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Original Article

The role of red cell distribution width in patients with Parkinson's disease

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Abstract: *Background:* There are increasing evidence that neuropathic inflammation may be implicated with the etiology and pathogenesis of Parkinson's disease (PD), and the inflammatory factors have been considered as a role in the development and progression of neurodegenerative disorders. Red cell distribution width (RDW) that can be easily measured in routine blood counts serves as an inflammatory marker. Therefore, we aimed to examine the association between RDW and PD. *Methods*: A total of 94 patients with PD and 279 healthy individuals were included in the study. We used the unified Parkinson's disease rating scale (UPDRS) motor score and the modified Hoehn and Yahr staging scale (H&Y score) to assess the severity of PD symptoms. *Results:* RDW was found to be increased in patients with PD compared to healthy subjects. The positively correlation between RDW and UPDRS motor score, H&Y score were observed in patients with PD (r=0.273, P=0.008; r=0.252, P=0.014). Increased levels of RDW were independently associated with PD in logistic regression analysis (OR=3.316, CI 95%: 1.150-9.559, P<0.001). The Receiver operating characteristic (ROC) curves analysis showed area under the curve of 0.747 (CI 95%: 0.684-0.809, P<0.001) with a sensitivity of 72.3% and a specificity of 55.2%. *Conclusions:* Our results suggest that RDW is independently associated with PD, and tends to correlate with motor deterioration in patients with PD.

Keywords: Red blood cell distribution width, parkinson's disease, inflammatory cytokines

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that caused by progressive dopaminergic neuronal degeneration, which mainly affects elderly population. Evidences suggest that oxidative stress, altered proteins and mitochondrial dysfunction have major role in neuronal degeneration of PD [1]. Accumulating data have indicated that several inflammatory cytokines are increased in the brain of PD patients [2, 3], and some inflammatory mediators such as tumor necrosis factor (TNF), interleukin-6 (IL-6) and interleukin-10 (IL-10) may cause nigral dopaminergic neuron death in patients with PD [4]. Very recently, increased levels of TNF in tear of PD patients have been reported by Çomoğlu SS et al. [5]. Similarly, recent investigations demonstrated that several peripheral cytokines are increased in patients with PD, including interleukin-2 (IL-2), interleukin-4 (IL-4) and interleukin-6 (IL-6) [6, 7]. Taken together, these results suggest that inflammatory mediators may be a key role in chronic neurodegenerative disorders.

Red cell distribution width (RDW) that can be easily measured in routine blood counts reflects variability and size of erythrocytes [8]. Increased RDW values have been recently reported in patients with ankylosing spondylitis, polymyositis and multiple sclerosis [9-11]. Epidemiological evidence suggests a relationship elevated RDW and major depressive disorder [12]. A strong association of RDW with inflammatory markers has demonstrated this parameter to be an indicator with respect to adverse outcomes in patients with acute pancreatitis, myocardial injury and hepatocellular carcinoma [13-15]. Increased RDW may result from an underling inflammatory status associated with clinically adverse outcomes [16]. In fact, RDW has been considered to be an inflammatory marker. However, to the best of our knowledge, there is no study in the literature regard-

Table 1. Demographic and laboratory characteristics of the Parkinson's disease (PD) patients and healthy subjects

Variables	PD patients	Control groups	*P*-value
	n=94	n=279	
Gender (Male/Female) [n]	48/46	176/102	0.036
Age [yr]	65.6±11.31	43.3±8.77	<0.001
Hemoglobin (g/L)	130.9±15.85	150.9±13.88	<0.001
Mean corpuscular hemoglobin (pg)	31.1±2.44	31.1±1.28	0.793
Mean corpuscular hemoglobin concentration (g/L)	332.3±11.80	334.1±8.35	0.163
Mean corpuscular volume (fL)	93.5±6.44	93.2±3.42	0.719
Lymphocyte count (10^9/L)	1.8±0.67	2.1±0.60	<0.001
Neutrophil count (10^9/L)	4.1±2.65	3.5±1.09	0.055
Platelet count (10^9/L)	236.9±48.30	200.4±52.12	<0.001
Red blood cell distribution width (%)	13.5±0.75	12.9±0.36	<0.001

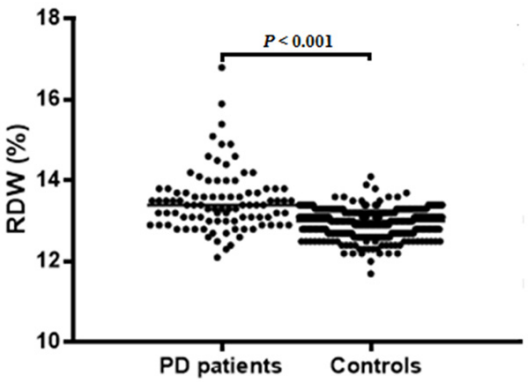

Figure 1. Elevated red blood cell distribution width (RDW) in Parkinson's disease (PD) patients compared with healthy controls.

ing the evaluations of RDW in PD patients. Therefore, we aimed to examine the association between RDW and PD.

