NEUROLOGY

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This information is current as of September 8, 2009

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AMERICAN ACADEMY OF NEUROLOGY

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M.L. Kuijf, MD
M. Eurelings, MD, PhD
A.P. Tio-Gillen, BsC
P.A. van Doorn, MD, PhD
L.H. van den Berg, MD, PhD
H. Hooijkaas, PhD
J. Stork, MD
N.C. Notermans, MD, PhD
B.C. Jacobs, MD, PhD

Address correspondence and reprint requests to Dr. Mark L. Kuijf, Erasmus MC, s'-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
m.kuijf@erasmusmc.nl

ABSTRACT

Background: Detection of serum antibodies to myelin-associated glycoprotein (MAG) by Western blot (WB) is a valuable assay to diagnose a distinct type of demyelinating polyneuropathy with immunoglobulin M (IgM) monoclonal gammopathy. In this study, the diagnostic accuracy of a new and more practical ELISA to detect these antibodies was validated.

Methods: Routine WBs from 2 independent laboratories and ELISA were used to detect anti-MAG IgM in serum from 207 patients with neuropathy and controls. The sensitivity and specificity of these assays were compared and related to the patient clinical and electrophysiologic characteristics.

Results: In ELISA, anti-MAG antibodies were found in serum from 49 (72%) of 68 patients with demyelinating polyneuropathy and IgM monoclonal gammopathy. However, in this subgroup of patients, only 30 (44%) and 37 (54%) were positive in the 2 WBs. All of the patients positive in the 2 WBs were also positive in ELISA. A high correlation was found for IgM activity in ELISA to MAG and sulfate-3-glucuronyl paragloboside (SGPG) (Spearman $\rho = 0.72$, $p < 0.0001$), supporting the notion that the shared sulfated glucuronic acid moiety of MAG and SGPG is preserved. Most patients positive in anti-MAG ELISA had a slowly progressive sensory–motor demyelinating polyneuropathy, even if the WB was negative. In control groups, however, 4 WB-negative patients with a nondemyelinating monoclonal gammopathy–related polyneuropathy were positive in anti-MAG ELISA. The remaining samples were negative in ELISA.

Conclusion: ELISA is more sensitive than Western blot to diagnose anti–myelin-associated glycoprotein related polyneuropathy, although a positive serology may be found in other forms of polyneuropathy as well. **Neurology® 2009;73:688–695**

GLOSSARY

BTU = Bühlmann titer unit; **IgM** = immunoglobulin M; **MAG** = myelin-associated glycoprotein; **ROC** = receiver operating characteristic; **SDS-PAGE** = sodium dodecyl sulfate polyacrylamide gel electrophoresis; **SGPG** = sulfate-3-glucuronyl paragloboside; **UMCU** = University Medical Center of Utrecht; **WB** = Western blot.

Patients with an immunoglobulin M (IgM) monoclonal gammopathy may develop a polyneuropathy if the monoclonal antibody binds to peripheral nerve antigens. In approximately half of these patients, serum antibodies to myelin-associated glycoprotein (MAG) can be detected by Western blotting (WB).[1,2] Most patients with anti-MAG antibodies have a slowly progressive, distal, sensory, or sensory–motor demyelinating polyneuropathy.[2-4] These antibodies recognize the HNK-1 carbohydrate epitope on MAG, which is also present on other peripheral nerve glycoconjugates, including sulfate-3-glucuronyl paragloboside (SGPG).[5] The majority of patients with antibodies to MAG therefore also have serum antibodies to SGPG.[2,4,6] In clinical practice, assays to detect anti-MAG and anti-SGPG antibodies are valuable diagnostic tools to diagnose a distinct subset of patients with chronic demyelinating polyneuropathy and IgM monoclonal gammopathy.

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Anti-MAG WB serology, however, may be negative in patients who otherwise have the typical phenotype of the anti-MAG related polyneuropathy. This may indicate that anti-MAG antibodies are present in these patients but that the sensitivity of the WB is insufficient. Recently, an ELISA was developed to determine serum anti-MAG antibody reactivity.[7] In general, ELISA is a highly reproducible and sensitive technique in which the antibody reactivity can be more easily quantified. At present, it is unknown whether ELISA is more sensitive than WB to detect anti-MAG antibodies and if testing for anti-SGPG antibodies has additional diagnostic value.

