Delusions Increase Functional Impairment in Alzheimer's Disease

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Key Words

Dementia · Delusions · Alzheimer's disease · Functional impairment · Caregiver burden · Behaviour

Abstract

Background/Aims: Delusions in Alzheimer's disease (AD) may be associated with functional impairment. No studies to date have used functional instruments sensitive to changes in frontal executive function, possibly underestimating the impact. **Methods:** Patients with AD with and without delusions were administered cognitive tests and questionnaires to assess depression and quality of life. Caregivers were administered questionnaires to assess functional impairment, caregiver burden and behavioural symptoms. **Results:** AD patients with delusions ($n = 19$) when compared to AD patients without delusions ($n = 19$) matched for age, education and global cognitive function were significantly more functionally impaired based on performance on the Disability Assessment for Dementia Scale ($p < 0.005$). **Conclusion:** AD patients with delusions have significantly worse functional performance.

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Introduction

Delusions are common symptoms in patients with Alzheimer's disease (AD). In fact, recent estimates sug-

gest that approximately one third of patients with AD may develop delusions at some point during the course of the disease [1]. While these symptoms may be common, prior research suggests that they may be associated with a number of adverse health outcomes, including increased morbidity/mortality and premature institutionalization [2, 3]. In spite of the prevalence of these symptoms and their association with adverse health outcomes, there has been comparatively little systematic research on how these symptoms affect clinical outcomes.

Much of the prior research assessing delusions in AD has attempted to localize delusions neuroanatomically. Past studies have consistently demonstrated an association with frontal executive dysfunction on neuropsychological testing. In a recent study, Nagata et al. [4] examined 48 patients with AD divided into two groups, namely those with and without delusions. After matching for age, sex, duration of illness and Mini-Mental State Examination (MMSE) score, they found a strong correlation between the presence of persecutory delusions and performance on the Japanese version of the frontal assessment battery. While these findings were of interest, the study did not attempt to correlate the difference in frontal executive function with relevant non-cognitive outcomes such as functional impairment, caregiver burden, quality of life and behavioural symptom severity. Frontal lobe findings have also been confirmed neuropathologically. Zubenko et al. [5] examined post-mortem

brain tissue of delusional and non-delusional AD patients and found a much higher concentration of senile plaques and neurofibrillary tangles in the middle frontal cortex of delusional AD patients when compared to non-delusional controls. Neuroimaging studies have produced similar results. Ismail et al. [6] recently conducted a comprehensive review of neuroimaging studies in delusional patients with AD. The review included structural imaging studies as well as functional imaging studies and showed a correlation between delusions in AD and hypofrontality, specifically in the right hemisphere. Matsuoka et al. [7] showed a correlation between delusional severity and hypoperfusion in the right anterior insula region using single-photon emission computed tomography imaging, suggesting that certain brain regions may modify symptom severity. Delusions have also been shown to correlate with lacunar infarcts in the basal ganglia [8], suggesting a possible neuroanatomical mechanism.

While the majority of research focusing on delusions in patients with AD suggests an association with malfunctioning of the frontal lobe, there has been considerably less focus on what this means clinically. In a recent review [9], we looked at studies comparing daily functioning in AD patients with and without delusions and found a correlation with impaired functioning, specifically in instrumental activity of daily living (IADL) performance, among AD patients with delusions compared to those without. Studies by Harwood et al. [10], Tekin et al. [11] and Liu et al. [12] all looked at functional outcome in AD patients with and without delusions using memory clinic samples. All three studies found worse functioning in the delusional AD subgroup compared to the non-delusional subgroup when controlling for global cognitive function. Other studies [13–15] found no such differences, although none of the studies conducted to date used instruments sensitive to picking up deficits in frontal lobe function. As impaired IADL performance is a common clinical marker of early AD, we were interested in comparing delusional and non-delusional AD patients in terms of their functional status, using a functional instrument that is very sensitive to detecting neuropsychological deficits in frontal executive function and validated in patients with AD, i.e. the Disability Assessment for Dementia Scale (DADS) [16]. While prior studies have examined this question [7], no studies have utilized instruments sensitive to neuropsychological deficits in frontal executive function, thus possibly underestimating the impact of delusions on functional performance. In addition, previous studies have suggested that delusions may be associated with greater behav-

ioral symptoms and increased caregiver burden [2, 3, 17], but no studies to date have examined these factors controlling for disease severity or in combination with functional measures. Based on the research done in this field, we hypothesized that delusional AD patients when compared to non-delusional controls would be more functionally impaired and have greater behavioural symptoms and increased caregiver burden for the same level of disease severity and that these differences would correlate neuropsychologically with frontal executive deficits.

