EDITORIAL



# The Importance of Being Significant: "Monoclonal Gammopathies of Neurological Significance"

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Paraproteinemic neuropathies (PPNs) are a heterogeneous group of neuropathies with a common denominator of an abnormal excess immunoglobulin in the serum.[1] The clinical phenotypes of these neuropathies tend to overlap and are a major source of morbidity in patients.[2] A wide array of disorders are on PPNs spectrum including monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis (AL), multiple myeloma, solitary plasmacytoma, Waldenström Macroglobulinemia, Polyneuropathy, Organomegaly, Endocrinopathy, M-protein spike, and Skin changes (POEMS) syndrome, Castleman disease, and a rare syndrome known as Chronic Ataxic Neuropathy, Ophthalmoplegia, Monoclonal gammopathy, cold Agglutinins, and Disialosyl antibodies (CANOMAD).

Approach to PPNs in clinical practice is a complex task both at diagnostic and therapeutic levels. This is particularly the case; if neuropathy is the initial presentation of an underlying hematologic disorder.[3] At times, it is challenging to determine if the paraproteinemia in a patient is solely a coincidence or has a causal relationship with the neuropathy. Furthermore, in some cases of PPNs, the differentiation from chronic inflammatory demyelinating polyneuropathy (CIDP) is difficult.

The role of the neurologist in PPNs is primarily in the initial diagnosis and implementation of therapy for the neuropathy in collaboration with the hematologist.[3] In cases where PPNs occur in patients with a known diagnosis of a hematological disorder, the neurologist's contribution is to determine whether the neuropathy is caused by the underlying hematological disorder or by the chemotherapy used for the disorder.[3,4] Once the diagnosis is made, neurologists usually face the challenge of selecting the appropriate therapy as there is no consensus on the immunotherapy for most cases of PPNs. When there is a hematologic malignancy, the optimal management is currently focused on the malignancy, but the parallel response of the neuropathy to the treatment remains unclear.[5]

In this issue of the journal, Mani et al. describe their experience in the diagnosis and treatment outcome on a large inpatient population with PPNs, who were admitted to a referral center in India between 2010 and 2019.[6] The study included patients who had presented with a neuropathy as the initial manifestation of paraproteinemia and those with a prior diagnosis of a plasma cell disorder were excluded. The major syndromes in their study in decreasing order of frequency were as follows: MGUS (45.9%), POEMS syndrome (24.3%), solitary plasmacytoma (17.6%), multiple myeloma (8.1%), and primary systemic AL (4.1%).[6]

Interestingly, a very high proportion of patients in their study had demyelinating features on electrophysiological studies (68.9%) reflected by a large number of patients with POEMS syndrome (24.3%) as well as demyelinating neuropathy in half of their patients with MGUS. The authors did not have access to antibody assay such as anti-MAG antibody. It is likely that some of the patients with demyelinating MGUS had anti-MAG-associated polyneuropathy/Distal Acquired Demyelinating Symmetrical (DADS) neuropathy. Mani et al. also described several electrophysiological features that can aid in differentiating POEMS and IgM MGUS from other types of PPNs, some of which had been previously described.[7,8,9] The outcome measures in their study were a response to therapy and residual neurologic disability. Majority of the patients were stabilized with standard therapies (65.3%), while only a smaller number of patients showed improvement (30.6%).[6]

Given the significant residual disability despite therapy and assuming the neuropathy as an end-organ damage in the PPNs, Mani et al. suggest using a novel terminology "Monoclonal Gammopathies of Neurological Significance".[6] By using this terminology, they raise awareness about the complexity, diagnostic challenges, and significant disability associated with PPNs. They hypothesized that this could help with earlier diagnosis of PPNs, hence earlier initiation of therapy, and hopefully reduction in the long-term disability. In this endeavor, the authors also propose a diagnostic algorithm for the workup of patients with PPNs.[6] Due to its retrospective nature and including only inpatient population with PPNs, this study is subject to the referral and selection biases. As a result, the findings are skewed toward the clinically more severe forms of PPNs with greater disability, which limits its applicability to the outpatient clinical setting. Mani et al. argue that earlier diagnosis of neuropathy and targeted therapy in patients with PPNs who have hematological stability may result in reduced long-term neurological disability.[6] To test this hypothesis, prospective controlled clinical trials are needed.

In conclusion, suggestions provided by Mani et al., which is based on their experience with a large inpatient population with PPNs, are a step forward that can be incorporated into the future prospective studies and clinical trials to explore the impact

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of timing of the diagnosis and implementation of a variety of therapies including novel biological treatments on neurological outcomes of patients with PPNs.

## Disclosures

The author has no conflicts of interest to declare.

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