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Differences in Rate of Cognitive Decline and Caregiver Burden between Alzheimer's Disease and Vascular Dementia: a Retrospective Study

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Abstract

Few studies have explored the rate of cognitive decline and caregiver burden within the context of a specialized memory clinic. When this was done, the focus was largely on functional decline related to Alzheimer's disease (AD). Our goal was to compare the longitudinal decline of AD patients to those with Vascular Dementia (VaD) on Mini-Mental State Examination (MMSE). We further explored the differential impact on caregiver burden. We retrospectively studied 237 charts from patients seen at our Memory Clinic between 2006 and 2012. The data was collected over 17 years. Cohorts were formed by excluding conditions other than AD and VaD, and including patients who had been assessed at least twice with the MMSE (AD: n = 83; mean age: 67.7 yo; VaD: n = 32; mean age: 73.3yo). A small group of 36 caregivers was surveyed by phone to explore caregiver burden. Results indicated that the natural history of MMSE changes in AD patients differed significantly from that of patients with VaD ($F = 10.41$, $p<0.0014$), with AD patients showing more cognitive decline over time. Sadness, stress/anxiety, fatigue, and sleep disorders were reported as the main preoccupations by caregivers and its impact was rated as 'severe' in 50% of cases. Altogether, this study provides further insight into the natural history of cognitive decline in AD and VaD. Future studies should explore the progression of dementing disorders in larger cohorts using prospective methodological designs.

Keywords: *Alzheimer's Disease; Vascular Dementia; Caregiver Burden; Natural History; Tertiary Memory Clinic*

Abbreviations: AD: Alzheimer's Disease; MMSE: Mini-Mental State Examination; Standard Deviation; VaD: Vascular Dementia; Non-Significant

Introduction

Alzheimer's disease (AD) is the most common cause of dementia associated with aging [1]. It is characterized by an insidious onset and slow deterioration in cognition, functional ability, behavior, and mood. While AD is responsible for the majority of dementias, Vascular Dementia (VaD) is thought to be responsible for no less than 20% [2-4]. VaD is associated with a variety of ischemic phenomenon (mainly large cortical infarcts, lacunae, white matter lesions, or microinfarcts) and is well-known for its impact on cognition and functional abilities [3,4].

A great deal of knowledge has been accumulated on the natural history of AD [5-8], yet very little is known on the longitudinal profile of patients with VaD and how this compares to AD cohorts. In a recent study, authors have estimated differences in rate of functional decline in a large cohort of patients with AD, dementia with Lewy bodies (DLB), and VaD [9]. Patients with VaD declined more slowly than

those with AD over time in their functional activities. There were no significant differences in rate of functional decline between patients with DLB compared with those with either AD or VaD. Another recent study suggested no difference in the rate of decline between DLB and AD [10]. Very little information was available on cognitive decline and caregiver burden.

To this date, the best longitudinal effort comparing the cognitive course of AD, VaD and AD with cerebrovascular disease (AD + CVD) found that patients with VaD showed the slowest decline over time when compared to AD+CVD and AD [11]. However, study period was limited to four years. The main objective of this study was therefore to explore the longitudinal decline of AD and VaD patients on MMSE scores over more than a decade. In order to further assess the natural history of both diseases, we studied their clinical charts dating from their first visit up to their most recent visit at our clinic. In light of increasing concerns raised by a group of Canadian experts, chaired by Dr. Howard Bergman [12] regarding the lack of tools to assess the situation of caregivers and lack of information regarding the extent of their difficulties, we further conducted a telephone survey to explore if caregiver burden differed between the two conditions.

Methods

Setting

Data was collected retrospectively from medical records using a standardized questionnaire designed to collect demographic information. Approval from local Ethics Review Board was obtained prior to conducting this study.

