Original article

Alzheimer's disease and co-morbidity: Increased prevalence and possible risk factors of excess mortality in a naturalistic 7-year follow-up

R. Heun a,1, D. Schoepf b,*,1, R. Potluri c, A. Natalwala d

a Department of Psychiatry, Royal Derby Hospital, Ultoxeter Road, Derby DE22 3WQ, United Kingdom
b Department of Psychiatry, University Clinic Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany
c Faculty of Medicine, Imperial College, London, SW7 2AZ, United Kingdom
d Southampton General Hospital, Tremosa Road, Southampton, Hampshire, SO16 6YD, UK

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A B S T R A C T

Background. – Subjects with late-onset Alzheimer’s disease (AD) have to be sufficiently healthy to live long enough to experience and to be diagnosed with dementia in later life. In contrast, neurodegeneration and cognitive deficits in AD may increase the frequency of co-morbid disorders and their possible influence on mortality. Consequently, we investigated whether the pattern of co-morbidity and its relevance for later death differed between hospitalized AD and age-matched controls subjects.

Methods. – Co-morbid diseases with a prevalence of more than 1% at hospital admission were compared between 634 hospitalized AD and 72,244 control subjects aged above 70 years admitted to the University of Birmingham NHS Trust between 1 January 2000 to 31 December 2007. Risk factors, i.e. co-morbid diseases that were predictors of mortality within the 7-year follow-up, were identified and compared.

Results. – Subjects with AD suffer more eating disorders, infections, brain diseases and neck of femur fractures than other hospitalized elderly patients. In contrast, some cardiovascular diseases and diabetes mellitus were less prevalent in AD subjects in comparison with hospitalized controls. Diseases that might have contributed to later mortality in AD were pneumonia, ischemic heart disease and gastroenteritis, but there were no significant differences in their impact on mortality compared to other hospitalized elderly subjects with the same co-morbidities in multivariate logistic regression analyses.

Conclusion. – Patients with AD have a different pattern of co-morbidity, but die from the same diseases as other hospitalized patients. Infections including pneumonia and diseases that may occur secondary to neurodegeneration and cognitive decline may need special attention in patients with AD who may not be able to identify or report the early symptoms. Preventive measures may be helpful to reduce the high risk and fatal consequences of undetected disease in AD.

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1. Introduction

In developed countries, the number of people affected by dementia will increase substantially with the aging of the general population. Dementia affects approximately 5–8% of individuals over the age of 65 years, 15–20% of individuals over the age of 75 and 25–50% of individuals over 85 [21]. It has been predicted that by 2050, the number of individuals with dementia will almost double worldwide, affecting over 1.7 million people in the UK [36]. The most common form of dementia is late-onset Alzheimer’s disease (AD), accounting for 50–75% of the total numbers of demented individuals, with a greater proportion in the higher age groups.

The psychopathology of AD is marked by cognitive deficits and psychosocial impairments in several domains. Deteriorations of short and long-term memory are characteristic initial features, which are followed by aphasia, apraxia, and agnosia after several years. Usually AD has an insidious onset and gradual decline [19]. Classically, the course of AD is described according to the level of functional psychosocial impairment. First stage: individuals with questionable psychosocial impairment show borderline functioning in several psychosocial areas but definite impairment in none. Second stage: individuals with mild psychosocial impairment have difficulties with complex activities in the household. Third stage: individuals with moderate psychosocial impairment have difficulties with simple activities of daily living. Fourth stage: individuals with severe psychosocial impairment require considerable assistance with personal care, including feeding, grooming, and toileting. Fifth stage: a patient has become largely oblivious to his surroundings and is almost totally dependent on caregivers [4].
The pathogenesis of AD is characterized by neurodegeneration with both genetic and environmental factors contributing to the development. Anatomically, the brain of a patient with AD undergoes morphologic changes including the development of extracellular neurofibrillary tangles and the deposition of β-amyloid plaques [55]. The presence of modified tau proteins in the brain tissue promotes additional cross-linking of both tau and β-amyloid, contributing to further neurodegeneration [9,57]. In addition, immune system dysfunction, dysfunctional processes at cell membrane level, endocytosis and lipid processing change affect neural brain tracts and central nervous neurotransmitter systems [24].

AD frequently interacts with other medical conditions that predispose to early death. Consequently, survival is discussed as to be determined by the multidirectional interaction of the following main factors: (1) mortality due to the risks of the resulting cognitive deficits of impaired cognition, impaired memory, or impaired performance that influence the pattern of physical health; (2) mortality due to a specific disease process that interferes with brain function especially if individuals present clinical features of both AD and vascular dementia; (3) mortality due to co-morbidity [41].

