Abnormal B-Cell and Tfh-Cell Profiles in Patients With Parkinson Disease

A Cross-sectional Study

Rui Li, MD, PhD, Thomas Francis Tropea, DO, Laura Rosa Baratta, BSc, Leah Zuroff, MD, MS, Maria E. Diaz-Ortiz, BSc, Bo Zhang, MD, PhD, Koji Shinoda, MD, PhD, Ayman Rezk, PhD, Roy N. Alcalay, MD, MS, Alice Chen-Plotkin, MD, and Amit Bar-Or, MD

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Abstract

Background and Objectives
There has been growing interest in potential roles of the immune system in the pathogenesis of Parkinson disease (PD). The aim of the current study was to comprehensively characterize phenotypic and functional profiles of circulating immune cells in patients with PD vs controls.

Methods
Peripheral blood was collected from patients with PD and age- and sex-matched neurologically normal controls (NCs) in 2 independent cohorts (discovery and validation). Comprehensive multicolor flow cytometry was performed on whole blood leukocytes and peripheral blood mononuclear cells to characterize different immune subsets and their ex vivo responses.

Results
The discovery cohort included 17 NCs and 12 participants with PD, and the validation cohort included 18 NCs and 18 participants with PD. Among major immune cell types, B cells appeared to be preferentially affected in PD. Proliferating B cell counts were decreased in patients with PD compared with controls. Proportions of B-cell subsets with regulatory capacity such as transitional B cells were preferentially reduced in the patients with PD, whereas proportions of proinflammatory cytokine-producing B cells increased, resulting in a proinflammatory shift of their B-cell functional cytokine responses. Unsupervised principal component analysis revealed increased expression of TNFα and GM-CSF by both B cells and T cells of patients with PD. In addition, levels of follicular T cells, an important B-cell helper T-cell population, decreased in the patients with PD, correlating with their B-cell abnormality.

Discussion
Our findings define a novel signature of peripheral immune cells and implicate aberrant Tfh:B-cell interactions in patients with PD.
Glossary

AUC = area under the curve; CU = Columbia University; GWASs = Genome-wide association studies; IgG = immunoglobulin; IRBs = Institutional Review Boards; LEDD = l-dopa equivalent daily dose; MHC = major histocompatibility complex; NCs = normal controls; PBMCs = peripheral blood mononuclear cells; PC1 = principal component 1; PCA = principal component analysis; PD = Parkinson disease; SN = substantia nigra; SOPs = standard operating procedures; Th = T-helper; UPA = University of Pennsylvania.

Parkinson disease (PD) is a neurodegenerative disease that affects more than 6 million people globally. The etiology of PD, which is characterized by a progressive loss of dopaminergic neurons, remains elusive. Emerging evidence suggests that immune system responses may be involved in PD pathogenesis. Genome-wide association studies (GWASs) relate haplotypes of the major histocompatibility complex (MHC) class II genes and other immune-related genes (e.g., TLR9, IL-1R2, SATB1, STAB1, GBA, CD38, CD19, NOD2, and FYN) to risk of developing the disease. Deposition of immunoglobulin (IgG) and infiltration of CD4+ T cells have been reported in the brains of both mouse models of PD and in patients with PD, implicating both humoral and cellular immune responses.

Studies of circulating immune cells in patients with PD have largely focused on T cells and have described a-synuclein–specific autoreactive T cells and increased levels of CD4+ T-helper (Th)17 cells (implicated as proinflammatory in other conditions) that are capable of mediating neuronal cell death in vitro. Although helper T cells are important orchestrators of many immune responses in both health and disease, their functions are commonly shaped by interactions with other immune cell types such as myeloid cells and B cells. Indeed, abnormal profiles and functional responses of such non–T cells are increasingly implicated across a growing range of complex human conditions traditionally thought to be principally mediated by T cells, and therapeutic targeting of the non–T cells has been shown to reverse abnormalities in these diseases. Little is known, however, about potential interactions between T cells and non–T cells in patients with PD. Efforts to link across cell types require simultaneous analysis of phenotypic and functional profiles of both T-cell and non–T-cell populations.

