.005) and the DN (r=0.41, p=0.006) throughout the whole cortex, but not with the NP (r=0.28, p=0.067). The duration of AD also correlated with the Braak score (r=0.38, p=.013), AD total score (r=0.42, p=0.005) and FAST score (r=0.32, p=0.034).

The Cornell score correlated significantly positive with the NP total score, a measure for the plaque density throughout the entire cortex, (r=0.34, p=0.027)
Relation between neuritic plaques and depressive state

When we looked at the four cortex areas separately we found a significant positive correlation between the NP score in the temporal lobe and the Cornell score ($r=0.38$, $p=0.012$). The correlation between the parietal NP score and the Cornell was almost significant ($r=0.29$, $p=0.061$). We found no correlation between the Cornell and the FAST score ($r=0.09$, $p=0.547$) nor between the Cornell score and the NFT, DN and Braak score (see table 1).

The hierarchical regression of NP in the temporal cortex on five predictor variables, entered in four blocks accounted for 30.1% of the variance ($p=0.017$). Sex and age of death were entered in the first block and accounted for 0.6% of the variance which was not significant ($p=0.882$). The Cornell score was entered in the second block and accounted for 17.2% of the variance ($p=0.007$). In the third block the FAST score was entered which accounted for a significant amount

<table>
<thead>
<tr>
<th></th>
<th>Last Cornell</th>
<th>Rho</th>
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</thead>
<tbody>
<tr>
<td>Frontal neuritic plaques (M:2.0,SD:1.0)</td>
<td>0.24</td>
<td>0.130</td>
<td></td>
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<tr>
<td>Frontal neurofibrillary tangles (M:2.0,SD:1.9)</td>
<td>-0.07</td>
<td>0.658</td>
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<tr>
<td>Frontal disruption of the neuropil (M:1.4,SD:1.0)</td>
<td>0.18</td>
<td>0.258</td>
<td></td>
</tr>
<tr>
<td>Temporal neuritic plaques (M:2.4,SD:1.8)</td>
<td>0.38*</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Temporal neurofibrillary tangles (M:2.1,SD:7)</td>
<td>0.14</td>
<td>0.384</td>
<td></td>
</tr>
<tr>
<td>Temporal disruption of the neuropil (M:2.4,SD:9)</td>
<td>-0.02</td>
<td>0.924</td>
<td></td>
</tr>
<tr>
<td>Parietal neuritic plaques (M:1.7,SD:9)</td>
<td>0.29</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>Parietal neurofibrillary tangles (M:2.1,SD:1.0)</td>
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<td></td>
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<tr>
<td>Parietal disruption of the neuropil (M:1.3,SD:1.2)</td>
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<td>0.674</td>
<td></td>
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<tr>
<td>Occipital neuritic plaques (M:1.9,SD:9)</td>
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<td>0.127</td>
<td></td>
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<tr>
<td>Occipital neurofibrillary tangles (M:1.0,SD:9)</td>
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<td>Occipital disruption of the neuropil (M:6.6,SD:9)</td>
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<tr>
<td>Braak score (M:5.1,SD:1.0)</td>
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<td>0.766</td>
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<tr>
<td>AD total score (M:21.5,SD:8.0)</td>
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<td>0.214</td>
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<tr>
<td>Neuritic plaques total score (M:8.1,SD:2.7)</td>
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<td>0.027</td>
<td></td>
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<tr>
<td>Neurofibrillary tangle total score (M:7.7,SD:2.8)</td>
<td>0.07</td>
<td>0.679</td>
<td></td>
</tr>
<tr>
<td>Disruption of the neuropil total score (M:5.7,SD:3.3)</td>
<td>0.06</td>
<td>0.686</td>
<td></td>
</tr>
<tr>
<td>FAST score (M:7.1,SD:5)</td>
<td>0.09</td>
<td>0.547</td>
<td></td>
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</table>

Table 1. Two-tailed Spearman’s rank correlations between the last Cornell score and the neuropathological Alzheimer’s disease scores.
of 10.0% of the variance (p=0.027). Finally the duration of AD was entered which accounted for an insignificant amount of 2.3% of the variance (p=0.279). Thus, in this model, only the Cornell score and the FAST score were significantly related to the amount of NP in the temporal lobe. The positive relationships indicated that people with higher scores on the Cornell and FAST will exhibit more NP burden in the temporal cortex.

When we performed the same hierarchical regression on the total amount of NP in the cortex, the model accounted for 30.9% of the variance (p=0.014). The Cornell and the FAST where again the only two variables accounting for a significant amount of the variance respectively 11.2% (p=0.029), 13.3% (p=0.012).

