Peripheral Leukocytosis Predicts Cognitive Decline but Not Behavioral Disturbances: A Nationwide Study of Alzheimer's and Parkinson's Disease Patients

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Keywords

Parkinson's disease · Alzheimer's disease · Leukocytosis · Dementia · Behavioral disturbances

Abstract

Introduction: Peripheral and central nervous system inflammation have been linked to the classic symptoms of Parkinson's disease (PD) and Alzheimer's disease (AD). However, it remains unclear whether the analysis of routine systemic inflammatory markers could represent a useful prediction tool to identify clinical subtypes in patients with Parkinson's and Alzheimer's at higher risk of dementia-associated symptoms, such as behavioral and psychological symptoms of dementia (BPSD). **Methods:** We performed a multivariate logistic regression using the 2016 and 2017 National Inpatient Sample with International Classification of Diseases 10th edition codes to assess if pro-inflammatory white blood cells (WBCs) anomalies correlate with dementia and BPSD in patients with these disorders. **Results:** We found that leukocytosis was the most common WBC inflammatory marker identified in 3.9% of Alzheimer's and 3.3% Parkinson's patients. Leukocytosis was also found to be an independent risk factor

for Parkinson's dementia. Multivariate analysis of both cohorts showed that leukocytosis is significantly decreased in patients with BPSD compared to patients without BPSD. **Conclusions:** These results suggest a link between leukocytosis and the pathophysiology of cognitive dysfunction in both PD and AD. A better understanding of the role of systemic neuroinflammation on these devastating neurodegenerative disorders may facilitate the development of cost-effective blood biomarkers for patient's early diagnosis and more accurate prognosis.

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Introduction

Chronic inflammation is a core pathophysiological factor contributing to neurodegenerative diseases [1]. Specifically, previous studies have shown that chronic inflammation may be involved in the early stages of Alzheimer's disease (AD) and Parkinson's disease (PD) [2–5]. Activation of central nervous system (CNS) resident immune cells produces neuronal death through the release of pro-inflammatory factors, such as cytokines,

prostaglandins, reactive oxygen species, and other complement proteins [6, 7]. Recent studies have also suggested that peripheral immune cell activation closely contributes to amplify or even trigger CNS immune response in the early stages of neurodegeneration [8–13].

AD and PD are the 2 most prevalent neurodegenerative diseases worldwide, which mainly affect the elderly population [14–17]. There are still many open questions regarding the mechanisms that trigger accumulation of pathological toxic protein species leading to neurodegeneration in AD and PD. Even though these diseases present different core symptoms – cognitive deficits in AD and motor dysfunction in PD – and unique neuropathology, in both the presence of systemic inflammation is a common denominator which correlates with clinical features [18, 19]. The prospective Framingham study, a multigenerational, community-based population study, revealed that cognitive-intact patients with higher levels of TNF- α and IL-1 β produced by peripheral blood mononuclear cells have nearly 3-fold higher risk of developing AD [19]. In PD patients, systemic inflammation is related not only to the onset of motor impairment, but also to its progression. Elevated blood levels of C-reactive protein were associated with early stages of PD [9], freezing of gait [18], and rapid progression of motor phenotype [20].

A wide range of other clinical features associated with the core symptoms of AD and PD can occur throughout the disease progression, and they have been related with reduced quality of life, clinical deterioration, and greater mortality risk [21–23]. In AD, up to 40–60% of patients exhibit behavioral and psychological symptoms of dementia (BPSD) [24], which include mood disorders, sleep disorders, psychotic symptoms, and agitation [25]. Cognitive and associated behavioral symptoms are also common in PD, which may occur even in the prodromal stages of the disease and worsen with its progression [26]. PD patients are 6 times more likely to develop mild cognitive impairment (MCI) or dementia, known as PD dementia (PDD), compared to healthy controls [27, 28]. Both cognitive impairment and BPSD are a major concern for AD and PD patients and their care providers due to its significant humanistic and societal impact [25, 27]. Patients with dementia and BPSD have substantially greater utilization of healthcare resources, therefore incurring in greater costs and economic expenses [25]. Suitable biomarkers to guide treatment decisions for these associated clinical features are lacking and urgently needed. A few diagnostic tests, such as positron emission tomography scans or cerebrospinal fluid analysis, have been proposed to predict different stages of AD and PD; yet the cost and invasiveness of

these methods represent an important limitation [29]. Thus, blood-based biomarkers that reflect the progression of the underlying neurodegenerative process in these diseases could improve clinical prediction of disease severity and clinical subtypes in large-scale populations [29].