Patients and methods

A total of 94 patients with PD who were admitted to the Affiliated Hospital of Youjiang Medical University for Nationalities were included in the study, two hundred and seventy-nine healthy individuals without history of PD were considered as control groups. All patients had definite PD in accordance with the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [17]. We used the unified Parkinson's disease rating scale (UPDRS) motor score and the modified Hoehn and Yahr staging scale (H&Y score) to assess the severity of PD symptoms [18, 19]. The demographic, laboratory and clinical information of the initial admission were collected from the medical records. Blood routine tests were performed by using automatic blood cell analysis instrument (Sysmex XN2000, Japan).

Exclusion criteria were: Diabetes, hypertension, cardiovascular disease, thyroid disease, autoimmune disease, metabolic syndrome, recent infection, hematological disorder, alcoholism, hepatic or renal insufficiency, cranial trauma, neoplastic disease and patients with use of corticosteroid, anti-inflammatory, immunosuppressive, anti-depressant, anti-parkinsonian and anti-cholinergic drugs within the last 6 months.

This study was approved by the Affiliated Hospital of Youjiang Medical University for Nationalities institutional review board, and obtained the requirement for informed consent of subjects. The research related to human use has been complied with the tenets of the Helsinki Declaration.

Statistical analysis

Continuous variables and categorical variables are presented as mean ± SD and percentages, respectively. We used Kolmogorov-Smirnov test to identify data normality. Differences between patients and control groups were evaluated by using Student's t test, U test and Chi-square test. Correlations between two continuous variables were analyzed by Pearson approach. We used binary logistic regression analysis to find the potential independent association between hematological parameters and PD. Receiver operating characteristic (ROC) curves analyzes were performed to estimate PD patients. Our data were analyzed by using

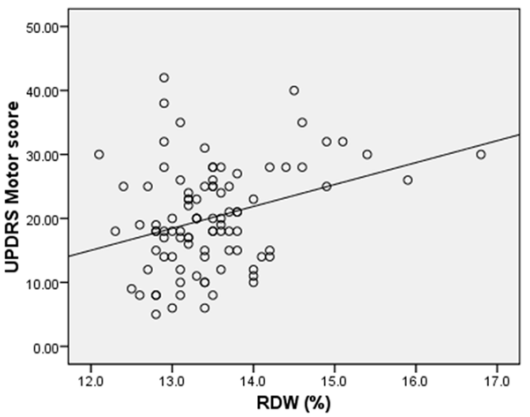

Figure 2. Scatter plot showing a correlation between red cell distribution width (RDW) and UPDRS motor score in patients with Parkinson's disease (PD).

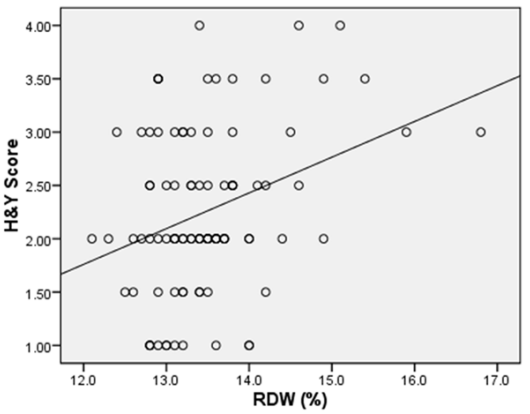

Figure 3. Scatter plot showing a correlation between red cell distribution width (RDW) and H&Y score in patients with Parkinson's disease (PD).

SPASS16.0 statistical software. Statistical significance was accepted at $P<0.05$.

Results

The demographic and laboratory data of all individuals are summarized as follows in **Table 1**. Patients with PD were statistically differences compared with control groups in regards to gender, age, lymphocyte count and platelet count, and RDW was found to be increased in patients with PD compared to healthy subjects (13.5±0.75 vs. 12.9±0.36, $P<0.001$), as shown in **Figure 1**.

