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History of depression prior to Alzheimer's disease and vascular dementia verified post-mortem

Hans Brunnström [a,*], Ulla Passant [b], Elisabet Englund [a], Lars Gustafson [b]

[a] Department of Pathology, Lund University and Regional Laboratories Region Skåne, Lund, Sweden
[b] Department of Geriatric Psychiatry, Clinical Sciences in Lund, Lund University, Lund, Sweden

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ABSTRACT

The aim of this study was to analyze the medical history, with regards to previous remote depression, in patients with neuropathologically verified Alzheimer's disease (AD), vascular dementia (VaD) and mixed AD/VaD. The 201 patients included (115 AD, 44 VaD and 42 mixed AD/VaD) had been referred to the Psychogeriatric/Psychiatric Department, Lund University Hospital, for psychogeriatric investigation and were followed-up with clinical records and detailed information on psychiatric history prior to the onset of dementia. Depression was considered to exist when the patient had consulted a psychiatrist or physician and had been diagnosed with a "depressive episode" or "depression" and when antidepressants and/or other specific treatments had been prescribed. Twenty patients (10%) had suffered from depression earlier in life well before the onset of dementia. Eight of the 9 AD patients with a previous diagnosis of depression had suffered from only one depressive episode and all had responded well to treatment, with complete recovery. In the VaD group, 8 out of 9 patients suffered two or more depressive episodes and only two recovered completely. Events with a possible significant relationship to depression were seen in 8 of the 9 AD patients but in only 1 of the 9 VaD patients. Psychotic symptoms were more common in VaD than in the AD group. The treatment modality of depression was similar in the groups. In conclusion, a history of depression prior to dementia is more common and more therapy-resistant in VaD than in AD.

1. Introduction

The relationship between depression and dementia is a complex issue. Non-demented patients with depression demonstrate an impairment of many cognitive domains (Christensen, Griffiths, Mackinnon, & Jacomb, 1997), and it may be difficult to differentiate between depression and dementia, especially in the elderly, in whom both conditions are prevalent. Furthermore, dementia and depression often coexist (Forsell & Winblad, 1998; Lyketsos et al., 2002), and depressive symptoms commonly appear at an early stage of dementia (Amieva et al., 2008). A number of prospective studies have shown a statistically significant association between the occurrence of depressive symptoms in the elderly and the risk of developing dementia or AD within a short period of time (Berger, Fratiglioni, Forsell, Winblad, & Bäckman, 1999; Devanand et al., 1996; Geerlings et al., 2000; Wilson et al., 2002), while other studies have shown no such association (Chen, Ganguli, Mulsant, & DeKosky, 1999; Henderson et al., 1997).

Depression as a risk factor for dementia has also been discussed (Byers & Yaffe, 2011; Jorm, 2001; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). There has been particular interest in AD, and several studies have found that a history of depression or depressive symptoms earlier in life relates to an increased prevalence of developing AD later in life (Green et al., 2003; Jorm et al., 1991; Jorm, 2001; Ownby et al., 2006; Steffens et al., 1997). However, the significance of these findings may be questioned, as the "history of depression" most often concerns only a limited number of years before the onset of a dementing disease.

The task of demarcating and studying the time period of "psychiatric history" prior to the onset of a dementing disease is rather difficult. A depressed mood may very well be an early symptom of the brain pathologies even when occurring many years prior to the onset of the mental deterioration, or could even be an early reaction or adaptation to the cognitive decline. To our knowledge, few studies of dementia have considered the psychiatric morbidity of early adulthood onwards, and there are no such studies entirely based on neuropathologically verified dementia cases.

* Corresponding author at: Department of Pathology, Regional Laboratories Region Skåne, S-22185 Lund, Sweden. Tel.: +46 46 173510; fax: +46 46 143307.
E-mail address: hans.brunnstrom@med.lu.se (H. Brunnström).

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The aim of the present study was to investigate the medical history with regards to earlier mental illness, especially depression, in patients with later-onset neuropathologically verified dementia in the form of AD, VaD and mixed AD/VaD, and to compare these groups with each other.

2. Methods

2.1. Study design

The study was based on a longitudinal prospective clinical work-up with a final post-mortem neuropathological examination, and covers the period from the late 1960s onwards. All patients had been referred to the Psychogeriatric or Psychiatric Departments at the University Hospital in Lund for psychogeriatric evaluation. All of the patients were systematically investigated, including anamnesis, physical examination, brain imaging and blood sampling. Patients who developed clinical dementia, which was neuropathologically verified upon death as AD, VaD or mixed AD/VaD, and who had been followed-up with clinical records including detailed information on previous psychiatric history before the onset of dementia, were included in the present study. For the years 1967–1998 consecutive cases included in the Lund Longitudinal Dementia Study (Brun & Gustafson, 1993; Gustafson et al., 2010) were selected, while for the years 1999–2008 consecutive cases referred to the Department of Psychogeriatrics were included.