In the current study, we used the ELISA to determine the frequency of anti-MAG antibodies in patients with various forms of chronic polyneuropathy and monoclonal gammopathy. These results were compared with those in anti-MAG WB and anti-SGPG ELISA and were analyzed in relation to the clinical and electrophysiologic characteristics following the criteria as proposed by the Standards for Reporting of Diagnostic Accuracy guideline.[8]

METHODS Patients. The study population comprised 154 patients with a chronic polyneuropathy who were recruited and diagnosed by neuromuscular specialists at the Departments of Neurology of the University Medical Center of Utrecht (UMCU) and the Erasmus MC in Rotterdam, The Netherlands, between 1986 and 2005. Medical history, physical examination, electrophysiology, and laboratory results, including immunoelectrophoresis and immunofixation, were obtained according to a predefined diagnostic protocol and eligibility criteria as reported elsewhere.[9]

Of these polyneuropathy patients, 87 had an IgM monoclonal gammopathy and were screened for (pre)malignancies. These studies demonstrated non-Hodgkin lymphoma in 1 patient, Waldenström disease in 2 patients, and breast cancer in 1 patient. No other causes for the neuropathy were found in the other 83 patients. Disease course was distinguished as either moderate progressive (deterioration reaching endpoint within 1 year) or slowly progressive (deterioration reaching endpoint at more than 1 year).[10] Endpoint was defined as a progression of the neuropathy leading to disability decrease of the Rankin disability score of 1 point or decrease of sensory function or strength according to scales as published previously.[11,12] The clinical phenotype was categorized as pure sensory, sensory–motor, or pure motor. Sensory ataxia was defined as disturbance of gait or limb movements, which intensified when the eyes were closed.[13] Nerve conduction and concentric needle examination identified a predominantly demyelinating neuropathy in 68 (77%) of these patients, according to previously described criteria.[14]

The remaining 67 patients with a chronic polyneuropathy had an IgG monoclonal gammopathy (n = 26), chronic inflammatory demyelinating polyneuropathy (n = 30), and chronic idiopathic axonal polyneuropathy (n = 11). For control studies, we also included 19 patients with an IgM monoclonal gammopathy without polyneuropathy and 34 healthy blood donors.

Data collection. Consecutive cases with polyneuropathy associated with a monoclonal gammopathy and patients with IgM monoclonal gammopathy without polyneuropathy were previously included (n = 132).[15] Recruitment of other patient groups was performed in a diagnostic workup context. These patients were selected randomly and not tested in anti-MAG ELISA before. Serum samples were tested in routine diagnostic WBs in 2 independent laboratories (reference standards WB-a and WB-b). All sera positive in anti-MAG or anti-SGPG ELISA and all patients with a demyelinating polyneuropathy and IgM monoclonal gammopathy (n = 74) were retested in WB-b. Data for the ELISA and WB-b were collected prospectively and for WB-a retrospectively. The flowchart of this study is presented in figure 1.

Standard protocol approvals, registrations, and patient consents. Institutional approval from ethical standards committees of the Erasmus MC and the UMCU on human experimentation was received for experiments using human subjects (Erasmus MC METC 2004-242, UMCU METC 02/321). Participants gave written informed consent.

Anti-MAG serology. Pretreatment serum samples from all 207 patients and controls were tested for anti-MAG IgM activity using an ELISA (Bühlmann Laboratories AG, Schönenbuch, Switzerland), according to the manufacturing instructions. Briefly, strips of wells precoated with human brain–derived MAG purified by monoclonal antibodies were incubated in duplicate with serum samples diluted in incubation buffer at 1:1,000 for 2 hours at 4°C. After washing, wells were incubated with anti-human IgM conjugate solution for 2 hours at 4°C. Next, the wells were rinsed and incubated with tetramethylbenzidine substrate solution for 30 minutes at room temperature. The reaction was stopped with an acidic stop solution within 30 minutes, and the extinctions were read at 450 nm using a multiscan reader (Bio-Rad, Hercules, CA). Serum antibody activity was determined by using a standard calibration run and expressed as Bühlmann titer units (BTU).

