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Immune profile of a patient with Parkinson's disease and autoimmune disease: A case report

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Abstract

While several studies have been conducted on the immune cell populations in systemic lupus erythematosus (SLE) and Parkinson's disease (PD) patients, very few works have focused on the relationship between both diseases. Being a purely autoimmune disease, SLE is known to exhibit high levels of proinflammatory cells. On the other hand, neuroinflammation is a key contributor to the death of dopaminergic neurons in PD. Herein, we report the case of a patient suffering from both SLE and PD, comparing it with a patient suffering from PD only. Our results are informative, showing decreased levels of regulatory populations like CD8+regs and functional Bregs in the SLE/PD patient. In contrast, the levels of tolerogenic dendritic cells were up to 10 times higher in this patient. Additionally, the levels of Tr1, Th3, and functional CD8 cells, as well as those of M2-like monocytes, were higher in the SLE/PD patient. Regarding the inflammatory response, increased levels of total CD8+ T cells and CD40-expressing DCs were observed. In conclusion, significant changes in the levels of immune cell populations were observed in a patient suffering from SLE and PD, suggesting that the immune response could impact the pathophysiology of PD.

Abbreviations: SLE: Systemic lupus erythematosus; PD: Parkinson's disease; DA: Dopamine; PBMCs: Peripheral blood mononuclear cells; RSBD: REM sleep behavior disorder; OSAS: Obstructive sleep apnea syndrome.

Introduction

Systemic lupus erythematosus: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ chronic inflammation [1,2] immune complex deposition [3], and the production of autoantibodies against nucleic acids and binding proteins, reflecting a loss of self-tolerance [4]. The clinical picture of SLE includes skin and joints symptoms; cardiovascular events; damage to kidneys, the nervous and hematopoietic systems; and treatment-derived infections [3].

Immune response in systemic lupus erythematosus: SLE is characterized by an aberrant immune response [3,5,6] In a study, SLE patients showed decreased levels of myeloid dendritic cells (mDCs, BDCA-1+CD11c+lin−) and increased numbers of plasmacytoid DCs (pDCs, BDCA-2+CD123+lin−) [7]; however, a decrease in the number of pDCs was reported in another study [8]. Dysfunctional antigen presentation by DCs could hamper T and B cell tolerance in SLE [5]. Other alterations in the activation and secretory functions of circulating and tissue-infiltrating macrophages have been reported [9], such as a defective phagocytosis and/or an increased expression of CD86 (monocyte derived-macrophage type 1, or M1 marker) and a decreased expression of CD163 (M2 marker) [10].

Lymphocyte function has also been reported as defective. A failure of T cells to produce IL-2 and a polarization toward Th17 from regulatory T (Treg) have been observed. An increase in the levels of CD4−CD8− double-negative T cells and of autoreactive B cells, as well as an overall B lymphopenia, was reported. Additionally, Treg (CD4+CD25+FOXP3+) cells have been found deficient or defective in SLE patients [11]. On the other hand, increased levels of T follicular helper (Tfh) cells are correlated with an increased frequency of flare-ups and with decreased Treg levels and/or function in SLE patients [12,13]. Another study indicated that IL-2- and IFN-γ-producing CD4+ Th1 cells are required for antibody production by autoreactive B cells [14]. Increased numbers of Th17 cells and levels of IL-17 have been found in SLE patients [15,16]. Finally, aberrant signaling pathways have been found in T cells from SLE patients, which affect their function and differentiation [17].

Parkinson's disease: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, after Alzheimer's disease [18]. The clinical diagnosis of PD relies on the criteria issued by the PD Brain Bank in the United Kingdom [18]. Patient performance and follow-up are evaluated with the MDS-UPDRS scale [18,19], while PD staging is based on the Hoehn and Yahr scale [20]. PD characteristic symptoms like bradykinesia, rest tremor, and rigidity are the result of a progressive degeneration of dopamine (DA)-producing neurons in the substantia nigra pars compacta (SNpc) and the resulting loss of DA signaling to the corpus stratium [21].

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Immune response in Parkinson's disease: The pathophysiological hallmark of PD is neuroinflammation, evinced by gliosis and T cell infiltration. Several studies have suggested that, in response to aggregations of α-synuclein, CD4+/CD25− effector T cells promote the activation of microglia and its neurotoxic effects, and that CD4+CD25+FOXP3+ Treg cells inhibit such process, as well as neuronal apoptosis [22-25].

Various works have reported alterations in circulating lymphocytes from PD patients [26], including decreased levels of helper T cells (Th cells, CD3+CD4+) [27-29] and changes in the CD4+:CD8+ ratio, with a reduction in the number of CD4+ cells [27,30,31]. An abnormal distribution of CD4+ Th cells has also been reported, with increased levels of memory effector cells (CD4+CD45RO+) and naïve T cells (CD4+CD45RA+) [27,29,32,33]. In addition, the reduced numbers of CD4+ Th cells have been attributed to a decrease in the levels of Th2, Th17, and Treg cells, while a biased immune response in CD4+ Th1 cells has been reported, with an increased production of IFN-gamma and TNFα, suggesting that CD4 Th1 cells are involved in the pathophysiology of PD [34].

