Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio may reflect differences in PD and MSA-P neuroinflammation patterns

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ABSTRACT

Aim of the study. To assess the usefulness of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in evaluating the inflammatory process in alpha-synucleinopathies.

Clinical rationale for the study. The role of neuroinflammation in PD and MSA pathogenesis is indisputable. However, there is no method available in everyday use that would enable its evaluation. We suggest that NLR and PLR, as non-specific parameters of inflammation, due to its approachability could be helpful in the assessment of inflammatory activity in alpha-synucleino-pathies in everyday clinical practice.

Material and methods. 98 patients with a clinical diagnosis of PD, 28 with MSA-P, and 99 healthy age-matched controls, were included in the study. Blood samples were analysed in order to count neutrophil and lymphocyte rates and, subsequently, NLR and PLR. The obtained parameters were compared between the groups. Results were statistically analysed.

Results. Our results indicate that patients with PD have higher values of NLR and PLR compared to controls. For MSA-P, only NLR was significantly higher in relation to the control group. There were no statistically significant differences between patients with PD and MSA-P in relation to NLR and PLR values. There was a positive average correlation between NLR and disease duration for MSA-P patients.

Conclusions. NLR and PLR values are significantly higher in alpha-synucleinopathies (MSA-P and PD) in relation to a control group. In PD patients, both NLR and PLR values are significantly higher in relation to a control group, whereas in patients with MSA-P, only NLR is significantly increased. The observed differences may reflect distinct neuroinflammatory patterns present in these entities.

Clinical implications. NLR and PLR are features of peripheral inflammation. Their specificity is relatively low, although increased values suggest possible inflammatory pathogenesis of clinical entities. NLR is based on the observations that in chronic and acu-te diseases the neutrophil rate has a tendency to rise, while the lymphocyte rate tends to decline. This aspect of inflammatory processes has been primarily evaluated in Intensive Care Units. PLR is a marker presenting changes in platelet and lymphocyte counts caused by acute inflammatory or prothrombotic states. Different values of NLR and PLR in PD and MSA-P compared to healthy controls suggest that in these two alpha-synucleinopathies, different patterns of neuroinflammation might be present. The role of inflammation in the differential diagnosis of parkinsonian syndromes remains unexplored.

Key words: PD, MSA-P, alpha-synucleinopathy, NLR, PLR, inflammation

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Introduction

Parkinson's Disease (PD) and Multiple System Atrophy (MSA) are progressive neurodegenerative disorders classified pathologically as alpha-synucleinopathies. PD was first described by James Parkinson in 1817 [1] and has been the subject of scientific interest ever since. Even so, the exact mechanism responsible for the process remains unclear. There are many theories concerning the pathogenesis of the disease. There is no doubt that mutations in several genes cause autosomal dominant or recessive forms of Parkinson's Disease. Many papers considering epigenetic abnormalities, exposure to toxins, oxidative stress, metabolic changes, telomere shortening, dysfunction of cellular proteolytic and mitochondrial system, or cardiovascular factors causing ischaemia, as potential causes of PD can be found in the literature [2–10]. Some studies have suggested that PD could be considered to be a prion-like disease [11]. Of all the discussed possible factors leading to PD pathology, the neuroinflammatory theory seems to be one of the most plausible.

It remains unclear, whether the prolonged inflammation in the cause or an effect of neurodegeneration, but the presence of this process is beyond doubt [12, 13]. It has been stated that chronic neuroinflammatory process and microglial activation play crucial roles in the neurodegeneration observed in PD [14, 15]. Chronic neuroinflammation can lead to blood-brain-barrier damage that opens the door to central nervous system (CNS) infiltration by peripheral immune system cells and chemokines. This process can activate glial cells, T-cells and mast cells in the CNS, leading to increased neuroinflammation, which becomes chronic and results in neuronal loss. Mutual activation of inflammation in the CNS and peripheral immune cells leads to the release of neurotoxic molecules and exacerbates neurodegeneration [16]. Pro-inflammatory cytokines and chemokines prompt oxidative stress and damage to dopaminergic neurons [17].