Serum IgM antibodies to SGPG were determined in all patients and in 17 of the 34 healthy controls using an ELISA (Bühlmann Laboratories AG). Instructions were the same as for the anti-MAG ELISA with a few modifications. Wells were precoated with SGPG purified from bovine cauda equine, also containing small amounts of lactosaminyl homologue, and sera were tested in 1:1,000 dilutions. Serum anti-SGPG antibody activity was expressed as the mean optical density ratio of the patient sample and the calibration sample.

The method of WB-a was previously described.[4] In short, human brain–derived myelin protein fraction was separated by polyacrylamide gel electrophoresis in sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to nitrocellulose blots. The blots were incubated with 1:500 serum dilutions, washed, and subsequently incubated with peroxidase-conjugated rabbit anti-human IgM antiserum. Positive sera, defined by the presence of a 100-kd band, were titrated by serial 2-fold dilutions until negative. The titer was defined as the highest serum dilution that showed the anti-MAG band. In WB-b, myelin was isolated from human brain by a protocol modified from Norton and Poduslo and loaded in 1 mg/mL in

Figure 1   Flowchart of study
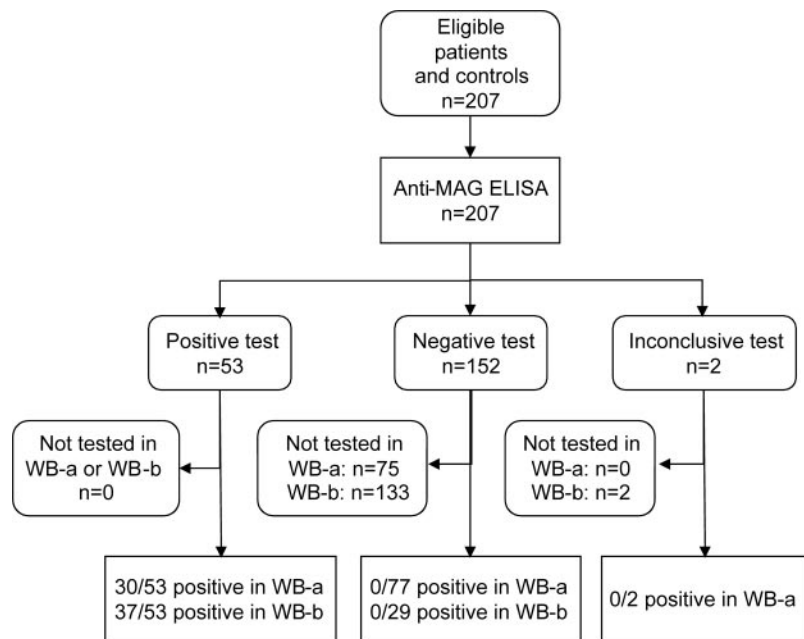
Flowchart of initial data collection according to Standards for Reporting of Diagnostic Accuracy criteria. Western blot (WB)-a and WB-b were used as reference test and applied on a selection of sera as depicted. MAG = myelin-associated glycoprotein.
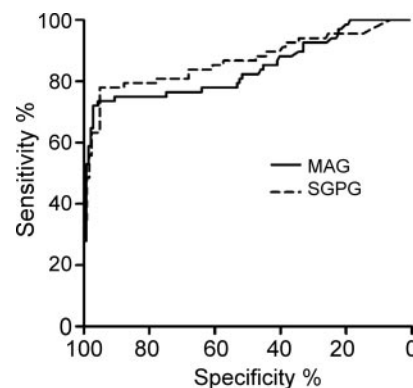
Figure 2   Receiver operating characteristic curve for the presence of serum IgM antibodies to MAG and SGPG determined by ELISA
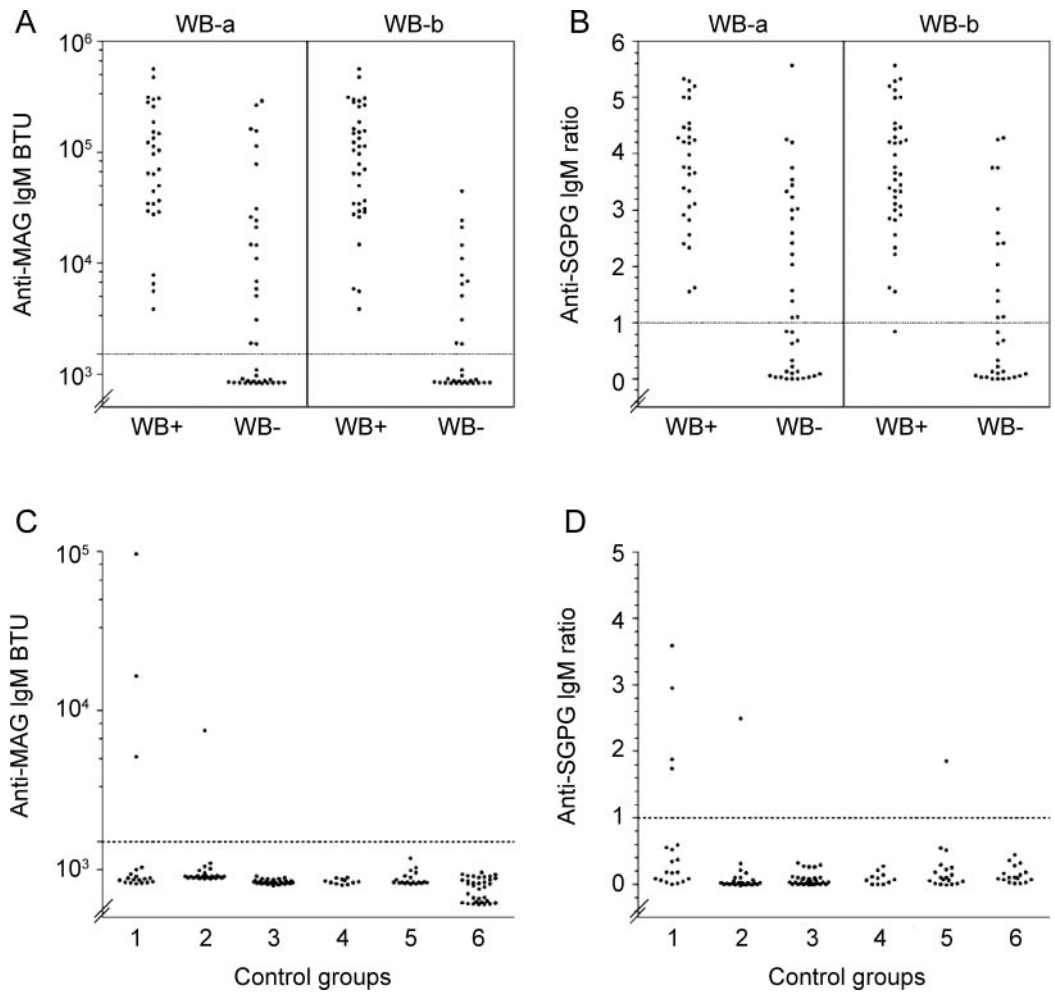

