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## ORIGINAL ARTICLE

# Monoclonal Gammopathy in Patients with Neuropathy

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## SUMMARY

***Background:*** **The incidence of monoclonal gammopathy of undetermined significance (MGUS) in the population of over 50-year-olds is approximately 3% and increases with age. The association between MG and neuropathy has been of interest for several years, but the causal relationship has not yet been clarified.**
***Methods:*** **For 682 patients who visited the Department of Neurology and requested tests for MG work-up, we retrospectively collected demographic and clinical information, such as age, gender, diagnosis, and neurologic and laboratory test results, from their medical records.**
***Results:*** **Out of a total of 682 patients who were suspected of neuropathy and tested for monoclonal gammopathy (MG), twelve (1.76%) showed MG on their serum protein electrophoresis. The most common form was IgM-κ with five patients, followed by IgG-κ, IgG-λ, and biclonal IgG-λ and IgA-κ. The results of the immunoglobulin quantitation test and free light chain assay showed that involved M-protein values in these patients were increased. Some patients were positive for anti-myelin-associated glycoprotein (MAG) antibody, anti-GD1b IgM antibody, anti-GM1 IgG & IgM antibody, and anti-cardiolipin IgM antibody. Also, some had antinuclear antibody (ANA) or antineutrophil cytoplasmic antibody (ANCA).**
***Conclusions:*** **In the future, it is necessary to investigate the pathogenic relationship between M-protein and autoantibodies in patients with neuropathies.**
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## INTRODUCTION

Monoclonal gammopathy (MG) refers to the presence of monoclonal proteins (M-proteins) in the serum and/or urine originating from abnormally proliferating plasma cells in the bone marrow. MG ranges from a highly prevalent, asymptomatic, low-burden precursor disease termed monoclonal gammopathy of undetermined significance (MGUS) to more advanced conditions, including active multiple myeloma (MM) [1,2]. MGUS is defined as a serum M-protein level of < 30 g/L, clonal plasma cells of < 10% in the bone marrow, and, most importantly, the absence of end-organ damage (i.e., hypercalcemia, renal failure, anemia, and bone lesions) or

amyloidosis [3,4]. The incidence of MGUS in the population of over 50-year-olds is approximately 3% and increases to 5% in those aged 70 and over [5]. In addition, because peripheral neuropathy also occurs in 2 - 5% of the general population [6,7], patients with MGUS also have peripheral neuropathy. However, it is difficult to determine whether MGUS and neuropathy occur simultaneously. Moreover, the data are limited. We investigated the incidence and patterns of MG in patients with neuropathy.

## MATERIALS AND METHODS

Among the patients who visited the Department of Neurology of Kyungpook National University Chilgok Hospital in Daegu, Korea, from January 2014 to March 2024, 682 patients underwent an MG work-up. For these patients, we retrospectively collected demographic and clinical information, such as age, gender, diagnosis, and neurological and laboratory test results, from their medical records. Laboratory tests to evaluate MG included serum and urine protein electrophoresis, immunofixation electrophoresis, immunoglobulin quantitation, free light chain assays, and tests for autoantibodies. Bone marrow examination was performed when necessary according to the clinical findings.
This study was approved by the institutional Review Board of Kyungpook National University Chilgok Hospital (IRB file no.: KNUCH 2024-04-027).

## RESULTS

### Incidence and demographic data

Out of a total of 682 patients who were suspected of having neuropathy and were tested for MG, 12 (1.76%) had MG positivity on their serum protein electrophoresis. The mean ages of patients with and without MG were 71.08 ± 14.53 and 63.07 ± 31.91 years, respectively, and there was no significant difference ($p = 0.0831$). Regarding gender, there were 406 male and 264 female patients without MG, and only one female patient out of 12 patients with MG. The clinical diagnoses of the patients are presented in Table 1.

### Patterns of MG

Among the twelve patients with positive MG results, the most common type was IgM-κ, with presence in five patients, including one patient with IgM-κ and IgM-κ, followed by IgG-κ, IgG-λ, and biclonal IgG-λ and IgA-κ (Table 1). Patient 1, who was diagnosed with neuralgic amyotrophy, had clear double bands of IgM-κ and IgM-κ in his serum (Figure 1). The results of the immunoglobulin quantitation test and free light chain assay showed increased M-protein values in these patients, which was consistent with the electrophoresis results. Moreover, there was no evidence of hematological cancer, such as multiple myeloma, in the bone marrow examination performed for confirmation in all 12 patients.

### Types of autoantibodies

The patients had several autoantibodies in their sera. Out of the five patients with IgM-κ, two were positive for anti-myelin-associated glycoprotein (MAG) antibody. Patient 1 was positive for anti-MAG, anti-GD1b IgM, anti-GM1 IgG, IgM, and anti-cardiolipin IgM antibodies. Patient 2 also exhibited anti-MAG and anti-cardiolipin IgM antibodies. Seven patients had antinuclear antibodies (ANA) or antineutrophil cytoplasmic antibodies (ANCA) (Table 1).

