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Association between subcortical lesions and behavioural and psychological symptoms in patients with Alzheimer's disease

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Running head: Association between subcortical lesions and BPSD in AD.

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Abstract

Background/Aims: The most devastating features of Alzheimer's disease (AD) are often the behavioural and psychological symptoms in dementia (BPSD). There is a controversy as to whether subcortical lesions contribute to BPSD. The aim of this study was to examine the relationship between BPSD and subcortical lesions (white matter lesions and lacunes) in AD.

Methods: CT or MRI from 259 patients with mild to moderate AD were assessed with the Age Related White Matter Changes (ARWMC) scale. Linear measures of global and temporal atrophy, and MMSE scores were used to adjust for AD pathology and disease severity in logistic regression models with the BPSD items delusions, hallucinations, agitation, depression, anxiety, apathy and irritability.

Results: Lacunes in the left basal ganglia were associated with delusions (OR 2.57, 95% CI 1.21–5.48) and hallucinations (OR 3.33, 95% CI 1.38–8.01) and lacunes in the right basal ganglia were associated with depression (OR 2.13, 95% CI 1.01–4.51).

Conclusion: Lacunes in the basal ganglia resulted in a 2- to 3-fold increased risk of delusions, hallucinations and depression, when adjusting for cognition and atrophy. This suggests that basal ganglia lesions can contribute to BPSD in patients with AD, independently of the AD process.

Introduction

Over 26 million people worldwide suffer from Alzheimer's disease (AD) [1]. The hallmark of AD is the loss of episodic memory and other cognitive functions. However, the symptoms that affect the patients, relatives, friends and society the most are the behavioural and psychological symptoms in dementia (BPSD). BPSD are present in more than 80 % of patients with AD [2] and have been associated with worse prognosis, earlier institutionalisation [3], increased caregiver distress [4], and reduced quality of life [5].

There has been much discussion about the pathophysiological processes behind BPSD. Some studies have found relationships between various BPSD and subcortical lesions (foremost in the white matter) in AD. These include positive associations with anxiety [6], aberrant motor behaviour [6,7], apathy [8], depression [9] as well as a trend for delusions [6]. However, other studies have failed to confirm these associations [10-13]. Some of the negative results could be explained by the hypothesis that different BPSD are associated with different regional white matter lesions (WML) and lacunes [14], since several studies only assessed the global WML burden. The negative results might also be explained by small sample sizes or by the heterogeneous nature of BPSD and subcortical lesions [13,15]. Nonetheless, a consensus regarding the association between BPSD and subcortical lesions in AD has not yet been reached.

Subcortical lesions, i.e. lacunes and WML, are overrepresented in patients with AD [16]. A causal relationship with cerebral amyloid angiopathy has been suggested [17], but more data indicates that most subcortical lesions are caused by small vessel disease [15,18,19]. The overrepresentation of the lesions in AD could be explained by the reserve capacity hypothesis, a mutual interaction or perhaps a common risk factor [20]. Patients with subcortical lesions have reduced cerebral perfusion [8] and recent data show that the lesions independently

predict functional and cognitive decline in healthy elderly [21,22]. The association with function and cognition in AD is less apparent or non-existing, probably due to the overshadowing effect of the AD pathology [7,17].

When examining associations between subcortical lesions and BPSD in patients with AD, it can be difficult to assess the independent effect subcortical lesions have on BPSD, since AD pathology also might cause BPSD. One way of examining its independent impact on BPSD is to adjust for atrophy (both global and temporal) and cognitive ability, which are closely related to AD pathology and disease severity [23-25]. Unfortunately, many previous studies have not adjusted for atrophy [6,8,9].

The aim of the present study was to examine the independent association between regional subcortical lesions and BPSD in a large population of AD patients, and adjust for atrophy and cognitive severity.

Materials and Methods

Subjects

All subjects were participants of the Malmö Alzheimer Study (MAS) and they were investigated during 1999–2003, at the Memory Clinic in Malmö, Sweden, at Skåne University Hospital. The study included 259 patients with an AD diagnosis (described in greater detail elsewhere [26]). A thorough dementia investigation was performed in all cases, including medical history, computerised tomography (CT) of the brain, analysis of the cerebrospinal fluid, somatic and neuropsychiatric examination and cognitive assessment with the Mini-Mental State Examination (MMSE) [27], among other tests. The MMSE is a test of orientation, memory, attention, visuo-construction and verbal ability, which takes about 15 minutes to administer and is measured on a scale from 0–30 points (worst to best).