Receiver operating characteristic curves are based on patients with demyelinating polyneuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy patients (n = 68) vs controls (n = 139). Dotted line represents the anti–sulfate-3-glucuronyl paragloboside (SGPG) results, and solid line represents the anti–myelin-associated glycoprotein (MAG) results.

10% SDS-PAGE.[16] Gels were run at 200 volts for 3–4 hours and subsequently transferred to nitrocellulose blots. Next, patient sera diluted 1:500 were incubated at room temperature and, after washing, visualized by horseradish peroxidase anti-human IgM and stained by enhanced chemiluminescences on Kodak x-ray films.

All studies were performed blinded for clinical data and results in other assays. Three individuals blinded for each other's observations screened WB-b readings. Positivity for WB results was then decided on consensus. WB-b was independently screened by 3 coworkers, and final scores were reached by consensus.

Statistical analysis. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values in the anti-MAG and anti-SGPG ELISA to discriminate between patients with typical anti-MAG–related polyneuropathy vs the other patients or healthy controls. Subgroups of patients defined by the test results in anti-MAG WB and ELISA were compared using the χ^2 test or Fisher exact test. Spearman correlation coefficients and κ values were used to compare the anti-MAG antibody activity found in ELISA and WB. Statistical analysis was performed with SPSS for Windows version 14.0 (SPSS Inc., Chicago, IL). P values <0.05 were considered to be significant.

