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Assessing brain vascular impairment, white matter lesions and ApoE status as predictors of behavioral and psychological symptoms of dementia (BPSD) in a multicentre sample of patients with Alzheimer's disease: a multidisciplinary retrospective study

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Abstract

Background. Understanding pathogenetic background and risk factors is the primary step to a better behavioral and psychological symptoms of dementia (BPSD) management. To this aim, this exploratory study is designed to sketch some indicative correlations between BPSD severity and vascular, genetic and cognitive variables.

Methods. A retrospective cross-sectional study conducted on medical reports of 135 Alzheimer Dementia (AD) patients from two memory clinics. Each subject underwent clinical examination and brain Magnetic Resonance Imaging (MRI), mini mental state examination (MMSE) and behavioral assessment using the neuropsychiatric inventory (NPI). This real-world cross-sectional study aimed to correlate the load of white matter lesions and global vascular compromise with clinical assessment. In addition, apolipoprotein E (ApoE) genotype was checked in 92 patients. Data were analysed performing Spearman correlation and principal component analysis (PCA).

Results. BPSD severity was independent from cognitive impairment, vascular impairment, white matter lesions and ApoE status.

Conclusions. Our results do not confirm the possible role for vascular impairment in BPSD severity as previously reported. Studies focusing on different biological features in relation to other structural, psychosocial and environmental factors are needed in order to get a more reliable model.

Key words

- behavioral symptoms
- dementia
- ApoE gene
- retrospective study
- vascular impairment

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INTRODUCTION

Cognitive impairment in Alzheimer's disease (AD) has been extensively studied from a clinical, biological and anatomical point of view [1, 2]. In contrast, the causes of behavioral and psychological symptoms of dementia (BPSDs) in AD are not so well known, although BPSDs affect nearly all patients with AD during their disease history, and they increase the risk for institutionalization and caregiver burden [3, 4]. Agitation, aberrant motor behaviour, anxiety, euphoria, irritability, depression, apathy, disinhibition, delusions, hallucinations, and sleep or appetite disturbances are the most reported BPSDs [1], and their treatment is often problematic [1, 5]. Accurate knowledge of predictors of BPSDs could help clinicians identify patients at risk, use preventive strategies and provide patients with appropriate timely care.

Since the detection and assessment of BPSDs are often based on caregivers' reports, previous studies have tried to further examine the burden on caregivers in order to better assess the onset, severity and nature of BPSDs [6]. On the other hand, many studies have analysed the correlations between biological factors and BPSD (general genetic risk factors), comorbidities (general vascular damage) and burden of white matter lesions [7].

The genetic background has been considered one of the main factors responsible for the predisposition of patients with AD to BPSDs [8]. Indeed, AD is sporadic in most cases, but there are also familial forms due to specific genetic mutations. However, it has long emerged that the main genetic risk factor for sporadic AD is a precise allele in the apolipoprotein E (ApoE) genotype [9]. The gene is found in the chromosome 19 and has three different allelic forms: ApoE-epsilon 2(ε2), ApoE-epsilon 3(ε3) and ApoE-epsilon 4(ε4). As reported in a seminal meta-analysis, there is a clear association between the ApoE(ε4) and AD. The presence of the ApoE ε4 allele (ε2/ε4 or ε3/ε4) confers risk, and ApoE ε4 homozygotes (ε4/ε4) have an increased risk compared with heterozygotes, whereas ApoE2 (ε2/ε4 or ε2/ε3) is protective against AD [10-12]. Furthermore, according to some studies, the ε4 allele is associated with specific BPSDs in AD [8-12].

The contribution of vascular factors in the pathogenesis of BPSDs has also been studied. The risk of developing AD is known to be increased in patients with vascular diseases (such as high blood pressure, atherosclerosis), as well as in metabolic diseases such as type 2 diabetes or hyperlipidemia [13]. Cerebrovascular disease and the burden of white matter hyperintensities (WMH) on the development of BPSDs have been later associated with anxiety, psychomotor agitation, and other neuropsychiatric symptoms in AD [7, 8-14]. Although previous literature showed conflicting results [15], understanding pathogenetic background and risk factors is the primary step to reach a better BPSDs management [16].

The aim of this study is to identify predictors of BPSDs using a multidisciplinary approach, in order to analyse the relationship between BPSDs severity and vascular risk factors, neuroimaging alterations, genetic markers and cognitive variables.

