MAYO CLINIC

Monoclonal Gammopathy—Associated Peripheral Neuropathy: Diagnosis and Management

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CME Activity

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Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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Learning Objectives: On completion of this article, you should be able to (1) recognize monoclonal gammopathy—associated peripheral neuropathy as an important diagnosis to consider when an M protein is detected during work-up of unexplained neuropathy; (2) differentiate monoclonal gammopathy—associated peripheral neuropathy from POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome and amyloid neuropathy; (3) select appropriate treatments for patients with patients IgM monoclonal gammopathy—associated peripheral neuropathy and non-IgM– related peripheral neuropathy.

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Abstract

Monoclonal gammopathies comprise a spectrum of clonal plasma cell disorders that include monoclonal gammopathy of undetermined significance, multiple myeloma, and Waldenström macroglobulinemia. In this review, we outline the epidemiology, etiology, classification, diagnosis, and treatment of monoclonal gammopathy—associated peripheral neuropathy. Monoclonal gammopathy of undetermined significance is relatively common in the general population, with a prevalence of 3% to 4% among individuals older than age 50 years. Therefore, the presence of M protein in a patient with neuropathy does not automatically indicate a causal relationship. Monoclonal gammopathy—associated peripheral neuropathy is often a difficult diagnosis with limited treatment options. Studies addressing the optimal approach to diagnosis and management of this entity are limited. In addition to a review of the literature, we present a diagnostic approach to patients with monoclonal gammopathy—associated peripheral neuropathy and discuss available data and options for treatment.

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Monoclonal gammopathies comprise a spectrum of clonal plasma cell disorders that include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), and Waldenström macroglobulinemia (WM). The hallmark of these disorders is the secretion of a monoclonal immunoglobulin,

referred to as a monoclonal (M) protein. Peripheral neuropathy is a well-recognized complication of monoclonal gammopathies and a difficult clinical problem in terms of diagnosis and treatment (Table). Because 3% to 4% of the general population older than age 50 years has a monoclonal gammopathy, it is very common to encounter patients with peripheral neuropathy in whom further work-up reveals an M protein. The vast majority of such patients do not have any evidence of overt malignant disease such as MM or WM but rather are at the premalignant MGUS stage in terms of plasma cell biology. Distinguishing patients in whom the M protein is causally related to the peripheral neuropathy from patients in whom the presence of an M protein is incidental and unrelated to the neuropathy is difficult. Further, despite the frequency of this condition and the diagnostic difficulties, there are very limited data to guide management. In this article, we review the epidemiology, etiology, classification, diagnosis, and treatment of monoclonal gammopathy–associated peripheral neuropathy.

Monoclonal gammopathy–associated peripheral neuropathy must be differentiated from 2 other well-characterized plasma cell disorders that cause neuropathy and have strict diagnostic criteria, namely immunoglobulin light chain (AL) amyloidosis and neuropathy associated with osteosclerotic myeloma (POEMS [polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes] syndrome) (Table).[1] In AL amyloidosis neuropathy and in POEMS syndrome, the causal relationship between the neurologic process and the underlying M protein is not in question, and therapy is aimed at the underlying disorder. These entities are reviewed in detail elsewhere.[2-4]

TABLE. Clinical Presentation of Peripheral Neuropathy in Plasma Cell Disorders

Monoclonal gammopathy–associated peripheral neuropathy
Monoclonal gammopathy of undetermined significance
• IgM
• Non-IgM: IgG, IgA
Multiple myeloma (including smoldering multiple myeloma)
Waldenström macroglobulinemia
POEMS syndrome
Systemic immunoglobulin light chain amyloidosis
Unrelated (coincidental neuropathy in patients with a monoclonal protein)

POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

EPIDEMIOLOGY

Peripheral neuropathy can occur in patients across the spectrum of plasma cell disorders from the premalignant MGUS stage to the overt malignant stages of MM and WM. In order to understand the epidemiology of monoclonal gammopathy–associated peripheral neuropathy, one needs to appreciate that MGUS is relatively common in the general population and that the mere presence of an M protein in a patient with neuropathy does not mean that a causal relationship exists. In fact, more often than not the association is probably coincidental, simply reflecting the relatively high prevalence of these 2 disorders in the population.

Monoclonal gammopathy of undetermined significance is present in more than 3% to 4% of the population older than age 50 years.[5] It is a premalignant precursor of MM. There are 3 major types of MGUS depending on the type of M protein secreted: IgM MGUS, non-IgM MGUS (includes IgG MGUS and IgA MGUS), and light-chain MGUS. Progression to malignant disease is the main clinical consequence of MGUS and occurs at a rate of 1% per year.[6] IgM MGUS is associated with a risk of progression to WM, while non-IgM MGUS carries a risk of progression to MM. Light-chain MGUS is a newly discovered entity that is associated with a risk of progression to light-chain type of MM. All forms of MGUS can progress to AL amyloidosis. The other main consequence of MGUS is the ability to cause organ damage due to the immunogenic properties of the M protein including peripheral neuropathy, membranoproliferative glomerulonephritis, and necrobiotic xanthogranuloma. The association of MGUS with neuropathy has been confirmed in a population-based screening study of 17,398 persons living in Olmsted County, Minnesota, 605 with MGUS and 16,793 negative controls.[7] With a mean follow-up of 24 years, totaling 14,373 person-years, there was a significantly higher risk of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in