RESULTS Reproducibility and validation of anti-MAG and anti-SGPG ELISA. ROC curves for serum anti-MAG and anti-SGPG IgM activity were constructed based on the 68 cases with demyelinating polyneuropathy and IgM monoclonal gammopathy vs the 139 other patients and controls (figure 2). A high discriminative power for the anti-MAG ELISA (area under the curve 0.84) and anti-SGPG ELISA (area under the curve 0.87) was found. The ROC analysis estab-

lished that the optimal diagnostic cutoff value for the anti-MAG ELISA was 1,500 BTU, and that for the anti-SGPG ELISA was a ratio of 1.0. The coefficient of variance was 6.8% for the anti-MAG ELISA and 6.1% for the anti-SGPG ELISA. The reproducibility of the anti-MAG ELISA was further determined by testing 64 patients with polyneuropathy and IgM monoclonal gammopathy a second time, in which 62 (97%) had the same test result. In a third measurement, the 2 discordant serum samples were negative and were further classified as such (figure 1).

Frequency of serum anti-MAG and anti-SGPG IgM antibodies in patients and controls. Using this diagnostic cutoff value for the anti-MAG ELISA, 53 (26%) of the 207 samples were positive (figures 1 and 3). From these, 49 (92%) had demyelinating polyneuropathy and IgM monoclonal gammopathy, 3 (6%) had nondemyelinating polyneuropathy and IgM monoclonal gammopathy, and 1 (2%) had nondemyelinating polyneuropathy and IgG monoclonal gammopathy. The sensitivity of the anti-MAG ELISA was 72.1% for demyelinating polyneuropathy and IgM monoclonal gammopathy and 100% for the subgroup positive in anti-MAG WB. The specificity of the anti-MAG ELISA was defined in the combined groups of patients with chronic polyneuropathy, excluding patients with a paraprotein without polyneuropathy and healthy controls, to reflect the situation in clinical practice. The specificity of the anti-MAG ELISA was 95.3% for identifying a demyelinating polyneuropathy and IgM monoclonal gammopathy.

Serum from patients and controls was tested in ELISA for the presence of immunoglobulin M (IgM) antibody activity to myelin-associated glycoprotein (MAG) expressed as Bühlmann titer units (BTU) and to sulfate-3-glucuronyl paragloboside (SGPG) expressed as antibody ratios. WB-a = Western blot performed in laboratory a; WB-b = Western blot performed in independent laboratory b. Dotted lines represent cutoff values for positivity. (A) Anti-MAG IgM activity in ELISA is shown for patients with demyelinating polyneuropathy and IgM monoclonal gammopathy (n = 68) and compared with activity in 2 routine diagnostic WBs (WB-a and WB-b), being positive (WB+) or negative (WB−). The left panel compares the activity in ELISA with the results in WB-a, and the right panel compares the activity in ELISA with the results in WB-b. (B) Identical to A except for anti-SGPG IgM activity. (C) Anti-MAG IgM activity of control groups including patients with 1) nondemyelinating polyneuropathy and IgM monoclonal gammopathy (all negative in WB, n = 19), 2) polyneuropathy and IgG monoclonal gammopathy polyneuropathy (all negative in WB, n = 26), 3) chronic inflammatory demyelinating polyneuropathy (n = 30), 4) chronic idiopathic axonal polyneuropathy (n = 11), 5) monoclonal gammopathy without polyneuropathy (all negative in WB, n = 19), and 6) healthy controls (n = 34). (D) Identical to C for anti-SGPG IgM activity.

The test results in ELISA were compared with the results from the 2 routine diagnostic anti-MAG WBs (WB-a and WB-b). In the 68 patients with demyelinating polyneuropathy and IgM monoclonal gammopathy, WB-a was positive in 30 (44%) patients, WB-b was positive in 37 (54%) patients, and anti-MAG ELISA was positive in 49 (72%) patients. All patients with a positive test result in WB-a or WB-b were also positive in the anti-MAG ELISA. In the 38 patients from this subgroup that were negative in WB-a, 19 (50%) were positive in anti-MAG ELISA. From the 31 patients negative in WB-b, 12 (39%) were positive in ELISA. The 2 routine WB-a and

WB-b showed only a moderate agreement ($\kappa = 0.62$): 3 patients were positive in WB-a only, and 10 patients were positive in WB-b only. WB-b showed a weak positive band in the patient with a nondemyelinating polyneuropathy and IgG monoclonal gammopathy that was positive in anti-MAG ELISA.

