Parkinsonism and Related Disorders 64 (2019) 340–341

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

Does peripheral inflammation contribute to multiple system atrophy?

ARTICLE INFO

Keywords:
Multiple system atrophy
Immune markers
Interleukin
Inflammation
Non-motor symptoms

Multiple system atrophy (MSA) is a neurodegenerative disease characterized by any combination of progressive autonomic failure, parkinsonian symptoms, and cerebellar and pyramidal features [1]. Although several lines of evidence suggest that central neuroinflammatory mechanisms are implicated in the pathogenesis of MSA [2], it remains unclear whether peripheral inflammation contributes to the disease. Research focusing on this aspect may provide not only a better understanding on the etiology of MSA but also information regarding its candidate biomarkers. Therefore, we assessed serum inflammatory markers in patients with MSA and explored their associations with motor and non-motor symptoms.

A total of 27 patients with MSA were included in this study. A diagnosis of MSA was made according to the consensus criteria [1]. Twenty healthy individuals with an overall age and sex distribution similar to that of the patients were the controls, as in our previous study [3]. We assessed motor symptoms using the Hoehn and Yahr stage and non-motor symptoms using the Montreal Cognitive Assessment, the Cross-Cultural Smell Identification Test, the Non-motor Symptoms Scale, and the Composite Autonomic Symptom Score 31. The following serum inflammatory markers in the serum samples were measured: interleukin (IL)-1β, IL-2, IL-6, and IL-10 and tumor necrosis factor (TNF)-α and high-sensitivity C-reactive protein (hsCRP). These markers were selected on the basis of the previous results from patients with Parkinson's disease [4] and those with multiple system atrophy [5]. The standard procedures for cytokine and hsCRP analyses have been previously described in detail [3]. The institutional review board of our hospital approved the study protocol, and written informed consent to participate was obtained from all the participants. We divided the MSA patients into two groups (low-level group vs. high-level group) according to the median value of each inflammatory marker, and then compared the clinical measures between the groups [6]. Quantitative variables were compared with the use of the Mann-Whitney *U* test, and qualitative variables were compared with the use of Fisher's exact test. All statistical tests were two-tailed, and a *P* value less than 0.05 was considered statistically significant. Calculations were done with the IBM SPSS software, version 22.

There were no differences between the MSA and control groups with respect to age and sex (Supplementary Table 1). The mean (standard deviation) disease duration of the MSA group was 3.4 (1.7) years. The IL-1β and IL-2 levels were below the lower limit of detection (LLOD) in 60% (MSA group: 59% vs. control group: 60%; LLOD: 0.03 pg/ml) and 43% (MSA group: 33% vs. control group: 55%; LLOD: 0.10 pg/ml) of the serum samples, respectively. The other cytokines and hsCRP were detectable in all the serum samples. As shown in Table 1, none of the inflammatory markers were significantly different between the two groups. Among the patients with MSA, the severity of the motor and non-motor symptoms did not differ between the low- and high-level groups for each inflammatory marker (Supplementary Table 2).

In this study, we did not find any evidence that peripheral inflammation is associated with MSA. In fact, unlike Parkinson's disease,

Table 1
Serum inflammatory marker levels.

	MSA (n = 27)	Control (n = 20)	*P* Value
IL-1β, pg/ml	0.03 (0.04)	0.03 (0.01)	0.868
IL-2, pg/ml	0.14 (0.22)	0.10 (0.07)	0.501
IL-6, pg/ml	0.95 (1.36)	0.64 (0.59)	0.389
IL-10, pg/ml	1.18 (3.58)	0.87 (2.75)	0.282
TNF-α, pg/ml	2.42 (0.64)	2.49 (0.61)	0.547
hsCRP, μg/ml	2.34 (7.84)	3.81 (11.55)	0.387

Data are the mean (standard deviation).
Abbreviation: hsCRP = high sensitivity C-reactive protein; IL = interleukin; MSA = multiple system atrophy; TNF = tumor necrosis factor.

https://doi.org/10.1016/j.parkreldis.2019.03.020
Received 22 January 2019; Received in revised form 21 March 2019; Accepted 22 March 2019

little is known about peripheral nervous system synuclein pathology in MSA. Furthermore, autonomic symptoms in MSA are generally caused by the involvement of the central nervous system including the autonomic centers of the brainstem, which suggests a primarily preganglionic disorder [7,8]. These observations may support the results of the current study. However, considering that the mean disease duration of our patients was 3.4 years, we cannot exclude the possibility that peripheral inflammation is vital to the initial pathogenesis of MSA but not relevant at this stage of the disease. Alternatively, the serum inflammatory markers used in this study may not adequately capture the immune responses of peripheral nervous system in MSA.