Study participants

A total of 237 charts from patients seen at Clinique Interdisciplinaire de Mémoire (CIME) between January 1st, 2006 and July 1st, 2012 were screened. This pool of patients had been followed up at CIME over 17 years, between 1995 and 2012. Several diagnoses composed the Memory Clinic population (Figure 1). For the purpose of the present study, only those with AD and VaD were selected. Inclusion criteria were chosen to obtain valid longitudinal data on a select group of patients: Demographics (Age at 'First Visit', Gender and Number of Years of Education). (1) demographics (age at 'First visit', gender, number of years of education), (2) initial diagnosis at 'First visit', (3) final diagnosis at the 'Most recent visit', (4) Mini-Mental State Examination (MMSE)(Folstein, Folstein and McHugh)scores at 'First visit', at 'Diagnostic visit' and at the 'Most recent visit', (5) medications, (6) main physical and psychiatric comorbidities, (7) habits (alcohol, tobacco, etc.), and (8) primary caregiver.

Data was collected directly from medical charts of patients who met the inclusion criteria. Any chart that did not include such information was excluded. All patients had standard dementia workup including a clinical interview by a dementia specialist, basic laboratory tests, brain imaging, cognitive screening using the MMSE, and in many cases a full neuropsychological evaluation (i.e., tests of attention, language, memory, visuospatial and executive functions). Our final sample was composed of an AD group (n = 83; mean age: 67.7 years old) and a VaD group (n = 32; mean age: 73.3 years old) (Table 1).

Among all 115 AD and VaD cases, a random group of 50 caregivers were selected and contacted. Thirty-six primary caregivers were available and consented to share their experience. A standardized clinical interview was administered to measure overall caregiver burden. More specifically, this interview used both open-ended and multiple choices questions, and focused on (1) personal difficulties they encountered as caregiver, and (2) the impact of being the primary caregiver on their daily lives. Overall severity of the impact on their health was subjectively graded as 'mild', 'moderate', or 'severe'. Further ethics approval was obtained separately for this prospective portion of the study.

Characteristics	AD (n = 83)	VaD (n = 32)	*P value*
Mean age (years) at diagnosis (SD)	67.7 (2.3)	73.3 (2.4)	N.S.
Gender (% female)	60.2	40.6	N.S.
Education (years)	11.4	11.1	N.S.
Comorbidity score (max = 3); mean (SD)	0.9 (0.3)	1.6 (0.3)	N.S.
Initial MMSE; mean (SD)	24.9 (4.5)	25.8 (5.7)	N.S.

Table 1: *Participant characteristics.*

A non-validated comorbidity score was calculated from the number of comorbidities found in three general categories (i.e., vascular, psychiatric, medical) each worth one point (max = 3). 'Vascular' included one of hypertension, diabetes, stroke, dyslipidemia, or heart disease. 'Psychiatric' included anxiety, depression, or another Axis I diagnosis. 'Medical' included general medical conditions such as hip surgery, gastrointestinal disease, etc.

AD: Alzheimer's Disease; VaD: Vascular Dementia; N.S.: Non-Significant; SD: Standard Deviation

