



# Neutrophil-to-lymphocyte ratio (NLR) at boundaries of Progressive Supranuclear Palsy Syndrome (PSPS) and Corticobasal Syndrome (CBS)

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## ABSTRACT:

**Aim of the study.** To examine possible features of neuroinflammation in progressive supranuclear palsy — Richardson syndrome and corticobasal syndrome (CBS).

**Clinical rationale for the study.** Neutrophil-to-lymphocyte ratio (NLR) is a parameter reflecting inflammation used in numerous branches of medicine. The search for pathogenesis of the diseases partly related to inflammatory processes confirms the need to obtain possible factors which could be relatively easily verified. NLR is a benchmark routinely evaluated in most hospitalised patients.

**Materials and methods.** 23 patients with a clinical diagnosis of PSP-RS, 18 patients with CBS, and 32 healthy controls, were included in the study. Blood samples were assessed in the context of neutrophil and lymphocyte rates. Subsequently, the results were transformed into neutrophil-to-lymphocyte ratio (NLR). The NLRs from each group were statistically assessed using a Kruskal-Wallis test and post-hoc analysis.

**Results.** Statistical analysis confirmed significant differences in NLR between PSP-RS and control group. No other significant differences were observed.

**Clinical implications.** The possible use of NLR in the additional examination of atypical parkinsonisms.

**Conclusions.** To the best of our knowledge, this is the first study comparing this aspect of neuroinflammation in PSP and CBS. It presents NLR as a promising non-specific parameter in neurodegenerative diseases.

**Key words:** progressive supranuclear palsy, PSP, corticobasal degeneration, CBS, NLR

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## Introduction

Neutrophil-to-lymphocyte ratio (NLR) is a non-specific parameter which has been assessed for almost two decades. It was initially introduced in the evaluation of intensive care unit patients. With the progress of knowledge, NLR has become one of the indicators of increased mortality [1]. Recent studies have evaluated the role of NLR in the examination of COVID-19 [2]. It has also been analysed in the context of ageing and various chronic and acute diseases. The role of NLR in the examination of movement disorders has been evaluated in Parkinson's Disease (PD), Progressive Supranuclear Palsy

(PSP) and Essential Tremor (ET). The results show that PSP is associated with higher NLR than PD. No differences in the NLR among PD subtypes were detected [3]. On the other hand, NLR was shown as significantly increased in PSP compared to PD [4]. ET was not associated with any significant changes in the level of NLR [5]. None of the studies considered blood parameters in Corticobasal Syndrome (CBS). Moreover, the issue of these quotients is not mentioned in the contemporary diagnostic criteria [6].

Progressive supranuclear palsy is a neuropathological term describing aggregation of microtubule-associated protein tau 4-repeats isoform (MAP/tau – 4R) with depositions in neurons

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and glial cells. Microscopically, neurofibrillary tangles associated with tufted astrocytes, oligodendroglial coiled bodies and threads, all comprising 4-R tau, are described as typical for PSP pathology. Lesions are located mainly in the rhombencephalon [7]. Corticobasal degeneration (CBD) is a neuropathological entity describing 4-R tau neuronal inclusions, threads, coiled bodies and, and this is the most characteristic, astrocytic plaques located predominantly in the forebrain [7]. Ante mortem diagnosing enables the identification of only clinical syndromes like progressive supranuclear palsy syndrome (PSPS) and CBS which may proceed not only from PSP and CBD pathologies accordingly.

The boundaries of CBS and PSPS are evaluated on various grounds. Due to overlapping clinical manifestations, interpreting PSPS and CBS as independent entities has become less obvious [8–10]. Contemporary criteria of PSP diagnosis mention PSP-CBS – a syndrome with mixed symptomatology, however multiple cases show dominant PSP or CBS syndrome, with insufficient evidence to diagnose PSP-CBS [11]. Contemporary literature has devised the term ‘4-repeat tauopathy’ (4RT), which is becoming a more popular diagnosis especially in patients with no evident symptomatology. The term is associated with a clinical diagnosis of joint PSP and CBD [8]. The evaluation of the accuracy of this diagnostic term was based on the examination of 195 patients with pathologically confirmed PSP and 55 with CBD. A total of 161 patients with non 4-repeat tauopathies with Multiple System Atrophy, Parkinson’s Disease and 4RT-negative Frontotemporal Lobe Dementia were additionally examined in the comparison. The authors of this research suggest that the diagnosis of ‘possible PSP-CBS’ may be doubtful in obtaining any benefit in the examination of 4RT. The term ‘4RT’ has been further analysed in the context of treatment perspectives and is interpreted as feasible in clinical trials [8, 12].