MATERIALS AND METHODS

A multicentre retrospective real-word cross-sectional study based on outpatients' clinical data from year 2014 was conducted. The patients' medical records came from two different Alzheimer Units: the Memory Clinic of Catholic University of Rome, and the Clinic for Memory and Cognitive Behavioural disorders of Sant'Eugenio Hospital of Rome. The outpatients' medical records were analysed and selected according to the presence of specific inclusion criteria: diagnosis of probable AD, as according at least to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCS-ADRDA) criteria of 1984 (as they were a common and reliable diagnostic method widely used, and because it required patients to undergo neuropsychological tests for the AD clinical diagnosis) [17]; suffering from BPSDs; having undergone a baseline cerebral MRI. Age, sex, education (in years), and vascular risk factors, including smoking (presence/absence), alcoholism, cardiovascular disease (hypertension, stroke, diabetes, cerebral vascular disease, and thromboendarterectomy) were recorded for all patients. The scores of cognitive and behavioral tests, scales for the differential diagnosis between primary dementia and vascular dementia and scores to measure white matter lesions on MRI were recorded. The carriers of the apolipoprotein E ε4 allele were identified (*Table 1*). Due to the outpatients setting, criteria were based primarily on clinical indicators. Clinical data from 2014 were found to be collected according to these criteria in both centers, making it possible to conduct a study with a standardized and consistent dataset across centers.

Cognitive deficits were assessed using the mini mental state examination (MMSE), which is commonly used as part of the dementia diagnostic process. MMSE score ranges from 0 (maximum cognitive deficit) to 30 (no cognitive deficit). It is necessary to correct the raw score based on variables potentially able to influence the result: age and years of schooling of the subject. A score of 24/30 or above is considered normal. As one falls below the threshold value of 24, cognitive impairment is indicated, which can be severe if the score is ≤9 points, moderate between 10 and 18 points, or mild between 19 and 23 points. In this study, patients with a MMSE score <24 were included [18]. MMSE adjustment coefficients for age and education classes in the Italian population were used [19].

BPSDs were assessed using the neuropsychiatric inventory (NPI) in the original version [20]. This test, through questions to the caregiver, investigates the frequency (score from 0 to 4 points) and severity (score from 1 to 3 points) of psychotic, affective and behavioral syndromes in patients with dementia. The following items were evaluated: Delusions, Hallucinations, Agitation/Aggression, Dysphoria/Depression, Anxiety, Euphoria/Elation, Apathy/Indifference, Disinhibition, Irritability/Lability, Aberrant Motor, Nighttime Behavior, Appetite/Eating. The higher the score for each symptom, the greater the severity, and the higher the overall score represents a greater severity of the BPSD. It also allowed us to evaluate the burden on the caregiver, for

the care burden was measured from 0 to 5 points, with a higher total score indicating a higher caregiver burden.

For the differential diagnosis between primary dementia and vascular dementia the Hachinski Ischemic Score (HIS) was used. This is a 13-item clinical scale. Each item is assigned a score of 1 or 2, with the latter indicating a vascular form. A total score of 4 or lower indicates Alzheimer's disease or a degenerative form, while a score between 5 and 6 suggests mixed dementia or an uncertain outcome. A score of at least 7 indicates vascular dementia. The presence of focal neurological symptoms was an important indicator of vascular dementia in cases where there was doubt [21].

The white matter hyperintensity (WMH) burden was assessed using the Fazekas Score (FS). It classifies lesions according to their hyperintensity at the MRI examination. Lesions were characterized as 0 (absence of lesions), 1 (non-confluent lesions), 2 (confluent lesions) and 3 (widespread lesions) [22].

The MRI examinations were performed at different scanners (magnetic field range 1.0-3.0 Tesla), without contrast administration. To mitigate the possible confounding effect of using different scanners, axial T2- and T1-weighted MRI images were analysed separately and blindly by a neurologist from each memory clinic and only scans that both neurologists judged suitable for the application of the FS were used for the retrospective study.

In order to identify the carriers of the apolipoprotein E ε4 allele, we extracted DNA from peripheral blood samples of 92 patients who gave consent for the examination. Genomic DNA was extracted by a standard salt-chloroform procedure [23] and it was amplified by a PCR in a thermal-cycler with specific oligonucleotide primers. The following primers were used according to previous literature: [24] upstream 5'-TCCAAGGAGCTGCAGGCGGCGA-3' and downstream 5'-ACAGAATTCGCCCCGCCTGGTACACTGCCA-3'. PCR was performed as described in [25].

