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Short communication

Peripheral blood monocyte count at onset may affect the prognosis in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a demyelinating neurological disease with unknown causes. In this study, we comprehensively studied blood cell counts in the early phase of MS and compared their values with eventual prognostic variables. We found that the blood monocyte count in the early phase of MS was robustly associated with the clinical severity of MS (rho = 0.64; p = 0.0002) but that the counts of the other blood cells were not associated with severity. This correlation between monocyte count and severity was not observed in neuromyelitis optica. In conclusion, blood monocytes could be a candidate for the prognostic prediction of MS.

1. Introduction

Multiple sclerosis (MS) is an autoimmune-related demyelinating neurological disease of the central nervous system (CNS) that shows relapsing-remitting clinical course with disseminated CNS lesions accompanied by brain atrophy in the early phase (Polman et al., 2011; Akaishi et al., 2017; Azevedo et al., 2015). Characteristic findings in MS include oligoclonal bands (OB) in the cerebrospinal fluid (CSF) and periventricular cerebral lesions (PVLs), but both of these findings have not been shown to affect disease severity or the risk of relapse (Akaishi et al., 2018a). There are many suggested aggravating factors in MS, such as smoking, EB virus infection with or without a past history of infectious mononucleosis, higher latitude with lower ultraviolet exposure, and vitamin D deficiency (Wingerchuk, 2012; Backhaus et al., 2016; Beretich and Beretich, 2009; Nielsen et al., 2007; Endriz et al., 2017; Zivadinov et al., 2016; Koduah et al., 2017; Kinoshita et al., 2015). However, the pathogenesis of MS cannot be fully explained by these known risk factors.

Recently, the significant role of activated monocytes and microglia in the pathogenesis of autoimmune-related CNS diseases, including MS, has attracted more and more attention (Datta et al., 2017; Shemer and Jung, 2015; Housley et al., 2015). Previous studies have shown that the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor is abnormal in MS lesions and that abnormal GM-CSF signaling could be a pathogenesis in MS (Imitola et al., 2018; Ifergan et al., 2017). However, an association between the peripheral blood monocyte count and disease severity in MS has not been reported yet. In this report, we show for the first time that the blood monocyte count at the beginning of the disease correlates with disease progression in Japanese patients with MS.

2. Materials and methods

2.1. Enrollment criteria

Among the MS patients who were treated at the outpatient center of Tohoku University Hospital, those who were currently diagnosed with relapsing-remitting MS (RRMS) before converting to secondary progressive MS were collected (n = 153). First, among the RRMS patients, those who had their first hospital visit after 2001 and a disease duration between 3 and 20 years were selected (Trojano et al., 2003; Gold et al., 2010; Davies et al., 2016). Then, those whose hemogram was studied at clinical onset without any kind of treatment were finally enrolled in this study (n = 29).

2.2. Studied variables

In these enrolled 29 patients, the counts of total white blood cells (WBC), neutrophils, eosinophils, basophils, monocytes, and lymphocytes in peripheral blood at their clinical onset were comprehensively collected. Also, their erythrocyte sedimentation rates (ESR; 30 min, 1 h, and 2 h), CRP, serum amyloid A (SAA), and 50% hemolytic complement (CH50) were collected.

The clinical variables sex, onset age, total number of relapses,

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annual relapse rate (ARR), present score of expanded disability status scale (EDSS), present MS severity score (MSSS), and baseline EDSS at the hemogram were collected. The hemogram was performed by automated hematology differential analyzers (XN-Series, Sysmex, Kobe, Japan).

To adjust for a possible confounding effect from treatment, the usage of disease modifying therapies (DMT) at the time of the hemogram was also verified for use in multivariate analysis. Also, to adjust for a possible effect from the time lapse from clinical onset to the time of the hemogram, we also collected the time period between the clinical onset and the time of the hemogram.

To verify that the correlation between monocyte count and disease severity was a specific finding to MS, we tentatively adopted the scale of EDSS and MSSS for patients with neuromyelitis optica (NMO) (n = 72) who were all positive for serum anti-aquaporin-4 (AQP4) autoantibody measured by a previously reported cell-based assay method and fulfilled the international diagnostic consensus for NMO spectrum disorders (Takahashi et al., 2006; Wingerchuk et al., 2015). Among the NMO patients, Spearman's rho between the blood monocyte count and the severity score was also calculated.

2.3. Statistical analysis and software

Because many of the studied variables showed non-normal distributions ($p < 0.01$, Kolmogorov-Smirnov test), correlations between the variables were evaluated with Spearman's rank correlation coefficients, which was followed by the test of no correlation. Because of simultaneous multiple tests of no correlation, $p < 0.01$ was regarded as statistically significant.