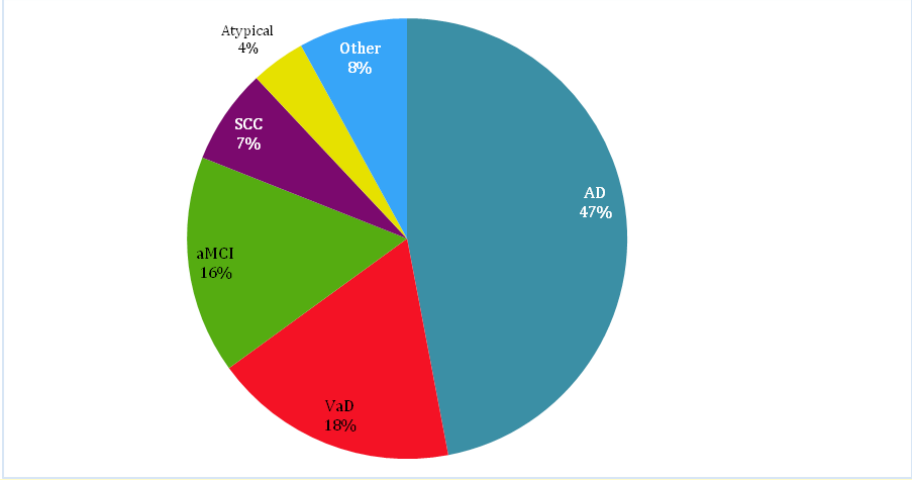

Figure 1: *Global clinical cohort.This is a portrait of the entire clinical cohort from which we selected AD and VaD subgroups. Abbreviations: AD (Alzheimer's disease); aMCI (amnestic mild cognitive impairment); SCC (subjective cognitive complaint); VaD (vascular dementia). 'Atypical' includes behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasasal degeneration, and progressive supranuclear palsy. 'Other' includes psychiatric conditions (eg, mood disorders, schizophrenia, and bipolar disorder).*

Analysis

In accord with the main purpose of this study which was to explore the rate of cognitive decline in patients with AD vs VaD, we selected 'control points' which represented comparable events throughout their history. Patients completed an MMSE at three different periods over their follow-up. The first time point that was chosen was their 'First visit' at CIME where they all completed an MMSE. Most patients presented with a prior MMSE done at their general practitioner's office but to ensure consistency of evaluation, these scores were not used. It was also calculated that out of our total cohort of patients at CIME, 41% of the 65% participants later diagnosed with AD and/or VaD were initially labelled Mild Cognitive Impairment (or equivalent depending on the decade) at 'First visit'. The second time point corresponded to the MMSE at the 'Diagnostic visit', that is when the clinician clearly outlined the diagnosis according to standard criteria for AD [14] and VaD [2]. This visit was considered the baseline point in the patient's evolution. This visit corresponded to Day 0 and we calculated the number of days between this date and the other two measurement periods (before and after). Hence for dates

before the 'Diagnostic visit', the number of days was negative and for dates after the 'Diagnostic visit', the number of days was positive. The final point in time was the 'Most recent visit' at CIME.

We used the Wilcoxon test to compare the mean number of days between time measurements of our groups. We performed two tests, one for the number of days between the 'First visit' and the 'Diagnostic visit' and one for the number of days between the date of the 'Most recent visit' and the 'Diagnostic visit'. Second, an analysis of covariance model (ANCOVA) with repeated measure was used to compare the change over time in MMSE scores between the two groups. The covariable was the number of days since diagnosis. The MIXED procedure in SAS [15] was used with a repeated statement to take into account the correlation between the three measurements on the same patient. The best covariance structure, based on the Akaike information criteria was chosen. Degrees of freedom were calculated using the Kenward-Roger method. Squared transformation of the MMSE score was used in order to meet the normality and homogeneity assumptions underlying the ANCOVA model. Multiple comparisons were made using protected Fisher least significant difference (LSD). The significance level was set at $\alpha = 5\%$.

Results

Natural history of Alzheimer's disease vs Vascular Dementia

To characterise the evolution of our two subgroups of dementia, we analysed the longitudinal history using three key points in patients' history. However, because these three points were not standard for each patient, the amount of time between evaluations amongst patient and groups were not the same. In fact, the average number of days between the 'First visit' and the 'Diagnostic visit' did not differ significantly (-671 days vs -756 days) between AD and VaD (Wilcoxon Two-Sample Test, $p = 0.41$), but there was a significant difference (Wilcoxon Two-Sample Test, $p < 0.003$) between the 'Diagnostic visit' and 'Most recent visit' (1123 days for AD vs 640 days for VaD). As a result of this, it implied that we had to factor in time as a covariate in an analysis of covariance model. To pursue this, we first verified whether there was a linear relationship between the dependent variable and the covariate. The results showed a Group X Time interaction ($F = 10.41$, $p < 0.0014$) suggesting that the relation between MMSE and time was different between our groups. This meant that the longitudinal evolution between our groups was significantly different. Therefore, we opted to compare the group's adjusted averages at specific time points: -2000, -1000, 0, 1000 and 2000. At days -2000 and -1000 (which corresponded to the period surrounding the 'First visit') the two groups did not differ significantly. However, they were significantly different at days 0 ('Diagnostic visit') ($t(0.05,126) = -2.70$, $p<0.008$), and at days 1000 ($t(0.05,192) = -3.57$, $p <0.0004$) or 2000 ($t(0.05,257) = -3.72$, $p<0.0002$) (which corresponded to the period surrounding the 'Most recent visit'), with lower scores for the AD group (Figure 2). These statistical analyses confirmed that the two groups, while initially comparable, evolved differently with a more pronounced deterioration in the AD group.