This study was conducted in adherence with the Helsinki Declaration as well as national ethical guidelines. All patients and their next of kin accepted the participation in all examinations. As the clinical information investigated here was integrated in the clinical routine diagnostic work-up, this study is classified as a descriptive investigation for which no formal approval from an ethics committee is needed according to Swedish law and ethical guidelines. This has been substantiated by a consultation with the Regional Ethical Review Board in Lund.

2.2. Material selection

In total, 201 patients with neuropathologically verified dementia (115 AD, 44 VaD and 42 mixed AD/VaD) met the criteria and were included in the study. The neuropathological diagnoses, taken from the original reports, were based on standardized neuropathological procedures and on criteria being developed and revised over the years, in line with the results of emerging new histopathological techniques. The brain examination typically included a semi-serial whole brain coronal section with extensive microscopic assessment of conventional and immunohistochemical stainings. The classification of dementia subtypes was in adherence to the Swedish Consensus on Dementia Diseases (Wallin, Brun, & Gustafson, 1994). A diagnosis of AD was based on neurodegeneration with a significant presence of tangles and plaques (Braak & Braak, 1991; Brun & Englund, 1981; Brunnström & Englund, 2010; Mirra et al., 1991). VaD was diagnosed when the brain damage was exclusively or primarily based on vascular and circulatory etiologies with a minimum admixture of other pathologies, e.g. a minimal tangle amount in the hippocampus-subiculum, corresponding to Braak Stage I or Alzheimer grade 0.5 (Braak & Braak, 1991; Brunnström & Englund, 2010). The pathological category of mixed AD/VaD, indicated patients showing both types of pathology to such an extent that both were likely to have caused or contributed to the dementia, whereas patients with a significant Alzheimer pathology and a minimal vascular component (such as a single minor infarct found in the entire brain) were classified as AD. The included cases exhibited no other significant neurodegenerative disorders, such as frontotemporal dementia.

2.3. Data collection

The medical records for all patients were retrospectively reviewed by two specialists in geriatric psychiatry (U.P. and L.G.) for a prior history of mental illness, with a focus on depression. The information from the medical records included an interview with the patients at the time of first examination for neuropsychiatric disturbances and an interview with close relatives and other informants in regard to their earlier psychiatric history, including stress-related events. Relevant clinical records from other hospitals and general practitioners were also evaluated systematically for a history of mental illness. The psychiatric history focused on the time period from early adulthood (20+ years) until the onset of dementia-related symptoms. The diagnosis of depression was considered when the patient had consulted a psychiatrist or a physician and the condition had been diagnosed as either a "depressive episode" or "depression" and when anti-depressants and/or other specific treatments had been prescribed by the doctor. The patient's age at the time of depression, psychotic symptoms, treatment, outcome, duration and possible significant events related to the depressive episode were registered. The age at onset of dementia was estimated, rounded to the nearest full year.

2.4. Statistical analysis

One-way analysis of variance (ANOVA) was used for the analysis of demographic data for the whole population set. Fishers' exact test was used for the analysis of differences between the groups with a history of depression. A p-value less than 0.05 was considered to be significant.

3. Results

Demographic data for the 201 patients included in the study are shown in Table 1. In total, 20 (10%) of the 201 cases were found to have had one or several depressive episodes earlier in life. The demographic data for the patients with a history of depression are also shown in Table 1.

Nine of the 115 AD cases (7.8%) had a history of depression prior to the onset of dementia, while the prevalence in the VaD group was 9 out of 44 (20.5%) and in the mixed AD/VaD group 2 out of 42 (4.8%). The prevalence in the VaD group was significantly higher than in the AD and the mixed AD/VaD groups (Fisher's exact test: $p = 0.046$ and $p = 0.049$, respectively with significances remaining when using the Chi^2-test), while there was no significant difference between the AD and mixed AD/VaD groups.

In Table 2, the clinical and social characteristics of the 20 cases with a history of depression are presented. 8 of the 9 AD cases with depression prior to the onset of dementia suffered from only a single depressive episode, and all 9 cases recovered completely from the depression. In the VaD group, 8 of the 9 cases with depression prior to the onset of dementia suffered more than one depressive episode, and only two had a complete recovery (plus one additional case of recovery after many years). Also, all but one patient in the AD group had possibly significant events related to the depression noted in the clinical records, while this was the case for only one VaD patient. Statistically, more than one depressive episode, no complete recovery and an absence of significant events related to the depression were significantly more common in VaD than in AD (Fisher's exact test: all $p \leq 0.003$). The two cases with mixed AD/VaD resembled the VaD group concerning the number of depressive episodes, recovery and depression-related events.