VOLUME 2002, ARTICLE 3
MAY 2002

Neurology and Clinical Neurophysiology

ISSN 1526-8748. MIT Press Journals, Five Cambridge Center, Cambridge, MA 02142, USA; tel.: (617) 253-2889; fax: (617) 577-1545; *journals-orders@mit.edu*, *journals-info@mit.edu*. Published one article at a time in html and PDF source form on the Internet. For more information and other articles see:

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The MIT Press

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Characterizing Neuropathies Associated With Monoclonal Gammopathy of Undetermined Significance (MGUS): A Framework Consistent With Classifying Injuries According to Fiber Size

■ Neuropathies associated with monoclonal gammopathy of undetermined significance (MGUS) occur frequently in the elderly. Data from 42 consecutive elderly patients with a MGUS-associated neuropathy—12 patients with IgM MGUS, 25 patients with IgG MGUS, 5 patients with IgA MGUS—were evaluated prospectively using quantifiable clinical criteria and quantitative sensory testing. Results consistent with preferential injury to large fibers were found in patients with IgM isotypes ($P < .005$) but not in patients with IgG isotypes ($P < .0005$ to $.0004$). These findings support an immunologic origin for at least some MGUS-associated neuropathies and provide information important for the clinical evaluation of neuropathies in the elderly. ■

Keywords: fiber size, immunologic, monoclonal gammopathy of undetermined significance (MGUS), neuropathy, quantitative sensory testing (QST)

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In the elderly, serum monoclonal proteins are frequently found in the absence of associated illnesses. MGUS (monoclonal gammopathies of undetermined significance) isotypes, which can be IgM, IgG, or IgA, are found in about 3% of the population older than 65 (Kyle and Dyck, 1993) and in 19% by age 95 (Radl et al, 1975). Twenty-nine percent to 71% of these patients have a neuropathy (Osby et al, 1982; Nobile-Orazio et al, 1992; Suarez and Kelly, 1993; Vrethem et al, 1993), which is considerably higher than the 6% of the population with a neuropathy by age 65. The immunologic dysfunction associated with MGUS has therefore been thought to be causative for neuropathies, and MGUS-associated neuropathies are important in the differential diagnosis of neuropathies in the elderly.

Clinically, patients with an IgM MGUS–associated neuropathy frequently have sensory ataxia consistent with large-fiber injury (Latov, 1995; Ropper and Gorson, 1998). Many of these neuropathies are associated with specific antineural antibodies—providing indirect support for an immunologic etiology. The most well-described neuropathies are those associated with antibodies to anti–myelin associated glycoprotein (anti-MAG) and to the related sulfate-3-glucuronyl paragloboside (SGPG; Kaku et al, 1994; Quarles and Weiss, 1999). Treatment of MGUS-associated neuropathies can be complicated and includes plasmapheresis and immunosuppressive therapy (Blume et al, 1995; Latov, 1995; Latov et al, 1999). For these reasons, clinical information that can be used to characterize these patients, and to characterize neuropathies in the elderly in general, is important for evaluation and management.

Patients and Methods

From 1995 to 1999, we prospectively studied 42 consecutive elderly patients with an MGUS-associated neuropathy—12 patients with IgM MGUS, 25 patients with IgG MGUS, and 5 patients with IgA MGUS. Mean ages (and ranges) were 73 years (68–81 years) for patients with IgM MGUS, 71 years (56–81 years) for patients with IgG MGUS, and 68 years (53–82 years) for patients with IgA MGUS. All patients were evaluated by either Dr. Fisher or Dr. Wilson, who were blinded to the immunologic studies. All patients had both clinical and electrodiagnostic findings consistent with a polyneuropathy. Clinical presentation of all neuropathies was distal, predominantly sensory, and symmetrical.

