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Relation between neuritic plaques and depressive state in Alzheimer's disease

Meynen G, Van Stralen H, Smit JH, Kamphorst W, Swaab DF, Hoogendijk WJG. Relation between neuritic plaques and depressive state in Alzheimer's disease.

Background: To investigate for the first time in a prospective study the relationship between depressive state and the neuropathological hallmarks of Alzheimer's disease, using a scale for depressive symptoms in dementia, while controlling for clinical severity of dementia.
Method: Within the framework of a prospective longitudinal study of depression in Alzheimer's disease, patients with dementia 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 correlation between the Cornell scores and the sum score for the density of neuritic plaques in the entire cortex ($p = 0.027$), and even stronger in the temporal cortex ($p = 0.012$). The observed correlations were independent of sex, age of death, clinical dementia severity and duration of Alzheimer's disease.
Conclusions: This study shows a positive relationship between depressive state at time of death and the presence of neuritic plaques in Alzheimer's disease, which is independent of the clinical severity of dementia.

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Keywords: Alzheimer's disease; depressive disorder; mood disorder; neuritic plaques; neuropathology; post-mortem

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Introduction

Depression occurs in 20–50% of the Alzheimer's disease (AD) patients during some time of the disease process (1). Depression can also be one of the earliest symptoms of AD (2–5). 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 (6–11). It has been hypothesised 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 (12).

The pathophysiology of depression in AD is unclear. The pathogenesis of idiopathic depression has been related to stress-regulating brain systems, such as the hypothalamo-pituitary-adrenal (HPA) axis and aminergic systems including the noradrenergic system (13,14). There are indeed similarities: in both major depression (15) and depression in AD (16), the number of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus, the origin of the HPA-axis, is increased. However, there are also differences between major depression and depression in AD. In previous studies, we did not find any difference between aminergic systems in depressed and non-depressed AD patients either in the total number of norepinephrine producing locus coeruleus neurons (17) or in the concentration of norepinephrine, serotonin, dopamine or their metabolites in de cerebral cortex, hippocampus, amygdala and locus coeruleus (18). Meanwhile, we have to note that others did find indications that the development of major depression in primary dementia is associated with a profile of neurochemical changes in aminergic systems largely consistent with existing

neurochemical hypotheses of major depression (19). Also, while in idiopathic depression an increased lumbar cerebrospinal fluid (CSF) cortisol level has been found (20), in AD patients post-mortem CSF cortisol levels are not higher in depressed AD patients than in non-depressed AD patients (21).

Rapp et al. performed a post-mortem study to determine the relationship between a history of depression and the neuropathological hallmarks of AD (22). Interestingly, they found that the 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 lifetime history of depression (22,23). However, Wilson et al. found no correlation between plaques and tangle formation and current depressive symptoms in AD patients (24). Taking these two studies together, it may still be that depressive episodes earlier in life contribute to the development of plaques.

Diagnosing a depressive disorder in AD patients is complex because, according to the DSM criteria, a depressive disorder can only be classified during the course of a neurodegenerative disease, using a dual diagnosis (25,26), of which the validity was showed by Zubenko et al. (27). 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 (28). To overcome these problems we used the Cornell scale, which is designed as a quantitative measure for depression symptoms in all stages of dementia (29). The scale has high inter-rater reliability, internal consistency and sensitivity. The 19-item scale is rated on a three-point score of 'absent' (0), 'mild or intermittent' (1) and 'severe' (2) symptoms, with a note when the score is unevaluable (a). An optimal cutoff score of '5/6' has been reported (30).

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

Patients

The sample and fieldwork are described in detail by Hoogendijk et al. (17,18). Patients with dementia were studied at 6-month intervals in the framework of a prospective longitudinal study of depression in AD in eight nursing homes. Clinical evaluation and post-mortem neuropathological data were available for 43 patients (33 women, 10 men) 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 patients entered the study, as part of the program of the Netherlands Brain Bank. The study was approved by the local ethics committee.

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 (31) and DSM-III-R criteria (26). The presence of depression was evaluated by the Cornell Scale for the Assessment of Depression in Dementia (29) at 6-month intervals, using information from both the patient and an informant. The Mini Mental State Examination (MMSE) (32) was used at baseline as an indication for the severity of clinical dementia, but the scores at follow-up were too low to be of discriminative value (floor effect). At 6-month intervals the Global Deterioration Scale (GDS) (33) and the Functional Assessment Staging (FAST) (34) were used as a measure for clinical dementia. The GDS provides a seven-point rating scale designed to stage the cognitive and functional capacity of individuals from normal ageing through profound dementia. The rating is made by clinically trained personnel based on observations, interviews with the patient and a knowledgeable informant. The GDS is composed of detailed descriptions of seven clinically distinguishable stages: no complaints of deficits (stage 1), subjective complaints of memory deficit (stage 2), earliest clear-cut cognitive deficits (stage 3), cognitive deficits that are clearly evident from a detailed clinical interview (stage 4), deficits that are severe enough to interfere with independent community survival (stage 5), deficits that are severe enough to interfere with basic activities of daily living (stage 6) and deficits severe enough to require continuous assistance with basic activities of daily living (stage 7) (33). The FAST is a rating scale that grades the progression of functional changes that occur with ageing and dementia. The rating is made by clinically trained personnel based on observations, interviews with the patient and a knowledgeable informant. The FAST consists of seven major stages that range from no functional difficulty (stage 1) to profound functional impairment (e.g. inability to speak, walk, or hold head up independently) (stage 7). Stage 6 is

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subdivided into five substages and stage 7 is subdivided into six substages. Thus, there are a total of 16 successive stages and substages (34).

