Journal of Systems and Integrative Neuroscience

Research Article ISSN: 2059-9781

Peripheral immunity in Parkinson's disease associated to chronic infections: A report of two cases

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Abstract

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder worldwide. PD is characterized by loss of dopaminergic neurons where neuroinflammation plays an important role. Moreover, there has been found changes in peripheral immune response that may contribute to its pathogenesis. Patients with PD aren't exempt to have concomitant diseases, such as chronic infections that may modify their immune response and contribute to the development of the disease.

In this study we present two cases of PD patients, one with concomitant syphilis and the other with chronic hepatitis virus C (CHVC) infection. We determinate their peripheral immune phenotypes by flow cytometry and plasma cytokines concentrations by ELISA.

In both patients, T CD4+ cells showed higher percentages than CD8+ T cells, total B cells, CD8+ lymphocytes, classical Tregs and active Tregs were higher in the CHCV infected patient as well as the levels of IFNγ and IL-10 compared to the syphilitic patient. On the other hand, the syphilitic patient showed a higher level of Th2 response than the CHCV infected patient.

The peripheral immune response in both patients is mostly due to the chronic infections, but the results suggest that PD could contribute to the progression of these diseases and promote worse outcome for the patients, specially the one with concomitant syphilis.

Introduction

Parkinson's disease

Parkinson's disease (PD) is the second most frequent progressive neurodegenerative disorder after Alzheimer's disease. In México, PD has an incidence of 40 to 50 per 100,000 people/year [1]. The cardinal manifestations of PD are bradykinesia, rigidity and resting tremor, but the clinical complex includes non-motor symptoms such as hyposmia, constipation, rapid eye movement sleep disorder and depression. These can be present in the initial phases of the disease [2]. The diagnosis of PD is clinical, and its progression can be established by two scales: MDS-UPDRS and Hoehn & Yahr [3].

In the pathogenesis of PD, it has been well stablished that immune system plays an important role in the disease progression and loss of dopaminergic neurons [4]. However, it has also been described that there are changes in peripheral immune cells, but its influence on the genesis or progression of the disease is not well understood yet.

Authors have demonstrated alterations in frequencies of T cells populations, indicating an activated adaptative immunity in PD. For instance, there's evidence of a reduced CD4+: CD8+ T cell ratios. Also, a decrease of CD4+ CD45RA+ "naive" T cells, and an increase of CD4+CD45RO+ "memory" T cells in peripheral blood. There´s a clear shift towards the Th1 type immune response [5]. Concerning Treg population, there´s contradictory evidence, some studies found reduce frequencies of these cells in PD patients compare with controls [6], while others sustained that there is no significant difference between patients and controls around these phenotypes [7]. Finally, a reduction of B lymphocytes as well as an increase in natural killer (NK) cells was described in PD patients [8-10].

Patients with PD are not excluded to present concomitant diseases, such as chronic infections, and it's quite probable that the presence of both pathologies can alter their immune response and clinical course. Therefore, the analysis of peripheral immune response in patients becomes important, so treatments can be modified if necessary.

Syphilis

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum* that is clinically characterized by three stages of the disease: an early phase where the skin lesion named chancre is found at the site of inoculation and can heal spontaneously after six weeks without treatment [11-15]. Secondary syphilis appears a few months later as a systemic illness characterized by fever, headache, anorexia and a diffuse

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Key words: *Parkinson's disease, syphilis, hepatitis C infection*

Received: November 18, 2019; **Accepted:** December 03, 2019; **Published:** December 06, 2019

macular rash [16]. Late syphilis develops approximately 30 years after primary infection like cardiovascular syphilis, gummatous syphilis and neurosyphilis [17]. The diagnosis of syphilis is most commonly made by serologic testing in symptomatic patients and high-risk population (HIV patients) [18]. Into the nontreponemal test, the most used in our country is Venereal Disease Research Laboratory (VDRL). In general, it reflects only the activity of the infection. The treponemal test include the Fluorescent treponemal antibody absorption (FTA-ABS), microhemagglutination test for antibodies to *T. pallidum* (MHA-TP), *T. pallidum* particle agglutination assay (TPPA), *T. pallidum* enzyme immunoassay (TP-EIA) and chemiluminescence immunoassay (CIA). All of these are usually used for confirmation of a nontreponemal test [19]. Parenterally-delivered Benzathine penicillin G is the treatment of choice for all stages of syphilis (2.4 million units intramuscularly [IM]) up to 30 days [20].