Mortality studies comparing subjects with AD and non-demented elderly controls demonstrated that mortality in AD depends on the patients’ age and the severity of the cognitive decline. Individuals with early stage AD have mortality rates equivalent to the general population, while those with late stage disease have elevated mortality rates [8,19,22,29].

Only a few earlier studies reported an effect of poor physical health on increased mortality in dementia [11,46]. A Canadian population-based study found that AD predicted increased pneumonia-related mortality in individuals with dementia in comparison with individuals without dementia [14]. Mortality studies have shown that patients with AD may be at reduced mortality risk from malignant neoplasm, type-2 diabetes mellitus and cardiovascular disease compared to the general population [14]. The types of general coexisting medical conditions that may occur in early stages of AD can include delirium, hearing and vision impairment, infections, falls and injury, urinary incontinence, constipation and fecal incontinence, pain, and oral health problems. With the progression of the disease, the general health care is often neglected and the disease frequently gives rise to complications that may result in loss of physical functions [60]. Medical problems including infection, bronchopneumonia, malnutrition and cachexia, dehydration, epilepsy and falls have all been reported to be more frequent in patients with severe dementia [13,17,34].

In summary, there is lack of information on the relevance of individual physical co-morbidity on mortality in AD [19,60]. Postmortem studies provide some evidence that causes of death differ in AD and elderly controls [5], but this has not been confirmed by others. Therefore, knowledge of the underlying and cause-specific co-morbidity of in-hospital mortality in patients with AD may be of major clinical relevance to help to intensify efforts aiming at the prevention of physical complications and at the reduction of mortality in AD.

1.1. Aims of study

The aims of this study are to evaluate in a non-selected hospital-based sample with up to 7-year follow-up if the prevalence of co-morbid disorders and their impact on later in-hospital mortality differ between patients with and without AD. Three specific hypotheses related to co-morbidity were tested: (1) co-morbid diseases at first admission to hospital for treatment are different between patients with AD and control patients; (2) some, but not all co-morbid diseases contribute to later in-hospital mortality in patients with AD (and control patients); (3) co-morbid diseases that are risk factors for later in-hospital mortality in patients with AD differ from those predictors of later in-hospital mortality in control patients.

2. Methods

The study was designed as hospital-based mixed case-control study with a 7-year follow-up (1 January 2000 to 31 December 2007). The design was retrospective and observational.

2.1. Study population

The 634 subjects with AD consisted of all patients that were consecutively admitted to University Hospital Birmingham NHS Trust for hospital treatment between 1 January 2000 and 31 December 2007. The hospital serves a multi-ethnic population of approximately 383,000 people (www.bpcs.nhs.uk). The inclusion criteria were discharge diagnosis of AD, age above 70 years, and inpatient care for at least 24 hours. The exclusion criteria were outpatient care, day or partial hospitalisation. The subpopulation of deceased AD subjects included all patients that had died as inpatients during the observation period ending 31 December 2007. The subpopulation of AD survivors included those subjects that survived the up to 7-year follow-up.

The control population consisted of other elderly patients that were admitted to the same hospital for hospital treatment during the same observation period. Control subjects were randomly selected to equalise the age distributions between the AD population and the control population (1 year intervals). The inclusion and exclusion criteria were the same as for the AD population (except for the diagnosis of AD). The subpopulation of deceased subjects included all control patients that had died during follow-up. The subpopulation of survivors included all control subjects who had finally survived at the end of 2007. The reason to randomly select a large hospital based control group that included all other types of diseases was to prevent a selection bias that would result by comparing hospitalised patients with AD with non-hospitalised control patients [7]. In addition, a large control sample prevents a random influence of chance on the comparison of somatic diagnoses that may have been resulted from the rarity of individual co-morbid somatic diseases in hospitalized subjects with AD and/or controls; furthermore this sample provides the opportunity to account for possible differences in age, gender and ethnicity in diagnostic subgroups for statistical analyses. It was not possible to match both samples for gender and ethnicity; the proportion of female AD subjects was significantly higher (65.1%) than in control subjects (51.0, p < 0.001); the number of Caucasians was significantly higher in AD subjects (92.7%) than in control subjects (80.0%, p < 0.001, see Table 1).