To evaluate the possible confounding effects from disease duration and the usage of DMT to the correlation between the data in the hemogram and clinical prognoses, multiple regression analysis using possible confounding factors (*i.e.*, disease duration at MSSS scoring, usage of DMTs at hemogram, time period between onset and the hemogram) with the data on the hemogram as explanatory variables was also performed. Variables with $p < 0.01$ were regarded as statistically significant as possible confounding factors.

Statistical analyses in this study were conducted using SPSS Statistics Base 22 software (IBM, Armonk, NY, USA) and MATLAB R2015a (MathWorks, Natick, MA, USA).

2.4. Ethics approval

This study was approved by the internal review board of Tohoku University Hospital, and written informed consent was collected in advance from all enrolled patients.

3. Results

3.1. Distributions of the studied variables in MS

The median and mean ± standard deviation (SD) of the current age were 40 and 43.0 ± 12.1 years old, respectively. The median and mean ± SD of the disease duration at the scoring of MSSS were 7.0 and 7.8 ± 3.3 years, respectively. The median and mean ± SD of the MSSS were 3.5 and 3.9 ± 2.9, respectively. The median and interquartile range (IQR) of the EDSS at the baseline were 2.0 and 1.5–2.5, respectively. The median and IQR of the ARR were 0.33 and 0.21–0.57, respectively.

The median and mean ± SD of the WBC count were 5800 and 6008 ± 1805, respectively; there was no patient with a WBC count over 10,000/μl at the hemogram.

3.2. Correlations between studied laboratory variables and prognosis in MS

The Spearman's rho between each type of the blood cell count in the hemogram and clinical prognosis (*i.e.*, MSSS and ARR) is shown in Table 1. The scatter plot showing the correlation between the monocyte count in the first year and eventual MSSS is shown in Fig. 1. There was no statistically significant correlation between the monocyte count and baseline EDSS at the hemogram (Spearman's rho = 0.228; p = 0.24).

Table 1
Correlation coefficients between the blood cell counts at onset and prognostic variables in the MS patients.

	MSSS		ARR	
	rho	p	rho	p
WBC [/mm^3]	0.23	0.13	0.27	0.074
Neutrophil	0.19	0.52	0.07	0.69
Eosinophil	0.12	0.67	0.14	0.47
Basophil	−0.08	0.67	0.02	0.91
Monocyte	0.64	0.00019	0.33	0.085
Lymphocyte	0.20	0.29	0.34	0.071

Statistical significance was confirmed only between the monocyte count and MSSS. As for the ARR, both monocyte and lymphocyte counts were suggested to be associated, but their associations did not reach the statistical significance. Abbreviations: ARR, annual relapse rate; MSSS, multiple sclerosis severity score; rho, Spearman's rank correlation coefficient; WBC, white blood cell.

As for other laboratory variables, none of the ESR (30 min, 1 h, and 2 h), SAA, CRP, or CH50 in the first year from clinical onset showed significant correlation between the eventual MSSS or ARR.

3.3. Confounding effects from disease duration and DMTs

During the clinical courses of the enrolled patients, 16 of the enrolled 29 MS patients were mainly treated with interferon-beta, 10 were untreated, and the remaining 3 were treated with oral prednisolone.

To evaluate the possible confounding effect of the usage of DMT at the time of the hemogram and disease duration as of 2017, multivariate regression analysis was performed by using the blood monocyte count in the first year, disease duration as of 2017, and usage of DMTs at the time of the hemogram as the explanatory variables and MSSS as the objective variable.

The derived regression model was suggested to fit the distributions (p = 0.00045). As for each of the studied variables, only the blood monocyte count was suggested to significantly affect MSSS ($p < 0.0001$), but the current disease duration (p = 0.13), time period between onset and the hemogram (p = 0.79), or the usage of DMTs at the hemogram (p = 0.86) did not show a correlation with MSSS.

3.4. Correlation between blood monocyte count and severity in NMO

The Spearman's rho between the blood monocyte count and tentatively adopted MSSS in the studied NMO patients was −0.22 (p = 0.16, test of no correlation). For reference, there was no differential leukocyte count or laboratory data that showed a significant correlation with the tentatively adopted MSSS or ARR in the NMO patients. Also, there was no significant correlation between the studied cell counts or laboratory variables and the latest EDSS in the NMO patients.

For reference, the distributions of the blood monocyte count were almost the same between the MS and NMO patients (388 ± 156 *vs* 358 ± 192; p = 0.30, Student's *t*-test).

4. Discussion

In this study, we showed that the blood monocyte count in the early phase of MS could strongly predict the subsequent clinical severity in MS patients. The correlation was still strong even after we adjusted for possible confounding effects from disease duration at EDSS scoring and the usage of DMTs at hemogram timing.

In the studied NMO patients, there was no significant correlation