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Tonsillar Alpha-Synuclein Accumulation on Parkinson's Disease

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ABSTRACT

Introduction: Parkinson's disease (PD) is a neurodegenerative disorder caused by the misfolding of alpha-synuclein (α-synuclein) proteins. Despite treatment, misdiagnosis rates can reach up to 50% within the first five years, highlighting the need for reliable biomarkers. However, the presence and role of α-synuclein in lymphatic tissues, such as the tonsils, have not been adequately investigated. The tonsils are accessible lymphatic organs that may serve as potential sites for α-synuclein accumulation due to their rich innervation and immune activity. Therefore, this study aims to investigate and compare α-synuclein levels in the tonsillar tissues of patients with Parkinson's disease and healthy controls. By evaluating the tonsils as a potential site of α-synuclein deposition, this study aims to explore their role as a possible biomarker.

Methods: After ethical approval, participants were selected from Neurology Outpatient Clinic diagnosed with idiopathic Parkinson's per UK Parkinson's Disease Society Brain Bank Criteria. The control group comprised individuals undergoing tonsillectomy with no neurological symptoms. We collected and analyzed tonsil tissues from 15 control and 11 PD patients using ELISA to determine α-synuclein concentrations. Data were analyzed using IBM SPSS 25.0, employing Mann-Whitney U and Kolmogorov-Smirnov tests to evaluate differences in α-synuclein levels, with significance set at $p<0.05$.

Results: No significant age or gender differences were noted between groups. PD patients showed higher α-synuclein concentrations in tonsillar tissues compared to controls, with statistical significance.

Discussion: Our results suggest that tonsillar tissue could serve as a novel peripheral biomarker, potentially reflecting α-synuclein accumulation in PD. Future studies are needed to clarify the underlying mechanism of α-synuclein deposition in tonsils, its correlation with disease severity and progression and its potential role in monitoring treatment response.

Keywords: Alpha-Synuclein, Parkinson disease, tonsil

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the misfolding and accumulation of the alpha-synuclein (α-synuclein) protein. Notably, α-synuclein deposits are detectable in the peripheral nervous system, including the myenteric plexus and olfactory areas, even before clinical symptoms develop. The spread of these protein aggregates correlates strongly with the clinical progression of PD (1,3).

The pathogenesis of PD involves the overexpression and misfolding of α-synuclein, which leads to the formation of toxic oligomers and fibrils. These misfolded proteins can propagate from cell to cell, inducing similar misfolding in neighboring cells, which is considered a critical mechanism in disease progression (4-6).

Despite advances, the diagnosis of PD remains primarily clinical and is still challenging, with misdiagnosis rates reaching up to 50% within the first five years of symptom onset (7). This diagnostic uncertainty has driven research efforts toward identifying reliable biomarkers. In recent years, studies have demonstrated that α-synuclein can be detected in various peripheral tissues, including the skin and submandibular gland, highlighting its potential as a biomarker.

However, the presence and role of α-synuclein in lymphatic tissues, such as the tonsils, have not been adequately investigated. The tonsils are accessible lymphatic organs that may serve as potential sites for α-synuclein accumulation due to their rich innervation and immune activity. Whether the tonsils act as a reservoir for misfolded α-synuclein and whether this accumulation correlates with disease severity or treatment response remains unknown.

Therefore, this study aims to investigate and compare α-synuclein levels in tonsillar tissues of patients with PD and healthy controls. By exploring the tonsils as a possible site of α-synuclein deposition, we hope to assess their diagnostic value and better understand their potential role in the disease process.

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Highlights

- **Parkinson's disease is a disorder caused by alpha-synuclein misfolding.**
- **Alpha-synuclein overexpression causes neuronal damage with prion-like spread.**
- **Lymphoid alpha-synuclein in Parkinson's suggests complex non-motor symptoms.**

METHODS

After approval by Kocaeli University Clinical Research Ethics Committee, the participants were selected from the patients who applied to the Neurology Outpatient Clinic and were diagnosed with idiopathic Parkinson's by UK Parkinson's Disease Society Brain Bank Criteria. The control group include the patients with no signs of neurological disease who would receive tonsillectomy at Otorhinolaryngology Department. Written informed consent was obtained from all patients. Tonsil biopsies of 15 participants in the control group (n = 15, age range: 50-80, mean age: 64) and 11 participants in the patient group (n = 11, age range: 60-75, mean age: 68) were analyzed. α-synuclein protein concentration was determined in the collected tonsillar tissues with Elisa method and examined the statistical difference from healthy control tissues.

Liquid nitrogen was used to shock-freeze tonsil materials in the first 1 hour and stored them at -80°C. The samples were thawed at +4°C and homogenized on ice with a hand homogenizer in 1 ml of 1X PBS (phosphate buffered saline) solution. Homogenates prepared in accordance with the BioVision Elisa kit protocol were read on Elisa reader. Concentration levels were calculated separately by the Linear Least Square Regression, Polynomial Quadratic Regression, and Polinomial Cubic Regression methods using standard readings. The samples were processed in duplicate. Since the tissue weights between samples were quite different from each other, we normalized the measured concentration values and weights and prepared them for statistical approaches for comparability.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS 25.0 package. Mann-Whitney U and Kolmogorov-Smirnov tests were used to compare PD+ patients with healthy controls. We considered sufficient with $p<0.05$ as statistically significant.

RESULTS

15 healthy participants were examined in the control group and 11 with PD in the experimental group. There was no significant differences between the two groups in terms of age and gender. The mean disease duration of the Parkinson's patient group was 6.4 years, the mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score was 13.7 and the mean mini mental state examination (MMSE) score was 25.3.