The nervous system is particularly vulnerable to damage in response to systemic inflammation. Cognitive dysfunction and delirium can be induced directly by inflammation-induced infiltration of immune cells and soluble factors such as TNF, IL-1, as well as indirectly through activation of CNS microglia and astrocytes. For example, activation of systemic inflammation by infectious agents has been linked to PD [30] and AD onset [31]; although, the level and chronicity of systemic inflammation required to develop cognitive impairment and BPSD is not fully understood.

We hypothesized that the higher levels of systemic inflammatory markers contribute to AD and PD cognitive features compared to healthy controls. A few studies reported systemic inflammatory biomarkers with a potential to identify patients at higher risk of dementia or BPSD in AD and PD [32–34]. However, due to the relatively small sample-size populations, it still remains unclear whether the analysis of routine systemic inflammatory markers could represent a useful prediction tool to identify clinical subtypes in patients with AD and PD at higher risk of dementia-associated symptoms, such as BPSD. In this study, we aimed to test our hypothesis that elevation in peripheral immune cell levels will correlate with cognitive deficit and BPSD in AD and PD using the large-scale National Inpatient Sample (NIS) database.

Material and Methods

Data Source

Our retrospective cohort study used the 2016 and 2017 NIS database. This large database contains discharges from a 20% sample of all US hospitals in states participating in the Healthcare Cost and Utilization Project. It contains demographic, diagnostic, and procedural data, with diagnoses and procedures captured in the form of International Classification of Diseases 10th edition (ICD-10).

Study Sample

Primary inclusion criteria were patients with a discharge diagnosis of MCI or dementia due to AD (ICD-10th: G30) [35, 36] or idiopathic PD (ICD-10th: G20) from January 1, 2016 to December 31, 2017. Secondary inclusion criteria were the presence of neurocognitive disorder with BPSD [37–39] and white blood cells (WBCs) anomalies in AD and PD. Exclusion criteria comprised of patients under 18 years old and a diagnosis of gastrointestinal, urogenital, respiratory infection, bacteremia, viral infection, sepsis, or fever. Two cohorts of age-matched healthy controls to AD or PD cases were also included in the analyses.

Fig. 1. Leukocytosis is the most prevalent pro-inflammatory WBC anomaly reported in AD and PD patients. Graph represents the total number of AD and PD patients registered in the 2016 and 2017 NIS and selected age-matched controls for the study. AD, Alzheimer's disease; PD, Parkinson's disease; WBCs, white blood cells; NIS, National Inpatient Sample.

Collected Data

The examined demographic data included age, sex, race, and median household income categorized in quartiles. Moreover, long-term (current) treatment with antibiotics was included. The analyzed comorbidities were hypertension, diabetes mellitus with and without complications, lipidemias, congestive heart failure, obesity, depression, history of cerebrovascular disease, current smoker status, and sleep apnea. Chronic pro-inflammatory diseases comprising ulcerative colitis, Crohn's disease, inflammatory polyarthropathies, systemic lupus erythematosus, multiple sclerosis, chronic obstructive pulmonary disease, and asthma were also included.

Dementia cases due to disorders which cause mild or major cognitive symptoms were taken into account when performing univariate analysis. These comprised Huntington's disease, frontotemporal dementia, dementia due to head trauma, schizophrenia, vascular dementia, and Lewy body dementia. The most prevalent pro-inflammatory WBC anomalies found in the 2016–2017 NIS database were selected, including eosinophilia, lymphocytosis, monocytosis, plasmacytosis, bandemia, and elevated WBC count (leukocytosis). Specifically, leukocytosis is defined as an elevated WBC count greater than $11,000 \text{ per mm}^3$ ($11.0 \times 10^9 \text{ per L}$) [40]. All the codes for this study are shown in the online suppl. Table S1; see www.karger.com/doi/10.1159/000516340 for all online suppl. material.

