Three Families With Polyneuropathy Associated With Monoclonal Gammopathy

Sanne M. Manschot, MD; Nicolette C. Notermans, MD; Leonard H. van den Berg, MD; Jan J. G. M. Verschuuren, MD; Henk M. Lokhorst, MD

Objective: To report familial occurrence of polyneuropathy associated with monoclonal gammopathy.

Design: Case reports.

Patients: We describe 6 patients (3 pairs) with a polyneuropathy associated with IgM monoclonal gammopathy. Four of the 6 patients had a demyelinating polyneuropathy on neurophysiological examination. Three patients had elevated antibodies against myelin-associated glycoprotein. No duplication on chromosome 17 or a mutation on chromosome 1 was found in any family.

Conclusion: Familial occurrence of polyneuropathy without the presence of hereditary motor and sensory neuropathy type 1 is a reason to search for the presence of monoclonal gammopathy.

Arch Neurol. 2000;57:740-742

The association between polyneuropathy and monoclonal gammopathy is well recognized.1,2 The finding of a monoclonal gammopathy in the serum of a patient may lead to the discovery of an underlying hematologic malignancy such as primary amyloidosis, multiple myeloma, Waldenstrom macroglobulinemia, or other related disorders. Frequently, none of these underlying diseases are found, and a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) can be made. An MGUS is found in 0.1% of the population older than 25 years, increasing to 3% in persons older than 70 years.3 Familial occurrence of monoclonal gammopathy has been described occasionally4-8 but the frequency of occurrence of familial monoclonal gammopathy is difficult to assess. The occurrence of monoclonal gammopathy with polyneuropathy in one family has only been described once in a mother and son by Busis et al9; however, these investigators could not definitively rule out hereditary motor and sensory neuropathy (HMSN). Herein we describe 3 patients and their relatives who all have a monoclonal gammopathy and polyneuropathy.

We report 3 sets of patients, each being first-degree relatives. None of the patients had a history of diabetes mellitus, systemic illness, or exposure to neurotoxins. None of the other first-degree relatives of all 3 families had similar complaints. Results of the laboratory and neurophysiological studies are presented in the Table.

CARES 1 AND 2

A 50-year-old woman (patient 1) noted stiffness of her feet and gait instability at age 44 years. She had paresthesias and gait instability in both hands and legs. She noted muscle cramps in her legs and muscle wasting of her hands and calves. On examination there was symmetrical weakness of the finger extensor muscles (Medical Research Council [MRC] 4), the anterior tibial muscle (MRC3), the gastrocnemial muscle (MRC4), the peroneal muscle (MRC3), and the extensor hallucis longus muscle (MRC0). All tendon reflexes were absent. Touch and pain sensation were impaired in her feet in a stockinglike distribution, and touch sensation was impaired in her hands. Vibration sense was absent to her knees and joint position sense was normal. The interossei muscles of her hands and her calves were wasted on both sides. The Romberg sign was positive. Serum IgM-κ was found in a concentration of less than 1 g/L. A biopsy examination of the sural nerve showed IgM deposits and a widening of
the myelin lamellae at the minor dense line in the external layers of myelin lamellae.

A 75-year-old woman (patient 2), mother of patient 1, had a known IgM-κ monoclonal gammopathy since the age of 69 years. At the age of 70 years, she developed Waldenström macroglobulinemia, for which she was treated with chlorambucil. During our investigation the Waldenström macroglobulinemia relapsed and she had been treated with one 5-day course of fludarabine phosphate 3 weeks earlier. She had no complaints in the first years of her disease, but since 6 months she complained about hypesthesias in her right leg and less strength in her right leg and both hands. Furthermore, she noted wasting of muscles in her left leg and she complained about gait instability. On examination there was symmetrical weakness of the extensor hallucis longus muscle (MRC4). Ankle jerks were absent. Touch and pain sensation were normal, the vibration sense was impaired in both toes, her joint position sense was not disturbed. She died at the age of 75 years from progressive Waldenström macroglobulinemia.

CASES 3 AND 4

A 57-year-old man (patient 3) noted paresthesias and hypesthesias in both hands and feet and numbness of his feet at age 50 years. He also noted stiffness of his calves and sometimes gait instability. On examination there was normal strength in all tested muscles. All tendon reflexes were absent, except for the triceps jerks, which were low on both sides. The pain sensation in his feet was impaired, he had a normal touch sensation, vibration sense was impaired in both hands and feet, and his joint position sense was not disturbed. The Romberg sign was negative. Serum IgM-κ was found in a concentration of 7 g/L.