Material and methods

Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples from a PD patient with no comorbidities and a patient suffering from both SLE and PD, paired by age and sex. Then, the immune cell populations and subpopulations were characterized by flow cytometry as described by Álvarez-Luquin et al, [35]. The definition of each cell phenotype is described in the Supplementary Table 1.

Patient with Parkinson's disease and systemic lupus erythematosus: A 60 years-old female patient, with a familial history of PD through her mother and maternal grandmother, was diagnosed in 2012 with SLE and hypothyroidism, and with PD in 2001. The clinical picture started with rest tremor in her right hand, adding right-half bradykinesia in 2004, and rigidity of the upper right limb in 2006. The patient suffered from biphasic dyskinesias since 2011, as well as insomnia, symptoms of REM sleep behavior disorder (RSBD), nocturia, and impulse control disorder, with depression and apathy added later. On physical examination, the patient showed akinetic-rigid syndrome, hypophonia, hyposmia, and masked facies. A polysomnographic analysis showed a moderate obstructive sleep apnea syndrome (OSAS) and RSBD. The UPDRS score was 48, the UPDRS III score was 22 in off; Hoen and Yahr stage was 4; Schwab & England scale score was 40%; and MOCA score was 18. A levodopa test was conducted in 2018, with a good response of 57%. Currently, the patient is under treatment with levothyroxine (150 mcg in the morning) for hypothyroidism; hydroxychloroquine (150 mg in the morning and the afternoon) for SLE; amantadine (150 mg in the morning and afternoon), levodopa/carbidopa/entacapone (150/37.5/200 mg every 4 hours), rasagiline (1 mg in the morning), and rotigotine (12 mg/day) for PD; quetiapine (150 mg in the evening) for neuropsychiatric symptoms; and continuous positive airway pressure (CPAP) for OSAS.

Patient with parkinson's disease: A 57 years-old female patient, with a familial history of PD through her father and paternal grandfather. No other relevant familial factors are reported. The clinical picture started in 2010 with a tremor disorder in the lower left limb. In 2015, the patient was diagnosed with PD by applying clinical questionnaires and a positive levodopa test. Recently, the patient showed sialorrhea, insomnia, and depression symptoms. Currently, she shows a clinical akinetic syndrome with bradykinesia and rigidity. The UPDRS score was 93, the UPDRS III score was 72 in off; Hoen and Yahr stage was 4; Schwab & England scale score was 40%; and she scored 33 points in a Beck questionnaire, a result suggestive of a severe depression. The patient is being administered with levodopa/carbidopa (250/25 mg, 4 times a day), pramipexol (3 mg, 3 times a day), and amantadine (100 mg, 4 times a day); no treatment for any other pathology is being given.

Results

The analysis of cell phenotypes showed that the levels of total CD8+ T lymphocytes were 2 times higher in the PD/SLE patient than in the PD patient. With respect to regulatory populations, the percentages of non-Tregs and resting Tregs were 2 times lower in the PD/SLE patient compared to the PD patient. In contrast, the percentages of Tr1 and Th3 cells were about 2 times higher in the PD/SLE patient. On the other hand, the levels of CD8+ reg cells were approximately 7 times lower in the PD/SLE patient that in the PD patient, while those of regulatory functional CD8 were more than 10 times higher in the PD/SLE patient. With regard to B cell subpopulations, the levels of functional Breg cells were about 2 times lower in the PD/SLE patient than in the PD patient. The levels of regulatory dendritic cells (B.7H1+ DCs, SLAM F1+ DCs, and CD205+ DCs) were 2-10 times higher in the PD/SLE patient than in the PD patient (Table 1).

Regarding monocyte subpopulations, the levels of non-classical HLA-DR+ monocytes were 8 times lower in the PD/SLE patient than in the PD patient, while the levels of IL-10+ non-classical monocytes were 4 times higher in the PD/SLE patient than in the PD patient. The levels of total and IL-10-producing intermediate monocytes were 2-5 times higher in the PD/SLE patient than in the PD patient. The levels of total and HLA-DR+ classical monocytes were 5 times lower in the PD/SLE patient than in the PD patient, while those of IL-12+ classical monocytes were 20 times lower. On the contrary, the levels of M2-like monocytes were 20-fold higher in the PD/SLE patient compared to the PD patient (Table 1).

With respect to the proinflammatory subpopulations of dendritic cells, the levels of CD40+ dendritic cells were about 3 times higher in the PD/SLE patient than in the PD patient. The levels of TNFα-producing Th1 cells were 3 times lower in the PD/SLE patient with respect to the PD patient. For Th2 cells, the levels of IL-4-producing Th2 cells were 2 times lower in the SLE patient than in the PD patient. Finally, the levels of IL-17-producing Th-17 cells were 3 times lower in the SLE patient than in the PD patient (Table 1).