2.2. Recording of diagnoses

Subjects above 70 with AD were diagnosed according to the International Classification of Disease, 10th edition (ICD-10, diagnostic category F00.1, Cooper 1994) by senior physicians responsible for the formulation of the individual treatment plans. The process of diagnosis included cognitive and mental state examination, documentation that symptoms were present for at least 6 months, the patient’s history of emotional, social and behavioural changes, assessment of decline in memory function and cognitive abilities such as judgement and thinking, physical examination and other appropriate investigations including blood tests and neuro-imaging at the time of admission which was also reviewed when a patient was discharged. Dementia subjects with
one or more cerebrovascular lesions, focal neurological signs and symptoms coupled with a more acute onset and stepwise decline were diagnosed with vascular dementia and thus included in the control sample. Subjects meeting the general criteria for dementia, but could not be classified as having a specific subtype of dementia, were grouped as having unspecified dementia. If a differential diagnosis of dementia (due to another psychiatric disorder like delirium, amnestic disorder, mental retardation, schizophrenia, major depressive disorder, pseudo dementia, malingering and factitious disorder or a differential diagnosis of dementia due to other causes like general medical conditions, structural brain lesions, head trauma, endocrine conditions, nutritional conditions, infectious conditions, derangements of renal and hepatic function, neurological conditions, effects of medications, effects of long-standing substance abuse) had to be ruled out, appropriate clinical investigations were performed. In subjects with AD, important diagnostic information frequently becomes available only after some time of assessment. Consequently, the final diagnosis at discharge that was registered in the hospital electronic diagnoses database was used. The accuracy of hospital registry data in identifying patients with an ICD-10 diagnosis of dementia has been confirmed in a recent Danish study [43]. Additionally, a clinical diagnosis of AD conforms to the definite pathological diagnosis 70–90% of the time [44].

As a limitation of the study design, motor disturbances, which may include gait differences and may help differentiate subtypes of dementia were not recorded [2]. The study also did not record visual hallucinations, Parkinsonism and a variety of abnormal movements which may be related to functional disability and to shorter survival [53]. The study also could not record pharmacologic treatment including anti-cholinergic drugs or sedating medication. In addition, it was not possible to collect comprehensive information on the use of other medication. Therefore, it was impossible to statistically analyse possible effects of pharmacologic treatment on dementia, on physical co-morbidity or on later in-hospital mortality.

2.3. Sampling strategy

Anonymous information of registered discharge diagnoses of all patients above 70 admitted for hospital treatment between January 1, 2000 and December 31, 2007 were received from the local health authority computerised hospital activity analysis register. The subset of subjects with AD that had a hospitalisation within the 8-year inclusion period and a control sample group-matched for age as described above were identified. For subjects with several hospitalizations the earliest hospitalization was chosen. Since complete data of final diagnoses at discharge are entered for each patient in the hospital electronic diagnosis database, the possibility of counting patients twice was excluded. Subsequently, on the 31st December 2007, patient records were linked to the National Health Tracing Services (NHS strategic tracing service 2009). Thus, the 8-year in-hospital mortality data from the NHS was crosschecked against the hospital case records and patient information system. For every individual subject, follow-up was commenced at the beginning of the first hospital treatment. Follow-up of subjects continued until 31 December 2007. Confidentiality of information was maintained in accordance with the UK Data Protection Act. The patient information was anonymous and non-identifiable when received by the authors. Ethical approval for this study was obtained from the relevant local ethics authorities.

There are two potential biases that might result from the selection method. As a rather rare occurrence, it is possible that a small number of subjects with AD went undetected because they died shortly after first hospitalisation in the hospital. A second bias may theoretically occur because of subjects with AD who were admitted to first hospital treatment shortly before the end of the observation period or because of patients who had long lasting first hospitalisations periods that went beyond the end of the observation period. These subjects went undetected because of the timing of the hospitalisation. There are three important limitations that result from the selection method: (i) the use of electronically registered discharge diagnoses from medical case records linked with 8-year all in-hospital mortality data of the NHS does not permit to differentiate between primary and secondary diagnoses of AD at admission and discharge; (ii) it is not possible to divide the course and the execution of a treatment into different phases or to discriminate between different settings in the hospital like emergency unit or regular ward; (iii) neither is it possible to control for other risk factors like marital status, socioeconomic class, environment or premorbid intelligence.

2.4. Definition of co-morbid disease

A co-morbid disease was defined as any diagnosis of a somatic or mental disorder other than AD registered at discharge after the first hospitalisation. We focussed on diagnoses that appeared in at least 1% of the study population. In the group comparisons a relative risk (RR) of less than 2 was considered low, a RR between 2–3 was considered moderate, whereas a RR of greater than 3 was considered high [23].

2.5. Definition of disease contributor to later in-hospital mortality

Possible diseases contributing to later in-hospital mortality represented any registered diagnosis other than AD registered at
discharge after their first hospitalisation. A predictor respectively risk factor of later in-hospital mortality was defined as a disease that contributed to the prediction of later in-hospital mortality in multivariate forward logistic regression analysis \( p < 0.05 \). The terms predictors, respectively risk factor, do not indicate that the causal chain of this connection with regard to the outcome of later in-hospital death is explained in individual patients. Therefore, the study design does not make it possible to distinguish between underlying and causal-specific risk factors of later in-hospital mortality.

