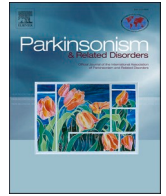




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Short communication



Peripheral Immune pattern in a genetic cohort of p.A53T alpha-synuclein carriers

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ABSTRACT

Introduction: Previous research has shown that inflammatory immune biomarkers including peripheral white blood cell subpopulations differ between Parkinson's disease (PD) patients and healthy controls (HC), with PD exhibiting higher neutrophil to lymphocyte ratio (NLR). The aim of the present report was to assess the peripheral immune profile in patients or asymptomatic carriers harboring the p.A53T alpha-synuclein (SNCA) mutation.

Methods: Data regarding 31 p.A53T SNCA PD patients, 9 asymptomatic mutation carriers and 194 HCs were obtained from the database of the Parkinson's Progression Markers Initiative (PPMI). Focus was placed on peripheral immune blood cells subpopulations and clinical/imaging parameters at baseline.

Results: NLR, Absolute Neutrophil cell count and Neutrophils to total Leukocytes ratio were increased in the p.A53T SNCA PD group as compared to HCs [2.77 vs 2.18 ($p < 0.001$), 4.32×10^3 cells/ μ L vs 3.67×10^3 cells/ μ L ($p = 0.001$), 65.67 % vs 59.55 % ($p < 0.001$)]. Differences in NLR were mainly driven by the male patient subgroup. Lymphocytes to total Leukocytes and Monocytes to total Leukocytes ratio were lower in the p.A53T SNCA cohort as compared to HC [($p = 0.001$) and ($p = 0.002$)]. Finally, we observed a positive correlation between the absolute Lymphocyte count and the mean putamen DATSCAN signal. Asymptomatic carriers did not differ statistically from either group.

Discussion: Our current study provides evidence of a specific pattern of peripheral immune response in the p.A53T SNCA PD group which aligns well with literature data in idiopathic and GBA-PD. Whether this peripheral immune activation represents a contributing cause or an effect of the neurodegenerative process will require further study.

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1. Introduction

The role of peripheral inflammation in Parkinson's Disease (PD) is increasingly recognized. Previous studies have reported alterations in subpopulations of leukocytes in peripheral blood of PD patients. The neutrophil-to-lymphocyte ratio (NLR) is particularly relevant to the peripheral inflammation in PD [1]. A lower lymphocyte count is associated with increased risk of PD [2]. In contrast, neutrophils can have a pro-inflammatory action and enhance inflammatory response by means of chemokines. Additionally, there is evidence that peripheral blood monocytes are also altered in PD and a putative proinflammatory impact of α -synuclein on monocytes has been suggested as a putative mechanism [3]. Notably, NLR has been associated with various indices of disease severity [4]. Whether these peripheral effects contribute to disease pathogenesis or are the result of the pathogenic process in PD is unclear.

Beyond idiopathic PD, Munoz-Delgado et al. assessed the impact of common genetic forms of PD (*GBA1* and *LRRK2* mutation carriers) on peripheral immune markers [5]. Patients with sporadic or GBA-associated PD showed a significantly lower lymphocyte count, a non-significantly higher neutrophil count and a significantly higher NLR than HC, while patients with *LRRK2*-associated PD did not differ from HC. Therefore, GBA-PD, but not *LRRK2*-PD, showed a peripheral inflammatory profile similar to sporadic PD, suggesting different pathophysiological links to the peripheral immune system in these two genetic forms.

The aim of our present report was to evaluate the peripheral immune profile in a genetic cohort of PD patients harboring the p.A53T alpha-synuclein (SNCA) mutation. This mutation was the first genetic defect identified in PD, representing thus the archetypal genetic synucleinopathy. Affected carriers resemble idiopathic PD, but suffer from a rapidly progressive course, especially regarding non-motor symptoms such as cognitive decline [6]. It is of special interest to examine relevant biomarkers in this group, in which aberrant alpha-synuclein is the primary pathogenic factor, to gain insights into the contribution of the peripheral immune component in PD.