The patient and the patient's closest caretaker were interviewed.

Neuropathological assessment

All brains were systematically assessed by a neuropathologist (35). The distribution of the AD changes was established according to the Braak stage for tangles (36). Moreover, one neuropathologist (W.K.) 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 (17). 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 NP or 30–60% of the normal network replaced by neuropil threads per 0.4 mm (2) area] and 3 = more than moderate. The NPs 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 and 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 (17,18,37).

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 analysed the ratio data and Spearman's rank correlation coefficients when we analysed the ordinal data. Multivariate analyses with the neuropathology variables as dependent variables were performed to investigate the inter-relationships between variables with general linear models (regressions). Statistical significance was set at <0.05, and accounted for multiple comparisons.

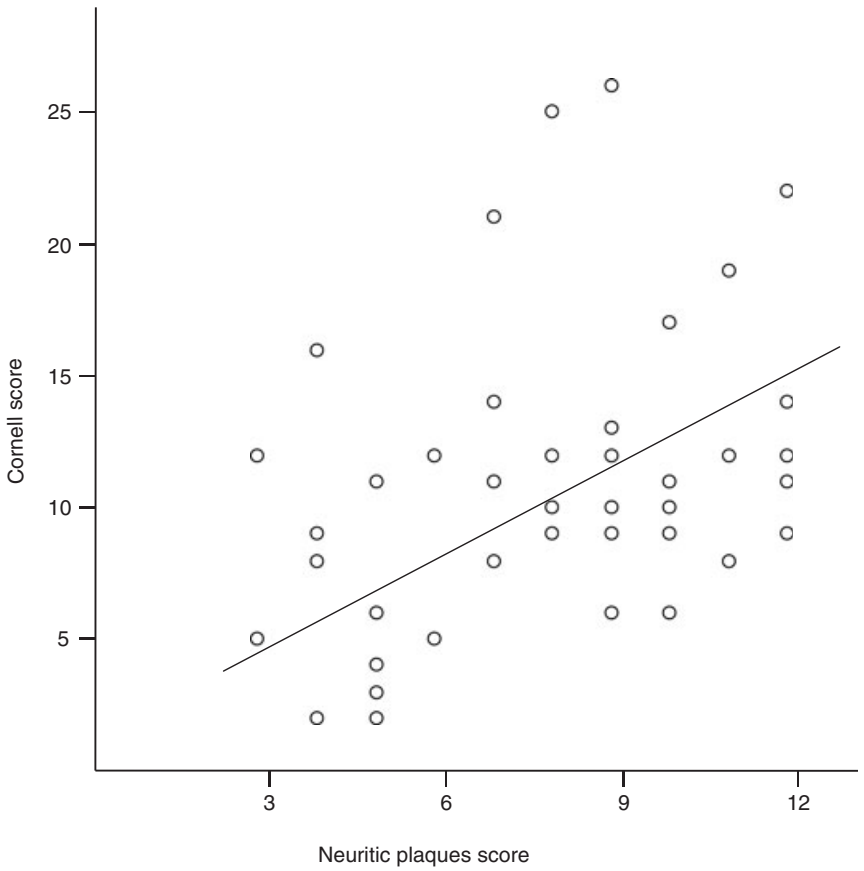

Fig. 1. Scatter plot of the correlation between the last Cornell score and the total score of neuritic plaques throughout the cortex ($\rho = 0.34$, $p = 0.027$).

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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 ± 7.2 years (range = 64−96) and a mean age at AD onset of 73.7 ± 8.1 years (range = 54 − 87). The duration of AD was on average 9.1 ± 3.3 years (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 (Mean = 0.8 ± 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 ± 5.5 (range = 2 − 26). Braak scores were on average 5.1 ± 1.0 (range = 3 − 6) and the mean AD total score was 21.5 ± 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 ($r = 0.38$, $p = 0.013$), AD total score ($r = 0.42$, $p = 0.005$) and FAST score ($r = 0.32$, $p = 0.034$).