2.6. Data analysis

SPSS version 15.0 (SPSS Inc. Chicago, IL) was used for data analysis. The Student’s t test and Chi\(^2\) analysis were applied for subgroup comparisons of demographic data and for group comparisons of co-morbid diseases possibly contributing to later in-hospital mortality. Initially, RR unaccounted for covariates were calculated in univariate analyses to allow comparisons with other studies. Ninety-five percent confidence intervals (CI) were provided. Multivariate forward logistic regression analysis using age, gender, ethnicity and duration of follow-up time as covariates were used to identify those diseases that were independent risk factors for later mortality in both groups, and to compare RR with regards to follow-up different time periods existed within time zero (1 January 2000) up to more than seven years (31 December 2007). Time zero was defined as the date a subject was admitted for first hospital treatment within the observation period. End-points were the outcomes in-hospital death; censoring date was the end of the observation period, i.e. the 31 December 2007. All p values were calculated as two-tailed analyses; \( p < 0.05 \) was taken as significant.

3. Results

3.1. Demographic description of sample

Table 1 represents the demographic characteristics of the study population of AD and control subjects, subdivided by deceased subjects during follow-up and survivors (at the end of the observation period 31 December 2007). The AD population consisted of 634 subjects with a mean age of 85.1 years, the control population of 72,244 subjects with a non-significantly lower mean age of 80.8 years. Females comprised 65.1% of the AD population compared to 51.0% in the controls \( (p < 0.001) \). Caucasians predominated in the AD population with 92.7% compared to 80.0% in the control group \( (p < 0.001) \). There was a significantly larger number of control subjects with unknown ethnicity at 13.8% compared to 4.9% in the AD population \( (p < 0.01) \).

In the AD population, 260 deaths (41.0%) were observed for the 8-year in-hospital mortality data of the NHS, but only 19,038 deaths (26.4%) were observed in the control population \( (p < 0.001) \). As a consequence, follow-up duration was shorter in the AD sample \( (p < 0.001) \). However, follow-up duration did not differ between deceased subjects with AD (539 days) and deceased control subjects (522 days, \( p > 0.05 \)).

3.2. Prevalences of co-morbid diseases at first admission to hospital

Table 2 represents the prevalences of co-morbid diseases at first admission to hospital in subjects with AD in comparison with hospitalized controls. In agreement with our first hypothesis, some co-morbid diseases were more frequent in the AD population in comparison to the control population: the most

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Study population at initial hospitalisation</th>
<th>Relative risk of co-morbid disorder (AD versus control subjects): [CI 95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD population N/634, (%)</td>
<td>Control population N/72,244, (%)</td>
</tr>
<tr>
<td><strong>Co-morbid diseases with increased prevalence in the AD population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating disorders</td>
<td>11 (1.7)</td>
<td>197 (0.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>54 (8.5)</td>
<td>1261 (1.7)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>25 (3.9)</td>
<td>620 (0.9)</td>
</tr>
<tr>
<td>Fractured neck of femur</td>
<td>41 (6.5)</td>
<td>1143 (1.6)</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>19 (3.0)</td>
<td>719 (1.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62 (9.8)</td>
<td>2490 (3.4)</td>
</tr>
<tr>
<td><strong>Co-morbid diseases with reduced prevalence in the AD population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>109 (15.9)</td>
<td>15824 (21.9)</td>
</tr>
<tr>
<td>Type-2 Diabetes Mellitus</td>
<td>40 (6.3)</td>
<td>6998 (9.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>58 (9.1)</td>
<td>13887 (19.2)</td>
</tr>
<tr>
<td>Angina</td>
<td>18 (2.8)</td>
<td>5389 (7.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (1.7)</td>
<td>5952 (8.3)</td>
</tr>
<tr>
<td><strong>Co-morbid diseases without significant differences in prevalence between AD and control subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>7 (1.1)</td>
<td>393 (0.5)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>11 (1.7)</td>
<td>679 (0.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (1.1)</td>
<td>449 (0.6)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>17 (2.7)</td>
<td>1380 (1.9)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>20 (3.2)</td>
<td>1825 (2.5)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>8 (1.3)</td>
<td>869 (1.2)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>40 (6.3)</td>
<td>6260 (8.7)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>12 (1.9)</td>
<td>1453 (2.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>33 (5.2)</td>
<td>4022 (5.6)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20 (3.2)</td>
<td>1717 (2.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18 (2.8)</td>
<td>2786 (3.9)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>8 (1.3)</td>
<td>1237 (1.7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>17 (2.7)</td>
<td>2685 (3.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21 (3.3)</td>
<td>3827 (5.3)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (1.6)</td>
<td>2020 (2.8)</td>
</tr>
</tbody>
</table>

Stars indicate significant group comparisons between Alzheimer’s disease- and control population.