Methods

This study received institutional approval from the St. Michael's Hospital Research Ethics Board. Participants were recruited from various outpatient clinics at St. Michael's Hospital, the Centre for Addiction and Mental Health and several affiliated Long Term Care Homes in Toronto. Participants were considered eligible for the study if they were over the age of 65 years, English speaking, met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for AD, had a baseline MMSE score greater than 16, had a caregiver available and had no history of significant sensory deficits that would interfere with neuropsychological testing. Participants were allowed to be on psychotropic medication provided that it had been started more than 1 month prior to inclusion in the study and they were clinically stable on it. Participants were excluded from this study if they were acutely delirious, suffered from a form of dementia other than AD or mixed dementia, had a significant history of substance abuse, psychiatric illness (such as schizophrenia or bipolar disorder), systemic or neurologic disease or were clinically depressed or medically unstable. After providing written informed consent, participants were screened for the presence of delusions. Delusions were detected using a clinical interview conducted by a qualified psychiatrist with the patient and caregiver and then confirmed using a behavioural scale (Behavioural Pathology in Alzheimer's Disease Rating Scale; BEHAVE-AD [18]) administered to the caregiver of the patient. In order for a patient to be confirmed as delusional, both a psychiatrist and neurologist had to assess the patient and come to agreement. In addition, patients needed to score above 1 on the delusional/paranoid ideation section of the BEHAVE-AD, and delusions had to be present for a minimum of 1 month prior to assessment. Patients were considered non-delusional on the basis that no delusions had been detected up to 6 months prior to assessment.

Different aspects of cognitive functioning, including memory, language, attention and executive functioning, were assessed through a series of neuropsychological tests and questionnaires. Patients were administered the National Adult Reading Test [19, 20], Word List Generation [21], the Wisconsin Card Sorting Task [22], the MMSE [23], the Trail

Table 1. Demographic/non-cognitive measures in delusional and non-delusional AD patients, controlling for age, education and MMSE scores

Variable	Mean $\pm$ SD	p value
Age, years		
Non-delusional	76.58 $\pm$ 6.327	0.274
Delusional	79.06 $\pm$ 7.223	
Years of education		
Non-delusional	13.94 $\pm$ 3.929	0.382
Delusional	12.76 $\pm$ 3.817	
Quality of Life in AD Questionnaire		
Non-delusional	36.32 $\pm$ 7.311	0.451
Delusional	35.74 $\pm$ 7.187	
Geriatric Depression Scale		
Non-delusional	4.47 $\pm$ 3.533	0.688
Delusional	4.00 $\pm$ 4.524	
Dysexecutive Questionnaire		
Non-delusional	18.79 $\pm$ 11.655	0.747
Delusional	18.78 $\pm$ 12.845	
DADS		
Non-delusional	80.11 $\pm$ 16.108	0.011
Delusional	54.44 $\pm$ 25.033	
DADS – basic ADLs		
Non-delusional	94.06 $\pm$ 15.910	0.071
Delusional	72.50 $\pm$ 34.692	
DADS – IADLs		
Non-delusional	72.11 $\pm$ 20.237	0.007
Delusional	41.56 $\pm$ 23.951	
DADS – leisure		
Non-delusional	80.83 $\pm$ 25.103	0.156
Delusional	55.00 $\pm$ 40.909	
BEHAVE-AD		
Non-delusional	2.83 $\pm$ 2.572	0.001
Delusional	14.22 $\pm$ 9.033	
BEHAVE-AD – paranoid and delusional ideation		
Non-delusional	0.28 $\pm$ 0.669	0.000
Delusional	5.33 $\pm$ 3.430	
BEHAVE-AD – hallucinations		
Non-delusional	0.06 $\pm$ 0.236	0.052
Delusional	1.50 $\pm$ 2.065	
BEHAVE-AD – activity disturbances		
Non-delusional	0.67 $\pm$ 1.085	0.091
Delusional	1.83 $\pm$ 1.689	
BEHAVE-AD – aggressiveness		
Non-delusional	0.11 $\pm$ 0.323	0.003
Delusional	1.33 $\pm$ 1.237	
BEHAVE-AD – diurnal rhythm disturbances		
Non-delusional	0.11 $\pm$ 0.323	0.179
Delusional	0.67 $\pm$ 1.085	
BEHAVE-AD – affective disturbances		
Non-delusional	0.44 $\pm$ 0.856	0.011
Delusional	1.83 $\pm$ 2.007	
BEHAVE-AD – anxieties and phobias		
Non-delusional	0.89 $\pm$ 0.963	0.354
Delusional	1.11 $\pm$ 1.079	