2. Methods

Data regarding 31 p.A53T SNCA PD patients, 9 asymptomatic p.A53T SNCA carriers and 194 HCs were obtained from the database of the Parkinson's Progression Markers Initiative (PPMI). Focus was placed on peripheral immune blood cell subpopulations and clinical data, including MDS-UPDRS part III in OFF and ON, MoCA score and DATSCAN imaging signal measurements during the initial study assessment.

Data used in the preparation of this article were obtained on 03/27/2023 (08/15/2024 last update) from the PPMI database (<http://www.ppmiinfo.org/access-data-specimens/download-data>), RRID:SCR006431. For up-to-date information on the study, visit <http://www.ppmi-info.org>. The present study was conducted in agreement with the principles of the Declaration of Helsinki. Signed informed consent was obtained from all participants recruited. The study was approved by the Scientific Board of all PPMI sites involved (including the Scientific Board of Eginition hospital).

Hematological and Biochemical analyses (including measurements of peripheral blood leukocyte subpopulations) have been carried out in Covance laboratories in a uniform fashion, as per the study protocol.

Statistical analysis for baseline comparisons between the p.A53T SNCA PD subjects, Healthy controls (HC) and asymptomatic carriers vs SNCA PD or HC was performed using univariate Analysis of Covariance (ANCOVA). Factors that could have an impact on measurements, including age and sex, were used as covariates in the analysis.

Pearson correlations were calculated between NLR, neutrophil or leukocyte counts and various baseline parameters (basal ganglia subregions DATSCAN signal measurements, MDS-UPDRS score part III in OFF and ON and Montreal Cognitive Assessment (MoCA) score) in the p.

A53T SNCA PD cohort.

3. Results

Demographic and clinical data regarding the p.A53T SNCA PD and asymptomatic carriers cohort have been included in Table 1. The mean age for PD was 50.58 ± 10.48 years and the mean disease duration was 3.81 ± 2.73 years. The average MDS-UPDRS III score in OFF was 23.21 ± 16.35 while in ON was 18.63 ± 12.19 . The mean MoCA score was 25.03 ± 5.28 . The mean age for asymptomatic carriers was 43.44 ± 13.49 years and the mean MoCA score was 27.11 ± 2.21 . (Table 1).

In our study the NLR ratio was significantly increased in the p.A53T SNCA PD group as compared to HCs [2.77 vs 2.18 ($p < 0.001$)]. Differences in NLR were mainly driven by the male patient subgroup [male p.A53T SNCA PD vs HC ($p < 0.001$) as compared to female p.A53T SNCA PD vs HC ($p = 0.071$)] (Fig. 1A). Neutrophil to Monocyte ratio (NMR) was also increased as compared to HCs, 12.85 vs 9.52 ($p < 0.001$).

Moreover, the absolute Neutrophil cell count and Neutrophil to total Leukocytes ratio were also higher than in HC [4.32×10^3 cells/ μ L vs 3.67×10^3 cells/ μ L ($p = 0.001$), 65.67% vs 59.55% ($p < 0.001$) respectively] (Fig. 1B). Differences in Neutrophil absolute cell count and ratio were again mainly driven by the male patient subgroup [male p.A53T SNCA PD vs HC ($p < 0.001$ for absolute count and $p < 0.001$ for ratio) as compared to female p.A53T SNCA PD vs HC ($p = 0.555$ for absolute count and $p = 0.013$ for ratio)].

The absolute Lymphocyte cell count showed a trend towards being decreased in p.A53T PD but did not reach significance [1.66×10^3 cells/ μ L vs 1.86×10^3 cells/ μ L ($p = 0.274$)]. However, Lymphocyte to total leukocytes ratio was lower in p.A53T SNCA cohort as compared to HC [26.16% vs 30.02% ($p = 0.001$)]. In contrast to NLR and Neutrophils, differences in Lymphocyte absolute cell count and ratio were not sex-specific [male p.A53T SNCA PD vs HC ($p = 0.93$ for absolute count and $p = 0.013$ for ratio) as compared to female p.A53T SNCA PD vs HC ($p = 0.045$ for absolute count and $p = 0.027$ for ratio)].

