Significant Elevation of Serum Pro-Inflammatory Cytokines in *GBA1*-Associated Parkinson's Disease: Implications for Immune-Mediated Pathogenesis

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Objectives

This study aimed to investigate differences in serum inflammatory and neurodegeneration markers between Parkinson's disease (PD) patients carrying GBA1 variants (mPD) and patients with idiopathic sporadic PD (sPD), focusing on the potential role of interferon-gamma (IFN-γ).

Materials

We enrolled 12 patients with GBA1-associated PD and 12 with sporadic PD

Mean	mPD(n=12)	sPD (n=12)	P value
Age (years)	62.3 ± 7.5	63.4 ± 8.0	0.732
Disease Duration	4.2 ± 2.5 years	4.4 ± 2.1 years	0.834
Men/women	10/2	10/2	1.0

Table 1. Patient characteristics by group (no significant differences)

Methods

PD diagnosis was established according to Movement Disorder Society criteria. Serum inflammatory biomarkers measured by ELISA included pro- and anti-inflammatory cytokines (**IL-1β, IL-17A, IFN-γ, IL-4, TNF-α, IL-10**, and **IL-6**). As neurodegeneration-related molecules, **neurofilament light chain** (NfL) and **brain-derived neurotrophic factor** (BDNF) were analyzed. Group differences were assessed with the Mann–Whitney U test, considering **p < 0.05** as statistically significant.

Results and Discussion

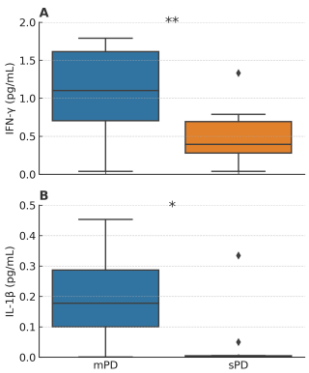

Fig.1 *Serum IFN-γ (A) and IL-1β (B) levels were significantly higher in mPD compared to sPD.* * p < 0.05; ** p < 0.01

IFN-γ levels were significantly elevated in the mPD group compared to the sPD group (**p = 0.00782**), highlighting a distinct inflammatory profile in GBA1-associated PD. Serum levels of IL-1β were also significantly higher in the mPD group (**p < 0.05**). The mPD cohort also showed a high prevalence of comorbidities including depressive disorders (66%) and melanoma (25%). Other markers showed no significant differences.

The **selective elevation of IFN-γ**, together with **increased IL-1β** levels (both key cytokines in innate immune signaling), suggests a specific systemic immune activation in GBA1 mutation carriers[1]. This immune signature may underlie the higher frequency of psychiatric and autoimmune comorbidities observed in these patients, supporting the notion that GBA1-associated PD represents **a biologically distinct subtype** with a prominent **immune-inflammatory phenotype[2]**. Although the sample size is small, our data reinforce the role of immune dysregulation in GBA1-PD pathogenesis and raise important questions about immune-mediated mechanisms contributing to disease heterogeneity[3]

Conclusions

Our findings highlight IFN-γ as a potential peripheral biomarker of immune dysfunction in GBA1-PD, warranting validation in larger cohorts. The distinct immuno-inflammatory profile observed suggests that targeting IFN-γ or its downstream pathways could open novel therapeutic avenues. Modulation of IFN-γ activity might mitigate both motor and non-motor symptoms linked to immune dysregulation, offering a promising strategy to personalize treatment in this PD subgroup.

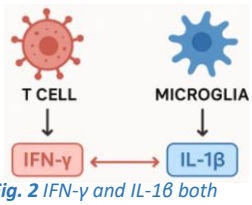

Fig. 2 *IFN-γ and IL-1β both significantly elevated vs. sPD → converging inflammatory pathway*

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3. *Schmidt FM, et al. Cytokine levels in depressed and non-depressed subjects: masking effects of obesity. J Psychiatr Res. 2014;55:29-34.*