The Cornell score was positively correlated with the NP total score, a measure for the plaque density throughout the entire cortex ($\rho = 0.34$, $p = 0.027$) (Fig. 1). When we looked at the four cortex areas separately, we found a significant positive correlation between the Cornell score and NP score in the temporal lobe ($\rho = 0.38$, $p = 0.012$), but not the frontal lobe. The correlation between the parietal NP score and the Cornell was almost significant ($\rho = 0.29$, $p = 0.061$). We found no correlation between the Cornell and the FAST score ($\rho = 0.09$, $p = 0.547$), between the Cornell score and the NFT, DN and Braak score (see Table 1). Post hoc analysis of individual Cornell items did not reveal additional correlations for these items, in particular apathy, which is in line with the lack of correlations with frontal lobe scores. 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 10.0% of the variance ($p = 0.027$). Finally, the duration of AD was entered, which accounted for a non-significant 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.

Table 1. Two-tailed Spearman's rank correlations between the last Cornell score before death and neuropathological Alzheimer disease scores

		Last Cornell	
	Mean (SD)	Rho	*p*
Neuritic plaques (NP)			
Frontal	2.0 (1.0)	0.24	0.130
Temporal	2.4 (0.8)	0.38	0.012
Parietal	1.7 (0.9)	0.29	0.061
Occipital	1.9 (.9)	0.24	0.127
Total score	*8.1 (2.7)*	*0.34*	*0.027*
Neurofibrillary tangles (NFT)			
Frontal	2.0 (.9)	−0.07	0.658
Temporal	2.1 (0.7)	0.14	0.384
Parietal	2.1 (1.0)	−0.01	0.957
Occipital	1.0 (0.9)	0.02	0.881
Total score	*7.7 (2.8)*	*0.07*	*0.679*
Disruption of the neuropil			
Frontal	1.4 (1.0)	0.18	0.258
Temporal	2.4 (0.9)	−0.02	0.924
Parietal	1.3 (1.2)	0.07	0.674
Occipital	0.6 (0.9)	0.04	0.814
Total score	*5.7 (3.3)*	*0.06*	*0.686*
Braak score	5.1 (1.0)	−0.05	0.766
AD total score	21.5 (8.0)	0.19	0.214
FAST score	7.1 (.5)	0.09	0.547

SD = standard deviation; AD = Alzheimer's disease.

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 were 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 until the time of death using the Cornell scale to overcome the problem of symptom overlap and post-mortem neuropathological data (29). We found a correlation between depression severity measured by the Cornell scale and the NP sum score of the four cortex areas, in particular in the limbic temporal cortex. The observed correlations were independent of sex, age of death, clinical dementia severity and duration of AD. The correlations were not driven by apathy-related items (e.g. psychomotor retardation) of the Cornell scale. This is in line with the fact that the Cornell scale was specifically developed and validated to measure depression in all stages of dementia.

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The six neuropathological developmental stages of AD developed by Braak et al. are based on the characteristic distribution pattern in the brain of the NFT and neuropil threads for the different AD stages (36). 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. This forms an internal validation of the used scores. In contrast to NFT and DN, NP varies widely within architectonic units and from one individual to another (36). 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 NP (22) and NFT scores (22,23), 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 (24). 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. 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 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 (38,39). Second, depression may be a risk factor for dementia in the presence of AD pathology (40). Third, the presence of NP in the cortex might contribute, possibly through a toxicity of Aβ-amyloid, to the occurrence of depressive symptoms, especially since we found the most significant changes in the limbic temporal cortex. 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 (41). This disinhibition of the HPA-axis is a major factor in the pathogenesis of depression (14,15,42). Fourth, stress-related disorders, such as depression, are frequently accompanied by hyperactivity of the HPA-axis, which in turn might contribute to the AD process through deleterious effects on the hippocampus (43). In this respect it is also of importance that depression is a risk factor for cardiovascular disease (44,45), while cardiovascular disease is a risk factor for AD (46). Both in depression (15,47) and in cardiovascular disease (48), the number of CRH neurons in the paraventricular nucleus of the hypothalamus, the origin of the HPA-axis, is increased. Considering the fourth option, depression in AD is in principle treatable with selective serotonin re-uptake inhibitors (SSRI) (49) or possibly also with a CRHR1-antagonist as a novel therapeutic tool (50). We did not find any associations between neuropathological AD changes and HPA-axis- or monoaminergic measures (data not shown). 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. At this stage, FAST scores may partly also relate to physical and cognitive deterioration. Therefore, we do not know whether the observed relationship between NP and depression scores is also present in earlier stages of the disease. The last Cornell scores provide an approximation of the actual score at time of death, since patients were studied at 6-month intervals, on average. However, we do not expect significant changes in depression score during the last months before death, since also during follow-up no clear changes in depression status were observed. We did not use an immuno cytochemical staining with antibodies against aβ and τ, since the Bodian silver staining we use for decennia is a stable staining with high resolution that is perfectly suitable to identify NP, NFT and DN. A considerable proportion of the patients died after the first assessment. Therefore, the statistical power was lacking to study the course of depressive symptoms. A study which would be able to look at the course of depressive symptoms would be valuable in order to better understand the pathophysiology of depression in AD.

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.

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