Table 1. (continued)

Variable	Mean $\pm$ SD	p value
Caregiver Burden Scale		
Non-delusional	24.31 $\pm$ 13.676	0.048
Delusional	34.82 $\pm$ 15.424	
MMSE		
Non-delusional	22.05 $\pm$ 2.121	0.408
Delusional	20.58 $\pm$ 3.580	

Making Test [24], the Boston Naming Test [25], the Token Test [26] and the California Verbal Learning Test (CVLT) [27]. Questionnaires such as the Dysexecutive Questionnaire [28], the Geriatric Depression Scale [29] and the Quality of Life in AD Questionnaire [30] were also administered to the patients to assess behaviour, mood and quality of life. Caregivers were asked to complete a series of questionnaires designed to measure behaviour (BEHAVE-AD [18]), daily functioning (DADS [16]) and caregiver burden (Caregiver Burden Scale [31]). Where available, patients were also compared in terms of psychotropic medication, including the numbers on cognitive enhancers and antipsychotic medications. The research assistant who administered the neuropsychological tests and questionnaires was blind to the delusional status of the patient at all times. Delusional and non-delusional AD participants matched for age and MMSE were then compared using an analysis of variance that controlled for the confounding effects of age, education and MMSE with SPSS 16.0 software. Significance was set at $p \leq 0.05$. All analyses were two tailed.

Results

A total of 49 AD patients meeting the eligibility criteria were recruited into the study and completed testing. Of these, 11 were later excluded, 9 because of incomplete testing and 2 because their MMSE scores were considered too high (26/30). In total, data for 38 patients were analyzed. Nineteen were non-delusional while 19 had delusions that had been present within 6 months of the assessment. Medication information was available for 13 non-delusional and 11 delusional AD patients. Eleven non-delusional versus 8 delusional AD patients were on cognitive enhancers, while 3 non-delusional and 5 delusional patients were on antipsychotic medications. One patient in each group was on no psychotropic medication, while data were missing for 8 non-delusional and 6 delusional AD patients. There were no significant differences noted between the two groups in terms of age, education or global cognitive function (MMSE score; table 1). In terms of other non-cognitive measures, sig-

Table 2. Cognitive measures in delusional and non-delusional AD patients, controlling for age, education and MMSE scores

Variable	Mean ± SD	p value
National Adult Reading Test – errors		
Non-delusional	33.39±16.500	0.802
Delusional	35.94±14.285	
National adult reading test – FSIQ		
Non-delusional	101.76±12.870	0.802
Delusional	99.77±11.142	
Trail Making Test A – sample time		
Non-delusional	11.37±6.272	0.369
Delusional	14.25±6.880	
Trail Making Test A – time		
Non-delusional	60.74±30.160	0.611
Delusional	77.87±92.058	
Trail Making Test B – sample time		
Non-delusional	23.76±14.417	0.126
Delusional	43.62±40.574	
Trail Making Test B – time		
Non-delusional	290.25±265.420	0.804
Delusional	270.30±192.549	
Trail Making Test B – errors		
Non-delusional	2.62±2.022	0.142
Delusional	1.50±1.434	
Trail Making Test – B minus A		
Non-delusional	229.51±263.756	0.899
Delusional	219.81±188.607	
CVLT – short delay		
Non-delusional	1.00±1.609	0.383
Delusional	0.87±1.060	
CVLT – long delay		
Non-delusional	0.89±1.323	0.851
Delusional	0.67±1.175	
CVLT – total		
Non-delusional	19.56±6.382	0.690
Delusional	18.13±7.279	
Boston Naming Test		
Non-delusional	42.69±12.758	0.144
Delusional	35.78±11.202	
Fluency – total		
Non-delusional	27.21±9.508	0.166
Delusional	21.39±12.210	
Fluency – first 15 s		
Non-delusional	011.05±4.731	0.049
Delusional	007.94±4.137	
Fluency – last 45 s		
Non-delusional	016.16±6.030	0.349
Delusional	013.44±8.396	
Switches (total)		
Non-delusional	020.68±9.516	0.044
Delusional	14.56±8.590	
Semantic (total)		
Non-delusional	9.42±3.626	0.617
Delusional	7.39±4.960	
Token Test		
Non-delusional	36.26±6.665	0.438
Delusional	33.00±7.036	
Fluency was tested by Word List Generation.		

