Immunoprofiling of Diabetic and Nondiabetic Lumbosacral Radiculoplexus Neuropathy

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Lumbosacral radiculoplexus neuropathy (LRPN) is a form of non-systemic vasculitis more commonly encountered among patients with type 2 diabetes mellitus. Among patients with diabetes mellitus, it is also referred to as diabetic lumbosacral radiculoplexus neuropathy (DLRPN) or diabetic amyotrophy. Population-based epidemiology study has demonstrated that incidence of diabetic and non-diabetic LRPN is more than twice the incidence of Guillain-Barré syndrome or chronic immune polyradiculoneuropathy, highlighting importance of early identification and management of this disease. Even though systemic vasculitic neuropathies or neuropathies associated with paraneoplastic conditions have validated diagnostic biomarkers, no such sensitive or specific biomarkers exist for LRPN/DLRPN. The diagnosis of these neuropathies continues to be based on clinical evaluation, and many cases require nerve biopsy. As most patients initially present with abrupt severe unilateral proximal lower extremity pain, many are misdiagnosed as compressive lumbosacral polyradiculopathy sometimes supported by the incidental spondylotic changes on magnetic resonance imaging (MRI), leading to unnecessary surgical interventions. Furthermore, even among patients correctly diagnosed, biomarkers for disease prognostication or assessment of risk of relapse are lacking. There exists, therefore, a critical need to identify serum and/or cerebrospinal fluid (CSF) biomarkers that can be utilized as a clinical assay for diagnosis as well as long-term outcome prediction. Without such biomarkers, LRPN/DLRPN diagnostics will continue to challenge many physicians or depend on invasive procedures. Our laboratory has a strong track record in antibody biomarker discovery over the past two decades including paraneoplastic neuropathy biomarkers such as CRMP5. We have utilized technologies such as phage immunoprecipitation sequencing to identify novel antibody biomarkers associated with unique autoimmune or paraneoplastic syndromes. We have also successfully demonstrated autoantigen specific T-cell responses among a subset of these conditions. We have the necessary infrastructure, expertise, and patient samples to carry out this unique project. Our long-term goal is to develop an understanding of immune mechanisms that contribute to the development and progression of LRPN/DLRPN. We also expect to develop diagnostic assays that will be accessible as non-invasive tests to support LRPN or DLRPN diagnosis and prognostication. We expect that by expanding the breadth of our understanding of the immune response, we will provide prognostic information or aid in treatment selection. Our overall objective in this application, which are the next steps towards attainment of our long-term goal, are to (i) identify LRPN/DLRPN specific autoantibodies; (ii) molecularly validate novel biomarkers; (iii) evaluate functional T-cell assay against specific autoantigens frequently detected among LRPN/DLRPN cases.

Hypothesis:

Our central hypothesis is that LRPN cases have humoral response to specific autoantigens, which is a biomarker of underlying CD8+ T cell-driven disease to cognate neural antigen. The rationale for

this project is that a clinically validated biomarker is going to be a useful high-throughput diagnostic assay, and we expect it will also be useful in outcome prediction. Furthermore, these findings may improve our understanding of this relatively common non-systemic vasculitic neuropathy.

Specific Aims:

1. Identify clinically relevant LRPN- and DLRPN-specific autoantibody biomarkers.

2. Assess molecular and clinical validity of novel IgG biomarkers of LRPN and DLRPN.

3. Evaluate autoantigen specific T-cell response among LRPN and DLRPN cases.

Impact:

The proposed project directly addresses multiple Fiscal Year 2022 Peer Reviewed Medical Research Program Topic Areas including peripheral neuropathy, autoimmune disorders, and diabetes mellitus. Upon successful completion of the proposed research, we expect our contribution to aid in better understanding of DLRPN/LRPN disease pathogenesis (Neuroscience strategic goal). The innovative methodology utilized for diagnosis of these immune-mediated neuropathies, has the potential to replace invasive procedures such as nerve biopsy (Autoimmune disease strategic goal). Autoantigen specific IgG and T-cell responses may also have the predictive potential to distinguish between monophasic or relapsing DLRPN/LRPN cases. Since some of the DLRPN cases have association with rapid correction of blood sugar among patients with diabetes, identification of diagnostic or prognostic biomarkers that can be further analyzed in future studies with prospective sample collection may also aid in identification of high-risk patients requiring careful insulin dosing and subsequently decreasing potential diabetes treatment complication (Diabetes strategic goal).