**Significance level: \( p \leq 0.05 \).

*** \( p \leq 0.001 \).
common, increased co-morbid disorder in the AD population was pneumonia with a frequency of 9.8% (RR, 2.8). Others more prevalent disorders in the AD sample included eating disorders (RR, 6.4), urinary tract infections (RR, 4.9), epilepsy (RR, 4.6), fractured neck of femurs (RR, 4.1) and Parkinson’s disease (RR, 3.0). In contrast, some cardiovascular diseases were less frequent in AD versus controls, i.e. hypertension (RR, 0.7), ischemic heart disease (RR, 0.5) and myocardial infarction (RR, 0.2). Type-2 diabetes mellitus (RR, 0.7) and angina (RR, 0.4) were also less frequent in AD than in control subjects. Other diseases including glaucoma, cellulitis, depression, gastroenteritis, ischemic stroke, acute renal failure, atrial fibrillation, breast cancer, peripheral vascular disease, hypothyroidism, chronic obstructive pulmonary disease, osteoarthritis, asthma, heart failure and anaemia were not significantly different in both groups.

3.3. Prevalences of co-morbid diseases contributing to later in-hospital mortality

Table 3 represents the co-morbid diseases that may have contributed to later in-hospital mortality in AD subjects and in the control sample (univariate analyses). In agreement with hypothesis 2, some, but not all co-morbid diseases contributed to later increased in-hospital mortality in the AD (as well the control population). In deceased subjects with AD, pneumonia was the most frequently recorded co-morbid disorder (17.7%) in comparison to the AD survivors (4.1), the risk of pneumonia was also highly elevated in deceased control subjects compared with the control sample survivors (RR, 7.1). Further contributors of later in-hospital mortality in both the AD- and the control population (CP) were peripheral vascular disease (RRAD 2.9; RRCP 1.5), ischemic stroke (RRA 2.7; RRCP 3.6) and gastroenteritis (RRA 2.6; RRCP 1.8).

In AD subjects only, specific single disease contributors of later in-hospital mortality were myocardial infarction (RR, 14.4) and ischemic heart disease (RR, 2.0); in contrast, in the control population, myocardial infarction and ischemic heart disease were no significant predictors of later in-hospital mortality.

Other co-morbid diseases that were significant predictors of later in-hospital mortality in the control sample, but not in the AD sample (partially due to increased statistic power as a consequence of higher sample sizes in the control sample) were: acute renal failure (RR, 7.2), heart failure (RR, 3.8), eating disorders (RR, 3.5), chronic obstructive pulmonary disease (RR, 2.3), fractured neck of femur (RR, 2.1), urinary tract infections (RR, 1.9), anaemia (RR, 1.8), atrial fibrillation (RR, 1.6), breast cancer (RR, 1.6), Parkinson’s disease (RR, 1.5), epilepsy (RR, 1.3), type-2 diabetes mellitus (RR, 1.1) 2.

Other diseases including osteoarthritis, hypothyroidism, asthma, hypertension, glaucoma, angina and depression did not contribute

| Table 3 |

| Prevalences of co-morbid diseases at initial hospitalisation (possible predictors) and their contribution to later in-hospital mortality in Alzheimer’s disease (AD) patients and control subjects: The prevalences of individual disease (%) were compared within the subgroups of AD and of control subjects between the population of deceased patients and the respective population of survivors. Relative risks and 95%-CIs are univariate and uncontrolled for follow-up duration, age, gender and ethnicity to allow comparison with other studies. In the first and second section diseases are ranked in descending order of relative risks in the Alzheimer’s disease population, in the third and fourth section diseases are ranked in descending order of relative risks in the control population. (Depression did not show any significant effect on mortality in any subgroup comparisons.). |

<table>
<thead>
<tr>
<th>Univariate comparisons</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alzheimer’s disease population</td>
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<tr>
<td></td>
<td>Deceased</td>
</tr>
<tr>
<td>Predictors of later in-hospital mortality in the Alzheimer’s disease- and the control population</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>46 (17.7)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>22 (8.5)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>13 (5.0)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>11 (4.2)</td>
</tr>
<tr>
<td>Predictors of later in-hospital mortality in the Alzheimer’s disease population (that did not significantly predict mortality in the control sample)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarct.</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Ischemic heart d.</td>
<td>34 (13.1)</td>
</tr>
<tr>
<td>Predictors of later in-hospital mortality in the control population (that did not significantly predict mortality in the AD sample)</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>11 (4.2)</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>5 (1.9)</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>6 (2.3)</td>
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<tr>
<td>Fractured neck of femur</td>
<td>17 (6.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>24 (9.2)</td>
</tr>
<tr>
<td>Anaemia</td>
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<tr>
<td>Atrial fibrillation</td>
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</tr>
<tr>
<td>Breast cancer</td>
<td>4 (1.5)</td>
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<tr>
<td>Parkinson’s disease</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Type-2 diabetes mellitus</td>
<td>16 (6.2)</td>
</tr>
<tr>
<td>Diseases at initial admission that did not contribute in the prediction of later in-hospital mortality</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Asthma</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (12.7)</td>
</tr>
<tr>
<td>Glaucosa</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Angina</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

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* p < 0.05.
** p < 0.01.
*** p < 0.001.
to later in-hospital mortality neither in deceased AD subjects nor in deceased control subjects.