nificant differences between the two groups were noted for the DADS ($p < 0.05$), specifically the IADL subscale, BEHAVE-AD scores ($p < 0.005$) and caregiver burden scores ($p < 0.05$). There were no differences noted between the two groups in terms of depression, frontal lobe behaviour or quality of life ($p > 0.05$).

In terms of neuropsychological status (table 2), there were significant differences noted between the two groups on measures of frontal lobe function, including phonemic fluency (first 15 s) and total switches ($p < 0.05$). There were no differences noted between the two groups on other neurocognitive measures, including the National Adult Reading Test, Trails A and B, total fluency, semantic fluency and the CVLT. Unfortunately, not enough patients were able to complete the Wisconsin Card Sorting Test so we excluded it. We also looked at the correlation between subtests of the BEHAVE-AD, daily functioning and caregiver burden (table 3). All behavioural symptoms, with the exception of affective disturbances, diurnal rhythm disturbances and anxiety and phobias, appeared to affect function, both the total score and IADLs ($p < 0.01$). Activity disturbances only mildly affected activities of daily living (ADLs; $p < 0.05$), and aggression did not correlate with ADLs at all. Affective disturbances correlated strongly with caregiver burden ($p < 0.01$), while anxieties/phobias and paranoid/delusional ideation correlated more weakly ($p < 0.05$).

Discussion

Our study showed that AD patients with delusions had significantly worse functional performance compared to AD patients without delusions. This difference in functional performance was not explained by demographic or global cognitive status as the two groups were well matched on these variables and we ran an analysis of variance co-varying for age, education and MMSE. Interestingly, while the overall IADL subscale of the DADS showed significance, the basic ADL subscale did not. As the IADL subscale is much more closely correlated with frontal executive impairment, this further supports our argument that delusions are highly correlated with frontal executive dysfunction. While we attempted to get medication data for all patients retrospectively from electronic charts, we were not successful, and this does represent a limitation of the study. However, with regard to the medication information we were able to obtain, the groups were fairly evenly matched in terms of the numbers of patients on antipsychotic medications

Table 3. Secondary analyses of BEHAVE-AD

BEHAVE-AD	Caregiver Burden Scale	DADS			
		total DADS	basic ADLs	IADLs	leisure
Total BEHAVE-AD	0.418**	−0.500**	−0.413**	−0.574**	−0.218
Paranoid and delusional ideation	0.342*	−0.473**	−0.465**	−0.493**	−0.244
Hallucinations	0.154	−0.438**	−0.436**	−0.429**	−0.208
Activity disturbances	0.222	−0.441**	−0.331*	−0.507**	−0.195
Aggressiveness	0.231	−0.400**	−0.276	−0.452**	−0.338*
Diurnal rhythm disturbances	0.204	−0.194	−0.130	−0.294	0.042
Affective disturbance	0.451**	−0.064	0.063	−0.204	−0.010
Anxiety and phobias	0.337*	−0.085	0.067	−0.229	0.146

* Correlation is significant at the 0.05 level; ** correlation is significant at the 0.01 level.

and cognitive enhancers. It is therefore unlikely that differences in psychotropic medication use between the two groups had a significant impact on functional outcome. Furthermore, there were no significant differences noted between the two groups on traditional neurocognitive measures such as the CVLT, MMSE or Trail Making Test. In fact, patients with delusions performed better than controls on Trail Making Test B. However, there were significant differences noted on some subtests of frontal lobe function, including phonemic fluency (first 15 s) and total switches. It has been argued by neuropsychologists that the first 15 s of the phonemic fluency task are more sensitive to frontal executive impairment. Although there were no significant differences in the total fluency score, this may have become significant with a larger sample size given that delusional patients on average produced 6 fewer words than non-delusional controls.

