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ORIGINAL ARTICLE

Prevalence and clinical profiles of anti-myelin-associated glycoprotein neuropathy in Japan: A nationwide survey study of 133 patients

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Abstract

Background and purpose: The aim of this study was to determine the prevalence of anti-myelin-associated glycoprotein (MAG) neuropathy and the current status of such patients in Japan.

Methods: We conducted a nationwide survey in 2021 using established epidemiological methods. Questionnaires were sent to all neurology and pediatric neurology departments throughout Japan to identify patients with anti-MAG neuropathy. An initial questionnaire was used to determine the number of patients, with a second one used to collect detailed clinical information.

Results: The estimated number of patients with anti-MAG neuropathy was 353, with a prevalence of 0.28 per 100,000 and an incidence of 0.05 per 100,000. The detailed clinical profiles of 133 patients were available. The median (range) age of onset was 67 (30–87) years, with a prominent peak in the age range 66–70 years, and the male-to-female ratio was 3.6. Most patients had distal sensory-predominant polyneuropathy, and neuropathic pain (50%), or sensory ataxia (42%), while 18% had Waldenström's macroglobulinemia or multiple myeloma. Intravenous immunoglobulin was the most frequently used treatment (65%), but the response rate was <50%, whereas rituximab was given in 32% of patients, and 64% of these showed improvement. At the last visit, 27% of patients could not walk independently.

Conclusions: This study on anti-MAG neuropathy provides updated insights into the epidemiology of this disease, clinical profiles, and treatment approaches in Japan. Rituximab therapy, used for only one-third of the patients, demonstrated efficacy. During the final visit, a quarter of the patients were unable to walk independently. Further studies are warranted to determine the optimal management of this rare and intractable disorder.

KEYWORDS
anti-myelin-associated glycoprotein, epidemiology, nationwide survey, neuropathy, neuropathy, prevalence

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INTRODUCTION

Demyelinating neuropathy with anti-myelin-associated glycoprotein (MAG) is an uncommon cause of chronic immune-mediated neuropathy, characterized by immunoglobulin M (IgM) paraproteinemia. Monoclonal gammopathy is usually a monoclonal gammopathy of uncertain significance (MGUS) or occasionally a hematological malignancy, such as Waldenström's macroglobulinemia or multiple myeloma. Polyneuropathies in MGUS patients encompass a heterogeneous group of nerve disorders lacking a clear classification, whereas anti-MAG neuropathy has the most homogeneous clinical and neurophysiological presentations. IgM paraproteins can bind to MAG in peripheral nerves, resulting in myelin uncompaction and consequent demyelinating polyneuropathy [1, 2].

In previous reports, the prevalence of neuropathy among MGUS patients varied considerably, from 5% to 17% [3–5]. Despite this, no systematic epidemiological study has focused on anti-MAG neuropathy, and its prevalence remains unknown.

In terms of treatment, two randomized controlled trials on anti-MAG neuropathy suggested a potential moderate effect of rituximab on neuropathy [6, 7]. Nevertheless, both studies failed to achieve the primary endpoints, preventing rituximab from gaining approval for treating anti-MAG neuropathy. Given such perplexing circumstances, real-world data on the proportion of patients treated with rituximab remains unknown.

The aim of this study therefore was to determine the prevalence and incidence of anti-MAG neuropathy and the current state of treatment in Japan, using a nationwide survey.

METHODS

Study design

This national survey was conducted in two parts: a primary and a secondary survey. The primary survey focused on assessing the prevalence of anti-MAG neuropathy, while the secondary survey focused on clinical characteristics, laboratory findings, treatment, and outcomes. This survey covered the entire Japanese population, which the National Bureau of Statistics reported to be approximately 125.48 million in March 2021, and followed the guidelines of the third edition of the Nationwide Epidemiologic Survey Manual for Rare Diseases established by the Research Committee on the Epidemiology of Intractable Diseases [8].

Ethics review

The research plan was approved by the Ethics Committee at the School of Medicine, Chiba University (approval no. M10011). Data were collected through standard medical practice, thus eliminating the need for written consent from patients. Information about the study and the option to opt out was provided on the website of the Department of Neurology, Chiba University Graduate School of Medicine.