Microglial activation seen as reactive oxygen species (ROS) synthesis is directly increased by α-synuclein, and this activity is even more severe in the case of mutated α-synuclein forms compared to the wild type [18]. Moreover, microglial-mediated inflammation (nuclear factor kappa-B and mitogen-activated protein kinase pathways) may be initiated by soluble α-synuclein when it binds to microglial TLR surface receptors [19, 20]. Inflammation initiated in microglia causes the activation of astrocytes and, *inter alia*, the upregulation of nitric oxide (NO) production [21]. A high concentration of NO causes α-synuclein aggregation [22] and promotes protein accumulation due to a decrease in proteasome activity [23]. This pathological cycle may be responsible for the prolonged neuroinflammation and progressive neurodegeneration seen in PD. In PD, neuroinflammation can be described as having a snowball-like effect with inflammatory activity gradually increasing over time.

MSA is often misdiagnosed as PD, especially the variant with predominant parkinsonism (MSA-P) and mainly in the early stages of the disease. Neuroinflammation is an important feature of MSA pathology, and can be observed as micro- and astrogliosis with increased proinflammatory cytokine levels [24]. Intensity of neuroinflammatory process is restricted to white matter regions due to the impact of oligodendrocytes containing α-syn inclusions [24]. MSA animal models indicate that the inflammatory response is more intense compared to a PD model, which may suggest that increased inflammation in MSA from its early stages is responsible for its more aggressive clinical course [25].

Animal models of MSA indicate that neuroinflammation has an early, pre-symptomatic, onset with explicit response of myeloid cells with proliferative and phagocytic activity in areas with more pronounced alpha-synucleinopathy [24]. In later stages of the disease, proliferation and activity of myeloid cells decreases to a lesser but continuant proinflammatory level [24].

These findings indicate a specific pattern of neuroinflammation characterised by very severe inflammatory response at the onset of the disease. Widespread microglial activation in the early stages of MSA-P has also been described in humans [26]. Data concerning the intensity of peripheral inflammation in the course of MSA remain ambiguous [27, 28].

There are several methods of assessing neuroinflammation activity *in vivo*, featuring mainly neuroimaging with the use of specific radiotracers, e.g. [^{18}F]-FEPPA PET [29] or 11C-PK11195 PET [30]. However, these methods are not available in everyday clinical practice. Finding evidence for connections between neuroinflammation and peripheral inflammation may provide a solution to this challenge [31], as there is data supporting the interrelationship of the peripheral inflammatory response and neuroinflammation, meaning that the activity of one should reflect the activity of the other.

Neutrophil-to-lymphocyte ratio (NLR) is a parameter which was introduced in 2001 by Zahorec [32]. The value of NLR is calculated by dividing the number of neutrophils by the number of lymphocytes. The purpose of evaluating this parameter was to examine patients affected by systemic inflammation who were in a critical condition [32]. It was interpreted as a simple non-specific tool. Since the introduction of NLR, many researchers have verified the usefulness of this parameter in various diseases, not only those directly related to inflammatory involvement.

The role of NLR in Parkinson's Disease has been assessed in several papers; in the study by Moghaddam et al. [33], the authors verified an association between NLR and striatal binding ratios in DaT SPECT. The study showed that increased NLR is concomitant with a decrease in the striatal binding ratio and more pronounced motor impairment [33]. One of the studies interpreted NLR to be a possible marker of peripheral neuroinflammation in differentiating PD from progressive supranuclear palsy (PSP) [34]. The increase of NLR in PD has also been associated with a loss of neural connections [35]. The

abnormalities were observed within cingulum bilaterally, body and left crus of fornix and corticospinal tract bilaterally [35]. An earlier work was based on the comparison of NLR in two variants of PD — the akinetic-rigid and the tremor-dominant [36]. This did not reveal any significant differences. To date, no study has evaluated NLR in the context of MSA.

Platelet-to-lymphocyte ratio (PLR) is calculated by dividing the number of platelets by the number of lymphocytes obtained from the same blood sample. As platelets are involved in peripheral inflammatory response, PLR is a parameter reflecting the level of inflammation. In the literature, this has mainly been discussed in the context of cardiovascular events [37], rheumatic diseases [38], cancer [39], and mental disorders [40]. This parameter has been assessed as a potential tool in differentiating PD from essential tremor [41], but there have been no papers considering this parameter in the context of MSA.

The aim of this study was to assess the intensity of peripheral inflammation in PD and MSA-P compared to healthy controls. We decided to use non-specific parameters, i.e. NLR and PLR, in order to evaluate the usefulness of tools available in everyday clinical practice.

Clinical rationale for the study

Neuroinflammation as an important factor involved in PD and MSA pathogenesis has been widely discussed in recent literature. It is possible that different patterns of ongoing neuroinflammatory process are responsible for its different clinical course and prognosis. However, the methods used in research facilities for neuroinflammation evaluation are not commonly available in everyday clinical practice.