### Clinical rationale for study

Recent research has shown possible differences in neuroimaging. However, evolving concepts regarding the pathogenesis of both entities show the necessity of the analysis of neuroinflammation as a possible common feature of PSP and CBD, which are pathologies associated with PSPS and CBS [13, 14]. The activation of microglia is shown to be one aspect of neurodegeneration [15]. Though the described entities are syndromes representing various pathologies, the correlation between pathophysiology and symptomatology remains unexplored.

The aim of this study was to assess whether NLR is a non-specific parameter which could differentiate between PSP, CBS and healthy subjects. The results of the study could contribute to the discussion as to whether, in terms of NLR, the boundaries between PSP and CBS are relevant.

### Materials and methods

23 patients (15 male, eight female) with a clinical diagnosis of PSP Richardson (PSP-RS), 18 patients (two male, 16 female) with a clinical diagnosis of CBS, and 32 patients (18 male, 14 female) who formed a control group, were included in the study. The age of patients with PSP-RS ranged from 61 to 82, in CBS from 56 to 86, and in the control group from 64 to 85. All the groups were age matched. All the included patients with PSP-RS and CBS matched the current criteria of diagnosis [6, 11]. All the patients diagnosed with PSP-RS demonstrated oculomotor dysfunction, bradykinesia, disturbances related to postural reflexes, and cognitive and speech deficiencies. Patients with CBS demonstrated asymmetric limb rigidity, axial rigidity, postural instability, bradykinesia, clumsy limbs, and asymmetrical manifestation of symptoms. Both groups experienced falls. All the patients were diagnosed with probable or possible PSP-RS or CBS. All the patients were evaluated using Unified Parkinson’s Disease Rating Scale – III to verify possible response to levodopa treatment. None of the patients included in the study had experienced any improvement after levodopa treatment. The duration of the disease varied from 2-6 years. No pathological examination was conducted. Patients with active inflammatory processes related to infectious, autoimmune and neoplastic diseases were excluded from the study.

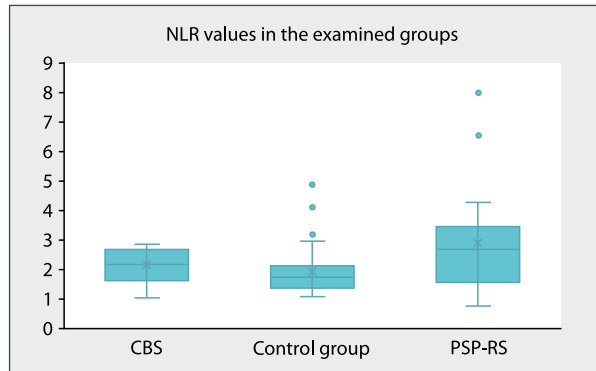
Every patient evaluated in the study underwent complete blood count (CBC) assessment, which was examined during their hospitalisation in the Department of Neurology. The CBC of the control group was evaluated in the occupational medicine department during regular check-ups. Each CBC enabled the analysis of the number of neutrophils and lymphocytes. The obtained data from each was automatically put into a database and was subsequently anonymously analysed. Further analysis was based on the age of the patient, sex, diagnosis, number of neutrophils, number of lymphocytes, NLR, and median of NLR in each group (Tab. 1). All the obtained data regarding NLR was evaluated using Statistica software, using a Kruskal-Wallis test to show possible differences of NLR between the three groups – the PSP-RS, CBS and control. The Kruskal-Wallis test was used due to the non-gaussian distribution in the three examined groups. The differences confirmed in Kruskal-Wallis were subsequently analysed using post-hoc Dunn test. Additionally, in order to obtain groups which were age-matched, statistical analysis was used to avoid the impact of age on possible differences between the groups.

### Results

The evaluation using a Kruskal-Wallis test showed significant differences in the comparison of control groups and patients with PSP-RS ( $p = 0.006413$ ) (Fig. 1, Tab. 2). No other

**Table 1.** Descriptive statistics

	Number of individuals	Gender proportions		AGE Median	AGE Range	NLR Mean	NLR Median	NLR Range	NLR Standard Deviation
		Male	Female						
PSP-RS	23	15	8	73	61–82	2.88	2.69	0.79–7.97	1.66
CBS	18	16	2	71	56–86	2.13	2.18	1.05–2.84	0.53
Control	32	18	14	71	64–85	1.92	1.72	1.08–4.87	0.84

**Figure 1.** Range of values within each group**Table 2.** Comparison of mean NLR values in each group. Post hoc p values (differences in NLR between groups)

	CBS	Control group	PSP-RS
CBS		0.295995 <b>(0.46)</b>	0.786741 <b>(0.75)</b>
Control group	0.295995 <b>(0.46)</b>		0.006413 <b>(0.96)</b>
PSP-RS	0.786741 <b>(0.75)</b>	0.006413 <b>(0.96)</b>	

significant differences were observed in the study ( $p > 0.05$ ). The differences between CBS and control were meaningfully beyond the level of significance –  $p = 0.295995$ . NLR did not show a differentiating potential in the examination of PSP-RS and CBS (Tab. 2).