3.4. Risk factors for later in-hospital mortality (multivariate analyses)

Table 4 represents the risk factors for later in-hospital mortality according to multivariate forward logistic regression analyses. In agreement with hypothesis 2, independent risk factors that predicted later in-hospital mortality in the AD population were pneumonia (RR, 3.0), ischemic heart disease (RR, 1.8) and gastroenteritis (RR, 2.1). Co-morbid disease that had contributed to later mortality in the AD sample in univariate analysis only were peripheral vascular disease, ischemic stroke and myocardial infarction (see Table 3) The lack of significance in multivariate analyses of the latter diseases may indicate that their contribution to the risk of later in-hospital mortality may be associated to the risk related to the above-mentioned three diseases identified in multivariate analysis (see first section of Table 4).

In disagreement with hypothesis 3, all diseases that represented independent risk factors or predictors of mortality in the AD population were not significantly different from the observed risk factors of mortality in hospitalized control subjects (i.e. the CI of the RR of mortality in AD subjects always included the corresponding RR of the control subjects, thus p > 0.05).

Diseases that were additional independent predictors of mortality in the control population were atrial fibrillation (RR, 1.2), heart failure (RR, 1.8), type-2 diabetes (RR, 1.2), peripheral vascular disease (RR, 1.3), chronic obstructive pulmonary disease (RR, 1.6), ischemic stroke (RR, 2.2), anaemia (RR, 1.3), acute renal failure (RR, 2.2), urinary tract infection (RR, 1.2), fracture of neck of femur (RR, 1.1) and eating disorders (RR, 1.8).

4. Discussion

This retrospective and observational university hospital based study investigates the prevalence of recorded co-morbid disorders and their impact on later in-hospital mortality in patients with AD.

In relation to our study hypotheses, we observed: (1) that in patients with AD, a different excess co-morbidity was found at first admission for hospital treatment in comparison to control subjects: disorders that were more frequent in AD included pneumonia, urinary tract infection, fractured neck of femur, epilepsy, Parkinson’s disease and eating disorders. (2) In univariate analyses some disorders including pneumonia, peripheral vascular disease, ischemic stroke, gastroenteritis myocardial infarction and ischemic heart disease significantly contributed to the mortality in AD. Diseases which may be the most relevant and independent risk factors of later mortality in multivariate analyses were pneumonia, ischemic heart disease and gastroenteritis, only. (3) However, in contrast to hypothesis 3, the contributions of these three diseases to later mortality were not significantly different between AD patients and hospitalised controls. Essentially hospitalized patients with AD suffer slightly different co-morbibd diseases in comparison with hospital controls at first admission to hospital; but die of the same reasons as other elderly patients.

4.1. Mortality in Alzheimer’s disease and gender

Concerning survival, we found that the mortality rate was twice as high in the AD population compared to elderly hospitalized controls. In full agreement with our results, a recent representative community based Canadian multicenter study demonstrated that the median survival after the onset of AD is much shorter than has previously been estimated. The mean survival in our hospitalised and later deceased AD sample was 1.5 years, the median survival for subjects with probable AD in the former study was 3.1 years [62]. This indirectly supports the assumption that the investigated AD population was characterized by a majority of patients that were highly cognitively- and psychosocially impaired.

The investigated clinical population is notable for its population of very elderly patients with AD: females comprised 65.1% of the AD population at first admission to hospital for treatment and 68.7% of the subpopulation of deceased patients at the end of follow-up. This result creates awareness of the relationship between gender differences, severity of dementia and the documentation of dementia on death certificates. In 1994, the Canadian Study of Health and Aging Working Group [12] published a report stating that the death rate based on the documentation of dementia as the underlying or non-underlying cause increased by a factor of 32 for the Canadian population aged between 65–74 up to...
those over 85 years. In general, women have a significantly longer life expectancy than men. In addition, the female gender has been reported to be a significant predictor of longer survival in AD in most studies on the subject [25,39,54,58,59]. Greater survival in woman with AD corresponds with an increased probability to develop severe to profound AD as well as an increased probability of documentation of AD on death certificates as the underlying or non-underlying cause [61]. Thus, the elevated number of female deaths in the AD population in our study is best explained by two reasons: (1) very elderly women are more likely to develop severe to profound dementia. In these deceased patients, AD may be more frequently reported on death certificates; (2) a potential survival bias that indicates that less healthy males with AD have been previously removed from the AD population by earlier death.