**Discussion**

To our knowledge, this is the first study to investigate the relationship between prospectively acquired data concerning the depressive state in AD patients at time of death using the Cornell scale to overcome the problem of symptom overlap and post mortem neuropathological data (Alexopoulos et al., 1988). We found a significant correlation between depression severity measured by the Cornell scale and the NP sum score of the four cortex areas, in particular in the temporal cortex and a trend for the parietal cortex. The observed correlations were independent of sex, age of death, clinical dementia severity and duration of AD.
The six neuropathological developmental stages of AD developed by Braak et al. are based on the characteristic distribution pattern in the brain of the neurofibrillary tangles and neuropil threads for the different AD stages (Braak et al., 1991). In accordance with the developmental stages of Braak et al. we found a significant positive correlation between the duration of the AD process and the Braak score, and in addition, between the duration of the AD process and the scores of the NFT and DN in the four cortical areas. In contrast to the NFT and the neuropil threads formation, the distribution of NP varies widely, not only within architectonic units but also from one individual to another (Braak et al., 1991). In line with this finding, we did not find a significant correlation between the duration of AD and NP.

While Rapp et al. reported a correlation between a retrospectively assessed history of depression and both NP and NFT scores (Rapp et al., 2006), we found a correlation between the prospectively obtained Cornell scores and NP scores. Previously, Wilson et al. studied plaques and tangle formation and depressive symptoms in AD patients (Wilson et al., 2003). They concluded that depressive symptoms in AD were not related to the level of AD neuropathology. However, in contrast to the present study they used a 10-item form of the Centre for Epidemiologic Study Depression Scale that was not especially designed to measure depressive symptoms in AD and they did not use classifications according to the DSM-IIIR or DSM-IV. In addition, in most of their analyses a global measure of AD pathology was used without distinguishing between plaques and tangles.

The correlation we found between the Cornell depression scores and the NP in the temporal cortex and the cortex as a whole may be explained in several ways. First, both the formation of NP and depression could be effects of a common underlying pathogenetic factor in AD, such as decreased cortical metabolism (Swaab et al., 2002).

Second, the presence of NP in the cortex might contribute, possibly via a toxicity of Aβ-amyloid, to the occurrence of depressive symptoms. For instance, neuronal damage in the temporal cortex could lead to disinhibition of the HPA-axis, since under physiological circumstances the hippocampus is an inhibitor of HPA-axis activity (Herman et al., 2005). This disinhibition of the HPA-axis could be a major factor in the pathophysiology of depression (Swaab et al., 2005). Another way in which NP in the cortex might contribute to the occurrence of depressive symptoms is via a chronic inflammatory response. There are clear indications that amyloid plaques are closely associated with a locally induced chronic inflammatory process (Eikelenboom et al., 2002). At the same time one of the hypotheses of the pathophysiology of depression concerns the involvement of the immune system in depression (Eikelenboom et al., 2002; Tilders et al.,
Therefore it has been hypothesized that an activation in the immune system is crucial in the pathophysiology of depression in AD (Eikelenboom et al., 2002).

Third, stress related disorders, such as depression are frequently accompanied by hyperactivity of the HPA-axis which in turn might contribute to the AD process via deleterious effects on the hippocampus (Sapolsky, 2000). Recently, higher HPA-axis activity, as reflected by increased plasma cortisol levels, was found to be associated with more rapid clinical disease progression in subjects with AD (Csernansky et al., 2006). In this respect it is also of importance that depression is a risk factor for cardiovascular disease (Ferkerich et al., 2000; Whooley, 2006), while cardiovascular disease is a risk factor for AD (Newman et al., 2005). Both in depression (Raadsheer et al., 1994; Raadsheer et al., 1995) and cardiovascular disease (Goncharuk et al., 2002) the number of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus, the origin of the HPA-axis, is increased. Considering the third option, it may be of relevance that depression in AD is in principle treatable with selective serotonin re-uptake inhibitors (SSRIs) (Lyketsos et al., 2002). Further research should be performed to clarify the pathophysiological relationship between the hallmarks of AD and the occurrence of depression in AD.

A limitation of the present study is that the AD patients in the present cohort suffered, in general, from end-stage AD. Therefore we do not know whether the observed relationship between NP and depression scored is also present in earlier stages of the disease. Since demented patients were studied at six-month intervals, the measurements were performed three months before the death of the subjects, on average. Therefore the last Cornell scores provide an approximation of the actual score at time of death.

In conclusion, the neuropathological hallmarks of AD are correlated to the depressive state in AD at time of death, which is independent of the clinical severity of AD.

Acknowledgements
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