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The Tregs Phenotype Characters for the Progression MCI Patients with or without Insomnia

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ABSTRACT

Objective: The aim of the present work was to investigate the risk factors for the rapidly progressive mild cognitive impairment (MCI) due to Alzheimer's disease (AD) with or without insomnia.

Method: A total of 150 patients ≥65y/o and with MCI were followed up. All patients were divided into two groups (progressive MCI group and unprogressive MCI group) according their cognitive levels at two-year time. These patients were divided into insomnia group and non-insomnia group according to whether their chief complaint of insomnia was more than three months. Tregs and other immune indicators were detected, and the differential changes of immune indicators were analyzed.

Results: Of the 150 patients enrolled, 23 patients were included insomnia group and 127 patients were included in non-insomnia group(N-insomnia). There were significant difference in CD3+CD4+/lymphocytes-β/Treg CD4 and CD56 between the insomnia groups and N-insomnia group($P<0.05$). Treg/CD4+ and TGF-β/Treg were negatively correlated with MCI progression in insomnia MCI people, meanwhile, PD-1+/Treg was positive correlated with MCI progression in non-insomnia MCI people, but CD8 was negatively correlated with that.

Conclusion: There were discernible differences in Treg cells between MCI individuals with insomnia and those without insomnia, which were associated with the progression of MCI.

Keywords: Insomnia; Alzheimer's Disease; Mild Cognitive Impairment; Immunization; Treg

Introduction

Alzheimer's disease (AD), the most prevalent form of dementia, represents a significant and growing global challenge [1]. The primary pathology of Al AD involves the abnormal deposition of amyloid-beta (Aβ) and tau proteins. Previous studies have shown that cerebrospinal fluid or PET detection of Aβ and tau protein was used as the gold standard for the diagnosis of AD [2]. Recently, serum Aβ1-42, Aβ1-40, ptau181, and Ptau217 have been recognized as alternatives to cerebrospinal fluid (CSF) or positron emission tomography (PET) detection methods for Aβ and tau proteins in the pathological diagnosis of AD [3]. Despite a pathological diagnosis of AD preceding clinical practice, individuals may experience a latency period of several years, or even over a decade, before exhibiting clinical symptoms. This delay is attributed to a combination of genetic, inflammatory, and environmental factors [4]. In fact, the current understanding of AD pathology encompasses various hypotheses, including cholinergic dysfunction, amyloid accumulation, tau protein abnormalities, neuroinflammation, oxidative stress, disturbances in metal ion homeostasis, glutamate excitotoxicity, interactions within the microbial-gut-brain axis, and disruptions in autophagy [1].

In recent years, neuroinflammation has been identified as a key pathogenic mechanism in AD, and several previous studies have shown that pharmacological modulation of neuroinflammation may alleviate AD symptoms, mainly by controlling neuroinflammatory signaling pathways such as NF-κB, MAPK, NLRP3, and their respective signaling cascades [5]. The role of neuroinflammation in disease progression has emerged as a significant research focus. Microglia and astrocytes are pivotal in mediating central nervous system immune responses [6]. Furthermore, inhibitors, natural products, and metabolites that target these inflammatory patterns have undergone extensive research. Many of these substances have demonstrated significant pharmacological efficacy and promising clinical applications [5]. In the current phase where the clinical efficacy of drugs targeting Aβ, such as lecanemab and donanemab, remains under verification in practical applications, the inflammatory mechanism has garnered increasing attention. Notably, peripheral immunity serves a protective function in AD, with regulatory T cells (Tregs) and monocytes emerging as promising targets for immunotherapeutic approaches [7].

In addition to inflammation, sleep disorders, including circadian rhythm disruption, have been identified both as risk factors and consequences of AD and a bidirectional relationship exists between sleep disturbances and AD [8]. The deposition of amyloid and hyperphosphorylation of tau protein, coupled with astrocytic hyperactivation, can induce alterations in neurotransmission dynamics within sleep-related brain regions, resulting in sleep disorders among AD patients [9], but the mechanism by which sleep disorders contribute to AD remains unclear. Previous study found that Th17/Treg was imbalance in obstructive sleep apnea (OSA) patients [10], but there's been little research on Tregs and insomnia. Our study aims to explore the Tregs phenotype characters for the progression MCI patients with or without insomnia.