Outcomes

The primary outcome analyzed for AD patients was the development of BPSD (ICD-10th: F02.81). For PD patients, the primary outcomes included MCI (ICD-10th: G31.84), major neurocognitive disorder (MND) with or without behavioral disturbances (ICD-10th: F02.80, F02.81), and 2 separate outcomes from the "major neurocognitive disorder" variable, PDD (ICD-10th: F02.80) and PDD with BPSD (ICD-10th: F02.81).

Statistical Analysis

Interactions between specific types of pro-inflammatory WBC anomalies and primary outcomes were assessed using the SPSS v.24 software. A univariate analysis was performed to identify unevenly distributed variables in the WBC anomalies that could constitute confounding factors. For this step, all continuous values are represented using mean $\pm$ standard deviation, or median and interquartile range. Categorical variables were described using frequencies and proportions. Comparisons were performed using Student's *t* test, the nonparametric Mann-Whitney test, or χ^2 tests as appropriate.

Factors with a *p* value <0.10 were then included in a multiple logistic regression analysis to reflect the adjusted association between WBC anomalies and each of the primary outcomes. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated, and a *p* value <0.05 was considered as statistically significant.

In order to test the extent to which pro-inflammatory WBC anomalies could predict the development of neurocognitive alterations and neurodegenerative disease itself, we performed a propensity matched score 1:1 with age-matched healthy controls for each AD and PD patient. The differences between cases and controls in sociodemographic, comorbidities, and other variables were assessed with a univariate analysis followed by a multiple logistic regression with the same criteria described above.

Results

A total of 179,102 patients with AD and 134,501 patients with a diagnosis of idiopathic PD were captured in the 2016 and 2017 NIS database. Out of those, 68,966 patients were excluded from the AD cohort and 43,969 from the PD cohort due to the presence of a diagnosis code of infection or fever. Four thousand four hundred seventeen AD patients (4%) and 2,995 PD patients (3.3%) had at least one of the pro-inflammatory WBC parameters included. The most prevalent anomaly was leukocytosis with 3.9% ($n = 4,244$) in AD and 3.2% ($n = 2,870$) PD patients. Eosinophilia and bandemia were reported in 0.1% of patients in both cohorts. The rest of WBC anomalies represented nearly the 0% of the cases (Fig. 1). WBC anomalies other than leukocytosis were not considered for further analyses due to the low number of cases in our cohorts (online suppl. Tables S2–S6 show the extended values for these analyses).

AD patients with MCI represented 0.3% of total cases ($n = 312$), while patients with dementia without BPSD represented 77.5% ($n = 85,418$) and patients with BPSD 22.2% ($n = 24,405$) of the entire cohort (Fig. 2a). In the AD cohort, the analysis between the primary outcomes and WBC anomalies showed that leukocytosis appears as frequent in MCI and dementia cases (3.9% $n = 13$ vs. 4.1% $n = 3,510$, n.s.). Interestingly, leukocytosis was significantly more prevalent in Alzheimer's dementia without

Fig. 2. Higher rates of leukocytosis are found in AD and PD patients with worsen neurocognitive decline. **a** Rates of MCI, dementia, and dementia + BPSD in AD. **b** Pro-inflammatory WBC anomalies in AD patients with MCI, dementia, and dementia + BPSD. **c** Rates of MCI and MND in PD patients. **d** Pro-inflammatory WBC anomalies in PD patients with normal cognition, MCI, and MND. **e** Rates of PDD and PDD + BPSD in PD patients with MND. **f** Pro-inflammatory WBC anomalies in PD patients with normal cognition, PDD, and PDD + BPSD. Graphs repre-

sent the percentage of AD and PD patients with WBC anomalies with respect to the total number of AD or PD patients registered in the 2016 and 2017 NIS database. Statistical analysis was carried out using the χ^2 test; * $p < 0.05$, ** $p < 0.001$. AD, Alzheimer's disease; PD, Parkinson's disease; WBCs, white blood cells; MCI, mild cognitive impairment; MND, major neurocognitive disorder; PDD, Parkinson's disease dementia; BPSD, behavioral and psychological symptoms of dementia; NIS, National Inpatient Sample.