Patients were stratified according to the presence/absence of at least one ε4 allele, and therefore divided in ApoE4 carriers (genotypes ε2 ε4+ε3 ε4+ε4 ε4) and non carriers (genotypes ε2 ε3+ε3 ε3). No ε2 ε2 genotype carriers were present in our sample.

The pairwise correlations between variables were assessed using Spearman correlation analysis, and to understand the mutual relation among different variables, we operated a principal component analysis (PCA). PCA is used to reduce the dimensionality of multivariate data sets while retaining the most important information [26]. The analysis decomposes the total variance (information) of the dataset into mutually independent patterns of variation (components) that best capture the structure of the data. In other words, when variables are correlated, PCA allows us to represent one variable in terms of another, simplifying the data. This allows to save the relevant part of information originally residing in N variables into P components (with P<<N), discarding the noise while retaining relevant "signal-like" information [27].

The number of components was determined using Cattel's test, which identifies significant differences between informative components ("signal-like" information) and noise [28].

To interpret the meaning of the components, we used the "component loadings", which is the Pearson correlation coefficient between original variables and components. The original variables with a higher correlation allow the researchers to attach a meaning to a specific component.

PCA was applied to the subset of patients with no missing values. Components were extracted in decreasing order of explained variance using eigenvalues obtained from Cattel's test. An eigenvalue represents the overall variance explained by each component. Since we standardized the variables to have a mean of 0 and a standard deviation of 1, an eigenvalue close to 1 means the component explains about as much as an average original variable. The percentage of variance explained by each component is calculated by dividing its eigenvalue by the total sum of eigenvalues, which equals the number of original variables analysed. The cumulative explained variance shows how accurately the components represent the dataset, reaching 100% when the number of components matches the number of original variables (*Table 2a*).

The names of the components reported below stem from the analysis of component loading pattern reported in *Table 2b*.

Analyses were carried out using SAS software version 9.4M1.

RESULTS

135 patients (52.1% with mild, 45.8% with moderate and 2.1% with severe AD) were selected based on their outpatient medical records

Demographic and clinical characteristics of the whole sample are detailed in *Table 1*, together with vascular risk factors and comorbidities of the sample. ApoE genotype distribution, which was analysed in 92 patients, is also shown in *Table 1*.

Table 2a reports the distribution of explained variance across the principal components: considering the four most important components, 77% of total variance is explained, with the first component (PC1) accounting for 34% of variance. The name assigned to the different components stems from the loading pattern as we will discuss below.

The most relevant variables (higher absolute loading) for the component interpretation are bolded in *Table 2b*. PC1 is a "cardiovascular" component (high loading hypertension, Fazekas and HIS). The second component PC2 is a "metabolic" factor (hypercholesterolemia and diabetes as main drivers). PC3 demonstrates the NPI singularity: BPSD severity in AD has a near to unity (0.94) loading on PC3. Given components are each other mutually independent by construction; this result implies that BPSD severity in AD is totally independent from the rest of the descriptors (cognitive impairment, vascular impairment, white matter lesions and ApoE status). The fourth component has to do with diabetes pathological features independent from general metabolic pattern shaping PC2.

Table 1
Descriptive statistics of measured features

Variable	Mean (SD)	Median	Minimum	Maximum
Age (years) n=135	74.45 (7.17)	75.00	55.00	90.00
Females/Males ratio	1.14			
MMSE n=132	18.66 (4.81)	20.00	7.00	29.00
ApoE4 carriers n=92	0.48 (0.50)	0	0	1.00
HIS n=126	2.83 (2.08)	3.00	0	12.00
NPI n=135	21.47 (18.26)	16.00	0	94.00
Fazekas score n=135	1.14 (0.86)	1.00	0	3.00
Education (years) n=131	8.00 (4.15)	8.00	1.00	19.00
Rivastigmine n=131	0.82 (0.38)	1.00	0	1.00
Hypertension n=132	0.61 (0.49)	1.00	0	1.00
Antiplatelet therapy n=131	0.47 (0.52)	0	0	1.00
Oral hypoglycemic drugs n=131	0.12 (0.33)	0	0	1.00
Insulin n=131	0.01 (0.09)	0	0	1.00
Antiarrhythmic drugs n=131	0.07 (0.25)	0	0	1.00
Statins n=132	0.39 (0.49)	0	0	1.00
Anticoagulants n=132	0.08 (0.27)	0	0	1.00
Folic acid treatment n=133	0.07 (0.25)	0	0	1.00
Familiarity for vascular diseases n=131	0.33 (0.52)	0	0	2.00
Smoking n=134	0.25 (0.44)	0	0	1.00
Alcoholism n=132	0.01 (0.09)	0	0	1.00

The mean of binary (0/1) variables corresponds to the proportion of patients having a 1 (yes) score to the variable itself; SD: standard deviation; HIS: Hachinski Ischemic Score; MMSE: mini mental state examination; NPI: neuropsychiatric inventory.