To quantify α-synuclein protein concentrations within tonsil tissues collected from Parkinson's disease patients and healthy controls, we employed the BioVision α-synuclein ELISA Kit. The analytical approach was designed to provide a robust quantification by adjusting for sample variability in interstitial tissue weights.

Quantitative determination of α-synuclein was achieved by interpolating from standard curves generated through first, second, and third-order polynomial regressions based on logarithmic standard concentrations provided by the ELISA kit. Subsequently, α-synuclein concentrations in the tissue samples were normalized against tissue weights to account for variations in interstitial tissue mass.

Due to the potential high variance induced by sample heterogeneity, non-parametric statistical tests were favored over their parametric counterparts. The Mann-Whitney U test was conducted to evaluate differences in normalized α-synuclein concentrations between PD+ patients and healthy individuals, yielding statistically significant results ($p = 0.0108$). Similarly, the non-parametric Kolmogorov-Smirnov test confirmed these findings, demonstrating significant disparities in distribution patterns between the two groups ($p = 0.0106$).

These results, depicted in Figure 1, underscore the enhanced presence of α-synuclein in PD+ patients compared to healthy controls, suggesting potential implications in the pathological processes of Parkinson's disease.

DISCUSSION

Historically, Parkinson's disease was primarily associated with dopaminergic neuronal loss in the substantia nigra due to mitochondrial dysfunction and environmental factors. However, extensive research over the past two decades has established that PD is a systemic neurodegenerative disorder characterized by the widespread misfolding and aggregation of α-synuclein, which can propagate through both the central and peripheral nervous systems.

While the presence of Lewy bodies and α-synuclein aggregates in regions such as the olfactory bulb, vagal nuclei and locus coeruleus is well documented (3,8–11), growing evidence indicates that non-neuronal structures, including peripheral lymphatic tissues, may also play an important role in the disease's pathophysiology. In this context, our study provides new insights by demonstrating significant α-synuclein accumulation in the tonsillar tissue of patients with idiopathic PD compared to healthy controls. This prion-like propagation mechanism further supports the hypothesis that α-synuclein pathology extends beyond the brain.

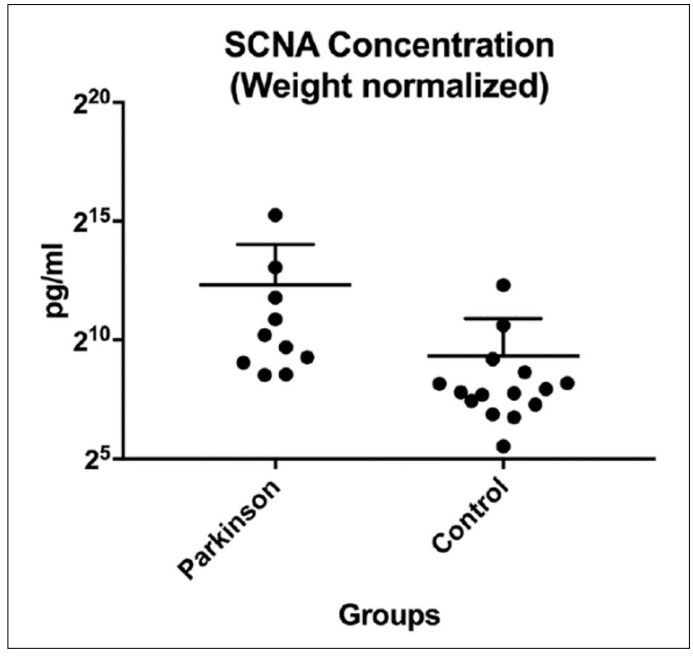

Figure 1. Scatterplot of Normalized Polynomial Cubic Regression Concentration Values for α-synuclein Protein

This finding gains further importance considering recent discoveries on the brain's lymphatic drainage system. It is now understood that the brain removes metabolic waste and misfolded proteins via the glymphatic system, which drains into the deep cervical lymph nodes through meningeal lymphatic vessels (12). Studies have shown that impairment of this drainage pathway may contribute to α-synuclein buildup, glial cell activation and dopaminergic neuronal loss in experimental models (12-14).

Despite advances in imaging modalities such as gadolinium-enhanced MRI or diffusion tensor imaging along the perivascular space practical and safe clinical tools for assessing brain lymphatic clearance are still limited (15-17). In this regard, the tonsils, as easily accessible lymphatic organs with rich neural and immune connections, may represent a promising peripheral site for detecting α-synuclein pathology.

Our results suggest that tonsillar tissue could serve as a novel peripheral biomarker, potentially reflecting α-synuclein accumulation in PD. Future studies are needed to clarify the underlying mechanism of α-synuclein deposition in tonsils, its correlation with disease severity and progression and its potential role in monitoring treatment response.

The detection of α-synuclein in lymphoid tissues such as the tonsils highlights that non-motor symptoms in Parkinson's disease may be more complex than previously understood, potentially involving distinct immunological responses among patients. These findings underscore the need for further research to clarify the role of peripheral lymphatic tissues and to evaluate the tonsils as an accessible biomarker site that could improve our understanding and monitoring of Parkinson's disease beyond its motor manifestations.

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Kocaeli University Ethics Committee with decision number number 270, dated 19.10.2016.

Informed Consent: Written informed consent was obtained from all participants.

Peer Review: External peer review.

Author Contributions: Concept- Pİ, Mİ; Design- Pİ, Mİ; Supervision-- Pİ; Resource: Pİ, Mİ; Materials- ÖÖ, CS, SÇ, Data Collection and/or Processing- Pİ, Mİ, CS, ÖÖ, SÇ; Analysis and/or Interpretation- CS, ÖÖ, SÇ; Literature Search- CS; Writing- CS, ÖÖ, Pİ; Critical Reviews- Pİ.

Conflict of Interest: The authors declare that they have no conflict of interest.

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