Table 1. Univariate analysis of AD and PD patients with/without elevated WBCs count (leukocytosis) from the 2016 to 2017 NIS database

Variables	AD			PD		
	WBCs count		<i>p</i> value	WBCs count		<i>p</i> value
	normal (<i>n</i> = 105,882)	elevated (<i>n</i> = 4,244)		normal (<i>n</i> = 87,658)	elevated (<i>n</i> = 2870)	
Age, mean (SD), years	81.73 (7.81)	81.84 (7.71)	0.357	75.9 (9.96)	76.19 (9.84)	0.098*
Female sex, <i>n</i> (%)	61,882 (58.4)	2,627 (61.9)	<0.001*	34,340 (39.2)	1,146 (39.9)	0.420
Race, <i>n</i> (%)						
White	76,461 (74.6)	3,183 (77.2)	<0.001*	68,452 (80.9)	2,311 (83)	0.012*
African-American	12,056 (11.8)	380 (9.2)		5,727 (6.8)	151 (5.4)	
Hispanic	9,037 (8.8)	390 (9.5)		6,290 (7.4)	176 (6.3)	
Other	4,943 (4.8)	169 (4.1)		4,171 (4.9)	147 (5.3)	
Socioeconomic status, <i>n</i> (%)						
Quartile 1	30,383 (29.1)	1,132 (27)	0.007*	22,217 (25.7)	720 (25.4)	0.624
Quartile 2	27,257 (26.1)	1,107 (26.4)		22,401 (25.9)	747 (26.3)	
Quartile 3	24,860 (23.8)	1,011 (24.1)		21,575 (25)	686 (24.2)	
Quartile 4	21,803 (20.9)	948 (22.6)		20,186 (23.4)	686 (24.2)	
Comorbidities, <i>n</i> (%)						
Hypertension	69,130 (65.3)	2,908 (68.5)	<0.001*	53,415 (60.9)	1,884 (65.6)	<0.001*
Diabetes mellitus simple	23,575 (22.3)	962 (22.7)	0.535	20,258 (23.1)	719 (25.1)	0.015*
Diabetes mellitus complicated	10,834 (10.2)	381 (9)	0.008*	10,278 (11.7)	294 (10.2)	0.015*
Lipidemias	48,984 (46.3)	1,978 (46.6)	0.656	40,419 (46.1)	1,279 (44.6)	0.103
Obesity	5,771 (5.4)	228 (5.4)	0.827	8,448 (9.6)	281 (9.8)	0.783
Congestive heart failure	25,591 (24.2)	853 (20.1)	<0.001*	20,535 (23.4)	562 (19.6)	<0.001*
Cerebrovascular disease	13,127 (12.4)	433 (10.2)	<0.001*	9,664 (11)	282 (9.8)	0.043*
Depression	21,263 (20.1)	827 (19.5)	0.344	17,923 (20.4)	578 (20.1)	0.689
Current smoker	5,429 (5.1)	253 (6)	0.016*	5,713 (6.5)	215 (7.5)	0.038*
Sleep apnea	5,107 (4.8)	141 (3.3)	<0.001*	8,828 (10.1)	252 (8.8)	0.024*
Other chronic inflammatory diseases, <i>n</i> (%)						
Ulcerative colitis	214 (0.2)	16 (0.4)	0.014*	280 (0.3)	10 (0.3)	0.787
Crohn's disease	237 (0.2)	11 (0.3)	0.634	320 (0.4)	14 (0.5)	0.286
Inflammatory polyarthropathies	5,745 (5.4)	231 (5.4)	0.960	5,277 (6)	190 (6.6)	0.184
Systemic lupus erythematosus	29 (0.03)	0 (0)	0.281	38 (0.04)	0 (0)	0.265
Multiple sclerosis	170 (0.2)	8 (0.2)	0.657	266 (0.3)	12 (0.4)	0.275
Chronic obstructive pulmonary disease	13,209 (12.5)	528 (12.4)	0.949	11,230 (12.8)	345 (12)	0.213
Asthma	4,393 (4.1)	189 (4.5)	0.330	5,047 (5.8)	197 (6.9)	0.013*
Other causes of dementia, <i>n</i> (%)						
AD	–	–	–	4,438 (5.1)	164 (5.7)	0.118
PD	4,430 (4.2)	172 (4.1)	0.676	–	–	–
Huntington	29 (0.03)	2 (0.05)	0.452	27 (0.03)	2 (0.1)	0.251
Frontotemporal dementia	224 (0.2)	9 (0.2)	0.994	87 (0.1)	5 (0.2)	0.215
Dementia due to head trauma	34 (0.03)	2 (0.05)	0.596	33 (0.04)	3 (0.1)	0.077*
Schizophrenia	1,561 (1.5)	63 (1.5)	0.957	1,995 (2.3)	74 (2.6)	0.286
Vascular dementia	4,765 (4.5)	152 (3.6)	0.005*	1,220 (1.4)	30 (1)	0.118
Lewy body dementia	710 (0.7)	36 (0.8)	0.166	641 (0.7)	28 (1)	0.133