A 65-year-old man (patient 4), brother of patient 3, was examined at the age of 63 years because of a persistently high erythrocyte sedimentation rate, which was discovered during a routine examination. He noted numbness of his feet but had no other complaints. On examination there was normal strength in all tested muscles. All reflexes were normal except for the ankle jerks, which were low on both sides. Touch and pain sensation were normal. The vibration sense in his right toe was impaired, and his joint position sense was normal. The Romberg sign was negative. Serum IgM-λ was found in a concentration of 13.1 g/L.

CASES 5 AND 6

A 78-year-old man (patient 5) noted numbness of his feet and a bandlike feeling around his lower legs at age 71 years. He also noted paresthesias in his lower legs and both his thumbs and gait instability. On examination there was symmetrical weakness in the anterior tibial muscle (MRC4) and the extensor hallucis longus muscle (MRC4) on both sides. Knee jerks were low, and ankle jerks were absent. Touch sensation of both his toes was impaired and pain sensation was impaired to his knees. Vibration sense was absent to his knees, and his joint position sense was disturbed. The interossei muscles of his hands were wasted. The Romberg sign was negative. Serum IgM-κ was found in a concentration of 7.6 g/L.

A 69-year-old man (patient 6), brother of patient 5, was diagnosed as having chronic lymphatic leukemia at the age of 62 years. In the same year he noted paresthesias in his feet and a painful sensation in his toes. Also he reported cold feet. On examination there was normal strength in all tested muscles. All reflexes were normal. Touch and pain sensation in both his feet was impaired. Vibration sense was impaired to his ankles, and his joint position sense was disturbed. The extensor digitorum brevis muscles of both his feet were wasted. The Romberg sign was negative. Serum IgM-κ was found in a concentration of less than 1 g/L. He died at the age of 69 years as a result of the chronic lymphatic leukemia.

COMMENT

We describe 6 patients with polynephropathy associated with IgM monoclonal gammopathy, with antibodies against myelin-associated glycoprotein in 3 patients. As
MGUS in the healthy population is frequently of the IgG isotype, it is not likely that the presence of IgM monoclonal gammopathy in our patients with polyneuropathy is coincidental. In addition, monoclonal gammopathy found in different members of a single kindred is often different.3 In all of our 6 patients a diagnosis of HMSN type I might be considered, but was deemed unlikely as the clinical presentation did not resemble that of HMSN type I, and on nerve conduction studies the demyelination that was found was multifocal, whereas demyelination found in HMSN type I is uniform. In addition, on nerve biopsy examination in patients with MGUS widening of the lamellae is found at the minor dense line in the external layers of myelin lamellae (as in patient 1), whereas in HMSN type I nerve biopsy examination reveals widening of the lamellae at the level of the internal layers of myelin lamellae.2 Furthermore, there was no duplication on chromosome 17 or a mutation on chromosome 1 found in any of the 3 families.10 The diagnosis HMSN type II could be ruled out on neurophysiological examination as the neuropathy was demyelinating in patients 1, 3, 5, and 6.

Another cause of the polyneuropathy might be the use of neurotoxic chemotherapy (eg, fludarabine in patient 2).11 This can be ruled out as the main cause of the polyneuropathy in patient 2, because her complaints started 6 months before she received this treatment. A paraneoplastic neuropathy is also unlikely as such neuropathies have a more progressive course. In patient 6 a paraneoplastic cause is unlikely because on neurophysiological examination he had a demyelinating polyneuropathy.12

We present these cases to describe the occurrence of familial polyneuropathy and the presence of a monoclonal gammopathy. In our opinion there is evidence for an association between the polyneuropathy and the IgM monoclonal gammopathy in all 6 patients, with serum antibodies against myelin-associated glycoprotein present in 3 of the 6 patients.

We conclude that if there is a familial polyneuropathy and HMSN type I can be ruled out as a cause, it is important to search for the presence of a monoclonal gammopathy.

Accepted for publication May 11, 1999.

We would like to thank J. H. van der Knaap, MD, and F. W. Smit, MD, for providing us with the necessary medical information of their patients.

Corresponding author: Sanne M. Manschot, MD, Department of Neurology, University Hospital Utrecht, C03.236, PO Box 85500, 3508 GA Utrecht, the Netherlands.

REFERENCES