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Cerebral white matter disease is independently associated with BPSD in Alzheimer's disease

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ABSTRACT

Objectives: To study the association between cerebral white matter disease and burden of behavioral and psychological symptoms (BPSD) among patients with moderate to severe AD.
Methods: Patients with moderate to severe AD having undergone MRI brain, cognitive and behavioral evaluations were studied. BPSD was diagnosed based on established clinical guidelines. White matter hyperintensity (WMH) and medial temporal lobe atrophy (MTA) were quantified by a blinded rater.
Results: 122 AD patients were studied. Age [76.84 vs. 72.70, $p = 0.014$] and MMSE [11.69 vs. 15.16, $p < 0.001$] was significantly higher in patients with BPSD. BPSD patients demonstrated higher periventricular [5.44 vs. 4.21, $p < 0.001$], deep subcortical [5.07 vs. 3.43, $p < 0.001$], and total WMH [10.51 vs. 7.65, $p < 0.001$] compared to non-BPSD patients. Higher proportion of BPSD patients had WMH in the highest tertile of severity (82.22% vs. 45.45%, $p < 0.001$). After correcting for age, baseline cognition and degree of MTA, total WMH remained significantly associated with a diagnosis of BPSD [odds ratio: 1.45 (1.14–1.85; $p = 0.002$)]. With severe WMH, the association is significantly increased [odds ratio: 4.3 (1.3–12.5); $p = 0.016$].
Conclusion: WMH is independently associated with BPSD in moderate to severe AD. Optimizing vascular risk factors may be a strategy to reduce the severity of BPSD in AD.

1. Introduction

Alzheimer's disease (AD) is a devastating illness characterized by a continuous decline in memory and other cognitive function [1]. In addition, many AD patients develop behavioral and psychological symptoms of dementia (BPSD), a term coined to describe non-cognitive features of dementia [2]. The prevalence of BPSD in AD patients stands at about 75–90% at least [3,4]. Apathy, depression, anxiety and aberrant motor activity are a few of the more frequently presented symptoms [5,6]. Clearly, such symptoms are associated with adverse outcomes such as, high levels of caregiver burden and distress, longer duration of hospitalization, increased rates of institutionalization and more rapid cognitive decline [3,7].

There is considerable interest in identifying the risk factors for developing BPSD among AD patients. Many researchers have identified a patient's premorbid personality as one of the reasons for developing BPSD. For instance, in a study conducted by Archer et al. in 2007 [8], it was found that premorbid neuroticism was positively correlated with anxiety while premorbid agreeableness was negatively correlated with irritability and agitation. Other factors that have been associated with BPSD include the severity of cognitive symptoms [9], environmental factors [10], and the burden of amyloid pathology [11].

Another factor that has been postulated to influence the onset and severity of both cognitive symptoms and BPSD has been cerebral ischemia. Cerebral ischemia, specifically small vessel ischemia is likely to contribute to both cognitive and behavioral changes in dementia. On MRI, white matter hyperintensity (WMH) has been demonstrated to be a reliable surrogate marker for white matter disease. Pathological studies have demonstrated a strong correlation between WMH and small vessel occlusion [12]. Disruption of white matter integrity, manifesting as WMH on T2 weighted MRI contributes to poor cognitive function and reduced functional status in the elderly and is associated with increased risk of several cognitive disorders including AD [13–15]. Furthermore, WMH has been demonstrated to increase risk of cognitive decline over time [16,17]. However the existing literature on the association between cerebral ischemia and BPSD is conflicting. In a paper by Berlow et al. [18], it was found that some symptoms of BPSD (anxiety, night time disturbance and aberrant motor behavior) are associated with increased WMH. On the other hand, disinhibition was associated with lower WMH volume. In contrast, a study conducted by Staekenborg et al. [19] failed to find any significant difference in WMH and hippocampal

List of abbreviations: AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; WMH, white matter hyperintensity; MTA, medial temporal atrophy; DSM IV-TR, Diagnostic and Statistical Manual version IV-text revision; MMSE, Mini-Mental State Exam; CDR, Clinical Dementia Rating; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; NPI-Q, Neuropsychiatric Inventory Questionnaire; PVH, periventricular; DSC, deep subcortical.

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volume, measured by medial temporal lobe atrophy (MTA) scores, in patients with and without non-cognitive symptoms.

The contradictory findings have led us to perform this study to delve deeper and examine the relationship between WMH and MTA scores with the presence of BPSD in AD patients. This relationship has not been well established. In addition, this study was undertaken due to a dearth of research looking into this area. We hypothesized that cerebral white matter disease is independently associated with BPSD among patients with moderate to severe AD.

2. Methods

A retrospective analysis of a prospective clinical database of patients attending a tertiary neurology center between 2008 and 2012 was conducted. The center manages patients with different types of dementia who are in various stages of disease severity. MRI imaging is performed as the standard neuroimaging for all patients with a clinical diagnosis of dementia. When there are contraindications to MRI, a CT brain is performed. Only AD patients having undergone MRI brain scan and classified as having either moderate or severe dementia were recruited into the study. AD was diagnosed based on the DSM IV-TR criteria [20] by a cognitive neurologist. To ensure that patients with moderate to severe dementia were studied, only AD patients with a Clinical Dementia Rating (CDR) [21] of 2–3 and a Mini-Mental State Exam (MMSE) [22] score of <20 were included in the study. The diagnosis of BPSD was made by consensus between the neurologist, dementia nurse and psychologist based on the presence of behavioral symptoms like "physical aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviors, sexual disinhibition, hoarding, cursing (and/or) shadowing", and/or psychological symptoms like "anxiety, depressive mood, hallucinations (and/or) delusions" as recommended by the International Psychogeriatric Association guidelines [23]. The study was approved by the institutional ethics review board, and informed consent was obtained from all subjects prior to data collection.