Here, we developed and applied a multiparametric flow cytometry platform to comprehensively assess both phenotypic and functional profiles of multiple (T cell and non–T cell) immune cell types in 2 independent (discovery and validation) cohorts of patients with PD and neurologically normal controls.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents
All subjects enrolled in this study provided informed consent as part of protocols approved by the University of Pennsylvania (UPA) and Columbia University (CU) Institutional Review Boards (IRBs) and in compliance with the Declaration of Helsinki principles.

Subjects and Study Design
Two independent cohorts of both patients with Parkinson disease (PD) and normal controls (NCs) from the 2 institutions enabled discovery and validation of findings. eTable 1 provides an overview of the cohorts. eTable 2 provides basic and clinical demographics for each patient. U Penn Discovery Cohort blood samples (NC, n = 17; PD, n = 12) were collected between October and December 2017, and the Validation Cohort samples (NC, n = 18; PD, n = 18) were collected between July and September 2018. All individuals with PD met the diagnostic criteria of the United Kingdom Parkinson’s Disease Brain Bank as previously described for these clinical cohorts. All normal controls had no known neurologic disorder. None of the participants had any suggestion of acute or chronic infection or on any immune-modifying therapy.

Sample Processing and Cell Culture
Antecubital venous blood was obtained contemporaneously from neurologically normal controls and participants with PD and used for fresh whole blood analysis and subsequent analysis of peripheral blood mononuclear cells (PBMCs) that were isolated by Ficoll density centrifugation (GE Healthcare) and then cryopreserved. All samples were processed at the University of Pennsylvania, with samples from the Columbia University samples (both NC and PD) overnight shipped to the University of Pennsylvania for next-day analysis and processing, using Credo Box shippers (Pelican Bio- Thermal) that ensure temperature stability during transport. All steps of sample handling, shipping, processing and storage, and whole blood staining and PBMC assays were performed using the identical standard operating procedures (SOPs).

Although the fresh whole blood analysis enables assessment of immune cell types that are less amenable to freeze and thaw, the cryopreserved PBMCs were thawed and cultured in batch, with samples selected to ensure age and sex balance between patients with PD and NCs, serving to both limit interassay variability and minimize batch effects.

Flow Cytometry
Multiple multiparametric flow cytometry antibody panels were developed to comprehensively characterize phenotypic and functional immune profiles of human peripheral immune cell subsets previously identified as proinflammatory or regulatory in the context of CNS-directed and other immune-
mediated conditions, as we have previously reported.20–24 eTable 3 lists the antibodies used for characterizing the phenotypes and functional response profiles of immune cells in both fresh whole blood and in cryopreserved PBMCs. For whole blood immune cell staining, 2 mL of peripheral blood was lysed with equal volume of 1X RBC lysis buffer (BioLegend). For PBMC staining, thawed cells were stained with Aqua (Thermo Fisher) to exclude dead/dying cells during analysis. Cells were incubated with surface antibody cocktails for 30 minutes at room temperature. After 2 washes, samples were fixed with Cytofix/Cytoperm buffer (BD Biosciences) at 4°C and then resuspended in PBS before acquisition by flow cytometry. For transcriptional factor staining, surface staining was followed by fixing cells with TF fixation and permeabilization buffer for 45 minutes (Thermo Fisher) and resuspending in the TF washing buffer (Thermo Fisher) overnight before incubation with TF antibody cocktail for 1 hour on the next day. For staining of cytokines from different immune cells, cells were first treated with PMA (20 ng/mL, Sigma-Aldrich), ionomycin (500 ng/mL, Sigma-Aldrich) and GolgiStop (Monensin, BD Biosciences) (B cell and T cell), or LPS (100 ng/mL, Sigma-Aldrich) and GolgiStop for 4 hours. After live/dead staining and surface staining, cells were fixed/permeabilized with Cytofix/Cytoperm buffer (BD Biosciences) and then resuspended in ICS buffer overnight (BD Biosciences). Intracellular cytokine staining was performed the next day. All flow cytometry was performed by a single operator who was blinded to the sample source and followed the same standardized protocols for acquisition and analysis. Samples were acquired by an LSRFortessa flow cytometer (BD Biosciences) stringently maintained by the flow cytometry core facility at the University of Pennsylvania. The raw data were further analyzed by FlowJo software analysis (BD Biosciences).