The aim of this study was to assess whether NLR and PLR, as non-specific widespread parameters reflecting peripheral inflammation, could contribute to the diagnosis of PD/MSA and describe differences of inflammation intensity in PD/MSA and healthy age-matched populations. The results of our study could introduce a feasible tool into clinical practice, and generate a discussion regarding a possible correlation between, and the implications of, central and peripheral inflammation in the pathogenesis of alpha-synucleinopathies.

Material and methods

This study was based on a retrospective analysis of blood samples taken from patients with a clinical diagnosis of either Parkinson's Disease or Multiple System Atrophy who were hospitalised in the Department of Neurology at the Medical University of Warsaw, Poland. Diagnoses were made according to the current criteria [42, 43]. The results of the control group were based on the routine examination of blood samples taken in the University's Department of Occupational Medicine. This study was approved by the Ethics Committee of Warsaw Medical University (AKBE151/2020).

Study participants did not suffer from any condition that could affect peripheral inflammation or blood count. The study included 98 patients with PD (43 females, 55 males, aged 39 to 85 years, mean 63), 28 patients with MSA-P (18 females, 10 males, aged 48 to 78, mean 61), and 99 healthy controls (58 females, 41 males, aged 37 to 86, mean 57). Disease duration ranged from 1-6 years for MSA and 2-20 years for PD. All patients were treated with levodopa (medications combined with benserazide or carbidopa); daily dose ranged from 150 to 1,450 mg for MSA patients (c.850 mg average) and from 400 to 2,100 mg for PD patients (c. 1,100 mg average). Less than 15% of patients with PD included in the study received low doses of ropinirole — maximum 4 mg. No changes in drug dosage were made before taking the blood sample. The minimum duration of treatment at a fixed dose was 10 weeks. Other medications in the analysed population included: donepezil, low doses of pyridostigmine (due to constipation), levothyroxine, and metformin.

The exclusion criteria were: age under 35, active infection, chronic inflammatory disease, neoplasm, haematopoietic abnormalities, drug use (including parkinsonian treatment) affecting blood count, diabetes, and significant cardiovascular disorders. Patient data was obtained by analysing their medical records. NLR and PLR ratios were compared between the groups.

The results were statistically analysed using the Shapiro-Wilk test, the Kruskal-Wallis ANOVA test with pairwise multiple comparison of mean ranks (PMCMR) in post-hoc analysis, and Spearman's correlation. p values < 0.05 were considered to be statistically significant.

Statistical analysis

All calculations were performed using Statistica software (version 13.1 Dell. Inc. Statsoft). Data distribution was assessed with a Shapiro-Wilk test. All results were expressed as medians with interquartile range. As the analysed data did not have a normal distribution, for group comparison we used Kruskal-Wallis ANOVA. Pairwise multiple comparison of mean ranks (PMCMR) was used for post-hoc analysis. Spearman's correlation coefficient was used to check the dependence of potential changes in NLR and PLR with disease duration for patients with PD and MSA-P.

Results

The WBC levels were within the normal range for all the subjects analysed (4–10 *10^3/ul).

Basic and subgroup analysis

Median values with interquartile range (Q1-Q3) of assessed parameters for whole groups and subgroups are set out in Table 1.

Table 1. Descriptive statistics of study group, PD, MSA-P, PD+MSA-P subgroups and control group

	Whole group (n = 225)		PD (n = 98)		MSA-P (n = 28)		MSA-P + PD (n = 126)		Control (n = 99)	
	Median	Q1–Q3	Median	Q1–Q3	Median	Q1–Q3	Median	Q1–Q3	Median	Q1–Q3
Age	60	54–66	62.5	54–71	62	54–67	62	54–70	59	54–63
Disease duration	–	–	9	6–12	4	3–5	7	5–10	–	–
Neutrophils	$3.6*10^3$	$2.8–4.7*10^3$	$3.6*10^3$	$2.8–4.7*10^3$	$4.3*10^3$	$3.7–5.1*10^3$	$3.8*10^3$	$2.9–4.8*10^3$	$3.4*10^3$	$2.7–4.6*10^3$
Lymphocytes	$1.9*10^3$	$1.5–2.3*10^3$	$1.7*10^3$	$1.4–2.1*10^3$	$1.8*10^3$	$1.4–2.2*10^3$	$1.7*10^3$	$1.4–2.1*10^3$	$2.1*10^3$	$1.8–2.5*10^3$
Platelets	$234*10^3$	$197–275*10^3$	$229*10^3$	$193–261*10^3$	$216.5*10^3$	$187.5–272*10^3$	$227.5*10^3$	$193–268*10^3$	$239*10^3$	$198–285*10^3$
NLR	2.01	1.44–2.65	2.2	1.54–3.04	2.12	1.77–3.27	2.2	1.6–3.04	1.72	1.31–2.26
PLR	124.59	95.24–160.75	134.49	100–179.29	124.43	$10^3.89$–160.08	130.23	101.58–177.69	111.76	89.82–148.35