Baseline demographic and vascular risk factor data was collected. Cognitive data included the MMSE [22] and the Montreal Cognitive Assessment (MoCA) [24]. Behavioral data included the 15-point Geriatric Depression Scale (GDS) [25] and the Neuropsychiatric Inventory Questionnaire (NPI-Q) [26]. The NPI-Q is an administered questionnaire that looks at 12 domains of behavioral symptoms [26]. Each domain is rated on a 3-point Likert scale for severity of symptoms and a 5-point Likert scale for distress caused to the caregiver as a result, adding up to a highest possible total score of 96.

Cerebral white matter hyperintensity and medial temporal atrophy were quantified by an independent trained rater using the modified Fazekas scale and the Schelten's scale respectively [27,28]. WMH was quantified using MRI T2-weighted axial images. Left and right periventricular hyperintensities (PVH) and left and right deep subcortical hyperintensities (DSC) were each rated on a scale of 0 (denoting no hyperintensities) to 3 (denoting severe and profuse hyperintensities), totaling up to a highest possible total WMH score of 12. MTA was rated using coronal spoiled gradient echo (SPGR) images. Left and right MTA were each rated on a scale of 0 (denoting no atrophy) to 4 (denoting severe atrophy), adding up to a highest possible total MTA score of 8.

Subjects were grouped according to BPSD diagnosis. Descriptive statistical analysis was run to look for significant differences in demographic, vascular, cognitive and neuroimaging data between the two groups. The two groups were compared using Student's t-test for parametric continuous or interval variables, Wilcoxon–Mann–Whitney test for non-parametric continuous or interval variables, and Chi-square test for categorical variables. Significance level was set at 0.05. For multivariate analysis, a logistic regression model was used to correct for all confounding variables, by setting presence or absence of BPSD as the outcome variable, and white matter scores and other statistically and clinically significant variables as predictor variables. Results of the logistic regression were analyzed to see if the significance of the white matter scores was maintained in a model that factored in the other possible confounding variables. All statistical analysis was performed using Stata 10.

3. Results

During the study period, a total of 196 patients with moderate to severe AD were identified. Of these 196 patients with moderate to severe AD, 49 patients without MRI and 25 with incomplete cognitive and behavioral evaluation were further excluded.122 patients with moderate to severe AD, having a mean age of 74.23 years, were studied. 45 patients were classified as having BPSD and 77 were classified as not having BPSD. In the descriptive analysis of the data, we found age to be significantly different, with the mean age of BPSD patients being higher than non-BPSD patients [76.84(7.37) vs. 72.70(8.88), $p = 0.014$]. MMSE scores were also significantly lower in the BPSD patients than in the non-BPSD patients [11.69(5.33) vs. 15.16(3.59), $p = 0.0005$]. We also found that a higher percentage of BPSD patients qualified as having severe dementia, defined as having an MMSE score ≤ 10 than in the non-BPSD patients (31.11% vs. 10.39%, $p < 0.001$). In spite of the BPSD diagnosis, GDS scores [3.64(3.72) vs. 3.31(3.10). $p = 0.961$] was not significantly different between the 2 groups. Patients with BPSD demonstrated higher total NPI-Q scores [18.30(15.73) vs. 11.07(11.34), $p = 0.123$] than AD patients without BPSD but this was not statistically significant (Table 1).

In terms of white matter changes, significant differences were found across all WMH scores. BPSD patients generally had higher total PVH scores [5.44 (1.08) vs. 4.21 (1.84), $p = 0.0001$], total DSC scores [5.07 (1.32) vs. 3.43 (1.77), $p < 0.0001$] and total WMH scores [10.51 (2.15) vs. 7.65 (3.26), $p < 0.0001$] than non-BPSD patients (Fig. 1). Using a cut-off point of total WMH >9 to define severe white matter disease, it was found that a higher percentage of BPSD patients had severe white matter disease than non-BPSD patients (82.22% vs. 45.45%, $p < 0.001$). Total MTA was found to be higher in BPSD patients, although the difference was not statistically significant [3.73 (2.17) vs. 3.13 (2.19), $p = 0.095$].

Logistic regression analyses were carried out with BPSD diagnosis as the outcome variable, and either total PVH, total DSC, total WMH, or total MTA as the predictor variable. Age and MMSE scores were used as the potential confounding variables, as they were the only variables that were significantly different, and thus were the most likely to be confounders. In addition, white matter scores were corrected for MTA, and MTA score was corrected for WMH scores. The results show that in models that accounted for confounding variables, total PVH (adjusted $p = 0.019$), total DSC (adjusted $p = 0.001$) and total WMH (adjusted $p = 0.002$) remained significant in predicting BPSD. Regression analyses demonstrated an odds ratio of 1.45 for the association between WMH and BPSD (Table 2). Logistic regression was also used to analyze WMH severity as a predictor variable, and found that BPSD patients were 4 times more likely than non-BPSD patients to have WMH scores in the most severe range (total WMH > 9). These findings demonstrate an increase in the predicted probability of having a diagnosis of BPSD with increasing severities of PCH, DSC, and WMH scores (Fig. 2). Models that used total MTA as a predictor variable did not show that MTA was significant or useful in predicting BPSD diagnosis.

4. Discussion

This study demonstrates that moderate to severe AD patients with BPSD have significantly higher burden of cerebral WMH compared to patients without BPSD. The association between WMH and BPSD persisted despite correcting for age, severity of cognitive impairment and medial temporal atrophy. Our findings have important clinical implications as WMH has been demonstrated to be a reliable marker for cerebral ischemia, and thus optimizing the management of vascular