Caregiver burden

Telephone interviews with 36 caregivers of patients with AD (n = 21) or VaD (n = 15) who reported on their experience revealed that the most frequent complaints were sadness (n = 15), stress/anxiety (n = 16), fatigue (n = 15), and sleep disorders (n = 11). Overall perception of the impact of dementia on caregiver health was severe in 50% of the sample (see Figure 3), but did not differ between the two groups.

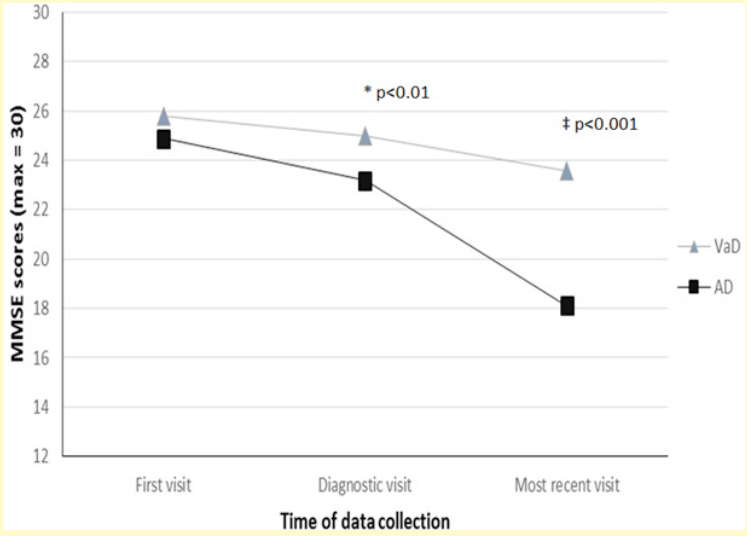

Figure 2: *Natural history of cognitive changes in AD vs VaD.*

This figure illustrates that the natural history of cognitive changes in AD patients differed significantly from that of patients with VaD, both at 'Diagnostic visit' and at 'Most recent visit', AD patients being significantly more affected over time. Within the context of our study, 'Diagnostic visit' means when the clinician clearly outlined the diagnosis according to standard criteria for AD and VaD. Statistical analyses confirmed that the two groups, initially comparable, evolved differently with a more pronounced deterioration in the AD group.

** p<0.01*

‡ p<0.001.