In correlation analysis, the levels of RDW were positively correlated with age ($r=0.291$, $P=0.004$) and were negatively correlated with mean corpuscular hemoglobin (MCH) ($r=-0.209$, $P=0.043$), mean corpuscular volume (MCV) ($r=-0.239$, $P=0.021$) and hemoglobin ($r=-0.210$, $P=0.043$). The UPDRS motor score and H&Y score were used as clinical assessment of PD disease status, the positively correlation between RDW and UPDRS motor score, H&Y score were observed in patients with PD ($r=0.273$, $P=0.008$; $r=0.252$, $P=0.014$) (**Figures 2**, **3**). Increased levels of RDW were independently associated with PD in logistic regression analysis when gender, age, hemoglobin, lymphocyte count and platelet count were considered as confounder (OR=3.316, CI 95%: 1.150-9.559, $P<0.001$) (**Table 2**). The Receiver operating characteristic (ROC) curves analysis showed area under the curve of 0.747 (CI 95%: 0.684-0.809, $P<0.001$) with a sensitivity of 72.3% and a specificity of 55.2% in estimating PD patients (**Figure 4**). Cut-off values of RDW for evaluating PD were 13.05%.

Discussion

The main findings of our study are that increased RDW is independently associated with PD in multivariable logistic regression analysis, and RDW is positively correlated with the UPDRS and H&Y score. These results first report the potential clinical value of RDW for the assessment the severity of PD symptoms.

RDW, an available and inexpensive parameter, has been regarded as an underling inflammatory marker. Higher RDW is positively correlated with inflammatory parameters including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and other inflammatory cytokines [12]. It has been demonstrated in recent studies that RDW is associated with sjögren's syndrome, prevalent dementia, rheumatoid arthritis and incident myocardial infarction [20-23]. In various inflammation related diseases, decreased life span of erythrocytes may be caused by some inflammatory factors, which would result in appearance of immature red blood cell in the peripheral circulation [24]. The increased levels of CRP in plasma have been shown to be associated with motor deterioration and prognosis in patients with PD [25]. In several earlier trials, several serum markers, such as sermonocyte chemoattractant protein-1, TNF and interleukin-8 (IL-8), are correlated with motor deterioration [6, 7]. In the present study, RDW was suggested in patients with PD to be correlated with motor deterioration as represented by the UPDRS and H&Y score. Compared with above mentioned serum

Table 2. Multivariate regression analysis of parameters associated with Parkinson's disease (PD)

Variables	OR	*P*-value	95% CI
Gender	1.207	<0.001	1.015-2.999
Age (yr)	1.176	<0.001	1.125-1.229
Hemoglobin (g/L)	0.862	<0.001	0.818-0.909
Red blood cell distribution width (%)	3.316	<0.001	1.150-9.559

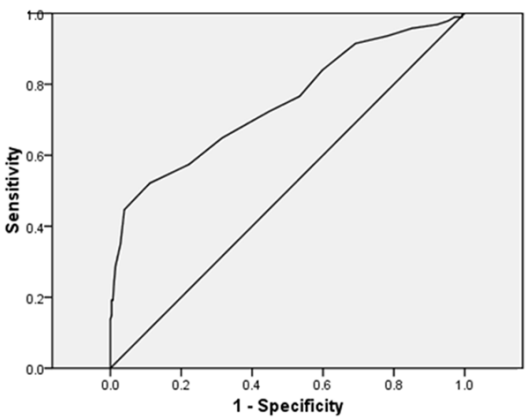

Figure 4. Receiver operating characteristic curve of red cell distribution width (RDW) for estimating patients with Parkinson's disease (PD).

indexes, RDW is easily measured in complete blood count tests with no additional costs for patients.

There are increasing evidence that neuropathic inflammation may be implicated with the etiology and pathogenesis of PD, and the inflammatory factors have been considered as a role in the development and progression of neurodegenerative disorders [6, 7]. It has been reported that the genetic polymorphism of inflammatory cytokines is associated with increased risk of PD [27]. TNF-induced signaling pathways can be activated in brain of PD by adjustment for target genes encoding inflammatory cytokines, suggesting a pivotal modulator for development and neurodegenerative processes of PD [26]. A remarkable relationship between inflammatory cytokines and PD also was suggested in a previous study, where TNF was thought to induce neurodegenerative processes [7]. Of note, activated microglia by some inflammatory cytokines such as TNF will produce inflammatory factors contributing neuronal death, which links peripheral inflammation to neuropathic inflammation for a clinical implication [28]. Interestingly, this alteration in the brain could be transferred to influence the peripheral immune system to product more inflammatory cytokines, peripheral inflammation will reverse amplify the neuropathic inflammation by cytokine network to aggravate neuronal damage and death [6]. Consequently, an interaction between neuropathic inflammation and peripheral inflammatory factors in PD patients is more plausible mechanism regarding the correlation between RDW and motor deterioration.

In the current study, we, however, noted several shortcomings. First, a relatively small sample size with retrospective design was a primary limitation. Second, a correlation between RDW and nerve severity were still unknown. Finally, the relationship between RDW and inflammatory markers such as CRP, IL-6 and TNF were not estimated in patients with PD. Nevertheless, our results suggest that RDW is independently associated with PD, and tends to correlate with motor deterioration in patients with PD.

Disclosure of conflict of interest

None.

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