Table 1

Epidemiological and clinical features of the p.A53T SNCA PD and asymptomatic cohorts. (Mean \pm SD).

Cohort Features	p.A53T SNCA PD (N = 31)	Asymptomatic p.A53T SNCA (N = 9)
Age (years)	50.58 \pm 10.48	43.44 \pm 13.49
Sex	16 F/15 M	8 F/1 M
Disease Duration (years)	3.81 \pm 2.73	N/A
MDS-UPDRS III score in "OFF"	23.21 \pm 16.35	0.11 \pm 0.33
MDS-UPDRS III score in "ON"	18.63 \pm 12.19	N/A
H & Y	1.8 \pm 0.71	0
MoCA score	25.03 \pm 5.28	27.11 \pm 2.21
DATSCAN Caudate Right	1.29 \pm 0.53	N/A
DATSCAN Caudate Left	1.26 \pm 0.35	N/A
DATSCAN Caudate Means	1.28 \pm 0.44	N/A
DATSCAN Putamen Right	0.60 \pm 0.30	N/A
DATSCAN Putamen Left	0.64 \pm 0.41	N/A
DATSCAN Putamen Means	0.62 \pm 0.36	N/A
NLR Index	2.77 \pm 1.17	2.34 \pm 2.3
White Blood Cells Absolute Number	6.50 \pm 1.82 $\times 10^3$	5.77 \pm 1.10 $\times 10^3$
Neutrophils Absolute Number	4.32 \pm 1.45 $\times 10^3$	3.59 \pm 0.89 $\times 10^3$
Lymphocytes Absolute Number	1.66 \pm 0.54 $\times 10^3$	1.7 \pm 0.51 $\times 10^3$
Monocytes Absolute Number	0.36 \pm 0.15 $\times 10^3$	0.34 \pm 0.1 $\times 10^3$
Eosinophils Absolute Number	0.13 \pm 0.08 $\times 10^3$	0.1 \pm 0.05 $\times 10^3$
Basophils Absolute Number	0.04 \pm 0.02 $\times 10^3$	0.04 \pm 0.02 $\times 10^3$

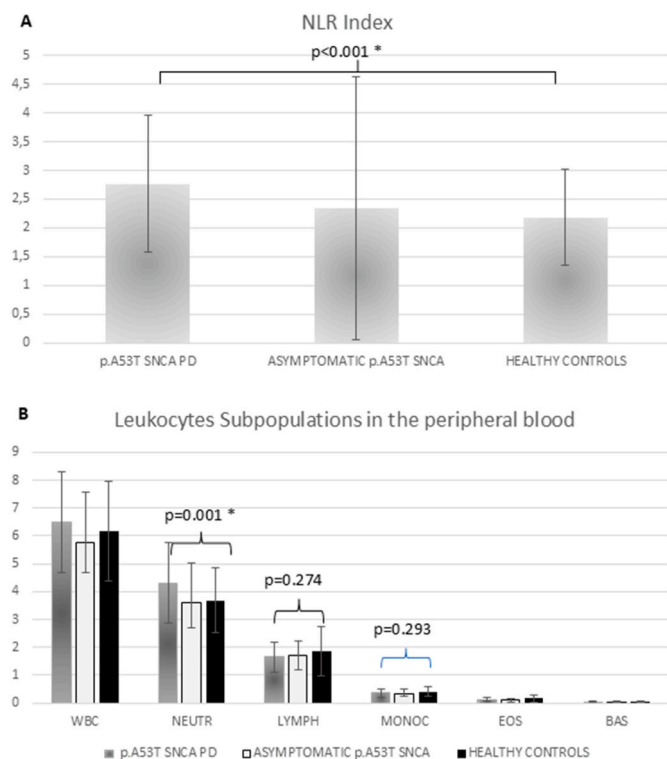


Fig. 1. A. NLR index in p.A53T SNCA carriers (PD and asymptomatic) and healthy control group (Means \pm SD). B. Peripheral Leukocyte subpopulations in p.A53T SNCA carriers (PD and asymptomatic) and healthy control group (Means \pm SD).