Table 2
Descriptive characteristics and composition of principal components

a) Variance of the principal components

Component	Eigenvalue	Proportion	Cumulative
1	**2.35**	**0.34**	**0.34**
2	**1.27**	**0.18**	**0.52**
3	**1.00**	**0.14**	**0.66**
4	**0.79**	**0.11**	**0.77**
5	0.69	0.10	0.87
6	0.47	0.07	0.94
7	0.42	0.06	1.00

b) Loading pattern corresponding to the correlation coefficients between original variables and extracted principal components

Variables	PC1	PC2	PC3	PC4
Hypertension	**0.78**	-0.08	-0.08	-0.27
Fazekas	**0.80**	-0.02	0.23	-0.10
HIS	**0.82**	-0.10	0.075	-0.07
NPI	-0.17	0.25	**0.94**	0.07
Age (years)	**0.40**	**-0.60**	0.14	**0.49**
Hypercholesterolemia	0.34	**0.70**	-0.03	-0.19
Diabetes mellitus	0.35	**0.59**	-0.20	**0.65**

PC1: cardiovascular component (high loading hypertension, Fazekas and Hachinski scores); PC2: metabolic component (hypercholesterolemia and diabetes); PC3: BPSDs; PC4: diabetes; PC: principal component; NPI: neuropsychiatric inventory; BPSDs: behavioral and psychological symptoms; HIS: Hachinski Ischemic Score; significant results are bolded.

As it can be seen in *Table 2b*, age (mean: 74.45, standard deviation: 7.17) was significantly related to most of the components but the BPSDs one. The loading pattern of Age variable points (as expected) to a pervasive role of age as for different pathological features but not influencing the severity of Alzheimer. This result stems from the observation that the data set is made only by Alzheimer patients so ruling out the well-established correlation between the onset of dementia and aging. The cardiovascular component had a positive and statistically significant correlation with presence of hypertension, FS and HIS (correlation coefficients of 0.78; 0.80; 0.82 respectively). The metabolic component was significantly related with presence of hypercholesterolemia and diabetes mellitus (correlation coefficients of 0.70 and 0.59). The BPSDs component was significantly related only with the NPI score (0.94), while the fourth component was related to diabetes (0.65).

The negative relationship between NPI score and rivastigmine use (correlation coefficient -0.52, $p<0.0001$) was of particular interest, since its values were correlated with PC3 scores obtaining a Spearman correlation coefficient equal to $r=-0.52$ ($p<0.001$), identical to the direct correlation between NPI and rivastigmine.

DISCUSSION

We correlated the load of white matter lesions and global vascular impairment with cognitive clinical assessment and ApoE genotype in a sample of AD patients with BPSDs. According to our results, BPSD severity (estimated by NPI total score) seemed to be independent from cognitive impairment (MMSE), vascular impairment (HIS), white matter lesions (FS) and ApoE status.

When comparing our results with those of the literature (cited below), it must be considered that similar studies have used other assessment tools for both AD and BPSDs, and that BPSD expression can vary or fluctuate in the different stages of Alzheimer's and in different settings. Therefore, it is important to keep in mind that we based our study on outpatients mostly with mild and moderate AD, as described below.

According to our data, we were not able to confirm a role for vascular impairment in BPSDs expression in our sample. This is inconsistent with some previous literature, according to which mood and psychomotor symptoms are more prevalent in patients with greater vascular cognitive impairment (VCI) compared to AD patients. On the other hand, VCI patients tend to show more psychotic symptoms [7, 29]. Also, VCI has been associated with WMH, and it is thought that VCI could have a moderating effect between WMH and BPSDs [30]. Notwithstanding this, BPSDs pathogenesis has not yet been completely elucidated [31].

While discussing our results, it must be noted that our sample consisted mostly of outpatients with mild and moderate cognitive impairment. Previous studies concluded that WMH is particularly evident with BPSD in moderate to severe AD [7, 32]. This may have influenced our results, as some initial structural changes in the brain, more common in patients with mild cognitive impairment, may not yet be detectable on neuroimaging (i.e., abnormal connectivity and circuitry between various areas of the brain) [32]. Therefore, our findings must be taken with caution.