Serum protein electrophoresis and immunofixation established the presence of monoclonal proteins as well as their specific type, including light chains (κ, λ). All MGUS patients also had a skeletal survey as well as a bone marrow biopsy. In IgG MGUS, the concentration of the monoclonal protein was less than 3 g/dL; in IgA MGUS and IgM MGUS, the concentration was less than 2.5 g/dL. Lymphocytic and plasmacytic infiltrates were less than 5% in the marrow. The bone marrow biopsies did

not provide evidence for amyloidosis, and patients did not have autonomic dysfunction, family history of a neuropathy, or a medical condition associated with secondary amyloidosis. Patients with a neuropathy of another origin (eg, uremia, a lymphoproliferative disorder, multiple myeloma, history of peripheral nerve trauma or compressive neuropathy, radiculopathy) were also excluded. Sera from 7 of the 12 patients with IgM MGUS were examined for antineural antibodies. In 5 of the 7, antibodies to anti-MAG and SGPG were present.

Five reflexes (biceps, brachioradial, triceps, patellar, Achilles) were each rated 1 (present) or 0 (absent) bilaterally. To enhance the reproducibility of the reflex quantification, no attempt was made to quantify diminished reflexes. As a result, a score of 10 (5/side) indicates that all reflexes were present, and a score of 0 indicates that all reflexes were absent.

Sensation was rated quantitatively using the criteria listed in Table 1. A total sensory score of 20 indicates an unremarkable sensory examination, and a score of 0 indicates prominent sensory loss for all modalities tested. This sensory quantification was chosen for its ease of use and reproducibility and for the clinical relevance of the information derived from it.

Using this quantitation of reflex and sensory findings (Table 1), we identified 3 injury patterns: (A) injury consistent with prominent injury to large fibers (reflex score, $\leq$7.0; vibratory sensation, 1 $\leq$ pinprick); (B) mixed injury (reflex score, $\leq$7.0; vibratory sensation, 1 $>$ pinprick); and (C) injury consistent with limited injury to large fibers (reflex score, 77.0). In other words, patients classified as having the type A injury pattern had a relatively prominent decrease in reflexes and vibratory sensation; those with the type B pattern had a less distinctive decrease in vibratory sensation; and those with the type C pattern had a limited decrease in reflexes.

Table 1 Criteria Used to Rate Sensation Quantitatively

Score	*Description*
Vibration and Proprioception	
5	Normal
4	Diminished or absent below ankles
3	Diminished or absent from ankles to below knees
2	Diminished or absent above knees or in fingers
1	Diminished or absent to wrist
0	More extensive
Pinprick and Light Touch	
5	Normal
4	Diminished or absent below ankles
3	Diminished or absent from ankles to below knees
2	Diminished or absent below knees and in hands
1	Diminished or absent in legs and in forearms
0	More extensive

Electrodiagnostic studies included at least median, ulnar, tibial, and peroneal motor conduction studies and sural, median, and ulnar sensory conduction studies in the limbs on either the right side or the left side. Study data—distal motor latencies (DMLs), conduction velocities (CVs), evoked response amplitudes, sensory conduction velocities, and amplitudes—were used to compare the 3 injury-pattern groups.

Seven of the 12 patients with IgM MGUS and 15 of the 25 patients with IgG MGUS underwent quantitative sensory testing (QST; CASE IV System; WR Medical Electronics, Stillwater, Minn) of vibratory-sensation (large-fiber) and cold- and heat-pain (small-fiber) thresholds (Suarez and Dyck, 1999). A person unaware of the patients' clinical information performed this testing. Each patient's left foot was studied. A 4–2–1 methodology was used, except when there were too many errors, in which case a forced-choice paradigm was used. A study was not considered abnormal unless its data were outside the 95th-percentile normal limit for age. QST studies were classified as being consistent with large-fiber injury if large-fiber thresholds were abnormal and small-fiber thresholds were within normal limits; consistent with small-fiber injury if small-fiber thresholds were abnormal and large-fiber thresholds were within normal limits; or consistent with mixed injury if both large- and small-fiber thresholds were abnormal.

A biopsy was performed on the sural nerve of 3 of the 12 patients with IgM MGUS and 1 of the 25 patients with IgG MGUS.

The Fisher exact test was used to compare proportions, and *t* tests were used to compare means. Results were considered statistically significant at $P <$ .05.