Calculation of Absolute Cell Count for Each Immune Cell Subsets Using Cryopreserved PBMCs

To estimate absolute counts in the absence of formal clinical laboratory testing, we first used fresh whole blood aliquots from the same samples to measure lymphocyte (CD45high SSClow), monocyte (CD45int SSCint), and granulocyte (CD45low SSChigh) counts, calculated as percentage of each population multiplied by the total white blood cell count. We could then estimate the counts of immune cell subsets within the PBMCs based on their percentages within the PBMCs, multiplied by either the lymphocyte count (for lymphocyte subsets) or the monocyte count (for monocyte subsets).

Statistical Analysis

Nonparametric Mann-Whitney 2-tailed testing was used for statistical comparisons between 2 groups with adjustment for multiple comparisons using the Benjamini-Hochberg procedure controlling for a false discovery rate <0.05 for each of the discovery and validation cohorts, separately. Linear regression modeling was used to test the correlation between different immune cell subsets. GraphPad Prism 9 was used to perform all the statistical analyses including ROC (Wilson/Brown Method) and PCA analysis. Data are represented using individual dots for each participant. p Values of 0.05 or less were considered statistically significant.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

Immunophenotyping Major Immune Cell Subsets in Whole Blood of Patients With PD and Neurologically Normal Controls

To broadly characterize the major circulating immune cell types of patients with PD and neurologically NCs we established a 15-color flow cytometry panel to immune phenotype in fresh whole blood: neutrophils (CD15+ CD16+), eosinophils (Siglec-8+), basophils (CD123high), monocytes (CD14+), dendritic cells (Lin− HLA-DR+), NK cells (CD14−, CD16−), T cells (CD3+), and B cells (CD19+), with the antibody panel and gating strategy summarized in eTable 4 and eFigure 1, respectively. Analysis of the (UPA) discovery cohort (eTables 1 and 2) suggested that absolute B-cell counts were decreased in the blood of patients with PD compared with NCs (Figure 1A), with no apparent differences in other major cell types including granulocytes, myeloid cells, NK cells, and T cells. This observation was confirmed in an independent (Columbia University) validation cohort (eTable 1 and eTable 2, links.lww.com/NXI/A676; Figure 1B), pointing to an abnormal B-cell immune compartment in patients with PD.

Comprehensive Immunophenotyping Within the B-Cell Compartment Reveals a Preferential Decrease of Transitional B-Cell Populations

To analyze distinct subsets more comprehensively within the B-cell compartment in patients with PD, we next developed and applied 3 15-color multiparametric flow cytometry panels to cryopreserved PBMCs isolated from patients and controls. These panels captured both phenotypic and functional profiles of B-cell subsets (eTable 4; eFigure 2A, links.lww.com/NXI/A676), including quantification of activation and proliferation markers, molecules associated with antigen-presenting function, and known B-cell cytokines previously implicated in immune activation (e.g., TNFα, IL-6, and GM-CSF) and immune regulation (e.g., IL-10). Interpretation of the PBMC analyses and validity of comparisons across groups were optimized by applying strict standard operating procedures20 and routinely confirming high cell viabilities (eFigure 2B). We observed that among B-cell subsets (eFigure 3), immature transitional B cells (including T1, T2, and T3 transitional B cells) were disproportionally decreased in patients with PD (Figure 2, A–F), resulting in substantial decreases of the ratios of transitional/mature B cells (Figure 2E). Within mature B cells, the numbers of CD27− IgD− memory B cells (also known as double-negative memory B cells previously implicated in
Altered Functional Responses of B Cells in Patients With PD

We next assessed functional markers of B-cell activation (Figure 3A), proliferation (Figure 3, B and C), and expression of costimulatory molecules including CD80 and CD86 (Figure 3D), used by B cells to interact with and activate T cells as part of their antigen-presenting cell (APC) capacity. We observed decreases in proliferating (Ki-67+ B-cell counts in patients with PD compared with controls in both discovery and validation cohorts (Figure 3B). The degree of decrease in Ki-67+ B cell counts positively correlated with the degree of decrease in the total B-cell counts in all groups (Figure 3C).