WBCs, white blood cells; AD, Alzheimer's disease; PD, Parkinson's disease; NIS, National Inpatient Sample. * Included in multivariate analysis.

BPSD compared to AD patients with BPSD (3 vs. 4.1%, $p < 0.001$) (Fig. 2b; online suppl. Table S2).

In the PD cohort, MCI was present in 0.9% ($n = 707$) of total cases, while MND was reported for 20.8% ($n = 18,815$) of total PD patients (Fig. 2c). Out of the PD pa-

tients with MNDs, 13.3% ($n = 2,499$) presented BPSD and therefore, 86.7% ($n = 16,316$) had PDD alone (Fig. 2e). Among the entire PD cohort, we found that leukocytosis prevalence was significantly higher in patients with MND compared to patients presenting normal cognition (3.6%,

Fig. 3. Leukocytosis is associated with higher odds of cognitive impairment and lower odds of BPSD in AD and PD patients with dementia. **a** Association of leukocytosis with risk of dementia + BPSD in AD patients. **b** Association of leukocytosis with risk of MND in PD patients. **c** Association of leukocytosis with risk of dementia in PD patients. **d** Association of leukocytosis with risk of PDD and BPSD. Graph values are based on the total number of AD and PD patients registered in the 2016 and 2017 NIS database. Lo-

gistic regression analyses show OR, and 95% CI, for unadjusted (crude) and adjusted (for demographics and comorbidities) leukocytosis contribution to neurocognitive features in AD and PD. AD, Alzheimer's disease; PD, Parkinson's disease; WBCs, white blood cells; MND, major neurocognitive disorder; PDD, Parkinson's disease dementia; BPSD, behavioral and psychological symptoms of dementia; NIS, National Inpatient Sample; OR, odds ratio; CI, confidence interval.

$n = 679$ vs. 3.0%, $n = 2,163$, $p < 0.001$) (Fig. 2d). Similarly, the rate of leukocytosis was higher in PD patients with MCI compared to cognitively normal patients, but this did not reach statistical significance (3.4%, $n = 2,163$ vs. 3.0%, $n = 24$, $p = 0.592$) (Fig. 2d).

A secondary analysis of PD patients with MND revealed that, compared to patients with normal cognition, leukocytosis was significantly associated with PDD (3.8%, $n = 621$ vs. 3.0%, $n = 2,163$, $p < 0.001$), whereas patients with PDD plus BPSD had significantly lower rates of leukocytosis (2.3%, $n = 58$ vs. 3.0%, $n = 2,163$, $p = 0.039$) (Fig. 2f).

Next, we carried out a univariate analysis to assess the unevenly distributed variables in patients with normal and elevated leukocytosis (Table 1). Compared to AD patients with normal WBC count, Alzheimer's patients with leukocytosis were significantly represented by females, Hispanics, hypertensives, current smokers, and individuals with ulcerative colitis ($p < 0.05$). Significantly fewer AD patients with leukocytosis suffered from complicated diabetes mellitus, congestive heart failure, cerebrovascu-

lar diseases, sleep apnea, and vascular dementia (Table 1). In the PD cohort, patients with leukocytosis were significantly ($p < 0.05$) represented by whites, hypertensives, diabetics without complications, and current smokers compared to PD patients without leukocytosis. Moreover, PD patients with leukocytosis had significant lower rates of diabetes with complications, congestive heart failure, cerebrovascular diseases, sleep apnea, and asthma (Table 1). All mentioned variables were included to adjust the multiple logistic regression models.