Anti-SGPG IgM antibodies were found in 55 (29%) of the 190 serum samples tested (figure 3). From these, 49 (89%) had a demyelinating polyneuropathy and IgM monoclonal gammopathy, 4 (7%) had a nondemyelinating polyneuropathy and IgM monoclonal gammopathy, 1 (2%) had a nondemyelinating polyneuropathy IgG monoclonal gam-
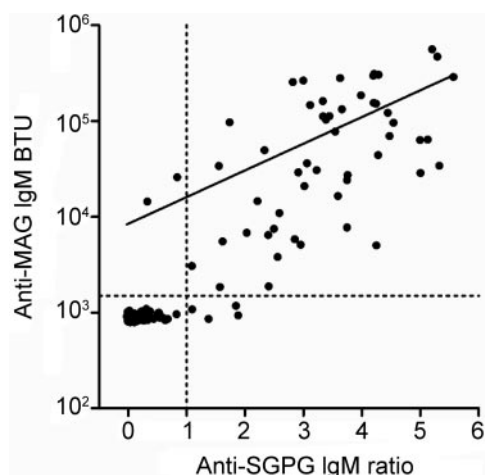
Scatter plot of serum immunoglobulin M (IgM) antibody activity to myelin-associated glycoprotein (MAG) and sulfate-3-glucuronyl paragloboside (SGPG) in ELISA, which shows that these activities are strongly correlated (Spearman ρ = 0.72, p < 0.0001). Dotted lines represent cutoff values for positivity, and solid line represents nonlinear regression line. BTU = Bühlmann titer unit.

mopathy, and 1 (2%) had an IgM monoclonal gammopathy without polyneuropathy. The sensitivity of the anti-SGPG ELISA for demyelinating polyneuropathy and IgM monoclonal gammopathy was 72.1% (and for the subgroup with a positive anti-MAG WB, 100%). The specificity of the anti-SGPG ELISA for demyelinating polyneuropathy and IgM monoclonal gammopathy defined in all patients with a chronic neuropathy was 94.2%.

There was a high correlation between the serum IgM activity determined in the anti-MAG ELISA and anti-SGPG ELISA (Spearman ρ = 0.72, p < 0.0001) (figure 4). Comparing the positive and negative test results of the anti-MAG ELISA and anti-SGPG ELISA, we found a high κ of 0.92. Four anti-SGPG positive patients were negative in anti-MAG ELISA. From these, 1 patient had a nondemyelinating polyneuropathy and IgM monoclonal gammopathy, 1 patient had a IgM monoclonal gammopathy without polyneuropathy, and 2 patients had a demyelinating polyneuropathy and IgM monoclonal gammopathy (figure 3). Two anti-SGPG–negative patients were positive in anti-MAG ELISA, and both had a demyelinating polyneuropathy and IgM monoclonal gammopathy. All sera positive with WB-a were positive in anti-SGPG ELISA. There was 1 patient positive in WB-b but negative in anti-SGPG ELISA. This patient had a

demyelinating polyneuropathy and IgM monoclonal gammopathy and was also positive in anti-MAG ELISA.

Clinical characteristics of patients with anti-MAG serum antibodies in ELISA. The clinical characteristics of the patients with a demyelinating polyneuropathy and IgM monoclonal gammopathy were compared in relation to the test results in anti-MAG ELISA, WB-a, and WB-b (table). Slow progression of disease was more frequently found in patients with positive anti-MAG serum reactivity in both ELISA and WB-a or WB-b compared with those negative in both tests (table). None of the other patient characteristics was associated with the presence of anti-MAG or anti-SGPG antibodies in either ELISA or WB. In addition, there were no differences between patients positive in ELISA only (negative in WB-a or WB-b) compared with patients positive in WB-a or WB-b. One of the patients who was positive in ELISA only was a 64-year-old woman with a slowly progressive demyelinating sensory–motor polyneuropathy. Immunohistologic investigation of a sural nerve biopsy in this patient showed the presence of IgM deposits at the myelin sheets, a finding frequently seen in patients with anti-MAG polyneuropathy.