## DISCUSSION

MGUS is relatively common in the general population, and further workup in patients with peripheral neuropathy often reveals M-protein. Progression to malignancy is the main concern in MGUS. In a retrospective cohort analysis [8], the risk of hematological malignant transformation was higher in patients with MGUS associated with polyneuropathy than in those without polyneuropathy. The authors suggested that all patients with polyneuropathy should be screened at diagnosis and monitored yearly [9].
A 24-year follow-up study in patients with MGUS and negative controls showed a higher incidence of chronic inflammatory demyelinating polyneuropathy and autonomic neuropathy in patients with MG [10]. Other studies have found M-proteins in 3 - 5% of cases of peripheral neuropathy, which is a statistically significant increase compared with the normal population [11]. In this study, there was a 1.76% incidence of neurologic symptoms in patients with MG. This was low compared with the results of other studies. This may be because our study group included not only confirmed neuropathic patients but also those who visited the hospital with suspected neurological disease. Therefore, it is necessary to conduct additional investigations in patients with confirmed peripheral polyneuropathy. Patients with MG were older, although there was no significant difference compared with those without MG. Notably, there was only one female patient among the 12 patients with MG. She had Guillain-Barre syndrome and IgG-κ M-protein. IgG is the most common type of M-protein in MG; however, in patients with peripheral neuropathy, IgM is much more common, accounting for over 50% of cases. IgG and IgA antibodies are less common in neuropathies [12-16]. Our results showed that five out of the 12 antibodies were IgM and the rest were IgG, which is different from the results of other studies. We could not find the cause of this difference; hence, further investigation is needed. In our study, one of the five patients with IgM-κ showed distinct biclonal bands-IgM-κ and IgM-κ (Figure 1). One patient, who had POEMS syndrome, showed biclonal gammopathy of IgG-λ and IgA-κ, which we previously reported [17]. Biclonal gammopathies are characterized by the production of two dis-

**Table 1. The clinical diagnoses and laboratory test results of twelve patients.**

| Patients' No | Gender | Age | Diagnosis | Type of Monoclonal Gammopathy | Presence of Autoantibodies |
|---|---|---|---|---|---|
| 1 | M | 74 | Neuralgic amyotrophy | IgM-κ and IgM-κ | Anti-MAG Ab, Anti-GD1b IgM, Anti-GM1 IgG & IgM, Anti-cardiolipin IgM |
| 2 | M | 69 | Chronic inflammatory demyelinating polyneuropathy | IgM-κ | Anti-MAG Ab, Anti-cardiolipin IgM |
| 3 | M | 70 | Cerebral infarction | IgM-κ | ANA |
| 4 | M | 68 | Sporadic amyotrophic lateral sclerosis | IgM-κ | ANA |
| 5 | M | 69 | Motor neuron disease | IgM-κ | Anti-GD1b Ab (weak) |
| 6 | F | 74 | Guillain-Barre syndrome | IgG-κ | ANCA |
| 7 | M | 79 | Peripheral polyneuropathy | IgG-κ | ANA |
| 8 | M | 77 | Peripheral polyneuropathy | IgG-κ | ANA |
| 9 | M | 78 | Miller- Fisher syndrome | IgG-λ | Anti-GQ1b Ab, ANA |
| 10 | M | 53 | Amyotrophic lateral sclerosis | IgG-λ | No test |
| 11 | M | 77 | Sporadic amyotrophic lateral sclerosis | IgG-λ | No test |
| 12 | M | 65 | POEMS syndrome | IgG-λ and IgA-κ | ANA, ANCA |