The crude analysis showed a reduced risk of BPSD in AD disease patients with leukocytosis (OR = 0.716, 95% CI: 0.658–0.778, $p < 0.001$). After adjusting for variables with $p < 0.1$ in the univariate analysis, the multiple logistic regression model (Fig. 3a) showed that leukocytosis was still highly significantly associated with decreased odds of developing BPSD (OR = 0.708, 95% CI: 0.651–0.769, $p < 0.001$).

In the PD cohort, WBC count had a crude significant association with an increased risk of MND (OR = 1.19,

95% CI: 1.09–1.31, $p < 0.001$) (Fig. 3b) but not with MCI (OR = 1.12, 95% CI: 0.743–1.68, $p = 0.592$) compared to PD patients without cognitive disturbances (online suppl. Fig. S1). The multiple logistic regression confirmed that leukocytosis was not significantly associated with MCI (OR = 1.14, 95% CI: 0.777–1.68, $p = 0.497$); however, it was independently associated with higher odds of developing major cognitive disorders (OR = 1.19, 95% CI: 1.08–1.30, $p < 0.001$) (online suppl. Fig. S1; Fig. 3b). Similarly, the multiple logistic regression confirmed a significant increased risk for PDD without BPSD in patients with leukocytosis (OR = 1.25, 95% CI: 1.14–1.38, $p < 0.001$) (Fig. 3c), and a significant lower risk for patients with PDD and associated BPSD (OR = 0.730, 95% CI: 0.561–0.95, $p = 0.020$) (Fig. 3d).

Finally, we performed a matched propensity analysis for both AD and PD cohorts. The AD cohort included 179,102 age-matched healthy controls out of which 43,617 were excluded due to a diagnosis of infection or fever. A total of 135,485 controls were included in the main analysis. After assessing the distribution of uneven variables between AD and controls through a univariate analysis (online suppl. Table S7), we proceeded with a multiple logistic regression which revealed a significant association of leukocytosis with risk of AD (OR = 1.458, 95% CI: 1.390–1.529, $p < 0.001$) (online suppl. Table S8). We carried out the same analysis in the PD cohort. A total of 134,501 healthy age-matched controls were included, and after excluding patients with infections or fever, 102,269 controls were considered for the main analysis. Variables with a $p < 0.1$ in the univariate analysis (online suppl. Table S7) were included in the adjusted logistic regression, which showed a significant association of leukocytosis with risk of PD [OR = 1.187, 95% CI: 1.121–1.257, $p < 0.001$] (online suppl. Table S9).

Discussion

With the move toward development of disease-modifying treatments, the identification of diagnostic and prognostic biomarkers that allow for an early characterization and accurate clinical follow-up of AD and PD patients with dementia is a major clinical objective. Easy-to-use blood-based assays able to provide high specificity and sensitivity are likely to play an important role. In this study, we analyzed the association between pro-inflammatory peripheral immune cells parameters found in routine blood tests and the presence of associated clinical features in AD and PD. We found that leukocytosis is an

independent predictor of MNDs in PD patients. Furthermore, a sub-analysis to distinguish between patients with PDD only and PDD with associated BPSD revealed that leukocytosis represents a risk factor for dementia, but at the same time is significantly associated with lower risk of BPSD. This association was also seen in the AD cohort where patients with leukocytosis had lower odds of developing BPSD compared to patients with cognitive impairment without behavioral symptoms. Finally, we performed a propensity matched score analysis which revealed that leukocytosis is significantly associated with risk of AD and PD, supporting our hypothesis that peripheral immune cell levels are elevated in AD and PD compared to healthy controls.

Systemic inflammatory burden product of multiple infections has been linked to PD [30] and AD onset [31]. The opposite association of leukocytosis with cognitive and noncognitive symptoms that was found in our study could be explained by the following reasons. First, it has been suggested that levels of systemic inflammatory markers are greater during early stages of PD and AD [9, 32–34], when they can amplify or even trigger chronic CNS neuroinflammation leading to neurodegeneration. Therefore, symptoms appearing at late stages of AD and PD, such as BPSD, could more significantly correlate with the progressive neurodegeneration rather than with systemic inflammation. In fact, several studies reported that appearance of BPSD symptoms strongly associate with the degree of functional and cognitive impairment [41, 42]. For instance, behavioral disturbances such as aggressive behavior tend to occur more often in late stages of AD, which are characterized by severe cognitive deficits and often result in impaired verbal communication [42, 43]. However, a study of the natural history of BPSD in AD reported that behavioral disturbances can occur almost at any time during the course of the dementia [41], suggesting that the different rates of leukocytosis observed in our study in dementia patients with or without BPSD may not be completely attributed to a chronological factor. Future clinical prospective studies are needed to clarify the dynamic change of peripheral immune cells in relation to the course of AD and PD.