Similarly, the absolute Monocyte cell count showed a trend towards being decreased in p.A53T PD but did not reach significance [0.36×10^3 cells/ μ L vs 0.41×10^3 cells/ μ L ($p = 0.293$)]. Monocyte to total Leukocytes ratio was lower in p.A53T PD 5.49 % vs 6.74 % ($p = 0.002$). No significant difference was evidenced regarding Eosinophils and Basophils.

We observed a strong positive correlation between the absolute Lymphocyte count and the mean putaminal DATSCAN signal [Pearson correlation: $r = 0.631$ ($p = 0.005$)]. There was no significant correlation between NLR, the absolute Neutrophil count or the absolute Lymphocyte count and MDS-UPDRS part III scores in OFF or ON, the MoCA score or mean caudate DATSCAN signal. Finally, we could not observe any correlation between disease duration in the p.A53T SNCA PD group and any of the indices of peripheral inflammation (NLR: Pearson correlation $r = 0.166$ ($p = 0.373$)).

As far as asymptomatic p.A53T SNCA carriers are concerned, no statistically significant differences between asymptomatic carriers and either p.A53T SNCA PD or HC could be evidenced regarding leukocyte subpopulations counts despite a trend for intermediate measurements between PD and HC (Supplementary material).

4. Discussion

Peripheral immune system activation, exemplified by an increased NLR, appears to occur in idiopathic and certain genetic forms of PD [5]. In the present study we have assessed the peripheral blood subpopulation profile in a genetic cohort harboring the p.A53T mutation in the alpha-synuclein (SNCA) gene. Our study results provide evidence of a pattern of peripheral immune response in A53T-PD (increased NLR ratio, increased neutrophils and reduced lymphocytes and monocytes) which is consistent with observations in idiopathic PD [1]. We have also observed a positive correlation between the absolute Lymphocyte count and the mean putaminal DATSCAN signal in this genetic PD group,

while correlations between NLR, absolute Neutrophil or Lymphocyte count and other clinical or imaging parameters were not significant.

In broad accordance with our results in the A53T-PD cohort, Munoz-Delgado et al. also found in idiopathic PD a positive correlation between lymphocyte count and DAT indices (and also, in their case, a negative correlation for NLR), indicating that peripheral immune alterations correlate with the extent of dopaminergic neurodegeneration [1,7,8]. Although in our cohort no other correlations of peripheral leukocyte counts with clinical parameters were significant, possibly due to the small number of subjects, our results also point to the general feature that such peripheral inflammatory indices correlate with disease severity.

Our results in A53T-PD would thus be more aligned with idiopathic and GBA-PD and be disparate from LRRK2-PD, where NLR and other indices of peripheral inflammation were not altered [5]. PD populations carrying pathogenic mutations in recessive PD genes like PRKN and PINK1 have not been studied in terms of peripheral immune alterations with the exception of the Cooperative Health Research in South Tyrol (CHRIS) study which assessed heterozygous PRKN mutation carriers in a large population sample and reported a marginally higher NLR ratio as compared to non-carriers [9].

Our study is thus one of a limited number of published reports addressing the impact of genetic forms of PD on peripheral immunity background and the first to assess SNCA mutation carriers. An important merit of our current study is that data we used from the PPMI database have been collected and processed uniformly across PPMI centers, with a thorough standardized clinical/laboratory assessment. On the other hand, a major limitation is the relatively small number of A53T SNCA subjects, albeit a rare condition.