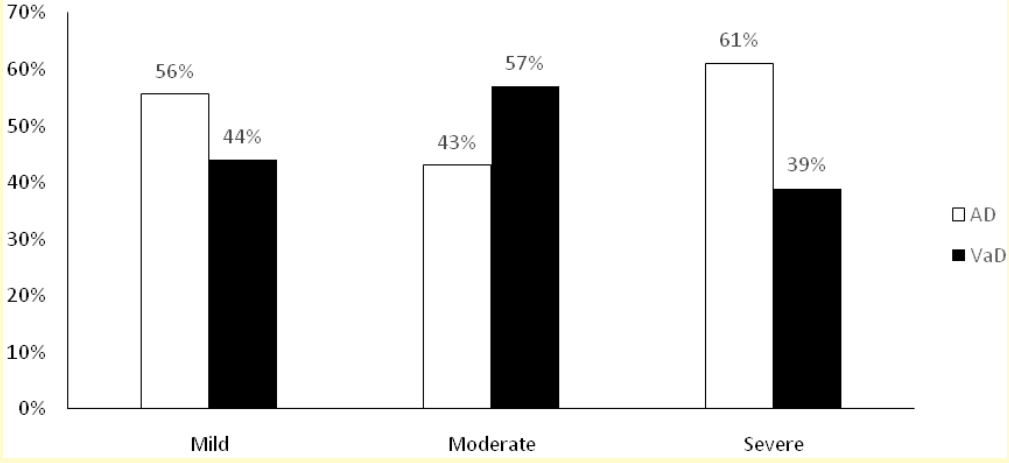

Figure 3: *Overall impact of the disease on the primary caregiver's health.*

This figure illustrates the percentage of caregivers who actually reported mild, moderate and severe overall impact on their health. Overall perception of the impact was severe in 50% of the sample (AD and VaD combined), but did not differ between the two groups. Sadness, stress/anxiety, fatigue, and sleep disorders, were reported as the main preoccupations by caregivers.

Discussion

The main goal of this research was to compare the longitudinal decline of patients with AD to those with VaD on MMSE scores. We further explored the differential impact of these conditions on caregiver burden. Results showed a significant difference between the rates of decline in patients with AD when compared to those with VaD, with AD patients declining the fastest. These findings are consistent with recent work on functional decline in different subgroups of dementing illnesses [9-11]. Very few authors, however, had explored their cognitive trajectories in the context of a tertiary memory clinic and over such a long period of time. Caregiver burden was high but did not differ significantly between AD and VaD.

Recent literature on common dementia syndromes shows that AD has a long, progressive prodromal phase [16-18]. When compared to AD, VaD also appears to be a progressive disease but its onset has not been specifically characterized in familial variants such as familial AD where it occurs approximately 25 years before the first symptoms [17,19]. Both conditions are modulated by vascular risk factors but VaD often presents as more sudden events causing progressive changes in cognition [20]. These pathophysiological differences in diseases may partly explain why our AD patients declined more rapidly over time. Moreover, diagnoses may have been influenced by progression between visits (i.e., time from 'First visit' to 'Diagnostic visit', which sometimes extended to two years).

Our findings in the VaD group are similar to other reports and suggest that VaD is a progressive disorder but may not progress as rapidly as AD [9,11]. This is also consistent with slower rate of decline in the placebo arms of randomized controlled trials in subjects with VaD versus AD (combined with cerebrovascular disease) [21]. One possible explanation is that patients with VaD have been recovering from vascular insults and thus are slowly improving over time. Alternatively, VaD may represent a milder form of dementia.

The retrospective nature of this study did not allow retrieval of brain scans that dated back to 1998, and therefore a great amount of brain imaging data collected as part of the dementia workup was unavailable. Brain imaging was available for only 31 patients (27%). This prevented us from a formal imaging comparison of AD with VaD and also with AD+CVD or the notion of 'mixed dementia'. It is unquestionable that the vast majority of our patients had dual pathology. A formal categorization, taking into account vascular burden should be considered in prospective efforts.

As for caregiver burden, our results appear consistent with prior literature, despite being flawed with several major limitations addressed below [22]. Indeed, as reported in a meta-analysis [23], stress and anxiety are often reported by caregivers. More than one in three individuals in our study reported these symptoms. The severity of these symptoms is of significant concern and should promote immediate responses from government authorities, as suggested in the Bergman report [12]. The fact that caregiver burden was similar in the two groups despite more severe cognitive impairment in the AD group came somewhat as a surprise. The retrospective methodology and limited sample size used for this exploratory portion of the study limits our conclusions. However, using an ecological perspective it appears that dementia, whatever underlying pathology or cognitive profile, generates significant caregiver burden. It appears that the sole experience of seeing a loved one go through phases of significant loss is sufficient to increase the amount of distress, irrespective of diagnosis.