Q1–Q3 — interquartile range

The PD patients had higher median values of NLR and PLR compared to controls, 2.2 vs 1.72 and 134.49 vs 111.76, respectively ($p < 0.05$, Tab. 2).

For MSA-P patients only, median of NLR was significantly higher in relation to the control group, 2.12 vs 1.72 ($p < 0.05$, Tab. 2).

Unfortunately, there were no statistically significant differences between patients with PD and MSA-P in relation to NLR and PLR values.

Spearman correlation

There was a positive average correlation between NLR and disease duration for MSA-P patients $R_s = 0.5$ ($p < 0.05$, Tab. 3). For PD patients, R_s values were low $R_s < 0.1$ ($p > 0.05$, Tab. 3).

Discussion

Studies looking into NLR as a potential parameter measuring inflammatory activity in PD have shown inconsistent results. Inci et al. [34] and Ataç Uçar et al. [36] reported no statistical difference in NLR values between PD and healthy controls, although Akıl et al. [44] observed a significantly higher NLR level in PD compared to a healthy population. This study proves that both NLR and PLR are significantly increased in a PD group compared to a control group.

The differences in the obtained results in the abovementioned studies might be explained by the size of the examined populations —the larger the studied group, the more pronounced were the differences in the NLR values observed. In a recently published paper analysing data obtained from 453 PD patients and 436 controls, it was also proven that NLR is significantly higher in PD patients, although this paper did not describe PLR [45]. NLR has been found to correlate with white matter changes in PD [46], which suggests that it may, at least partially, reflect inflammatory and degenerative processes ongoing in the CNS. Some papers have proved that significantly increased peripheral inflammatory indices are correlated with the akinetic-rigid PD phenotype, whereas low peripheral inflammation markers are characteristic for patients with the tremor-dominant or mixed phenotypes [47].

In our study, increased NLR and PLR values distinguished PD and MSA-P from healthy controls and indicated the inflammatory process involved in disease pathogenesis, although for MSA-P patients, only the NLR value was sensitive enough. In MSA-P, the level of lymphocytes was not significantly higher than in PD. This resulted in the fact that the difference between the level of lymphocytes among MSA-P patients and the control group was much less pronounced than between PD and controls. This, combined with the relatively low number of platelets, was the cause of significant differences between PLR in PD patients and controls. This observation was not maintained in the comparison of MSA patients and controls. On the other hand, a high increase of neutrophils compared

Table 2. Comparison of PD, MSA-P, and control groups

	PD vs MSA-P *vs.* control	PD *vs* control	MSA-P *vs.* control	PD *vs.* MSA-P
	p*	p**	p**	p**
Age	0.0041	0.0034	1.0000	0.3079
Neutrophils	0.1047	0.9812	0.1064	0.4420
Lymphocytes	< 0.001	< 0.001	0.0487	1.0000
Platelets	0.2990	0.5719	0.6631	1.0000
NLR	< 0.001	< 0.001	0.0176	1.0000
PLR	0.0127	0.0105	0.4868	1.0000

p* — p-value for Kruskal-Wallis ANOVA; p** — p-value for pairwise multiple comparison of mean ranks (post-hoc test); in red are marked statistically significant p-values < 0.05

Table 3. Correlations between PD, MSA-P, and disease duration

	PD (n = 98)	MSA-P (n = 28)
	disease duration Rs	disease duration Rs
Neutrophils	−0.17	0.47
Lymphocytes	−0.11	−0.01
Platelets	0.00	0.10
NLR	−0.08	0.50
PLR	0.07	−0.06