The role of immune system in syphilis is quite complex. In early syphilis, lipoproteins from *T. pallidum* are recognized by TLR2 on antigen presenter cells which interact with naïve T cells in the primary lesion and in peripheral blood (PB). There is an important role of monocytes in this stage of disease, and those are better found on the chancre and few percentages in PB. Also, there is predominance of CD4+ T cells over CD8+ T lymphocytes. On the contraire, this ratio is inversed in secondary syphilis, and cytokines like IFNγ, IL-12 and IL-2 had been found [21]. Also, monocytes are polarized to an M1 phenotype and express higher levels of IL-1β and TNFα [22]. In late syphilis, particularly neurosyphilis, the number of CD3+CD8+ lymphocytes are higher; meanwhile, CD3+CD4+ T cells and B lymphocytes presented no difference between patients and controls [23].

Chronic Hepatitis C virus infection

This infection is usually slowly progressive and may not result in clinically apparent liver disease in many patients. Approximately 5 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period. Patients usually present generalized symptoms such as fatigue, abdominal pain, myalgia, arthralgia, weakness and weight loss [24]. The diagnosis is made by serologic assays that detect antibodies to hepatitis C and quantification of HCV RNA that is the confirmatory test [25,26]. Antiviral therapy is the cornerstone of treatment of chronic hepatitis C virus (HCV) infection. The standard care of treatment for CHCV has until recently been pegylated IFN-γ and ribavirin. Nowadays, direct-acting antiviral (DAA)-based regimens result in dramatically higher sustained virologic response and less adverse effects [26].

The immune response against HCV infection starts with NK cells, that have been suggested to be responsible for clearance of HCV since they are source of IFNγ. Among the contributors, HCV-specific CD8+ T cells inhibit viral replication by secretion of IFNγ and cytolytic effector functions. However, sometimes, HCV-specific CD8+ T cells fail to clear the virus, resulting in chronic HCV (CHCV) infection. Also, their cytokine production (IL-2, IFNγ and TNFα) is reduced in peripheral blood as well as intrahepatically [27-29]. On the other hand, CHCV infection has been associated with increased Treg proportion and function, suggestive to contribute to failure of spontaneous clearing of HCV [30-32]. Also, the anti-inflammatory cytokines IL-10 and TGFβ have increased levels in CHCV infection. It has been suggested that TGFβ contribute to development of liver fibrosis and subsequently cirrhosis [33].

So far, we have shown the characteristics of peripheral immune response in PD, syphilis and CHCV infection. Our group of study detected a couple of patients with diagnosis of PD who also presented these chronic infections. Therefore, the aim of this study was to determinate if the peripheral immune profile changed in patients with PD and concomitant chronic infections such as syphilis and CHCV infection.

Case report: Parkinson's disease and syphilis

A 66-year-old male, who have personal history of systemic arterial hypertension and dyslipidemia started ten years ago, with constipation. Three years later, with hyposmia. He also has history of 10 episodes of non-specified ulcer in penis, treated just once with three doses of penicillin. His current condition started 2 years ago with slowness of movement and depression; 6 months ago, resting tremor in right hand was added and later, on right leg with abnormal gait. He was diagnosed with idiopathic Parkinson's disease, with a rate in Hoehn and Yahr scale of 2 and 17 points in UPDRS total scale. He started treatment with pramipexole 3 mg/day. Because of his history of an ulcer in penis, he was tested for VDRL that was found positive (hemogram, blood chemistry, hormone, viral and inflammatory profiles are shown in Supplementary Table 1). Confirmatory tests were made and found antibody anti-treponema by ELISA in 60.15 UI/mL and FTA for *Treponema pallidum* IgG reported as reactive. After these findings, the patient received treatment with Benzathine penicillin G 2.4 million of units IM daily for 7 days.

Case report: Parkinson's disease and Hepatitis C infection

A 65-year old woman, who didn't have relevant personal history; started her current condition three years ago, with slowness of movement and abnormal gait. Two years later, the patient presents resting tremor in the left hand and rigidity on both legs. At the time, she also has hypomimia, resting tremor on the left side of her face and gait without bracing. She was diagnosed with idiopathic Parkinson's disease, with a rate in Hoehn and Yahr scale of 2, and 52 points in UPDRS total scale and started treatment with pramipexole 3 mg/daily and levodopa/carbidopa 250/25 mg/daily.

General tests were ordered and found reactive anti-HCV antibodies (hemogram, blood chemistry, hormone, viral and inflammatory profiles are shown in Supplementary table 1). Therefore, confirmatory test was made; quantification of HCV RNA that reported 963735 UI/mL. Unfortunately, the patient couldn't afford the treatment for hepatitis C viral infection, so she´s only under surveillance and continues her treatment for Parkinson's Disease.