Many aspects have been found to significantly affect caregiver burden, including behavioural and psychological symptoms of dementia (BPSD) [24-27]. For example, D'Onofrio., et al. (2014) [23] attempted to characterize the differences of caregiver burden in patients with AD and VaD in order to improve the care counselling and management plan by testing 506 patients on the MMSE, Clinical Dementia Rating, Hamilton Rating Scale for Depression and Neuropsychiatric Inventory (NPI) [24]. AD patients at baseline showed higher grade of cognitive impairment and increased severity stage of dementia than VaD patients. AD caregivers, mainly females, devoted significantly more length of time care and time of daily care and showed a significantly higher burden level than VaD caregivers. AD caregivers showed a higher burden level than VaD caregivers, and this appeared to be associated with sex and length of time care. Huang et al. (2012) [25]. showed that symptom frequency of anxiety, delusions, and agitation/aggression correlated positively with

caregiver's NPI score [26]. Their findings suggest that improvement of treatments for delusions, agitation/aggression, anxiety, irritability/lability, and dysphoria/depression among dementia patients may reduce caregiver burden.

Finally, Rosa., *et al*. (2010) [27]. have argued that symptoms more often found in VaD than AD such as physical limitations (loss of strength, balance and/or sensation) may be associated with greater caregiver burden. These authors also found that better knowledge of the disease (i.e., what to expect physically, cognitively and emotionally) were among the most important needs expressed by caregivers [28].

Limitations

This study has several important limitations which significantly limits the strength of its conclusions. First, it uses a retrospective design that is flawed by a number of uncontrolled variables, including different timing of diagnoses, various diagnostic definitions between clinicians and across time. Although CIME's neurologists use the most recent diagnostic criteria in their practice, because the extent of follow-up covered up to 17 years, several criteria changed throughout the study. Indeed, some forms of dementia that were not very well defined 10 years ago are clearly underrepresented in our study. Second, the results are based on a small number of patient records. However, the data included in our study was collected over up to 17 years and we believe the quality of longitudinal information is of great value. Further studies should include a larger sample of patients diagnosed with modern criteria. Third, there was no quantification of cerebrovascular disease either in the form of higher vs. lower vascular burden or number of vascular lesions in each of our groups. This creates a situation where our AD group may be a mixed group as suggested in current literature. In addition, we provide very limited insight into the synergistic effects of AD on CVD and vice-versa. One could expect a more rapid decline in AD + CVD than in AD, and possibly also more than in VaD, given the fact that for example the Nun Study and the Religious Disorders Study have shown that much less beta-amyloidosis and neurofibrillary tangles are required with CVD to reach the same degree of cognitive impairment. Fourth, it is possible that vascular comorbidities were better documented in VaD patients than in AD patients. However, it is unlikely that this affected our findings on longitudinal MMSE scores. Fifth, we used the MMSE scores to compare the rate of cognitive decline in patients with AD and VaD. However, the MMSE generally reflects cognitive deficiencies better in the majority of typical AD (i.e., episodic memory, naming) than in the majority of VaD (i.e., poor instrument to measure frontal-subcortical deficits such as problems with attention, working memory and executive skills).

Our post-hoc study of caregiver burden was simply exploratory. It was based on a very small sample size, did not include standardized objective measures of BPSD or other variables well documented to have an impact of caregiver burden. [24-27] Future studies should focus on prospective efforts using both quantitative (NPI, structured neuropsychiatric interviews) and qualitative measures (e.g., focus groups).

Concluding comments

We focused on two common late-life dementias and found that their longitudinal evolution on MMSE was significantly different. Our retrospective design allowed an ecological perspective on the issue but at the same time many limitations (outlined above) reduced our ability to generate firm conclusions. Understanding cognitive decline in AD and VaD, and how trajectories among them differ can be important for clinical care but also stimulate further research endeavours into their pathophysiological mechanisms. Because of the large predicted increase in dementia prevalence in the coming years, our results may nonetheless help clinicians better inform patients and families of the expected trajectories of these diseases.

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