The patients were community-dwelling, suffered from mild to moderate dementia [28], and fulfilled the NINCDS-ADRDA criteria for probable AD [29]. The patients were reviewed longitudinally, as previously described [30], and would retrospectively also fulfil the new criteria for probable AD with increased level of certainty [31]. The mean ± standard deviation (SD) age of the 259 patients was 75.0 years ± SD 6.4 years. The mean ± SD MMSE score was 21.4 points ± 5.0 points and 68% were female. Thirty-one percent of the patients used some kind of sedative, anxiolytic or anti-psychotic medication. The following vascular risk factors were prevalent in the population: any kind of heart disease 30%, orthostatic hypotension 28%, hypertension 23%, hypercholesterolemia 11% and diabetes 7%. The study was approved by the Regional Ethics Committee of Lund, Sweden.

Assessment of BPSD

The studied BPSD variables were delusions, hallucinations, depression/dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability, apathy and aberrant motor behaviour.

These 10 BPSD variables followed the description in the Neuropsychiatric Inventory [32]. The BPSD items were retrieved by a thorough review of patient records performed by a specialist in dementia disorders. Each BPSD item was assigned a dichotomous value; either present or absent. A BPSD item was registered as present if it was apparent at the visit or in the daily life of the patient (even if it was not present at the actual assessment visit).

Atrophy measures

Eight subjects underwent MRI-scanning. All the other subjects underwent non-contrast cranial CT using the Somatom Plus 4 scanner (Siemens, Erlangen, Germany). Axial images with 5-mm slice thickness were taken parallel to the orbitomeatal plane. To adjust for the effects the AD pathology might have on the BPSD, linear CT/MRI measurements of atrophy were included in the logistic regression models. The measures for medial temporal atrophy were the suprasellar cistern ratio, the temporal horn ratio and the cistern ambiens ratio. Measures for global atrophy were the ventricle index and the cella media index. The measurements were performed by an experienced neuroradiologist and have been previously published [33].

Scoring of the subcortical lesions

The Age Related White Matter Changes (ARWMC) scale by Wahlund et al. was used to rate the presence and severity of subcortical lesions [34]. The assessed areas were (1) the frontal area (the frontal lobe anterior to the central sulcus); (2) the parieto-occipital area (The parietal and occipital areas were separated from the temporal areas by an approximated line between the posterior part of the Sylvian fissure and the trigone areas of the lateral ventricles. Lesions here are later referred to as parietal WML since most white matter are located in the parietal lobe) and; (3) the basal ganglia, which consist of the striatum, globus pallidus, thalamus, internal and external capsules, and insula. The areas were assessed separately in the left and right hemisphere. Temporal and infratentorial lesions were left out since these are uncommon

regions for WML. According to the scale, the WML were rated the following way: 1 point if there were at least one lesion ≥5 mm; 2 points if the lesions were beginning to aggregate; 3 points if there was a diffuse involvement of the entire region. Lacunes in the basal ganglia were rated the following way: 1 point if there was one lesion of at least 2 mm; 2 points if there were more than one lesion; 3 points if there were confluent lesions.

The rater of the ARWMC scale (SP) was blinded to all clinical data of the patients. Intra-rater reliability for each measurement was assessed by comparing repeated measurements from 29 subjects selected randomly. The mean kappa (κ) value of the intra-rater agreement was 0.76 with a range from 0.66 (basal ganglia dx) to 0.86 (parietal dx). The inter-rater reliability was assessed by having SP and LB (an experienced neuroradiologist who co-developed the ARWMC scale) individually rate 11 randomised patients. The mean k-value of the inter-rater agreement was 0.83, with a range from 0.72 (frontal dx) to 1.00 (parietal dx). All given κ-values are weighted and linear. Poor agreement is indicated by a κ -value of 0.40 or less, moderate agreement from 0.41 to 0.60, good agreement from 0.61 to 0.80, and excellent agreement for κ -values above 0.8 [35].

Statistical Analysis

A binary logistic regression analysis was performed for each BPSD item (as the dependent variable). BPSD variables with a frequency of less than 10 % were not analysed. The independent variables in each model were gender, age, MMSE score, the ARWMC score for the left and right parietal region, frontal region and basal ganglia, as well as the atrophy measures cella media index, cistern ambiens, ventricle index, suprasellar cistern and temporal horn ratio. The ARWMC scale is an ordinal scale with only 3–4 levels and it had a skewed distribution (Fig. 1). Due to the low number of patients at the more impaired levels, the variables were dichotomised as 0 or 1 before entered in the logistic regression. Each WML

region was assigned the value 1 if the ARWMC score was > 1 point and each basal ganglia region was assigned the value 1 if the ARWMC score was > 0 points (to reflect the clinical relevance of the lesions [34]). The different atrophy measures differed greatly in magnitude and their z-scores were therefore computed for an easier interpretation of the odds ratios (OR). The independent variables were entered using the backward LR method. The entry limit was set to $p = 0.05$ and the limit of removal was set to $p = 0.051$. There was a strong relationship between the ARWMC score of the left and right parietal as well as frontal region. Therefore, the left and right regions were entered separately to reduce collinearity. The total amount of white matter load (the sum of all regions) correlated moderately to highly with the different subcortical regions and was entered separately from the other WML and the basal ganglia variables. The statistical analyses were performed with SPSS Statistics, version 19.0 [36].