Results

Eight of the 12 patients with IgM MGUS but only 2 of the 23 patients with IgG MGUS (in comparison to IgM MGUS) met the clinical criteria for the type A injury pattern—that is, prominent injury to large fibers (Table 2). All 5 patients with antibodies to anti-MAG and SGPG met the criteria for the type A pattern, but so did the 2 patients who tested negative for these antibodies.

QST findings indicated large-fiber injury in 4 of the 7 patients with IgM studied but in none of the 15 patients with IgG ($P <$ .005; Table 3). In all 4 patients with IgM and QST large-fiber injury, clinical classification was type A; in 1 patient with IgM and QST

Table 2 MGUS Isotypes and Clinical Classifications (Nerve Injury Patterns)*

Isotype	*Clinical Classification*		
	Type A	*Type B*	*Type C*
IgM	8	1	3
IgG	2	3	20
IgA	3	2	

*MGUS indicates monoclonal gammopathy of undetermined significance; see text for descriptions of type A, type B, and type C injury patterns.

Table 3 MGUS Isotypes and QST Classifications*

Isotype	*QST Classification*			
	Large Fiber	*Mixed Fiber*	*Small Fiber*	*NDA*
IgM	4 (4A)	1 (1C)	2 (1B, 1C)	0
IgG	0	3 (2A, 1B)	9 (2B, 7C)	3 (3C)

*Associated clinical classifications (nerve injury patterns) are in parentheses. QST studies were not performed for the 5 patients with IgA. MGUS indicates monoclonal gammopathy of undetermined significance; QST, quantitative sensory testing; NDA, no diagnostic abnormality.

large- and small-fiber (mixed) injury, clinical classification was type C. QST was abnormal in all patients studied with IgM MGUS. In 3 patients with IgG and QST mixed injury, clinical classification was type A (2 patients) or type B (1 patient); in 9 patients with IgG and QST small-fiber injury, clinical classification was type B (2 patients) or type C (7 patients); and, in 3 patients with IgG, QST changes were not statistically significant (these patients' clinical classification was type C). In short, for all 6 patients with the type A injury pattern (prominent large-fiber injury), QST studies indicated large-fiber injury.

QST findings did not indicate large-fiber injury in any of the 12 patients with limited clinical evidence for large-fiber dysfunction (type C). Nine of these patients had QST small-fiber injury; in the other 3 patients, meaningful QST abnormalities were not present. One of the 4 patients with the mixed (type B) pattern had QST mixed-fiber injury; the other 3 patients had QST small-fiber injury.

Three of the 5 patients with IgA had the type A pattern; the other 2 patients had the type B pattern. QST studies were not performed for these patients.

Median and peroneal DMLs were significantly longer ($P < .014$ and $P < .005$, respectively) in patients with predominant large-fiber dysfunction (type A injury pattern) than in patients with limited large-fiber dysfunction (type C pattern). Statistically significant differences were not found for ulnar DMLs ($P > .08$), for tibial DMLs ($P > .13$), or for other parameters evaluated—median, ulnar, tibial, and peroneal motor and sensory CVs and evoked response amplitudes and sural CVs and amplitudes ($P < .08$ to .93). For all motor and sensory nerves, mean CVs were slower in patients with the type A pattern than in patients with the type C pattern, but none of these differences were statistically significant—except the difference for peroneal motor CVs ($P < .035$). Sural nerve action potentials were absent in 2 patients with prominent large-fiber injury (type A pattern) and in 7 patients with limited large-fiber injury (type C pattern). This difference was not statistically significant ($P = .44$).

In 3 patients with IgM and the type A injury pattern, a biopsy specimen from the sural nerve showed extensive loss of myelinated fibers. In 1 patient with IgG and the type C pattern, loss of myelinated fibers was limited, though consistent with an axonal neuropathy.

Discussion

The clinical and QST findings in this study are consistent with preferential injury to large fibers in IgM MGUS versus IgG MGUS. The number of patients with IgA MGUS was too small for meaningful analysis.