Second, this phenomenon could be related to the specific mechanisms implicated in cognitive and noncognitive impairment. Loss of cognitive functions in the early stage of dementia is highly associated with neuronal death boosted by the crosstalk between peripheral and CNS inflammation [44, 45], which includes different mechanisms such as vagal reflex-induced inflammation from

the periphery to the brain [46, 47], blood-brain barrier disruption [13], and direct entry of peripheral immune cells into the brain parenchyma [12]. Decline of noncognitive functions has been related to changes in anatomic structures [48], circadian rhythm dysfunction [49], metabolic changes [50], and imbalance in the production of neurotransmitters [51, 52], but less is known about how much systemic inflammation aggravates noncognitive symptoms. Hence, our results open a debate on whether there is an underlying mechanism that produces a negative feedback in leukocytes, especially in late stages of dementia with BPSD, making leukocytosis values a reliable biomarker to identify CNS inflammation and damage at the time of BPSD onset.

Our work supports previous evidence of leukocytes anomalies with risk of dementia [53], and to our best knowledge, it is the 1st study that reveals this association on a large national scale. We also provide new insights into the role of systemic inflammatory markers found in routine lab tests with regards to BPSD, which may aid future research to address the identification of clinical subtypes, and to develop prevention and management strategies of currently unmet needs in both AD and PD.

Although having a routine laboratory marker, such as leukocyte count, that predicts neurocognitive deterioration would be ideal, the variability and similarities of the complex mechanisms involved in AD and PD make a single blood biomarker not sufficient for specific early diagnosis and accurate prognosis of these 2 neurodegenerative diseases. Therefore, our work should be seen in the light of limitations inherent to the nature of a retrospective study. The predictor variable of interest, leukocytosis, is presented in the NIS database as a categorical variable rather than continuous variable and, therefore, it did not allow the identification of a cutoff threshold that could be used to increase the sensitivity and specificity to predict dementia or BPSD. Moreover, an ICD-10th code for preclinical AD is not available. As suggested by the National Institute on Aging and Alzheimer's Association guidelines, identification of preclinical AD is not meant to be used in the routine clinical diagnostic decision-making [54]. Thus, an association of cognitive decline from preclinical AD to dementia due to AD with leukocytosis in this cohort was not possible. Last, for the main outcomes of dementia and BPSD, the degree of severity, time of onset, and BDSP subtype were not available in the NIS data set.

In view of this, our conclusions are not aimed to be generalized for every PD or AD case, but rather to overcome limitations of previous relatively small single-cen-

ter studies and, to contribute to the clinical evidence of a critical role of systemic inflammation on the progression of the most prevalent neurodegenerative diseases worldwide.

Conclusions

In our large-scale retrospective study, we found that peripheral leukocytosis is an independent risk factor for PDD, and is significantly associated with reduced risk of developing behavioral and psychological symptoms in both AD and PD. Although our results need further elucidation on how leukocytes interact with global cognition and BPSD and its predictive value, we believe the communication of this 1st national study will aid future works in the search of biomarkers that improves physicians' strategies of prevention and management.

Statement of Ethics

An IRB approval was not required due to the anonymized and retrospective nature of this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: S.R.U. and R.M.; methodology: S.R.U.; formal analysis: S.R.U.; resources: A.M.A. and D.J.A.; investigation: S.R.U., A.M.A., and R.M.; data curation: S.R.U.; writing – original draft preparation: S.R.U. and R.M.; writing – review and editing: S.R.U., A.M.A., D.J.A., and R.M.; supervision: R.M.; funding acquisition: R.M.; project administration: R.M. All authors have read and agreed to the published version of the manuscript.

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