Results

The frequency of BPSD and subcortical lesions

The frequencies of the BPSD items are illustrated in Fig. 2. Eighty percent of the patients had at least one BPSD item present. The most frequent was depression (55%), followed by anxiety (33%). Further, apathy was present in 31%, irritability in 26%, delusions in 15%, agitation/aggression in 14%, hallucinations in 10%, disinhibition in 9%, aberrant motor behaviour in 6%, and euphoria in only 2%. The frequencies of the white matter changes and lacunes assessed by the ARWMC scale are illustrated in Fig. 1. More than 72% (n=187) of the patients had $\geq$1 point on the ARWMC scale. The most common location of lesions was the frontal lobes.

Logistic regression analysis of the BPSD

The results from the significant logistic regression models are presented in table 1. The presence of lacunes in the left basal ganglia was significantly associated with delusions (OR 2.57, 95% CI 1.21–5.48) and hallucinations (OR 3.33, 95% CI 1.38–8.01). Lacunes in this region yielded the highest OR of all independent variables in predicting the presence of any BPSD item. Lacunes in the right basal ganglia was significantly associated with depression (OR 2.13, 95% CI 1.01–4.51). None of the WML in the frontal or parietal regions or the total amount of lesions was significantly associated with any BPSD item. Increased global atrophy (cella media index) was significantly associated with agitation (OR 1.54 for each SD, 95% 1.05–2.25). A lower MMSE score increased the risk for several BPSD items. It was significantly associated with hallucinations (OR 0.92, 95% CI 0.85–0.997), agitation (OR 0.91, 95% CI 0.85–0.98), apathy (OR 0.96, 95% CI 0.87–0.99) and irritability (OR 0.93, 95% CI 0.87–0.98). If the patient was female the OR was 2.03 (95% CI 1.16–3.56) for depression, 2.48 (95% CI 1.29–4.75) for anxiety and 2.44 (95% CI 1.32–4.53) for irritability. Age was not associated with any BPSD item.

Discussion

In a large population of patients with mild to moderate AD, we found that lacunes in the basal ganglia increased the risk of delusions, hallucinations and depression when adjusting for atrophy and cognitive ability in logistic regression models. The result indicates that these subcortical lesions affect BPSD in AD patients independently of AD pathology and disease severity.

Frequency of BPSD in AD

Consistent with other studies we found BPSD to be very frequent in AD [6,13,37]. BPSD could be seen in 80% of our patients, with depression and anxiety being the most prevalent. The presence of specific BPSD items such as delusions, depression, and anxiety was similar to a large AD study by Fuh et al. [38] However, our study identified a lower frequency of hallucinations, apathy, irritability, euphoria, agitation, disinhibition and aberrant motor behaviour. This could be explained by the population of the other studies, which had patients with more severe dementia (mean MMSE score 17.1 points compared to 21.4 points in our study). It could also be explained by how the BPSD variables in our study were retrieved (present or absent in medical records at the memory clinic), which could underestimate the presence of mild BPSD. However, we argue that the symptoms were clinically more relevant and with less caregiver bias than if the NPI scale [32] would have been used prospectively, since the BPSD variables were based on medical records written by physicians with experience in assessing the presence of BPSD.

Subcortical lesion correlates of BPSD

To the best of our knowledge, the present study is the largest to evaluate the association between BPSD and subcortical lesions in AD patients, when adjusting for atrophy and cognition. We found that patients with lacunes in the left basal ganglia had a 3-fold increased

risk of delusions and hallucinations. These are two closely related BPSD and this finding fits well with the hypothesis of how delusions and hallucinations can occur. Many studies have found that pathology or lesions in the basal ganglia result in delusions in various disorders [39-44], presumably through disrupted fronto-subcortical circuits [42]. In AD, delusions and hallucinations have previously been associated with extrapyramidal symptoms (as signs of basal ganglia damage) [45,46], but to our knowledge not directly with visualised lesions in the basal ganglia.