In keeping with our hypothesis, these results suggest that the worse functional status in AD patients with delusions in our study may have been mediated by worse frontal executive function neuropsychologically. It is possible that the changes detected would have been more significant if a more comprehensive neuropsychological battery had been used and if the sample size had been larger. Behavioural symptoms were also significantly worse in the delusional AD subgroup, as was caregiver burden, and it is possible that this was also mediated by impaired frontal executive function. These findings are also consistent with the literature, which suggests that psychotic symptoms in AD are often associated with greater caregiver burden [15]. The fact that there were no significant quality of life differences noted between the two groups and no differences on the frontal lobe ques-

tionnaire (Dysexecutive Questionnaire) is somewhat more difficult to explain. It may be that changes were present but did not reach the threshold for significance and would have with a larger sample size. Another possibility is that delusions may correlate better with damage to the prefrontal cortex, which is more closely associated with problems with planning and multi-tasking and less closely associated with behaviour. Quality of life measures are notoriously unreliable in patients with frontal lobe damage given that patients often develop problems with awareness that may affect their assessment.

In terms of our secondary analyses, behavioural symptoms correlated very strongly with functional impairment, both ADLs and IADLs, and more weakly with caregiver burden. With respect to subtypes of behavioural symptoms, delusions, hallucinations, activity disturbance and aggression correlated strongly with functional impairment, while affective symptoms correlated less with functional impairment and more with caregiver burden. It is likely that neuropsychological impairments in frontal lobe function mediate both these subtypes of behavioural symptoms (delusions, hallucinations, activity disturbance and aggression) and functional decline. Affective disturbances in our study did not significantly correlate with changes in function but caused more distress for caregivers, second to delusions and other phobias. Apathy and mood changes have been well documented to be associated with significant caregiver stress based on previous research [32].

Our findings, namely that AD patients with delusions have significantly worse functional status, worse behavioural status and greater caregiver burden compared to AD patients without delusions, provide strong support

for the existence of a psychotic subtype of AD. This is particularly the case given that the changes noted were independent of other cognitive measures of disease severity. In a recent review of this area, Ismail et al. [33] suggest that AD patients with delusions differ from those without delusions in terms of genetics, neurotransmitters, neuropathology and clinical course. They suggest that in fact different delusional subtypes (misidentification delusions vs. persecutory delusions) may have different neural mechanisms. In our study, we did not subtype patients based on their delusion type given the relatively small sample size. We also did not attempt to correlate dementia severity with delusional subtype. Research in this area by Sweet et al. [34], who compared AD patients with psychosis with those without psychosis, points to the existence of possible biomarkers. In a post-mortem magnetic resonance spectroscopy study, they found that AD patients with psychosis had greater neuropil disruption in multiple brain regions, including the dorsolateral prefrontal cortex, superior temporal gyrus and inferior parietal cortex. Similar accelerated biomarker changes have been shown in the anterior cingulate gyrus of AD patients with delusions compared to those without delusions [35].

The fact that AD patients with delusions had significantly worse functional performance in this study compared to those without delusions has implications for clinical care. AD patients with delusions should be

screened more aggressively for the presence of functional impairment.

In addition, interventions that assist with function, such as increased community-based support, caregiver training and placement in a long-term care home, should be made available to such patients. Cognitive enhancers and AD-specific treatments should be administered as soon as possible, and change in function should be used to gauge improvement. Antipsychotic medications that have shown benefit in the treatment of delusions in AD and related dementias [36, 37] should be administered where appropriate. The high correlation between the presence of delusions, caregiver burden and other behavioural symptoms suggests that this subgroup may require more aggressive psychiatric management compared to other subtypes.

In conclusion, our study contributes to the growing body of literature suggesting that AD patients with delusions may represent a distinct subtype of the illness with unique biomarkers, neuropathology, genetics and clinical course. Future work in this area should continue to explore the clinical and neuroanatomical differences between AD patients with and without delusions.

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