Materials and Methods

Ethics Statement

The study received approval from the Medical Ethics Committee of Shanghai Pudong New Area People's Hospital, Shanghai, China (Approval Number: 2022-K48). Written informed consent was obtained from all participants or their legally authorized representatives. All methods were carried out in accordance with relevant guidelines and regulations.

Subject Recruitment

All participants were recruited from the local community. In 2019, we established a community-based cohort focusing on cognitive function among individuals aged 65 and older [11]. Annually, individuals ≥65y/o voluntarily join the program, with the current cohort comprising 400 participants diagnosed with MCI. This study commenced enrollment on September 20, 2022. Our team endeavored to include all individuals with MCI who voluntarily participated in the physical examinations, providing informed consent. The follow-up period extended to September 20, 2024, at which point cognitive function was assessed. The screening flow chart was shown in Figure 1.

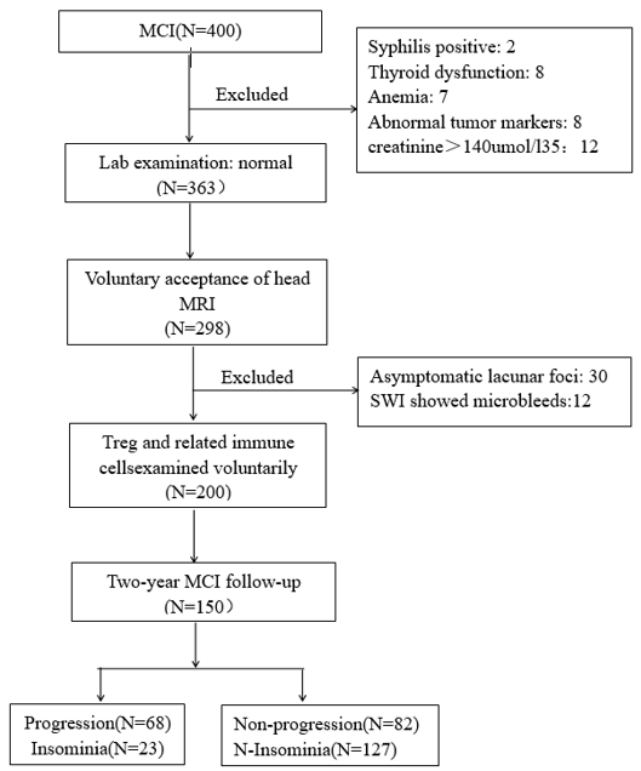

Figure 1: The screening flow chart.

MCI Diagnostic Criteria and MCI Progression Standards

In our study, MCI was defined by the following criteria:

1. Cognitive concern or complaint expressed by the subject, informant, nurse, or physician, with a Clinical Dementia Rating (CDR) less than 0.5;
2. Objective impairment in at least one cognitive domain, evidenced by performance 1.5 standard deviations below the mean, as determined by norms from the pilot study;
3. Essentially normal functional activities, as assessed by both the CDR and the Activities of Daily Living (ADL) evaluation;
4. Absence of dementia, as diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. The participants were screened by MoCA, with the score of 23 being the threshold of normal and MCI. MCI progression was judged by Cognitive Function Scale (CFS) scores ≥1 was defined as progression group (PG) [12], otherwise, it was judged as non-progression group(N-PG).

Methods for Detection of Treg and Related Immune Cells

Activation of Cells: Three steps were needed in activation of cells.

- **Step 1:** Take a flow tube with a cover, add 500 μl of mixed whole blood, add 500 μl of 1640 culture medium, after mixing, 2 microliters of Cell Activation Cocktail and 2 microliters of BD GolgiStop™ Protein Transport Inhibitor (containing monensin) were added and mixed again.
- **Step 2:** The cells were incubated for 5 hours at 37° C in a 5% CO2 incubator.
- **Step 3:** Remove from the incubator, wash the cells twice with PBS at room temperature, and centrifuged at 350g for 5 minutes. PBS was resuspended to 300 microliters.

Antibody Staining (Intracellular Cytokine Assays): Detection was performed by flow cytometry. Detailed procedures are provided in the Supplementary Material.

Statistical Analysis: SPSS Statistics 25 statistical software ((SPSS Inc., Chicago, IL) was used in our study. The chi-square test was used to assess the differences between different subgroups in terms of gender, smoking, drinking alcohol, and the diseases of diabetes and insomnia; T-test, to assess the differences of age, body weight and serum indexes between PG and N-PG; Regression analysis, to evaluate the correlation of immune cells with progress MCI. There were no missing data in this study, so no statistic method used for missing data addressed.