Materials and methods

We isolated peripheral blood mononuclear cells (PBMC) from both patients' hole blood samples by density gradient and characterized by flow cytometry their cell populations and subpopulations as described by Álvarez-Luquin, 2019 [34]. The definition of each phenotype is described in Supplementary Table 2.

We also measured the concentration of inflammatory cytokines (TNFα, INFγ, IL-12p70, IL-13, IL-4, IL-1β, IL-6 and IL-17) and anti-inflammatory cytokines (IL-10, TGFβand IL-35) in patients' plasma, also described by Álvarez-Luquin, 2019 [34].

Results

The analysis of cell subpopulations phenotypes showed among the proinflammatory profile, that total CD4+ lymphocytes were 64% higher in the CHCV infected patient than the syphilitic patient. The CD4+:CD8+ ratio of the syphilitic patient was 4.8. The CD4+:CD8+

ratio of the CHCV infected patient was 3.8. The percentages of CD8+ lymphocytes, B lymphocytes and plasmatic cells were around 2-fold higher in the CHCV infected patient than in the syphilitic patient. The syphilitic patient presented around two- or three-times higher levels of cytolytic CD8+ T lymphocytes, CD14+ monocytes, classical monocytes, effector dendritic cells (HLA-DR+DCs, CD40+DCs and CD86+DCs) and Th2 CD4+ T lymphocytes compared to the CHCV infected patient (Table 1).

As for the anti-inflammatory profile, the levels of regulatory T cells and active Tregs cells were almost twice higher on the CHCV infected patient than in the syphilitic patient (Table 1).

Regarding the plasma cytokine analysis, IFNγconcentrations were around 8-fold higher in the CHCV infected patient than in the syphilitic patient. On the other hand, IL-13 concentrations were almost twice higher in the syphilitic patient than in the CHCV infected patient, IL-17 was 9-fold higher in the CHCV infected patient than in the syphilitic patient. Finally, concentrations of IL-10 were around 20% higher in the CHCV patient than in the syphilitic patient (Table 2).

Discussion

The phenotype and cytokine analysis of both cases showed interesting differences in the percentage of several subpopulations of cells. According with the reviewed literature, in PD and CHCV infection, there are reduced levels of CD4+ compared to CD8+ T cells [7,27], however, in early syphilis there are more total T CD4+ lymphocytes than T CD8+ [21]. In this study, the syphilitic patient presented increased CD4+:CD8+ ratio, which suggest that the peripheral immune response in this patient is probably associated with the infection. From the T CD4+ cells, higher levels of regulatory T cells and active regulatory T cells were found on the CHCV patient compared with the syphilitic patient, as well as levels of IL-10 and TGFβ on plasma. This could be explained by the theory that propose that Tregs contribute to the chronicity of HCV infection [30-33]. Apparently, there is no change in T regs frequencies due to PD in these patients, because these would tend to diminish in the disease [6]. On the other hand, the higher level of IFNγ in plasma on CHCV patient may indicate an attempt to clear HCV from the patient, and the level of the cytokine may be exacerbated for the Th1 response seen peripherally in PD patients [10,29].

Interestingly, both Th2 analyzed phenotypes and plasmatic IL-13 were found higher in the syphilitic patient; this could be explained by Fitzgerald's theory, proposed in 1992 [35], where he said that when syphilis infection progress, there is a shift from a Th1 response to a Th2 predominance, due to decrement of monocytes action in the site of inoculation. The findings in this study suggest that the syphilitic patient could be starting to develop progression of the infection, so he must be followed to determinate symptoms of secondary syphilis and be able to have the right treatment.

It has been described [36] that in CHCV infection, there are increased frequencies of immature transitional and mature activated B cell subsets. Immature transitional B cells may serve as a precursor for plasma cells involved in innate antibody production. Therefore, the finding of increased plasmatic cells in the CHCV infected patient could be explained by this phenomenon and could be related with the antibody production against HCV reflected on the laboratory finding.

The finding of higher total CD14+ monocytes in the syphilitic patient compared to the CHCV infected patient is expected due to the main response that these cells promote during the early stages of

Table 1. Percentages of immune cells subpopulation in syphilitic patient vs CHCV infected patient