Rs — Spearman correlation coefficient; in red are marked Rs values with p < 0.05

to controls resulted in the fact that the comparison of NLR between MSA-P and controls showed significant differences, whereas in PLR the significance of differences was not confirmed. The tendency towards increased levels of neutrophils in MSA-P may be influenced by the differences in neuroinflammatory pattern of PD and MSA. Based on previous studies regarding cytokine profiling in the prefrontal cortex of PD and MSA patients, it has been shown that increased mRNA levels of GSK3β are observed in MSA but not in PD [48]. GSK3β is a relevant factor in the inhibition of AMP-activated protein kinase (AMPK). GSK3β inhibition of AMPK is an enhancer of lipopolysaccharide inflammatory responses resulting in stimulation of neutrophils [49]. The role of platelets in neurodegeneration is currently being widely discussed in the literature; due to neurotransmitters like γ-aminobutyric acid (GABA), glutamate, serotonin, epinephrine, dopamine, and histamine which are present in platelets cytoplasm or exosomes, these cells are thought to act as messengers connecting the CNS to the peripheral environment [50]. It is known that platelets release serotonin when exposed to glycolipid structures specific for neurons and astrocytes' lipid rafts [51], and this phenomenon occurs as a response to blood-brain-barrier damage and promotes neuroinflammation, *inter alia* in neurodegeneration [52]. According to Rydbirk et al. [48], there are no statistically significant differences in PDGF levels between PD and MSA, and therefore a disparity in platelet number should not be expected.

Another possible explanation for partially similar results of NLR and PLR obtained from patients with PD and MSA-P

may lie in different inflammatory patterns. Taking into account the pace of deterioration and the previously described inflammatory patterns, it is possible that analysed parameters are similar due to inflammation in MSA fading over the course of time and incompletely developed neuroinflammation in middle-stage PD.

We hypothesise that the curves showing the severity of inflammation over time run in opposite directions, only to converge in the intermediate period of the diseases. Initially, the severity of inflammation should be much higher in MSA, while in late-stage PD, the severity of inflammation should exceed that seen in late-stage MSA. However, our theory requires verification. This hypothesis was not directly confirmed by our results, but they were obtained with the use of non-specific parameters of inflammation, and recent research concerning this issue suggests a multicausal background to this phenomenon. Kouli et al. [53] proved that at the earliest stages of PD there is a reduction in terminally differentiated effector memory (TEMRA) lymphocyte T CD8+ population compared to healthy controls. A study by Csencsits-Smith et al. [54] revealed that in MSA the dynamics of neuroinflammation acceleration measured by levels of serum cytokine secretion is four times greater than in PD, which could explain faster progression.

However, due to the fact that the neuroinflammatory processes present in the pathogenesis of both the diseases under discussion is complex and includes multiple variables, it is very difficult to exactly determine which components of the immune system play the dominant role. Increased parameters of peripheral inflammation may be used as one of the biomarkers of alpha-synucleinopathies, among others, in non-invasive assessments [55].

To the best of our knowledge, this is the first study to assess NLR or PLR in MSA.

The fundamental limitation of this study is its retrospective character, which precluded an assessment of genetic features of included patients or other markers of the inflammatory process. All patients included in the study remain alive, and therefore all diagnoses were made according to current diagnostic criteria without neuropathological confirmation.

NLR and PLR are non-specific parameters, although their assessment could be useful in everyday clinical practice. The exact mechanism of a possible association between peripheral inflammation and neuroinflammation must be further explored.

Therefore, it seems crucial to search for more specific parameters reflecting neuroinflammatory intensity that are accessible in everyday use. This is a topic that requires further investigation.

Conclusions

NLR and PLR values are significantly higher for alpha-synucleinopathies (MSA-P and PD) compared to a control group.

In PD patients, both NLR and PLR values are significantly higher compared to a control group, whereas in patients with MSA-P only, NLR is significantly higher.

NLR and PLR values do not help differentiate PD from MSA-P patients.

NLR and PLR values suggest the presence of different patterns of ongoing inflammation in PD and MSA-P.

Clinical implications/future directions

This study has identified a possible role of the everyday use of laboratory tests in the clinical diagnosis of PD and MSA-P. Our obtained results contribute to the discussion considering neuroinflammation and its possible peripheral markers in the context of alpha-synucleinopathies. This study highlights the need to search for accessible tools facilitating the management and diagnosis of Parkinson's Disease and Multiple System Atrophy. To the best of our knowledge, this is the first paper evaluating PLR in the context of atypical parkinsonian syndrome; this parameter should be assessed in patients with atypical parkinsonian syndromes, as previously published studies have shown interesting results in the context of peripheral inflammation markers [56].

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