Results

Demographic Analysis

A total of 150 MCI participants≥65y/o underwent the detection of Tregs and immune cells including CD19, CD8, CD4, the CD4/CD8 ratio, and CD56. A total of 150 participants volunteered to undergo a follow-up assessment of cognitive function on September 20, 2024. The group included 68 individuals from the PG group and 82 from the N-PG group. A list of their demographic characteristics was compiled (Table 1). The results indicate that, apart from CD19 and age, which exhibited significant differences between the two groups ($P<0.05$), no other factors demonstrated significant differences ($P>0.05$). In our study, all MCI patients were categorized into an insomnia group and a non-insomnia group based on their reports of insomnia persisting for over three months. As indicated in Table 2, there were 23 individuals in the insomnia group and 127 individuals in the non-insomnia group. There were significant differences in CD3+CD4+/lymphocytes, TGF-β/Treg, CD4, and CD56 between the two groups ($P<0.05$).

As illustrated in Table 3, the ratios of CD4+CD25+FOXP3+/CD4+ and TGF-β/Treg in individuals with MCI and insomnia were significantly different between the progressive and non-progressive groups ($P<0.05$). Conversely, the ratios of PD-1+/Treg, CD19, CD3, and CD8 in individuals with MCI without insomnia exhibited significant differences between the progressive and non-progressive groups ($P < 0.05$). (Table 3) The progression-related factors were different between the two groups of MCI patients with and without insomnia. As shown in (Table 4) the CD4+CD25+FOXP3+/CD4+ and TGF-β/Treg ratios in MCI patients with insomnia exhibited a negative correlation with the progression of MCI. Furthermore, the PD-1+/Treg ratio in MCI patients without insomnia showed a positive correlation with MCI progression, whereas CD8 demonstrated a negative correlation with MCI progression.

Table 1: The general information of MCI progression group and non-progression group.

	PG(n=68)	N-PG(n=82)	P
CD3+CD4+/lymphocytes (%)	28.56±7.17	29.94±8.02	0.274
CD4+CD25+FOXP3+/CD4+(%)	3.20±1.31	2.97±1.07	0.254
TIM3+/Treg (%)	4.68±3.37	4.76±3.13	0.891
PD-1+/Treg (%)	5.87±3.54	6.91±3.96	0.098
IL-10+/Treg (%)	1.65±1.00	1.70±1.09	0.786
TGF-β/Treg (%)	1.31±1.05	1.08±0.97	0.179
IL-17A+/CD4+ (%)	0.89±0.35	0.84±0.39	0.399
IFNr+/TH17(%)	3.23±2.75	2.76±2.49	0.274
CD19(%)	9.18±4.83	11.26±7.12	0.042*
CD3(%)	65.72±11.49	62.60±12.09	0.11
CD4/CD8(%)	1.63±0.86	1.75±1.04	0.464
CD4(%)	38.62±10.40	37.00±10.36	0.343
CD56(%)	8.06±5.14	8.34±4.05	0.71
CD8(%)	29.23±14.37	25.28±10.01	0.051
Age(years)	74.01±6.32	71.56±5.30	<0.001*
Body weight(kg)	61.69±10.01	62.15±10.50	0.798
Systolic blood pressure(mmHg)	151.66±22.10	146.87±19.67	0.182
Diastolic blood pressure(mmHg)	78.21±11.98	75.93±10.26	0.233
Smoking (Yes)	12（17.60%)	19(23.20%	0.266
Drinking alcohol (Yes)	8（11.80%）	11（13.40%）	0.48
Diabetes (Yes)	10（14.70%)	22(26.80%)	0.053
Female (Yes)	42（61.80%）	44（53.70%）	0.202
Insomnia (Yes)	12(17.69%)	11(13.40%)	3.12

Table 2: The factors associated with insomnia.

	Insomnia(n=23)	Non-insomnia(n=127)	P
$CD3^+CD4^+$/lymphocytes (%)	32.42+8.42	28.75+7.40	0.034
TGF-β/Treg (%)	1.58+1.24	1.12+0.95	0.04
$CD4^+$ (%)	41.55+8.82	37.04+10.52	0.044
$CD56^+$ (%)	6.23+2.58	8.58+4.76	0.023

Table 3: The progression-related factors were different between the two groups of MCI patients with and without insomnia.