4.2. Excess co-morbidity at first admission to hospital

In this population of hospitalized patients with AD, the most frequent excess co-morbidity was pneumonia. The increased prevalence of pneumonia is in line with most studies on the subject [6,14,30,41,61]. A variety of reasons may account for this finding. From an epidemiological perspective, community-acquired pneumonia is among the most common infectious diseases and represents the third most frequent hospital diagnosis among patients above the age of 65 [16,20,37]. From a clinical perspective, the elderly and especially those with more severe disease and lower forced expiratory volume in 1 s are at the highest risk of recurrent pneumonia for several years after the first episode has taken place [32]. Further explanations that are associated with features of AD are lack of physical exercise, lack of mobility, communication difficulties and self-neglect. In addition, impaired swallowing function and pharmacological treatments with sedative agents may further increase the risk of aspiration pneumonia [42]. In summary, our finding highlights the fact that hospitalised AD subjects are a sample highly loaded with pneumonia. Furthermore, the finding may implicate and support that, despite current diagnostic and therapeutic possibilities; the prophylaxis of pneumonia during long term care programs for patients with AD is not optimal [35]. In general, age-related decline in immune function is considered to increase the risk of infection in the elderly, and hospitalised patients with AD who are unable to self-care are at greater risk [26].

Problems with mobility can be a major risk factor of urinary incontinence and associated urinary tract infections [49]. In line with possible poor mobility, the prevalence of fractured neck of femur was increased four-fold in the AD compared to the control population. The highly increased falls risk in very elderly individuals with AD can be viewed as the result of interaction of several factors: due to age- and related autonomic dysfunction in association with a high prevalence of co-morbid medical conditions, polypharmacy [31], due to anticholesterinase- or antipsychotic agents [10,11,48] and due to increased risk through impaired visuospatial and gait functions [2,50,56]. In summary, both urinary tract infections and fractured neck of femurs have direct negative effects on psychosocial functioning and a negative impact on cognitive-emotional functioning and communication.

In agreement with others, we observed an increased risk of epileptic fits and Parkinson’s disease in AD [3,34,52]. However, it might have been possible that in some of the cases co-morbidity for AD and Parkinson’s disease might have been better diagnosed as dementia of Lewy body type [27]. This might be a lesser problem in future studies when the awareness of dementia of Lewy body type might have increased in the medical community.

There is limited published evidence on how many individuals with severe to profound AD suffer from eating disorders. In one representative overview and two representative recent epidemiological studies, it has been reported that patients with dementia are at a higher risk of malnutrition because of a diminished capacity to recognize hunger and thirst, a decreased sense of taste and smell, and required assistance with eating [15,63].

4.3. Decreased co-morbidity at first admission to hospital

In the AD population, some co-morbid diseases were decreased in comparison with control subjects. These included cardiovascular diseases like ischemic heart disease and myocardial infarction as well as other cardiovascular risk factors like hypertension and type-2 diabetes mellitus. We explain this finding due to a possible combination of three effects: (1) a hospitalization bias indicating that elderly patients without AD are more frequently referred to hospital for treatment of cardiovascular diseases. In contrast, patients with AD may more frequently be referred due to infectious disease related reasons, fractures after falling and epilepsy; (2) an awareness bias indicating that a serious mental illness like AD with its functional problems may imply a tendency to ignore secondary or tertiary somatic conditions [33]; (3) a survival bias indicating that patients with AD and several co-morbidities may have died at a younger age and thus may have evaded inclusion in our study.

The prevalence of angina was more than twofold decreased in the AD sample. As far as we are aware, there are no representative comparable epidemiological studies on the prevalence of angina in AD. This may be the result of the fact that others might not have seen the diagnosis as sufficiently relevant or specific to AD to be included in relevant comparisons.

4.4. Risk factors of later in-hospital mortality

One main finding is that that this study shows that pneumonia, ischemic heart disease and gastroenteritis are the most relevant independent predictors for later mortality in AD, as well as in the control sample. The highest co-morbidity in deceased patients with AD was pneumonia with 17.7% compared to 9.5% in the deceased control population, but the RR did not significantly differ in both samples, as 95% intervals overlap. In addition, the risk of ischemic heart disease was elevated in deceased patients with AD (RR, 1.8) compared to the deceased control population (RR, 1.3). Bronchopneumonia and cardiovascular disease are the most relevant causes of death in AD and elderly controls [5,14,17,39,45,61,62]. In contrast, in this sample of hospitalized AD patients specific cardiovascular risk factors like hypertension, type-2 diabetes mellitus and depression were not positively associated with mortality of deceased AD patients. Concerning the increased risk of gastroenteritis, we could not find a comparable study that directly corroborated the evidence of gastroenteritis as a risk factor of mortality in dementia. However, other authors observed that malnutrition is a risk factor of mortality in dementia [18].

