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Proceeding Paper

Inflammatory Bowel Disease, Alpha-Synuclein Aggregates and Parkinson's Disease: The InflamaSPark Protocol †

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Abstract: The hallmark of Parkinson's disease (PD) is the accumulation of alpha-synuclein (AS) aggregates. Prior to the central nervous system involvement, PD establishes itself in the gut as a result of the complex interplay between microbiota, the host's immune/neural systems and increased intestinal permeability. Inflammatory Bowel Disease (IBD) patients present a higher number of AS aggregates in the intestinal wall and an increased risk of developing PD. By studying AS aggregates in gut biopsy specimens of IBD patients and controls, this project aims to further clarify the pathophysiology of PD and to explore the potential of gut a biopsy for AS aggregates as a biomarker for prodromal PD.

Keywords: inflammatory bowel disease; gut alpha-synuclein aggregates; Parkinson's disease

1. Introduction

Recent pathophysiological models of Parkinson's disease (PD) suggest that, prior to the central nervous system involvement, the disease establishes itself peripherally, most likely in the gut, as a result of a complex interplay between the microbiota and the host's immune and neural systems facilitated by changes in intestinal permeability [1]. Inflammatory bowel disease (IBD) is a paradigm of inflammation and disruption of intestinal wall integrity, and provides a favorable setting for the formation of alpha-synuclein (AS) aggregates that characterize PD early stages. IBD patients present a higher number of AS aggregates in the intestinal wall and an increased risk of developing PD (risk ratio of 1.28 for Crohn's disease [CD] and 1.30 for Ulcerative Colitis [UC]) [1]. This study aims to evaluate and characterize the presence of AS aggregates in IBD intestinal biopsies, correlating this presence with clinical features to further clarify the pathophysiological of the PD cascade, and to explore the usefulness of gut AS aggregates as biomarkers for PD diagnosis in prodromal stages. This may prove to be particularly useful for populations at higher risk of PD, such as IBD patients [2].

2. Materials and Methods

This is an observational, noninterventional, case-control study with an 18 months enrollment of IBD patients. Sample: (50 patients/50 controls). (a) Cases: convenience sample from patients with IBD under active follow-up in the IBD Outpatient Clinic of Gastroenterology Department. Inclusion criteria: willingness to participate; ability to understand, provide informed consent and comply with all the proceedings; adult patients with a confirmed diagnosis of IBD according to the appropriate diagnostic criteria under follow-up by a gastroenterologist specialized in IBD. Exclusion criteria: IBD limited to the rectum; comorbidities and/or abnormalities in the physical exam with the potential to develop an undue risk during the procedures; clinical suspicion or prior diagnosis of synucleinopathy. (b) Controls: convenience sample from consenting patients undergoing upper and/or lower gastrointestinal endoscopy, whose biopsies, obtained from normal-appearing mucosa, are considered exempt from changes of pathological significance. Variables: demographics; general clinical data; screening for motor and nonmotor symptoms of PD; evaluation of olfaction and IBD-related data (just for the cases). (a) IBD clinical data: age at diagnosis, type (CD or UC) and phenotype of IBD, disease activity, history of surgical procedures and admissions related to IBD, as well as the ongoing and previous medication related to IBD. (b) IBD laboratory data: fecal calprotectin and serum c-reactive protein levels. Processing and analysis of gut biopsies. (1) Optical microscopy (OM): standard analysis in clinical practice for structural and histological characterization. (2) Immunohistochemistry: identification/quantification of AS aggregates in the gut wall of patients and controls. (3) Electron microscopy: ultrastructural analysis of the tissue. At this stage, only the samples of the subjects with high burden of AS aggregates on OM will be evaluated (top 10% of cases and top 10% of controls). Appropriate statistical analysis will be performed. The project will be conducted in accordance with the Helsinki Declaration and will seek approval by the local Ethics Committees. Data collection/analysis will be conducted in compliance with all ethical principles, including proper protection of confidentiality of the participants.

3. Results and Discussion

In line with the current knowledge in this field, we expect to find that compared to controls: (1) IBD patients have a higher burden of AS intestinal aggregates, mainly those with more disease activity/poor response to treatment and, as such, more inflammation and disruption of intestinal wall integrity; and (2) IBD patients have more motor and nonmotor clinical markers of prodromal PD. Additionally, by employing electron microcopy techniques, we expect to fully characterize the AS aggregates at an ultrastructural level. Since the research will be conducted on human subjects (not animal models) with a higher theoretical risk of developing PD (IBD patients), from a "real-world" clinical setting, our results can be a valuable contribution to the field. Ultimately, the InflamaSPark has the potential to further elucidate the complex and mostly unknown cascade of events that occurs in the gut at the prodromal stages of PD.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Instituto Universitário Egas Moniz (protocol code 113/2021; date of approval: 8 July 2021).

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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