		PG(n=12)	N-PG(n=11)	P
Insomnia(n=23)	$CD3^+CD4^+$/lymphocytes (%)	31.46±7.14	33.46±9.89	0.583
	$CD4^+CD25^+FOXP3^+/CD4^+$ (%)	2.15±0.90	3.49±1.55	0.021*
	$TIM3^+$/Treg (%)	7.11±6.14	4.44±2.56	0.195
	$PD\text{-}1^+$/Treg (%)	8.09±4.27	6.40±1.62	0.232
	$IL\text{-}10^+$/Treg (%)	1.86±0.75	2.07±1.19	0.609
	TGF-β/Treg (%)	0.84±0.54	2.26±1.31	0.003*
	$IL\text{-}17A^+/CD4^+$ (%)	0.92±0.42	0.86±0.41	0.713
	$IFNr^+$/TH17(%)	2.73±2.61	3.14±2.00	0.676
	CD19(%)	9.86±4.74	10.01±7.53	0.954

	CD3(%)	66.07±11.99	69.92±9.94	0.413
	CD4/CD8(%)	1.73±0.85	1.71±0.56	0.946
	CD4(%)	39.06±9.82	44.27±7.03	0.162
	CD56(%)	5.84±2.28	6.66±2.92	0.458
	CD8(%)	26.47±9.87	27.66±6.87	0.742
N-Insomnia(n=127)				
	$CD3^+CD4^+$/lymphocytes (%)	27.94±7.09	29.40±7.63	0.273
	$CD4^+CD25^+FOXP3^+/CD4^+$(%)	3.13±1.27	3.10±1.04	0.869
	$TIM3^+$/Treg (%)	4.16±2.18	4.81±3.22	0.204
	$PD\text{-}1^+$/Treg (%)	5.40±3.22	6.98±4.22	0.021*
	$IL\text{-}10^+$/Treg (%)	1.60±1.05	1.64±1.08	0.859
	TGF-β/Treg (%)	1.11±0.87	1.12±1.01	0.915
	$IL\text{-}17A^+/CD4^+$(%)	0.89±0.32	0.84±0.33	0.466
	$IFNr^+$/TH17(%)	3.34±2.78	2.70±2.57	0.184
	CD19(%)	9.03±4.88	11.45±7.09	0.031*
	CD3(%)	65.65±11.50	61.46±12.05	0.05*
	CD4/CD8(%)	1.61±0.87	1.76±1.10	0.428
	CD4(%)	38.52±10.61	35.87±10.37	0.159
	CD56(%)	8.54±5.47	8.61±4.16	0.94
	CD8(%)	24.82±15.16	28.92±10.50	0.033*

Table 4: The correlation analysis of risk factors between insomnia and non-insomnia in progressive MCI patients (logistic regression analysis).

		B	Standard error	Wald	P	Exp(B)
Insomnia	CD4+CD25+FOXP3+/CD4+ (%)	-0.905	0.442	4.19	0.041	0.405
	TGF-β/Treg (%)	-1.528	0.682	5.019	0.025	0.217
N-Insomnia	$PD\text{-}1^+$/Treg (%)	0.119	0.053	4.963	0.026	1.126
	CD8(%)	0.034	0.016	4.416	0.036	0.967