Lacunes in the right basal ganglia doubled the risk of depressive symptoms in the present study. As with delusions and hallucinations, depression in AD is also thought to at least partly arise from damage to fronto-subcortical circuits [9,47]. This is in agreement with studies associating depression with extrapyramidal signs [48,49] and frontal WML [50]. However, in other studies no association has been found with subcortical lesions [11] or the association was found with other structures [51].

Apathy is closely related to depression and has previously been associated with subcortical lesions [8], but it was not associated with any lesions in the present study. A reason for this might be the large number of missing cases for apathy (its presence or absence was only registered in 187 or 259 patients, see Fig. 2). Another explanation could be the differences in the structural and neurochemical correlates of depression and apathy [52].

Other correlates of BPSD

Lower MMSE score was associated with an increased risk of hallucinations, agitation, apathy and irritability, which supports the fact that a higher prevalence of BPSD is found in more severe dementia. No association was found between MMSE score and depression. This result is in agreement with a large review, which found that depression was not related to disease severity [53]. Another study confirmed this, but on the other hand found that apathy was

associated with disease severity [54]. One explanation might be that executive ability, which deteriorates with disease severity, is often mistaken for apathy. The patient's mood, on the other hand, can clinically often improve with the progression of the disease due to impaired insight.

Women had an increased risk of depression, anxiety and irritability compared to men. Whether this is a true finding or simply the result of the female patients being better at expressing these symptoms at the doctor's visit, is difficult say. Atrophy was not significantly associated with any BPSD, except for global atrophy (cella media index) and agitation. Contradictory results have previously been published regarding the influence of atrophy on BPSD in AD [6,55]. It is important to note that volumetric measures of atrophy were not used in the present study. Instead we used linear measures on axial slices, which give an indirect assessment of the amount of atrophy. Further, atrophy and cognitive ability were used as surrogate markers to adjust for AD pathology and disease severity in the models. However, there is a lack of true disease markers for AD. Therefore, our measures for atrophy and cognition cannot entirely correct for the influence of the AD process, or allow for a completely independent examination of the association between BPSD and subcortical lesions.

Conclusion

We found that lesions in the basal ganglia increased the risk of delusions, hallucinations and depression 2- to 3-fold in a large population of AD patients, when adjusting for atrophy and cognition. This adds evidence to the hypothesis that subcortical lesions, not just the AD pathology itself, can contribute to BPSD. It as also supports the literature that suggests that disrupted fronto-subcortical circuits can give rise to these symptoms. However, subcortical lesions are of course not the only cause of BPSD, and physical, environmental and social factors must also be considered.

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Tables

Table 1. Logistic regression analysis of BPSD and significantly associated variables

BPSD item (dependent variable)	**Significant independent variables**	**p-value**	**OR (95% CI)**
Delusions	Lacunes in basal ganglia, left	0.014	2.57 (1.21–5.48)
Hallucinations	Lacunes in basal ganglia, left	0.007	3.33 (1.38–8.01)
	MMSE score	0.043	0.92 (0.85–0.997)
Depression	Basal ganglia, right	0.049	2.13 (1.01–4.51)
	Gender (female)	0.014	2.03 (1.16–3.56)
Agitation	Cella media index	0.026	1.54 (1.05–2.25)
	MMSE score	0.007	0.91 (0.85–0.98)
Anxiety	Gender (female)	0.006	2.48 (1.29–4.75)
Apathy	MMSE score	0.017	0.96 (0.87–0.99)
Irritability	Gender (female)	0.005	2.44 (1.32–4.53)
	MMSE score	0.009	0.93 (0.87–0.98)

Binary logistic regression analysis of delusions, hallucinations, agitation, depression, anxiety, apathy and irritability. Hosmer and Lemeshow test was >0.05 for all dependent variables, which indicate a good fit of the models. The table only shows the significant independent variables. The independent variables were: The left and right frontal and parietal WML (dichotomised at ARWMC >1), left and right basal ganglia lacunes (present or not present), total amount of WML (ARWMC score), gender, age, MMSE score (0-30 points), cella media index and ventricle index (global atrophy), as well as the suprasellar cistern ratio, temporal horn ratio and cistern ambiens ratio (temporal atrophy). Atrophy measures were entered as z-scores.

ARWMC: Age Related White Matter Changes scale; BPSD: Behavioural and psychological symptoms in dementia; MMSE: the Mini-Mental State Examination; WML: White Matter Lesions.