Four patients from the other chronic neuropathy groups were also positive in anti-MAG ELISA but negative in WB-a. Three patients had a nondemyelinating polyneuropathy and IgM monoclonal gammopathy. One of these patients developed Waldenström disease, and another developed amyloidosis. The electrophysiologic studies performed in these patients did not show signs of demyelination. The other patient also had a nondemyelinating polyneuropathy but with an IgG monoclonal gammopathy and a non-Hodgkin lymphoma.

DISCUSSION The current study showed that in patients with demyelinating polyneuropathy and IgM monoclonal gammopathy, serum anti-MAG antibodies are more frequently detected by ELISA compared with WB. More than 70% of these patients were positive in ELISA, whereas 44% to 54% were positive in the 2 routine diagnostic WBs, a percentage comparable to previous reports on WB.[3,4] Our study indicates that patients who are positive in ELISA but negative in WB may have a polyneuropathy with the typical anti-MAG phenotype. First, these patients had a similar slowly progressive, sensory or sensory–motor demyelinating polyneuropathy as seen in the anti-MAG WB-positive patients. Secondly, nearly all ELISA-positive but WB-negative patients had additional IgM serum antibodies to SGPG (96%), indicating that the antibodies are directed to the shared sulfated glucuronic acid moiety in MAG and SGPG, which is typical for patients with anti-MAG polyneuropathy.[4,6] Third, a sural nerve bi-

Table Characteristics of 68 patients with a demyelinating polyneuropathy and IgM monoclonal gammopathy in relation to serum anti-MAG reactivity in WB and ELISA

	WB-a		WB-b		WB-a or WB-b
	WB⁺ ELISA⁺ n = 30	WB⁻ ELISA⁺ n = 19	WB⁺ ELISA⁺ n = 37	WB⁻ ELISA⁺ n = 12	WB⁻ ELISA⁻ n = 19
Demography					
Age, mean (SD), y	60 (10)	58 (11)	59 (10)	61 (11)	61 (8)
Sex, F:M	7:23	7:12	11:26	3:9	5:14
Slow progression (%)	21 (70)*	8 (42)	24 (65)†	5 (42)	5 (26)
Ataxia (%)	15 (50)	6 (32)	15 (41)	6 (50)	5 (26)
Classification (%)					
Sensory	0 (0)	1 (5)	0 (0)	1 (8)	1 (5)
Sensory–motor	30 (100)	17 (90)	36 (97)	11 (92)	17 (90)
Motor	0 (0)	1 (5)	1 (3)	0 (0)	1 (5)
IgM light chain (%)					
κ	22 (74)	14 (74)	29 (78)	7 (58)	13 (68)
λ	4 (13)	3 (16)	4 (11)	3 (17)	3 (16)
Both	4 (13)	2 (11)	4 (11)	2 (25)	3 (16)
Anti-SGPG positive (%)	30 (100)	17 (89)	36 (97)	11 (92)	2 (11)‡

*p = 0.003 compared with Western blot (WB)⁻ ELISA⁻.

†p = 0.006 compared with WB⁻ ELISA⁻.

‡p < 0.0001 compared with WB⁺ ELISA⁺ and WB⁻ ELISA⁺ in Western blot performed in laboratory a (WB-a) and Western blot performed in independent laboratory b (WB-b).

IgM = immunoglobulin M; MAG = myelin-associated glycoprotein; SGPG = sulfate-3-glucuronyl paragloboside.

opsy from these patients positive in ELISA only showed myelin sheet IgM deposits in myelin sheets, a finding frequently seen in anti-MAG polyneuropathy.[17-21] Together, these observations suggest that ELISA is more sensitive than WB for identifying patients with an anti-MAG–related polyneuropathy.

