**Progress Report**

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**Title of Project:** Improving the early diagnosis of amyloid- and paraprotein-associated neuropathies: a heterogeneous group with emerging treatments.

***Summary: (approximately 1,000 words****)*

Amyloid- and paraprotein-associated neuropathies (APAN) are a complex group of neuropathies that are frequently misdiagnosed, leading to progressive disability in affected individuals. The incidence of APAN increases with age and patients with these diseases often have poor quality of life and limited functional capacity. However, despite the apparent need, the diagnosis and management of these disorders is limited by uncertain causality, diagnostic pathways and optimal treatment paradigms.

The aim of the funded research is to determine the early diagnostic features of the amyloid- and paraprotein-associated neuropathies (APAN), in order to refine diagnostic algorithms and thereby improve time to diagnosis and patient outcomes. Specifically, this research uses deep phenotyping to identify the key clinical and imaging characteristics of this disease group and assess for biomarkers of disease progression and disability that can be used to guide and monitor treatment, and prognosticate.

This research hypothesises that the characteristics of the individual diseases comprising the APAN differ in their key clinical, biochemical, electrophysiological and imaging features, and are dissimilar to commonly misdiagnosed entities such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Furthermore, we hypothesise that these defining attributes can be used to enable earlier, more accurate, diagnosis and targets for disease monitoring.

**Research progress:**

Aim 1: Identify the distinguishing clinical and investigative characteristics (neurophysiology, imaging, biochemical and histological) of APAN and compare the causes of previous misdiagnosis and treatment delay for APAN between regional cohorts.

To date, 152 individuals have been recruited, consented and evaluated for this study. Predominantly this includes individuals with Waldenstrom’s Macroglobulinaemia/ MGUS (n=60), hereditary TTR Amyloidosis (n= 58), and CIDP with a paraprotein (n=7). Individuals with rare APAN, including those with neurolymphomatosis, T cell lymphoma and light chain deposition, have also been enrolled in the study. Recruitment is ongoing for an additional year, to improve the breadth, reproducibility and generalisability of our findings. We expect that analysis of this data will be completed in late 2020.

Aim 2: Evaluate potential neurophysiological and imaging biomarkers of APAN in pre-symptomatic and symptomatic patients.

Axonal excitability studies are a non-invasive technique which explores, in vivo, the ion channel expression and membrane properties of axons. This technique can provide insights into the pathophysiology of nerve diseases and is hypothesised in this research to be an early marker of nerve involvement in the APAN. Commonly the median nerve is studied at the wrist, however given the prevalence of carpal tunnel syndrome in the APAN, in particular in amyloidosis, this typical methodology could not be used. As a result, we developed a variation on the traditional technique evaluating the ulnar and superficial radial nerves. We then conducted a pilot study to evaluate the new protocol’s effectiveness, provide normative values and identify the optimal protocol for testing in the APAN cohort.

The preliminary study indicated that the ulnar motor and sensory axons were the most comparable to median motor and sensory axons, with only minimal alteration observed (Figure 1), and hence should be used preferentially when conducting axonal testing on individuals with carpal tunnel syndrome. This data was presented at the Peripheral Nerve Society meeting (Genoa, June, 2019) and is currently under review for publication in an international peer reviewed journal. We have subsequently tested 15 patients with TTR amyloidosis using this new protocol displaying either symptomatic or asymptomatic disease, with analyses underway. Concurrently, phenotypic, imaging, autonomic and further neurophysiological data has been collected for future analyses. We look forward to sharing these results with the Brain Foundation as they become available.

Aim 3: Evaluate potential biochemical markers of APAN in pre-symptomatic and symptomatic patients.

IgM levels are frequently elevated in patients with particular APAN subsets including Waldenstrom’s Macroglobulinaemia (WM), MGUS, MAG neuropathies and some lymphomas. IgM can be easily and inexpensively measured in both serum and CSF. We hypothesised that CSF IgM could be used to distinguish between disease subsets of the APAN, as well as between the APAN and commonly misdiagnosed conditions, such as CIDP. We initially reviewed all instances of CSF IgM testing between July 2011 and 2017 and stratified these according to disease subtype. We found that the combination of elevated Serum and CSF IgM was both sensitive and specific for Bing Neel Syndrome - a subset of WM. Unfortunately, there was insufficient power to detect differences between other APAN and inflammatory nerve conditions. Therefore, this project has been extended to include further samples collected between July 2017 and 2019, to increase statistical power and broaden the applicability of the work. Analyses are ongoing but suggest possible distinction of the IgM associated APAN from other inflammatory nerve diseases. Blood samples have also been taken and stored for further analysis of axonal and demyelination biomarkers in the APAN patients. These have been bio-banked and will be tested in 2020.

Early diagnosis remains the bottleneck to improved patient outcomes and quality of life for individuals with APAN. While novel therapies have the potential to prevent disability, early intervention is essential for success. Our research is working towards clarifying the underlying pathophysiology and improving diagnostic algorithms for the APAN, which with time will improve long term outcomes for individuals with APAN. We look forward to sharing future developments and patient outcomes as these become available*.*



A

B

C

D

Figure 1: Axonal excitability recordings from the Median (Red), Ulnar (Blue), Radial (Green), motor (A,B) and sensory axons (C,D) in normal controls. A, C: Threshold electrotonus (TE), B: Recovery cycle, D: Current/threshold relationship (I/V).