The reflex arc for phasic myotatic reflexes depends on conduction in large afferent (1A) and large efferent (α) fibers. Vibratory sensation is conducted through large afferent (A-β) fibers; pain sensation and temperature sensation, by contrast, are conducted through small unmyelinated or poorly myelinated fibers. As a result, the degree of loss of phasic myotatic reflexes and vibratory sensation is related to large-fiber dysfunction. Using clinical criteria to identify the size of injured fibers is invariably empiric. The clinical criteria used in this study provided a quantifiable clinical framework for classifying injuries according to fiber size—a framework consistent with accepted concepts of the pathophysiology of nerve dysfunction.

QST is an established, quantifiable method for identifying the types of sensory fibers that have been injured (Suarez and Dyck, 1999). QST studies do not identify all fiber injury that has occurred but rather determine whether sensation subserved by specific fibers is abnormal at a statistically significant level (≥95th percentile for age). QST data help us validate our clinical criteria. For our patients with definable QST abnormalities, QST findings and clinical classifications were in concordance. For all patients with prominent large-fiber dysfunction, QST studies indicated prominent large-fiber injury (type A injury pattern). Such findings were not present in all patients with limited large-fiber disturbances (type C pattern). Further, for all such patients in whom QST abnor-

malities were present, the studies indicated small-fiber injury.

Patients with an IgM MGUS–associated neuropathy and anti-MAG/SGPG antibodies have clinical findings consistent with prominent injury to large fibers, but the same may be true of patients with an IgM MGUS–associated neuropathy without these antibodies. These findings are consistent with other clinical, pathologic, and physiologic reports involving patients with IgM MGUS and neuropathy (Latov, 1995; Ropper and Gorson, 1998). Pathologically, widening of myelin lamellae may occur with deposition of complement and IgM on myelin sheaths (Ritz et al, 1999). Demyelination has been produced experimentally by intraneural injection of patient sera (Hays et al, 1987; Willison et al, 1988; Trojaborg et al, 1989; Tatum, 1993).

Electrodiagnostically, patients with an IgM anti-MAG neuropathy have prominent distal slowing (Kaku et al, 1994). Relatively prolonged DMLs in patients with prominent large-fiber injury (type A injury pattern) are explained by the IgM anti-MAG neuropathies in a subgroup of these patients. Although patients with an MGUS-associated neuropathy may have a distinctive electrodiagnostic pattern of nerve dysfunction, standard electrodiagnostic criteria for axonal versus demyelinating injury are of limited value in characterizing MGUS-associated neuropathies (Fisher and Wilson, 1999; Wilson et al, 2001). Although the tendency for CVs to be slower in patients with predominant large-fiber dysfunction would be consistent with large-fiber injury in these patients, standard electrodiagnostic studies are unsurprisingly not sensitive in defining clinical patterns of large- versus small-fiber injury. To varying degrees, these patients have both large- and small-fiber injuries, and the basis for the resulting clinical manifestations is complex. Electrodiagnostic findings, however, invariably reflect the large-fiber injury, as small-fiber injury is not monitored by conventional electrodiagnostic studies. Further, electrodiagnostic studies might not be expected to be sensitive in making clinical classifications based on sensory findings, as electrodiagnostic abnormalities correlate poorly with these findings.

As the MGUS isotype can be used to identify the type of nerve injury present, this study supports an immunologic origin for at least some MGUS-associated neuropathies. This origin, in turn, supports use of immunomodulating therapy for patients with such a neuropathy. The different effects of IgM MGUS and IgG MGUS could reflect isotype-dependent immunologic reactions or differences in the physiology and vascular supply of large- versus small-fiber nerves. The finding that the different MGUS isotypes have different effects on nerves is important clinically, as findings consistent with prominent large-fiber injury argue for an IgM MGUS and increase the importance of evaluating for associated antineural antibodies.

Acknowledgments

Our study was supported by the Hines Veterans Affairs Hospital, Hines, Illinois.

This article was presented in part at the Annual Scientific Meeting of the American Association of Electrodiagnostic Medicine (AAEM), September 14–16, 2000, Philadelphia, PA.

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