The combination of pneumonia, ischemic heart disease and gastroenteritis may highlight the relevance of pneumonia associated complications that are fatal in hospitalized AD patients: (1) in general very elderly individuals with AD whose general health is often compromised by the related psychosocial impairments are likely to be less resistant to opportunistic infections like pneumonia [61]; (2) severe dementia with co-existing factors like gastroenteritis, dehydration and malnutrition indirectly makes the likelihood of cardiovascular- and respiratory mortality more probable through a decrease in cardiorespiratory function [40]; (3) multiple pharmacologic agents or atypical antipsychotic drugs might be prescribed with less stringency in
these patients with further direct- and indirect effects on unexpected cardiovascular- and respiratory deaths [47]. In addition, in deceased AD patients myocardial infarction and ischemic stroke represented two single disease contributors of later in hospital mortality in univariate analysis. Both diseases may be related to pneumonia: a reduced oxygen supply as well to the heart muscle as to the extra- and intracerebral arteries is associated with cardiorespiratory associated complications in undetected or non symptomatic atherosclerosis of coronary- and cerebral arteries.

Even though some of these issues cannot be proven in this study, our results clearly demonstrate that pneumonia associated complications may play a dominant role in AD-related mortality. With regard to this main finding, there is a pressing need to address the deficiencies in healthcare of very elderly patients with AD in which physiological deterioration such as difficulty eating, incontinence, motor dysfunction and eventually immobility occur as dementia progresses. Reducing the risk of pneumonia associated complications by strict prophylaxis of avoidable- and recurrent infections, early referral to healthcare professionals, early detection in combination with aggressive treatment of pneumonia in hospital, controlling for side effects of psychotropic and somatic medication and creating awareness about preventive strategies for cardiovascular respiratory complications of pneumonia may help in reducing pneumonia associated mortality in our patients.

4.5. Limitations

Our study being retrospective and observational by design has several limitations. No data were provided whether or not patients with AD were treated with antipsychotic and anticholineresterase agents, nor data were provided concerning the use of multiple pharmacologic agents. These missing data make it impossible to compare possible drug effects on cognitive functions, falling risks, cardiovascular- and respiratory complications between the AD and the control population. The use of diagnostic information from medical case records at discharge and later in-hospital mortality data of the NHS does not permit to differentiate between primary diagnoses and secondary- or tertiary diagnoses. The quality of diagnoses and the possible effects of diagnostic awareness may have influenced the results and there may be a diagnostic awareness bias that is even more pronounced in the AD population than in the control population. The accuracy of entering secondary or tertiary somatic diseases into the medical record of very elderly patients with dementia strongly depends on the habits of the senior clinicians diagnosing and treating dementia that often do not stand in the foreground of hospital treatment. On the other hand, the degree to which patient and provider factors contribute to the fact that very elderly patients with AD may be less likely to report physical symptoms of illness is not clear. The observed awareness bias may explain a possible systematic underreporting of somatic conditions like angina pectoris and early respiratory dysfunctions in the AD population. This bias may explain at least in part the excess frequency of myocardial infarction in deceased patients with AD. Another important bias may be that patients with AD and control patients have different hospital admission rates. Very elderly controls with multiple somatic risk-factors and multiple diseases may have a higher probability of being hospitalized than subjects with early stages of AD and less physical diseases.

However, the validity of our results has been corroborated by studies from other samples including those from postmortem studies. Reasons for minor disparities between our study and others may be explained by differences in the sample as well as admission criteria of hospitals and nursing homes. Performing a large prospective follow up study on physical co-morbidity in dementia and its effect on mortality may be difficult for logistic reasons and intended blinding may be impossible for additional ethical reasons. Thus, further research in different settings i.e. hospital, nursing homes and the general population is needed to evaluate the specific effects of physical co-morbidity on patients with AD. In summary, even though we accept the possibility of possible awareness and hospitalization bias, we assume that these bias would not have completely changed our results.

5. Conclusions

Patients with AD have a slightly different pattern of co-morbidity, but they die from the same diseases as other hospitalized patients. Infections including pneumonia and diseases that may result as a consequence of neurodegeneration and of confusion may need special attention in patients with AD who might not be able to identify or report the early symptoms. Preventive measures may be helpful to reduce the high risk and fatal consequences of infections in AD.

References


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