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November 10, 2020

Detecting Alpha-Synuclein in Parkinson's and Other Synucleinopathies: Proper Pathological Methods Matter

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The identification of a reliable biomarker in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease is an essential step toward treatment of the underlying problem. It is essential to diagnose these diseases early in order to begin appropriate therapeutic agents. Researchers have worked for decades to identify just such a biomarker. Investigations into radiographic analyses, cerebrospinal fluid assays, blood tests, and assessment of other body fluids have failed to uncover a sensitive and specific biomarker. One of the difficulties in this investigative work has been that different laboratories may look for the same biomarker in different ways, and it has become clear that it is not just the target that is critical, but it is also the methodology used to analyze the specific biomarker.

Since the 1990s it has become clear that Parkinson's disease belongs to a family of diseases in which the protein alpha-synuclein accumulates inappropriately within the nervous system and leads to eventual cell death. These diseases, now termed the synucleinopathies, include Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, pure autonomic failure, and REM sleep behavior disorder. For the past 30 years, researchers have searched for a reliable way to identify this abnormal alpha-synuclein protein. Investigations into spinal fluid, blood, saliva, salivary gland biopsies, and skin have all emerged as potential ways to identify the abnormal protein.

One of the largest studies of synuclein, the Systemic Synuclein Sampling Study (S4), found synuclein deposition in skin was highly specific, but it was seen in only 24% of patients with Parkinson's disease. These results contradict the findings of numerous other investigators, including researchers from the US, Germany, and Italy, who have shown that phosphorylated alpha-synuclein can be seen in the skin of 80-95+% of Parkinson's patients.

A recent editorial in the journal Neurology sought to explore how differences in methodologies explained the discrepant sensitivity findings. Dr. Gibbons, et al highlight that the S4 study used formalin-fixed and paraffin-embedded tissue, a method that has never

gained acceptance in the study of peripheral nerve tissue. The S4 study also used thinly cut sections, which disrupt nerve fiber structure and reduce the ability to visualize intra-neural synuclein deposition. This procedure is in contradiction to international standards for skin biopsy processing to visualize nerves in which only thick, paraformaldehyde-fixed tissue can be used. As the authors of the S4 study note, the deposition of alpha-synuclein is “patchy.” Therefore, a standard 4-micrometer-thick paraffin-embedded tissue section provides only a fraction of the tissue volume obtained with a 50-micrometer section. A significant sampling error is introduced by using thin paraffin sections as was done in the S4 study.

These widely differing study results emphasize the importance of using the best possible methodology when searching for something as important as the first biomarker for the synucleinopathies. At CND Life Sciences, we utilize methods initially developed by researchers from across the world and then further refined in our state-of-the-art lab. We are proud to offer this test as a diagnostic tool for patients and doctors, and we will continue to work with pharmaceutical companies to track their progress in finding better treatments for these diseases.