Whether the peripheral immune activation observed here and in other studies contributes to PD pathogenesis or is merely a response to the disease (reverse causation) remains unclear. Given the very high penetrance of the p.A53T SNCA mutation [6], which suggests that the presence of the mutation alone almost invariably leads to disease manifestation, our results would seem to argue more for the latter. However, in this genetic form penetrance is not full and age of onset is variable, suggesting that factors such as peripheral inflammation could still play a role in initiating and possibly sustaining the disease process. It is important in this context to consider the data from the other two genetic PD cohorts (GBA1 and LRRK2). An explanation for the discrepancy between LRRK2 PD carriers and other genetic forms like SNCA or GBA1 mutation carriers (or even idiopathic PD) might lie in the widespread systemic Lewy body (LB) pathology in the latter conditions that could be the cause of the peripheral immune activation that seems to be lacking in LRRK2-PD, which is generally more restricted to the CNS and often occurs in the absence of LB pathology.

On the other hand, there is accumulating evidence supporting the crucial involvement of T lymphocytes subpopulations in PD [8]. In some previous studies an increased proportion of Th1 and Th17 cells (which have a pro-inflammatory effect) and a decreased number of Th2 cells (which exert anti-inflammatory functions) has been recorded in PD, leading to a pro-inflammatory Th1-biased immune response in these patients [5,10]. According to the aforementioned studies, an increased proportion of neutrophils has been linked to chronic inflammation whereas decreased populations of lymphocytes possibly represent an inadequate regulatory pathway. Moreover, another argument in favor of a pathogenic role of inflammatory dysregulation in PD is that in many previous studies, peripheral inflammation (as exemplified by markers like NLR) is robustly related to disease severity [1,4,7,11,12], something also nominally observed in our present study, as previously mentioned. But, again, this could just reflect the fact that a more intense intrinsic pathogenic process of PD leads to enhanced peripheral leukocyte effects.

The peripheral leukocyte profile of asymptomatic p.A53T SNCA carriers was either similar to HC or intermediate between HC and PD, suggesting that a more marked leukocyte subpopulation disequilibrium might occur closer to conversion to clinical PD. Any interpretations

however are limited by the rather low number of asymptomatic carriers.

It appears that there is some degree of sexual dimorphism in the association of peripheral inflammation with PD. In our study, differences in NLR and Neutrophil count were mainly driven by the male patient subgroup, thus implying that A53T-PD males, possibly due to their hormonal background, might manifest more peripheral immune dysregulation compared to female carriers. In accordance, it has been shown that prodromal intestinal inflammation promotes the pathogenesis of PD endophenotypes in male mice expressing the mutant LRRK2 G2019S transgene, through mechanisms that depend on genotypic sex and involve early accumulation of α -synuclein within the gut [13].

Gender differences regarding the role of peripheral immunity on PD neurodegeneration could have implications in future treatment strategies, considering the fact that there are some promising inflammation-related/immunomodulatory approaches in the current pipeline.

Our present results combined with those from other genetic cohorts could help elucidate the role of peripheral indices of inflammation in PD. Longitudinal prospective studies with multimodal data and biomarker collection, with particular attention to PD subtypes, may be especially helpful in this regard. It will be crucial to decipher through such and other studies in animal models whether peripheral immune activation is a driver or just a consequence of the widespread neurodegenerative process in synucleinopathies.

CRediT authorship contribution statement

Christos Koros: Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Athina-Maria Simitsi:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Nikolaos Papagiannakis:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Roubina Antonelou:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis. **Anastasia Bougea:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Dimitra Papadimitriou:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Ioanna Pachi:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Ion Beratis:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Dionysia Kontaxopoulou:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Stella Fragkiadaki:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Evangelos Sfikas:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Ioanna Alefanti:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Chrysa Chrysovitsanou:** Writing – review & editing, Validation, Investigation, Formal analysis. **Efthalia Angelopoulou:** Writing – review & editing, Investigation, Formal analysis. **Marianna Bregianni:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Konstantinos Lourentzos:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Vasilios C. Constantinides:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Georgios Velonakis:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Vasilios Prassopoulos:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Anastasios Bonakis:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Sokratis G. Papageorgiou:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Constantin Potagas:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Marina Picillo:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Paolo Barone:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Maria Stamelou:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Leonidas Stefanis:** Writing – review & editing, Investigation, Formal analysis, Data curation.

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Declaration of competing interest

The authors declare no conflict of Interest.

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Appendix A. Supplementary data

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