Discussion

The pathogeny of PD and SLE could share an autoimmune base. Very few studies on the possible relation between these pathologies have been conducted. PD has been proposed to be an autoimmune spectrum disorder, since the migration of B cells to the central nervous system has been observed to cause activation and proliferation of Th17 cells, accelerating the ongoing degeneration. Additionally, the presence of anti-α-synuclein, anti-tau, and anti-β amyloid antibodies has been detected in PD patients [36,37]. The high levels of proinflammatory cell populations are a hallmark of autoimmune diseases [38]. In PD, the immune response by itself is a chronic process that plays a role in neurodegeneration; by adding a highly inflammatory environment like SLE, the progression of PD will be faster.

The levels of regulatory cell populations herein analyzed are decreased in the PD/SLE patient, except for Tr1, Th3, and tolerogenic dendritic cells; while the differences were not significant, they could have some effect on inflammatory cell populations. Similarly, since

Table 1. Percentages of immune cells subpopulation in a PD/SLE patient compared to a PD patient. DCs: Dendritic cells

	PD/SLE patient	PD patient
Population markers (% of cells)		
T CD4+ lymphocytes	43.435	32.540
T CD8+ lymphocytes	21.414	10.599
B CD19+ lymphocytes	10.649	13.089
CD14+ monocytes	10.663	13.942
CD11c+ dendritic cells (DCs)	28.963	29.099
Regulatory cells (% of cells)		
Regulatory T cells		
Suppressive regulatory T cells	1.789	1.806
Active Tregs	3.363	5.305
Non-Tregs	4.808	8.961
Resting Tregs	12.715	21.212
Tr1	1.341	0.682
Th3	2.326	0.987
Regulatory CD8+ cells		
Cytolytic CD8+	9.226	14.903
CD8+ regs	6.307	44.247
Functional CD8+	0.298	0.023
Regulatory B cells		
IL-10-producing plasma cells	18.851	11.268
Functional B regs	4.215	9.067
IL-10-producing functional B regs	3.706	2.470
Bregs cells	0.247	0.107
Regulatory dendritic cells		
B7.H1+ DCs	5.338	2.199
SLAM 1+ DCs	10.933	5.684
ILT3+ DCs	17.447	12.747
CD205+ DCs	10.808	0.959
Monocytes (% of cells)		
Non-classical monocytes	3.115	2.053
IL-12-producing non-classical monocytes	0.889	0.698
HLA-DR-producing non-classical monocytes	0.228	1.806
IL-10-producing non-classical monocytes	0.737	0.186
Intermediate monocytes	2.275	1.190
IL-12-producing intermediate monocytes	0.913	0.653
HLA-DR-producing intermediate monocytes	0.559	1.184
IL-10-producing intermediate monocytes	1.096	0.241
Classical monocytes	0.378	2.057
IL-12-producing classical monocytes	0.009	0.191
HLA-DR-producing classical monocytes	0.353	2.047
IL-10-producing classical monocytes	0.08	0.114
M1-like monocytes	0.09	0.010
M2-like monocytes	0.179	0
Proinflammatory cells (% of cells)		
Proinflammatory dendritic cells		
HLA-DR+ DCs	28.135	26.804
CD40+ DCs	5.413	1.661
CD86+ DCs	33.55	20.044
CD80+ DCs	8.457	5.693
Proinflammatory T CD4+ cells		
IFNγ-producing Th1 cells	0.392	0.328
TNFα-producing Th1 cells	0.651	1.882
IL-13-producing Th2 cells	0.682	0.961
IL-4-producing Th2 cells	0.374	0.743
IL-17-producing Th17 cells	0.124	0.406

SLE is an autoimmune disorder mediated by autoantibodies, the observed decrease in the levels of functional Breg cells is interesting, considering that functional Bregs have been described to suppress the proliferation of other immune cells by secreting immunosuppressive cytokines like IL-10 and IL-35 [39,40]. However, our results do not show a significantly higher inflammation in the SLE/PD patient with respect to the PD patient [41,42]. Only the levels of CD40-expressing DCs were increased, because CD40 is involved in B cell activation; this finding could be linked to the pathophysiology of PD. It is noteworthy that the PD/SLE patient was under treatment with immunosuppressive drugs (hydroxychloroquine); this could explain the increased levels of regulatory cells (Tr1, Th3, and functional CD8 cells, as well as M2-like monocytes) in the PD/SLE patient [43,44].

Additionally, this drug interferes with autoantibody presentation, block antigen-induced response in T lymphocytes, decrease the production of inflammatory mediators, and inhibit the activation of Toll-like receptors [45].

The PD/SLE patient showed a chronic inflammatory response, common, but lower than a typical PD patient. This could be influenced by the base treatment. The coexistence of PD and SLE could accelerate the future progression of PD because the rate of dopaminergic neurodegeneration could be increased by the continued migration and signaling of proinflammatory cells [38].

Conclusion

The coexistence of PD and SLE in a patient led to an immune profile characterized by altered levels of some immunoregulatory and proinflammatory cell phenotypes, along with increased levels of CD40-expressing DCs. Since the latter factor is linked to auto-antibody production and inflammation, thus favoring he clinical deterioration in PD patients, the comorbidity with SLE could have impacted the progression of PD in this patient.

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Conflicts of interest

The authors report no conflict of interest.

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