Also decreased in the circulation of patients with PD were 2 B-cell subsets known for their efficient APC capacities, CD11c+ CD86+ B cells (referred to as age-associated B cells; Figure 3E), and CD43+ CD27+ B cells (referred to as B1 cells; Figure 3F). Because B cells can regulate local immune responses through expression of distinct cytokine combinations (and particularly the balance between proinflammatory and anti-inflammatory cytokines,15,28–37 we next used intracellular cytokine staining to examine cytokine expression profiles of B cells. We observed that patients with PD, in both the discovery and validation cohorts, harbored decreased counts but not frequencies of IL-10–producing (anti-inflammatory) B cells compared with NC (Figure 4A). Frequencies, but not the counts, of both GM-CSF and TNFα expressing (proinflammatory) B cells were increased in the patients with PD (Figure 4B), which was reflected in significant increases in the GM-CSF/IL-10 and TNFα/IL-10 cytokine expression ratios of the PD patient B cells (Figure 4, C and D).

Immune Profiling of Innate Immune Cells and T Cells Reveals a Reduction of Follicular T Cells in Patients With PD

Given the growing recognition of the importance of interactions between subsets of B cells, T cells, and innate cells, we next considered whether the B-cell abnormalities we observed

autoimmune and infectious disease25-27) were decreased in patients with PD (Figure 2G), whereas no appreciable abnormalities were noted for other B-cell subsets (Figure 2G).
in patients with PD (including diminished proliferation, decreased transitional B-cell counts, and the proinflammatory cytokine profile shift) could be understood on the basis of changes in potentially interacting non-B cells. To this end, we developed a series of multiparametric flow cytometry panels to capture the functional phenotypes of T cells and myeloid cells (eFigure 4, links.lww.com/NXI/A676). Similar to B cells, Ki-67+ (proliferating) CD4+ T cells counts were also reduced in patients (Figure 5A). We further found that the numbers of lymphoid-tissue homing central memory (TCM) CD4+ T cells (but not effector memory T-cell subsets) are decreased in the patients with PD (Figure 5B). In particular, levels of CD4+ follicular T cells (Tfh, CXCR5+ CD45RA−) and especially the ICOS+ PD-1+ Tfh subset known to interact with B cells to help them form and maintain germinal centers were significantly reduced in patients with PD compared with NCs (Figure 5, C and D). Absolute counts of the Tfh cells correlated with the Ki-67+ B-cell counts (Figures 5, E and F) consistent with the possibility that decreased numbers of Tfh cell and hence decreased Tfh:B cell interactions may account for the observed decreases in transitional B cells of patients with PD.

Unique Signature of the B- and T-Cell Compartments Characterizes Patients With PD Compared With Neurologically Normal Controls

To follow-up on our directed analyses of immune cell subsets previously implicated in inflammatory CNS conditions, we next performed an exploratory data-driven principal component analysis (PCA) on the full data set (198 features in total, comprising both immune cell counts and frequencies) across all 65 individuals. As shown in Figure 6A, the first 10 principal components accounted for 65.5% of the total variance, with principal component 1 (PC1) explaining 16.5% and PC2 explaining 11.7% (Figure 6B). Notably, PD and NC samples separated well along PC2 (Figure 6B) regardless of the cohorts (Figure 6C). ROC curve application to PC2 values indicated an area under the curve (AUC) of 0.88, with p value <0.0001 suggesting that PC2 showed good ability to discriminate PD from NC (Figure 6D). This separation was not driven by age or sex (data not shown). Among the top 30 immune markers within the PC2 loadings, 6 belonged to the set of markers that define B-cell populations, whereas 7 belonged to the set of markers that define Tfh cells (Figure 6E). Increased expression of TNFα and GM-CSF by both B cells and by CD4+ and CD8+ T cells (Figures 6, F–G) contributed to the immune signature enriched in patients with PD compared with NCs.

Discussion

In the current study, we interrogated the phenotypic and functional profiles of peripheral immune cells in 2 independent (discovery and validation) cohorts of patients with PD and matched neurologically normal controls. We demonstrate decreased total B-cell counts (driven by decreases in immature/transitional B-cell subsets), as well as diminished B-cell proliferation, in the circulation of patients with PD. Decreased Tfh counts in the patients with PD were associated
with their decreased B-cell counts. We also observed a shift toward a more proinflammatory cytokine response profile in both B cells and T cells of patients with PD. Together, these data reveal previously unexpected abnormalities in the B-cell compartment of patients with PD and implicate aberrant B-cell:T-cell interactions in their dysregulated immune state.

