

Poster

ALPHA-SYNUCLEIN AND PHOSPHORYLATED ALPHA-SYNUCLEIN IN RESECTED APPENDICEAL SPECIMENS FROM CHILDREN WITH APPENDICITIS: A CROSS-SECTIONAL STUDY

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Background. The pathogenesis of Parkinson's disease (PD) is increasingly hypothesized to originate in the gastrointestinal tract, where acute and chronic inflammatory insults play a crucial role in triggering the upregulation and post-translational modification of alpha-synuclein (a-syn). While the adult vermiform appendix is recognized as a lifelong reservoir for aggregated a-syn, it remains unknown whether this dense accumulation represents a constitutive physiological baseline present from early childhood or a consequence of cumulative aging and inflammatory exposure. Investigating this early inflammatory neuro-immune interaction during childhood could potentially identify the initial spark linking mucosal stress to the clinical onset of Parkinson's disease decades later.

Methods and Data. This cross-sectional study provides the first comprehensive quantitative characterization of native (total) and phosphorylated at serine 129 (pS129) a-syn in resected appendices from a cohort of 65 pediatric patients with acute appendicitis. Histological grading categorized samples into catarrhal, phlegmonous, gangrenous, and perforated groups. Standardized immunohistochemistry, double immunofluorescence, and automated morphometric image analysis (QuPath) were utilized to quantify and localize a-syn species across discrete anatomical layers, including the mucosa, submucosa, lymphoid follicles, and both muscular layers. Finally, these immunohistochemical profiles were systematically correlated with clinical, demographic, and surgical inflammatory parameters.

Results. Both total and pS129 a-syn are constitutively and abundantly expressed within the pediatric appendix, involving both the enteric nervous system and local immune cells. Total a-syn is primarily concentrated in neuronal fibers innervating mucosal glands, submucosal and myenteric plexuses, and muscle layers. Conversely, pS129 a-syn distinctly localizes to nerve fibers surrounding peri-glandular immune infiltrates, intraganglionic macrophages, and the central zone of lymphoid follicles. While absolute levels of total and pS129 a-syn did not significantly differ across appendicitis severity, the pS129/total a-syn ratio exhibited highly dynamic, topographically specific shifts. Phlegmonous appendicitis showed an elevated phosphorylation ratio in the circular muscular layer, which expanded to both muscular layers in gangrenous cases, and localized heavily to the submucosa in perforated cases. Crucially, this pS129/total a-syn ratio strongly and directly correlated with systemic inflammatory markers, including core body temperature, white blood cell count, absolute neutrophils and C-reactive protein, across all anatomical compartments.

Conclusions. This study presents the novelty of being the first to investigate these mechanisms directly in a pediatric population, establishing the vermiform appendix as a highly reactive anatomical epicenter for neuro-immune a-syn crosstalk from early childhood. Our results confirm a strong correlation between acute systemic inflammation and localized shifts in a-syn phosphorylation. However, while these experimental positivities might correlate with long-term outcomes, we cannot definitively declare without a doubt that the pediatric appendix is the absolute site of adult neurodegeneration. Further research is required to fully understand the underlying mechanisms of this expression. Ultimately, following these children longitudinally into adulthood will be essential to establish any true clinical link between early-life appendiceal inflammation and the subsequent development of Parkinson's disease.