In contrast to our findings, a recent study reported increased plasma levels of IL-6 and TNF-α in patients with MSA compared to the controls, and the higher TNF-α levels were associated with less severe motor symptoms [5]. However, these results were obtained from only 14 patients with MSA, limiting any conclusions that can be made. Therefore, further studies with a larger number of patients with MSA should be done to clarify this issue.

Authors' contributions

Study concept and design: RK, HK.
Data acquisition: HK, AK, MJ, AK, YK, DY, JI, JC.
Data analysis: RK, HK, AK, MJ, AK, YK, DY, JI, JC, BJ.
Drafting the manuscript: RK, HK.

Conflicts of interest

No conflicting relationship exists for the authors.

Disclosure statement

All authors report no disclosures relevant to the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.03.020

Funding source

This work was supported by grant No. 0320160420 (2016-1085) from the SNUH Research Fund.

References

[1] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski, N.W. Wood, C. Colosimo, A. Dürr, C.J. Fowler, H. Kaufmann, T. Klockgether, A. Lees, W. Poewe, N. Quinn, T. Revesz, D. Robertson, P. Sandroni, K. Seppi, M. Vidailhet, Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (2008) 670–676.
[2] B.D. Vieira, R.A. Radford, R.S. Chung, G.J. Guillemin, D.L. Pountney, Neuroinflammation in multiple system atrophy: response to and cause of α-synuclein aggregation, Front. Cell. Neurosci. 9 (2015) 437.
[3] R. Kim, H.J. Kim, A. Kim, M. Jang, A. Kim, Y. Kim, D. Yoo, J.H. Im, J.H. Choi, B. Jeon, Peripheral blood inflammatory markers in early Parkinson's disease, J. Clin. Neurosci. 58 (2018) 30–33.
[4] X.Y. Qin, S.P. Zhang, C. Cao, Y.P. Loh, Y. Cheng, Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: a systematic review and meta-analysis, JAMA Neurol 73 (2016) 1316–1324.
[5] E. Kaufman, S. Hall, Y. Surova, H. Widner, O. Hansson, D. Lindqvist, Proinflammatory cytokines are elevated in serum of patients with multiple system atrophy, PLoS One 8 (2013) e62354.
[6] D. Iacobucci, S.S. Posavac, F.R. Kardes, M.J. Schneider, D.L. Popovich, Toward a more nuanced understanding of the statistical properties of a median split, J. Consum. Psychol. 25 (2015) 652–665.
[7] L. Zange, C. Noack, K. Hahn, W. Stenzel, A. Lipp, Phosphorylated α-synuclein in skin nerve fibres differentiates Parkinson's disease from multiple system atrophy, Brain 138 (2015) 2310–2321.
[8] J.Y. Kim, B.M. Illigens, M.P. McCormick, N. Wang, C.H. Gibbons, Alpha-synuclein in skin nerve fibers as a biomarker for alpha-synucleinopathies, J. Clin. Neurol. (2019) [Epub ahead of print].

Ryul Kim[a], Han-Joon Kim[a,*], Aryun Kim[b], Mihee Jang[c], Ahro Kim[d], Yoon Kim[a], Dallah Yoo[a], Jin Hee Im[a], Ji-Hyun Choi[a], Beomseok Jeon[a]
[a] *Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea*
[b] *Department of Neurology, Chungbuk National University Hospital, Cheongju, South Korea*
[c] *Department of Neurology, Presbyterian Medical Center, Jeonju, South Korea*
[d] *Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea*
E-mail address: movement@snu.ac.kr (H.-J. Kim).

[*] Corresponding author. Department of Neurology, College of Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, South Korea.