Discussion

The etiology of AD is multifaceted, with key contributing factors including inflammation, oxidative stress, genetic and epigenetic variations, and cerebrovascular abnormalities [13]. Neuroinflammation has emerged as a pivotal factor in the pathogenesis of AD. Increasing evidence underscores the interaction between the peripheral immune system and the central nervous system (CNS) in driving neuroinflammation, with T lymphocytes playing a critical role in both regulatory and effector functions [14,15]. Moreover, Tregs, which play a crucial role in maintaining immune tolerance and exhibit neuroprotective effects in various diseases, including animal models of AD demonstrate significant therapeutic potential [16]. The impact of immune inflammation on the cognitive progression of MCI patients experiencing insomnia has been scarcely investigated. Our study revealed that both age and CD19 levels are associated with the progression of MCI. It has been acknowledged that AD is an age-dependent neurodegenerative disorder [17]. CD19 is a transmembrane protein uniquely expressed on the surface of B cells. It constitutes a fundamental element of the B cell receptor co-receptor complex, interacting with molecules such as CD21 and CD81. It plays a crucial role in regulating B cell activation, proliferation, and antibody production. Its expression level directly reflects the functional status of B cells [18]. So, it was speculated that the decline of B lymphocyte function may related to the progression of MCI.Our study revealed that elevated levels of CD3+CD4+/lymphocytes, TGF-β/Treg, and CD4+, coupled with decreased levels of CD56+, are strongly correlated with insomnia, indicating a close relationship between insomnia and immune inflammation. CD3+CD4+/lymphocytes represent the proportion of helper T cells (CD3+CD4+) among lymphocytes, commonly utilized as an indicator of immune function [19]. Previous research has established a causal link between immune cells and insomnia, specifically through the leucine-mediated interaction between CD4/CD8 cells and insomnia [20], which was consistent with our conclusion.

Transforming growth factor-β (TGF-β) is a multifunctional cytokine, which mainly plays a role in inhibiting inflammation and maintaining peripheral tolerance in the immune system, which can induce the differentiation of naive T cells into Treg and inhibit the differentiation of pro-inflammatory Th17 cells [21]. In our study, the ratio of TGF-β/Treg is elevated in patients with insomnia compared to those without insomnia. This may be attributed to the activation of self-protective immune functions following T cell activation. CD4+ T cell subsets generally exhibit aging-related features, which are adaptive immune cells that originate from the bone marrow and mature in the thymus. Upon antigen activation, naive CD4+ T cells (TN cells) can differentiate into different functional subsets, including helper T cells (Th cells) such as Th1, Th2, Th9, Th17, Th22 and follicular helper T cells (Tfh)as well as Tregs and memory CD4+ T cells. CD56 (also known as neural cell adhesion molecule, NCAM) is the main surface marker of natural killer cells (NK cells), which is used to distinguish different immune cell subsets. NK cells with high expression of CD56 mainly secrete cytokines and regulate immune responses. NK cells with low expression of CD56 had stronger cytotoxic activity. In our study, the ratio of TGF-β to Tregs in patients with insomnia is lower than that in patients without insomnia, suggesting the potential production of cytotoxic activity in insomnia individuals and it also reflects the protective effect of Tregs on sleep from another perspective.

Our study reveals that the levels of CD4+CD25+FOXP3+/CD4+ (Treg/CD4+) and TGF-β/Treg are lower in individuals with MCI and insomnia who exhibit progressive MCI. Regression analysis indicates a negative correlation between Treg/CD4+ and TGF-β/Treg and the progression of MCI in individuals with insomnia. Conversely, in MCI patients without insomnia, the PD-1+/Treg ratio is elevated among those with progressive MCI, whereas CD8 levels are reduced. The regression analysis indicated a positive correlation between PD-1+/Treg and the progression of MCI among individuals without insomnia. Conversely, CD8 exhibited a negative correlation with MCI progression. The results indicate that there are differences in immune cells associated with the progression of MCI between individuals with insomnia and those without. Previous studies have suggested that regulatory Tregs may modulate the pathology of AD by inhibiting neuroinflammation, in addition, a study found that CD8 T cells induce plaque and tangle-like deposits, modulate AD-related genes, and ultimately lead to progressive neurodegeneration with global and fine features of sporadic human AD. These findings align with our conclusions.

Conclusion

We pioneered the immune-cell profiling of MCI progression in individuals with and without insomnia. Our study found that Tregs phenotypes associated with MCI progression were different in MCI individuals with and without insomnia. Specifically, Treg/CD4+ and TGF-β/Treg demonstrated a negative correlation with the progression of MCI among individuals with insomnia. Conversely, PD-1+/Treg exhibited a positive correlation with MCI progression in those without insomnia. Additionally, CD8 showed a negative correlation with MCI progression.

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Conflicts of Interest

There was no conflict of interest.

Author Contributions

LHQ and CYJ wrote the manuscript. WLL and LYX and YS and YJ conducted the assessment of cognitive impairment. WYJ and LMY perform data collection, QXT perform the statistics. SHH supervised the whole experiment. YJ conceived and designed the research and performed all the experiment and reviewed the manuscript. All authors reviewed the manuscript.

Data Availability Statement

Data is provided within the manuscript or supplementary information files.

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