B cells have traditionally been considered based on their contributions to humoral immune responses, through their potential to generate antigen specific protective antibodies (or, in the context of autoimmune diseases, auto-antibodies that recognize self-antigens). Deposition of IgG1 antibodies has been described in the substantia nigra (SN) of PD patients, which may be associated with local microglial activation. More recent studies identified that α-synuclein–specific autoantibodies are increased in the peripheral blood and CSF of patients with PD compared with controls. Although these findings were taken to suggest a pathologic role of antibodies in PD, a more recent study by Li et al. reported that naturally occurring antibodies against α-synuclein may be disease protective because they may neutralize the seeding of intracellular synuclein aggregates. These studies highlight the potentially complex ways in which antibody-related B-cell responses may participate in PD disease pathogenesis.

In addition to generating antibodies, it is now well known in other fields of immunology that B cells are actively involved in regulating local immune responses through multiple antibody-independent cellular functions, such as antigen presentation to T cells and via secretion of either pro- or anti-inflammatory cytokines that can modulate the activation of other immune cells, including T-cell subsets and innate cells. Our findings indicate that patients with PD have preferential decreases in numbers of circulating anti-inflammatory B-cell subsets (including transitional B cells and IL-10+ producing B cells), which is consistent with previous work by Alvarez-Luquin et al. showing that CD24high CD38− atypical memory B cells (E) and CD43+ CD27− B1 cells (F) are decreased in the circulation of patients with PD. ns = not significant, *p < 0.05, **p < 0.01, and ***p < 0.001. Discovery cohort (comprising n(NC) = 12, n(PD) = 17) and validation cohort (n(NC) = 18, n(PD) = 18). NC = normal control.
innate cells in traditionally considered T cell–mediated diseases.29,31,33,49,50 Although our study did not assess antigen-specific responses, it is interesting to speculate that the B-cell abnormalities we discovered in patients with PD may be linked with previously reported abnormalities in the T-cell compartment of patients, including observations of abnormally increased Th17 and α-synuclein–reactive T cells.9–11

In contrast to a prior study48 that suggested increased proportions of circulating Tfh cells in patients with PD, we observed decreased absolute counts of Tfh cells in patients with PD compared with controls in both our discovery and validation cohorts and further noted that the reduced Tfh cell numbers in patients correlated with their diminished B-cell counts. Crosstalk between Tfh cells and B cells is known to be important for proper function of both cell types,35,51 and we speculate that decreased Tfh cells in patients may underlie their diminished B-cell proliferation also resulting in preferentially lesser generation of transitional/regulatory B cells. In keeping with this, IL-21 (produced by Tfh cells) is known to be particularly important for the generation of IL-10–producing regulatory B cells.30

There are several potential limitations to our study. From a technical perspective, the use of cryopreserved PBMCs has the important advantage of reducing interassay variability and batch effects, although the freeze/thaw of PBMCs may impact cell yields and viability and unevenly influence different immune cell subsets. We cannot exclude an impact of such influences on our results, although the strict SOPs applied consistently across all sample likely contributed to the reassuringly high yields and viabilities of our samples, and we have no reason to suspect that any processing artifact would systematically affect the PD patient samples differently than the control samples. From a study design standpoint, although the independent discovery and validation cohorts enable us to ascertain PD immune abnormalities more confidently, our study is cross-sectional, thus capturing only a snapshot of PD patients’ immune status and limiting our ability to relate our findings to the course and outcome of patients. Future studies that serially assess immune profiles in patients may provide additional insights into the sequence and dynamics of immune cell subset interactions involved in the disease. Interpreting the immunologic differences that we observed between patients with PD and controls might be confounded by medications used to treat PD. In particular, immune cells can both secrete and respond to dopamine,52–58 and the effects of dopamine can be complex as it has been shown to either enhance or limit responses of both B cells and T cells (which may depend in part on the dopamine receptor