We did not find correlations between ApoE4 genotype and BPSDs in our sample. This is similar to previous literature, since both positive and negative correlations have been described over time [33, 34]. Although correlations of ApoE4 genotype with specific clusters of BPSD have been proposed [8, 12], this has not been always supported [35].

BPSDs are thought to be the result of complex interplay between biological (brain changes due to multiple causes), sociological (social network, living arrangements) and psychological factors (e.g., personality) [31]. Some researchers also point at specific conditions – such as chronic neuroinflammation – in which histaminergic neurotransmission could have a pivotal role in microglia inflammation [36]. Serotonergic and dopaminergic circuitry are known to be involved as well [37, 38]. Furthermore, grouping BPSDs into "clusters of symptoms" – as we also did – could distort relationships with different variables, because BPSDs are not grouped consistently across studies, with each "cluster" reflecting a different prevalence, timeline and bio-psychosocial correlates [31]. This often increases the difficulty in interpreting data [1]. For instance, previous research suggested that specific clusters of symptoms did not affect the progression of cognitive decline, while the greater the cognitive impairment, the more severe were the BPSDs.

An important aspect to note is that although the NPI is a largely diffused tool for studying BPSDs in dementia, our results – and some others as well [7, 39, 40] – underlie an emerging need to investigate bio-psychosocial and environmental factors in pathogenesis of BPSDs too. NPI is a useful measure to assess BPSD in people with dementia, but is a caregiver-dependent measure. The caregiver's personal characteristics (e.g., age, educational level, personality, psychological conditions, coping skills, etc) may modify levels of perceived stress and burden, impacting his/her reliability [1]. Moreover, it is known that the patient-caregiver emotional relationship and communication can have effects on BPSDs expression. Experience, emotional relationships, or familiarity could have a role in this process [41]. Therefore, it is essential to assess caregivers' burden including measures of objective and subjective caregiver stress and analysis of environmental conditions.

The association between the use of rivastigmine and less BPSDs we found is consistent with existing literature. It is widely known that cholinergic deficits cause cognitive impairment and are involved in BPSDs and delusional thinking [42,] and the positive clinical response to acetylcholinesterase inhibitors of patients with such symptoms (especially apathy, psychosis) are well known [43, 44].

Cardiovascular and metabolic components that came out from the PCA were consistent with previous literature [41]. Regarding the association of age with most of the PCA components: its role, even if statistically significant, is ambiguous. Indeed, it is important to remember that we analysed an aged population, imposing a range restriction to the age variable that is detrimental to the discovery of meaningful correlations with other variables [45].

Considering the high prevalence, and the often early occurrence of BPSDs – particularly of mood disorders – a rigorous assessment of psychiatric features in cognitively impaired patients should be part of the routine examination. Characterizing the behavioral profile of these patients may lead to a wholesome comprehension of their condition during the evolving of the disease, and may allow both caregivers and professionals to use more effective treatments for improving patients' and caregivers' quality of life [29].

LIMITATIONS

Our study has several limitations. Radiologic images were taken using different MRIs with different magnetic fields (range 1.0-3T) and different protocols by different centers. Independent confirmation of the FS from an external neuroradiologist was not taken. Since BPSDs symptoms fluctuate over time, estimating their prevalence using a cross-sectional approach may not be completely appropriate. Moreover, the cross-sectional design precludes causal inferences and reverse causality cannot be excluded. In future research, a longitudinal design could be accurate to study the causality of this study's topic. NPI is a broad-spectrum screening test: in future research, it may be useful to administer tests for specific symptoms of interest. The lack of a control group prevented us from conducting a case-control study. Limitations of our study include also its retrospective nature and the relatively small sample size.

CONCLUSIONS

In conclusion, we did not find in our sample and according to our study design the expected associations between vascular, genetic and imaging factors with expression of BPSDs. Our results could therefore underline the complex interactions between the above mentioned factors in the expression of BPSDs, being unable to identify a specific one. Conducting further studies in real-world contexts will be necessary to better understand other factors, aside from the biological ones, that may influence BPSD expression in AD patients, also through a more structured data collection on family members and patients. BPSDs are a very complex aspect of neurologic care, as they increase the risk of patients' hospitalization, death and caregiver exhaustion, and their pathogenesis is yet to be fully comprehended. The challenge for future studies may be to better understand this complex interaction of variables in the pathogenesis of BPSD by analysing the bio-psychosocial factors that are the least identified. Different methodological approaches could help deepening the knowledge on this topic. Also, further studies on brain circuitry could improve knowledge on this topic.

Conflicts of interest statement

The Authors have no conflit of interest to disclose.

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