## Discussion

The obtained results probably suggest that PSP-RS and CBS are factors increasing NLR. Only in PSP-RS did the increase of NLR obtain a significant difference compared to the control group. The increase of NLR in CBS was less pronounced, and was not associated with significant differences compared to the control group. The increase of NLR in both syndromes (PSP-RS and CBS) diminishes the possibility of significant differences between these clinical entities.

Regarding the lack of possibility of pathological verification of the diagnoses, the singular effect in PSP-RS could be related to the fact that PSP-RS is highly predictive for PSP pathology [16]. The CBS correlation with possible CBD pathology is not as common, being associated with about 55% of CBS cases [17]. The fact that PSP-RS is more likely to be a manifestation of 4RT, whereas there was a lack of significant differences between CBS and the control group, could be partly explained by the diverse pathological basis. Additionally, CBS may be based on 4RT as PSP, CBD, Agryophilic Grain Disease, Globular Glial Tauopathies, 3-repeat tauopathies as Frontotemporal Dementia and 3/4R tauopathies as Alzheimer's Disease and Primary Age-Related Tauopathy [18].

To the best of our knowledge, this is the first study evaluating patients with CBS in such a context. The results concerning PSP-RS are convergent with those obtained in a study by Inci et al, however in this study PSP was a homogenic group, without the indication of the disease's variants [4].

The potentially underlying mechanisms which are related to the increase of NLR in the presented tauopathies may be related to microglial activation. Its role in the neurodegeneration in atypical parkinsonisms is not fully understood, and in the case of CBS it is practically unexplored. Microglial activation is interpreted as an inflammatory explanation for neurodegeneration [13]. Most studies have concentrated on the association of tauopathic pathologies and neuroinflammation [13]. The correlation between neuroinflammation and clinical manifestations (PSPS or CBS) is unexplored [13].

The results from our study show that atypical parkinsonism based on tauopathic pathology is a feature causing an increase of inflammatory parameters. However, this does not provide information as to whether it is related to the cause of the disease, or perhaps more likely to its effect.

We are aware of the limitations of our study such as the relatively small number of patients. However, various studies evaluating other features, possibly facilitating the examination of CBS, have been based on smaller numbers of patients [9, 10, 20]. The disparity between the number of male and female patients in the CBS group is related to the rarity of this syndrome. There is no information on the impact of sex. Additionally, it should be stressed that our study is based only on clinical manifestations and does not examine the

pathological background. This factor could possibly impact upon the results of patients with CBS, due to the heterogenic pathological basis of this syndrome. All of the examined patients are alive. Moreover, the main intention of the authors was to evaluate accessible methods in vivo. The NLR is also a non-specific method, providing information on the ongoing inflammation. However, it is examined routinely and can be evaluated rapidly and possibly provide general information.

### Clinical implications/future directions

This study shows that 4RT may be a factor accelerating inflammatory processes, as well as a consequence of these reactions. The obtained results contribute to the discussion on the pathogenesis of 4RT. Another issue emerging from this study is the controversy as to whether to regard PSPS and CBS as separate entities. The boundaries between the diseases are often questioned due to their overlapping symptomatology, especially PSP-RS and CBS. The recent criteria of diagnosis of PSP show PSP-CBS syndrome. This seemed to be a way of diagnosing ambiguous cases. Further analyses of PSP and CBS symptomatology led to the introduction of the diagnosis of '4-repeat tauopathy' [8]. Earlier studies conducted by our research team revealed similar results in neurological and neuropsychological examination and neuroimaging. Patients diagnosed with advanced PSP-RS presented postural deficits and oculomotor dysfunction accompanied by asymmetrical syndrome with limb dystonia. Asymmetrical atrophy tended to occur with midbrain and cerebellar peduncle decreases of volume. Additionally, no significant differences in perfusion were detected [9, 10, 20].

The issue of NLR seems to be one of many factors in this discussion. The evaluation of neuroinflammatory factors in PSPS and CBS requires further research based on larger groups of patients. Studies evaluating the role of inflammatory processes in CBS should verify the possible impact of different pathologies standing behind this syndrome.

**Ethics:** *The Bioethical Committee of the Medical University of Warsaw approved this study. The number of the approval is AKBE151/2020.*

**Conflict of interest:** *None.*

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