Figure 4 Cytokine Profiles of B Cells in Normal Controls and Parkinson Disease

Cryopreserved peripheral blood mononuclear cells were thawed and rested overnight before stimulation with PMA and ionomycin in the presence of GolgiStop for 4 hours. B-cell expression of IL-10, GM-CSF, TNFα, and IL-6 was detected by flow cytometry using intracellular cytokine staining. IL-10–producing B-cell counts are reduced in patients with Parkinson disease (PD) (A), whereas GM-CSF and TNFα-expressing B-cell frequencies are increased in patients with PD (B), which together results in decreases of both GM-CSF/IL-10 ratios (C) and TNFα/IL-10 ratios (D) of cytokine-expressing B cells in PD compared with normal control (NC). ns = not significant, *p < 0.05, and **p < 0.01. Discovery cohort (comprising n(NC) = 12, n(PD) = 17) and validation cohort (n(NC) = 18, n(PD) = 18).
profiles and the context of exposure, such as the immune cell state of activation). For example, dopamine can inhibit T-cell activation through its D1 and D2 receptors, whereas it may favor proinflammatory Th1 and Th17 T-cell responses when signaling through its D3 and D5 receptors. Dopamine can also preferentially induce apoptosis of cycling B cells, but not of resting B cells, and when released from Tfh cells can strengthen T-B synapse within germinal centers, thereby boosting B-cell responses. To gauge the possible impact of dopamine, we obtained LEDD (L-dopa equivalent daily dose) scores (eTable 2, links.lww.com/NXI/A676), considered by some authors to provide an estimation of a patient’s daily medication exposure. We found no apparent relationship between LEDD scores and PD-associated immune abnormalities, though we cannot entirely exclude effects of PD medications on our findings. Other (non-PD) medications were common in both our participants with PD and NCs, who also harbored a range of comorbidities. Although these other medications and comorbidities may also impact immune measures, they did not appear imbalanced between the participants with PD and NCs in either the discovery or validation cohorts. Finally, although our findings provide intriguing insights into a dysregulated peripheral immune compartment in patients with PD, how such dysregulation relates to disease-relevant processes within the CNS remains to be elucidated. In this regard, future studies interrogating immune cells in the CSF and/or within the CNS parenchyma of patients will be of interest.

In summary, our study uncovers a novel B-cell signature in PD and suggests that aberrant interactions between T cells and antibody-independent functions of B cells may be involved in PD pathogenesis. Further investigation of the significance of such interactions in PD is warranted. If confirmed to be pathogenic, there may be potential to therapeutically target B-cell:T-cell interactions in PD, an approach increasingly applied across a growing range of human immune-mediated (including neurologic) conditions.

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**Disclosure**

R. Li, L.R. Baratta, L. Zuroff, M.E. Diaz-Ortiz, B. Zhang, K. Shinoda, A. Rezk, R.N. Alcalay, and A. Chen-Plotkin report no
Principal component (PC) analysis was applied to the complete data set containing 198 features comprising both counts and frequencies of different immune cell subset/functional markers. (A) Percent variance accounted for by each of the first 10 principal components. (B) Plot of PC1 vs PC2 showing separation between Parkinson disease (PD) and normal control (NC) along PC2. (C) Boxplot of PC2 values grouped by disease status and cohort. (D) ROC curve of PC2 values (area under the curve (AUC): 0.88, \( p < 0.0001 \)). (E) Top 30 features within the PC2 loadings. (F) TNF\( \alpha \) and GM-CSF expressing B-cell and T-cell subsets are increased in patients with PD. ns = not significant; **p < 0.001 and ****p < 0.0001. Discovery cohort (comprising \( n(\text{NC}) = 12, n(\text{PD}) = 17 \)) and validation cohort (\( n(\text{NC}) = 18, n(\text{PD}) = 18 \)).

**Appendix** Authors

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<thead>
<tr>
<th>Name</th>
<th>Location</th>
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<tbody>
<tr>
<td>Rui Li, MD, PhD</td>
<td>The Center for Neuroinflammation and Neurotherapeutics and the Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
</tr>
<tr>
<td>Thomas Francis Tropea, DO</td>
<td>Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data</td>
</tr>
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Appendix (continued)

Name | Location | Contribution
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Amit Bar-Or, MD | The Center for Neuroimmunology and Neuroinflammation and the Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA | Drafting/revision of the manuscript for content; study concept or design; and analysis or interpretation of data

References


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