	PD + syphilis patient	***PD + CHCV patient***
Population markers (% of cells)		
T CD4+ Lymphocytes	27.997	43.315
T CD8+ Lymphocytes	5.849	11.678
B CD19+ Lymphocytes	11.811	27.713
CD14+ Monocytes	38.062	17.430
CD11c+ Dendritic cells (DCs)	83.626	39.421
Regulatory cells (% of cells)		
Regulatory T cells		
Regulatory T cells	1.001	1.811
Active T regs	1.001	2.283
No T regs	4.720	3.943
Resting T regs	3.116	3.743
Tr1	0.291	0.781
Th3	1.659	2.545
Regulatory CD8+ cells		
Cytolitic CD8+	20.958	9.506
CD8+ regs	12.122	10.314
Functionals CD8+	0.089	0.434
Regulatory B cells		
Plasmatic cells	22.478	41.573
IL-10-producer plasmatic cells	1.141	2.056
Functional B regs	3.693	7.210
IL-10-producer functional B regs	0.215	0.363
B regs cells	1.757	2.114
Regulatory Dendritic Cells		
B7.H1+DCs	5.446	16.916
SLAM 1+ DCs	18.173	8.997
ILT3+ DCs	74.967	32.111
CD205+ DCs	16.108	28.708
Monocytes (% of cells)		
Non-classical monocytes	2.217	1.006
IL-12-producer Non-classical monocytes	1.105	0.165
HLA-DR-expressing Non-classical monocytes	0.570	0.359
IL-10-producer Non-classical monocytes	2.122	0.480
Intermediate monocytes	3.384	1.256
IL-12-producer Intermediate monocytes	0.946	0.435
HLA-DR-expressing Intermediate monocytes	3.265	1.230
IL-10-producer Intermediate monocytes	2.828	1.287
Classical monocytes	6.601	3.662
IL-12-producer Classical monocytes	0.162	0.159
HLA-DR-expressing Classical monocytes	6.513	3.614
IL-10-producer Classical monocytes	2.806	1.522
M1-like monocytes	0.001	0.010
M2-like monocytes	0.122	0.041
Proinflammatory cells		
Proinflammatory Dendritic cells		
HLA-DR+ DCs	81.140	33.204
CD40+ DCs	6.8	3.288
CD86+ DCs	77.328	32.785
CD80+ DCs	15.619	20.991
Proinflammatory T CD4+ cells		
IFNγ-producer Th1 cells	2.588	2.385
IL-13-producer Th2 cells	31.168	1.753
IL-4-producer Th2 cells	14.504	2.217
IL-17-producer Th17 cells	1.616	0.322

Table 2. Concentration of plasmatic cytokines in syphilitic patient vs CHCV infected patient

	PD + syphilis patient	***PD + CHCV patient***
Proinflammatory cytokines [pg/mL]		
Th1 cytokines		
TNFα	9.836	5.738
IFNγ	3.571	27.857
IL-12p70	0	0
Th2 cytokines		
IL-13	16.424	9.475
IL-4	0	1.556
IL-1β	0	0
Th17 cytokines		
IL-17	409.4	3730.4
IL-6	0	6.960
Regulatory cytokines [pg/mL]		
TGFβ	4190.385	4500.641
IL-10	1.554	8.674
IL-35	0	0

infection [21]. We also found an increased in classical monocytes in this patient. It has been described in an animal model of Parkinson's disease an augment of classical monocytes that is corresponding with our findings; however, is has been suggested that these cells are lack of phagocytosis function [37], so in further studies, this should be analyzed to determine if the non-functional monocytes could be a factor that promotes progression of the chronicity of infection.

It has been demonstrated the activation of dendritic cells in an animal model of syphilis, concluding that these are the first cells that are in contact with the bacteria and their activation conduce to its phagocytosis [38]. That's why we were not surprised to find extraordinarily high levels of total an effector dendritic cells in the syphilitic patient.

In this study we found that the peripheral immune response in both PD patients is mostly due to their concomitant chronic infection; however, as we had shown, the influence of Parkinson's disease could be deleterious for the clearance of chronic infections, specially, in the syphilitic patient. Therefore, in this kind of patients, which are not rare to find in Mexican population, the treatment for syphilis should be complete and the follow-up must be carefully taken to prevent progression of the chronic infection. On the other hand, the peripheral immune response of the CHVC infected patient doesn't seem to be influenced by the concomitant PD because the observations discussed earlier coincide with the normal response described in the literature [27-31].

Conclusion

This study suggests an augmented risk of progression of concomitant chronic infections such as syphilis in Parkinson's disease patients due to the increased proinflammatory profile and the decrease of Tregs subpopulations that was demonstrated. The decreased Tregs subpopulations could be deleterious for the maintenance of the immunologic homeostasis in both pathologies so the patients could have worse outcomes that could be prevented with the right treatment and follow-up.

Acknowledgments

The authors thank the LABNALCIT-UNAM (CONACYT) for technical support, especially to Carlos Castañeda Barba. The authors also thank the Programa de Maestría y Posgrado en Ciencias Médicas, Odontológicas y de la Salud, Universidad Nacional Autónoma de México. Thanks to CONACYT SALUD [grant No. 2015-1-261455].

Conflicts of interest

The authors report no conflict of interest.

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