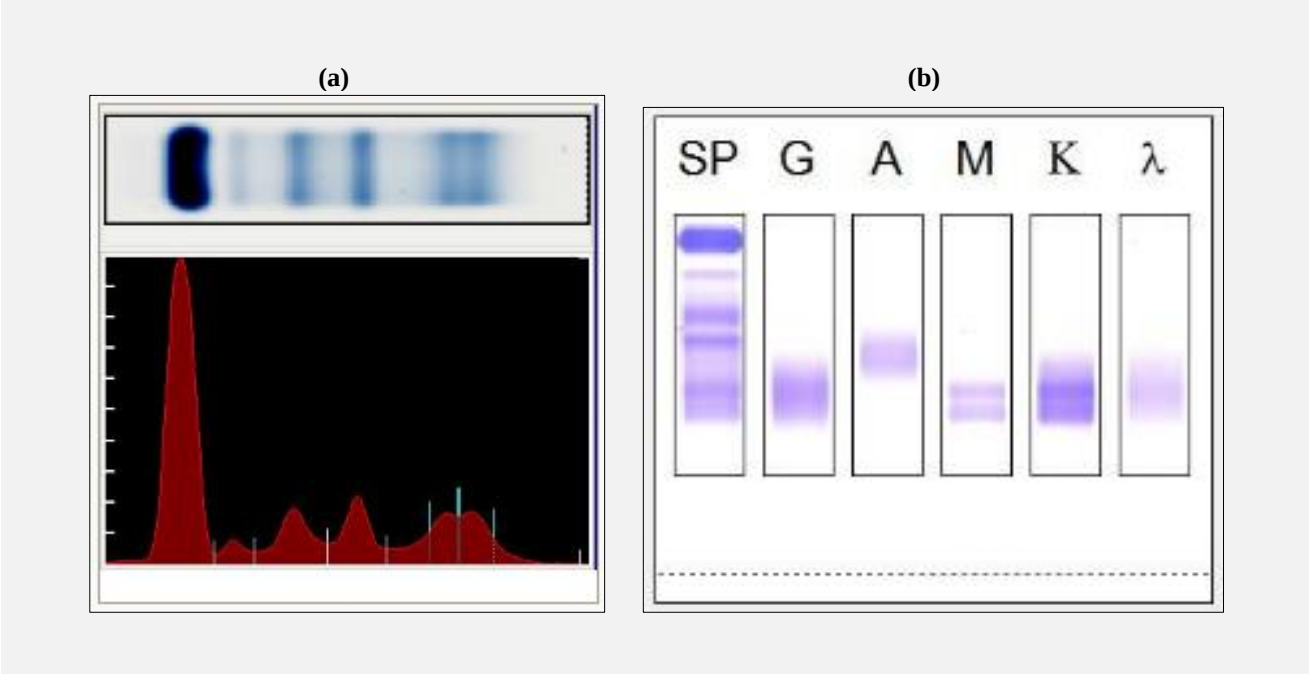


**Figure 1. Clear double bands of IgM-κ and IgM-κ in a patient with neuralgic amyotrophy.**

**(a) Serum protein electrophoresis, (b) Serum immunofixation electrophoresis.**

tinct monoclonal proteins and, therefore, the presence of two monoclonal bands on serum protein electrophoresis. Biclonal gammopathy appears in approximately 1 - 2% of the patients with multiple myeloma [18,19]. Nonetheless, it can also be seen in patients with peripheral neuropathy [20,21], such as IgM-κ and IgG-λ in a patient with demyelinating neuropathy, as reported by Julien et al. [20]. There was no significant difference in

biclonal gammopathy in patients with peripheral neuropathy. In our study, Patient 1 showed a persistent pattern of biclonal gammopathy of IgM-κ and IgM-κ during the follow-up period of three years after diagnosis. Although the cause of peripheral neuropathy in patients with MG has not been fully understood, there is evidence that M-protein reacts with neural antigens and has autologous and homologous anti-nerve activity [22,23]. In patients with neuropathy who are positive for autoantibodies to myelin or nerve components, the most common type of M-protein is IgM and the condition is mainly associated with the presence of MAG antibodies [15,22,24-26]. Patients 1 and 2 in our study had MG of IgM-κ with anti-MAG antibody. Patient 1 was diagnosed with neuralgic amyotrophy and had several autoantibodies, including anti-GD1b IgM, anti-GM1 IgG and IgM, anti-cardiolipin IgM, and anti-MAG. Notably, he had clear double IgM-κ and IgM-κ in his serum immunofixation electrophoresis (IFE), which is thought to be due to the presence of several IgM antibodies. Patient 5, who had motor neuron disease, had anti-GD1b antibody positivity with MG of IgM-κ, and Patient 9, diagnosed with Miller-Fisher syndrome, had anti-GQ1b antibody positivity with IgG-λ. Moll et al. [27] and Tschernsch et al. [28] reported ANA in paraneoplastic neuropathies. In the present study, although no patients had cancer, ANA and ANCA were positive in a few patients, necessitating the need for future research.

The association between MG and neuropathy has been of interest for several years; however, the exact mechanism has not yet been established. The prevalence of MGUS is higher in people of older age, male gender, black race, and those with a family history of MGUS [4]. Although MGUS itself does not show any specific symptoms, symptomatic neuropathy can be found in 8 - 37% of patients with MGUS [13,29]. M-protein can cause an immunological reaction with nerve tissue; therefore, should be approached differently during treatment.

We investigated the incidence and patterns of MG in patients with neuropathy. The present study did not investigate neuropathy in patients with known MG but identified MG in patients with neurological diseases, which poses a limitation to our study. Future studies should investigate the relationship between M-proteins and autoantibodies in patients with neuropathy.

**Declaration of Interest:**

None.

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