Figures

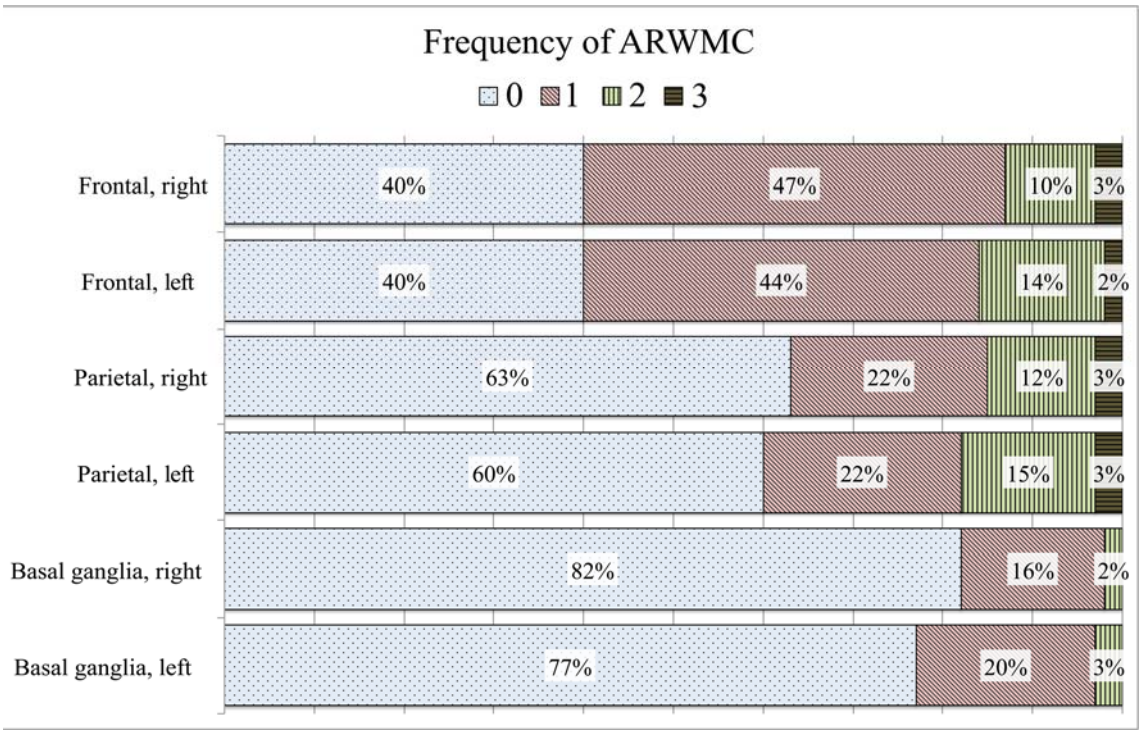

Figure 1. Frequency and severity of subcortical lesions assessed with the ARWMC scale.

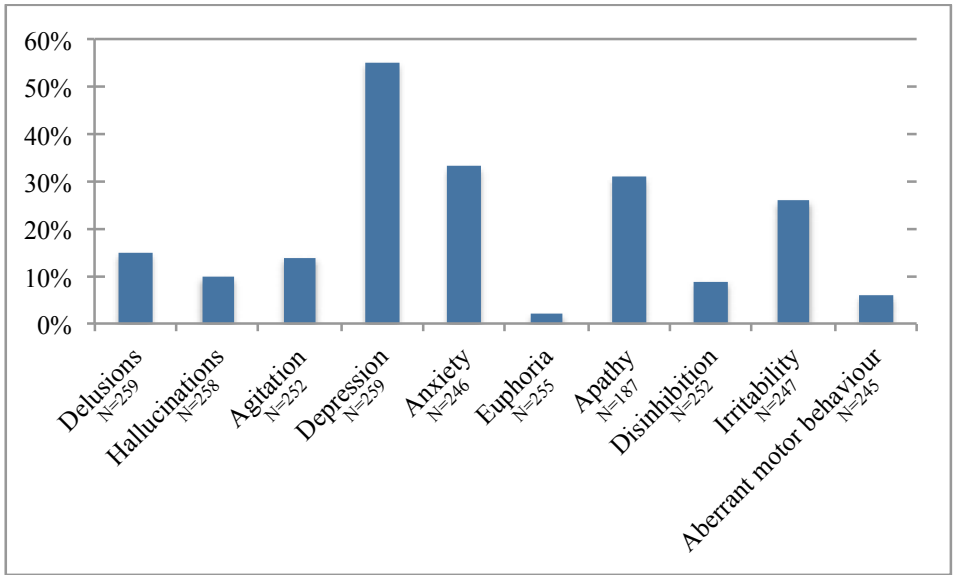

Figure 2. Frequency of BPSD. N = number of patients where the specific BPSD item was assessed (of 259 in total).