At present, however, the WB method is considered to be the gold standard technique to determine serum anti-MAG antibodies.[22] An important advantage of WB compared with ELISA is the possibility to verify that the antibodies are directed to the typical 100-kd protein and not to a contaminant in the purified myelin fraction. The ELISA validated in the current study, however, uses a highly purified MAG fraction, showing no contaminants in silver staining, Coomassie blue staining, or immunoblotting (figures e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). Disadvantages of WB compared with ELISA are the difficulties to control the quality of the used myelin fractions and to quantify the staining band. This may limit not only the sensitivity to detect anti-MAG antibodies, but also the interlaboratory reproducibility, as illustrated in the comparison between WB-a and WB-b in our study. Previous studies comparing ELISA and WB also reported the moderate agreement in antibody activity to MAG measured by the 2 techniques.[4,6] Detection of serum antibodies may be influenced by differences in ELISA and WB to capture MAG and present reactive epitopes. Our finding that all patients positive in WB have high anti-MAG antibody activity in ELISA indicates that ELISA at least can be used as a first screening method in the clinical workup of patients with chronic demyelinating polyneuropathy and IgM monoclonal gammopathy. Following the guidelines of the European Federation of Neurological Societies and the Peripheral Nerve Society, it may be useful to confirm the anti-MAG ELISA-positive sera in WB.[23]

The anti-MAG ELISA was also positive in 4 patients with a nondemyelinating polyneuropathy. These patients all had a monoclonal gammopathy (3 IgM and 1 IgG) but were negative in anti-MAG WB. The additional positive serology for SGPG in these patients suggests that their serum antibodies recognized the shared sulfated glucuronic acid moiety in MAG and SGPG. Previous studies indicate that in exceptional cases patients with axonal neuropathy can be positive for anti-MAG antibodies, even in WB.[24] Serum antibodies from anti-MAG–positive patients may bind to peripheral nerve axons, especially if there is additional serum reactivity for SGPG.[25] This staining pattern may reflect the presence of SGPG in human peripheral nerve axons.[26] These findings indicate that electrophysiologic studies are required in the diagnostic workup and cannot be replaced by anti-MAG serology. If the routine testing for anti-MAG antibodies is restricted to patients with a demyelinating form of polyneuropathy, this may

not influence the specificity of the ELISA in the diagnosis of the classic anti-MAG polyneuropathy.

Disease markers for chronic immune-mediated neuropathy are required to classify diseases and predict the response to therapy. The presence of serum IgM antibodies to MAG defines a distinct type of neuropathy in which these antibodies are probably involved in the pathogenesis of disease.[19,27-29] Previous studies using WB indicate that approximately half of the patients with demyelinating polyneuropathy and IgM monoclonal gammopathy have anti-MAG antibodies.[3,4] The current study indicates that anti-MAG antibodies are found in more than 70% of patients with a typical IgM monoclonal gammopathy–related demyelinating polyneuropathy. This may indicate that the group of patients with demyelinating polyneuropathy and IgM gammopathy is more homogenous than previously thought. Patients with a nondemyelinating polyneuropathy or with a demyelinating polyneuropathy without detectable IgM gammopathy incidentally may have anti-MAG antibodies.[17,24] Nerve biopsy studies are needed to determine whether these patients also have the typical anti-MAG–related immunopathology. Detection of anti-MAG antibodies is also relevant because it may help to target immunotherapy. It has been shown that IgM anti-MAG neuropathy usually responds poorly to most conventional immunomodulatory therapies.[30] Recent studies in IgM anti-MAG neuropathy, however, indicated promising results using rituximab, a chimeric monoclonal that targets B cells, in which anti-MAG titers decay with clinical improvement.[31-34] Interestingly, most clinical improvement was reported in patients with the lowest baseline anti-MAG titers,[33] further illustrating the clinical relevance of a sensitive technique to demonstrate anti-MAG antibodies. Our study shows that the ELISA can be used as a sensitive and reliable screening method for determining anti-MAG antibodies.

AUTHOR CONTRIBUTIONS

Mark L. Kuijf and Bart C. Jacobs conducted statistical analyses.

DISCLOSURE

Dr. Kuijf received a non–industry-sponsored travel grant from the Peripheral Nerve Society. Dr. van Doorn serves on a scientific advisory committee for Octapharma. Dr. van den Berg received a travel grant from Baxter to attend an American Academy of Neurology Annual Meeting. Dr. Eurelings, Ms. Tio-Gillen, Dr. Hooijkaas, Dr. Stork, Dr. Notermans, and Dr. Jacobs report no disclosures.

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