Primary survey

The primary survey was carried out in September 2021. The selection of hospitals offering neurology and pediatric services was based on the registry of medical institutions insured under the Ministry of Health, Labour and Welfare of Japan. Inclusion criteria for patients with anti-MAG neuropathy were based on the 2010 electrodiagnostic standards of the European Federation of Neurological Society and the Peripheral Nerve Society [9]. The cut-off for anti-MAG antibodies was set at over 1000 BTU (Buhlmann titer units) as measured by enzyme-linked immunosorbent assay, consistent with criteria used in previous clinical studies [6].

Secondary survey

The secondary survey was conducted in December 2021. This included examination of clinical and laboratory characteristics, treatment, and outcomes; the presence or absence of muscle weakness in the arm or leg; and the distal or proximal distribution of the weakness. The analysis of long-term prognosis was based on patient data from the initial treatments. The primary outcome measure was the degree of change in Overall Neuropathy Limitation Scale (ONLS) score. Positive response to treatment was defined as an improvement of at least 1 point on the ONLS. The timing of the treatment response evaluation was not specified in order to collect as much data as possible.

Statistical analysis

In the primary survey, special-tier hospitals were defined as those hospitals to which members of the Japanese Society of Neuroimmunology belong that had an exceptionally high prevalence of anti-MAG neuropathy. The prevalence of anti-MAG neuropathy patients in these hospitals was estimated, stratified by hospital size (number of beds), with a 100% sampling rate for thoroughness. This approach, previously validated in a national study of chronic diseases in Japan [10], also included the calculation of a 95% confidence interval (CI) using a multinomial hypergeometric distribution model. For the secondary survey, patient data were summarized using means, standard deviations, and percentages. Statistical tests, including Student's t test, the Mann–Whitney U test, and the chi-squared or Fisher's exact tests, were used for comparative analysis, with significance set at $p < 0.05$. SAS software (version 9.4) and JMP Pro 16.2.0 were used for these analyses.

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RESULTS

Estimated number of patients and prevalence rate

A total of 4966 departments were selected from all over Japan, and 1919 departments (39%) responded to the primary survey (Figure 1). In total, 194 patients were reported. The number of prevalent cases was estimated to be 353 (95% CI 287–419; males: 282 [95% CI: 226–338]; females: 68 [95% CI: 48–87]). The prevalence rate was 0.28 per 100,000 and the incidence was 0.05 per 100,000 individuals.

Clinical characteristics

A secondary survey was sent to departments that identified patients in the primary survey. Detailed clinical information was obtained for 137 patients. Of these, four duplicate cases were excluded, with 133 patients included in the analysis (Figure 1).

The patients' clinical profiles are shown in Table 1. The male/female ratio was 3.6/1 (78% male), and the age of onset was predominantly late 60s (Figure 2). The median disease duration was 22 months. Hematological tumor comorbidities were present in 18% of the patients; 95% of these were Waldenström macroglobulinemia. In total, 83% of patients could walk independently before the initial treatment, but at the final visit, this number had decreased to 73%. Most patients had distal sensory-predominant polyneuropathy. Muscle weakness was observed in 60% of the patients, mostly in the distal leg. Of these, 16% developed slight proximal muscle weakness in the late stage. Neuropathic pain (50%) and sensory ataxia (42%) were frequently present.

Laboratory findings

Table 2 presents the laboratory findings. Electrophysiological data were available for 98 patients. Consistent with the previous study results, distal latency was prominently prolonged, and nerve conduction velocities were moderately decreased in all the nerves tested.

Monoclonal gammopathy was found in 95% of patients, and IgM class was found in 99%. A total of 94% of patients were both MAG- and sulfated glucuronyl paragloboside-positive. Only six patients did not have monoclonal gammopathy, and their median (range) anti-MAG antibody titer was 256,000 (256,000–8,192,000) BTU. Table S1 shows the characteristics of patients with and without monoclonal gammopathy. The characteristics of patients without monoclonal gammopathy were not different from those of patients with monoclonal gammopathy.

Anti-MAG antibody titer data were collected from 60 patients (45%), of whom six (10%) had anti-MAG antibody titers lower than 7000 BTU. The characteristics of patients with anti-MAG antibody titers of 7000 BTU or less ($n=6$) and those with more than 7000 BTU ($n=54$) were generally similar (Table S2).

Treatment and outcome

Treatment outcomes are shown in Table 3. The median time from disease onset to the first treatment was 25 months. Patients were treated most frequently with intravenous immunoglobulin (IVIg; 65%, possibly because the initial diagnosis was chronic inflammatory demyelinating polyneuropathy), followed by rituximab (32%) and corticosteroids (23%). Ten patients (8%) received systemic chemotherapy due to association of macroglobulinemia. Rituximab

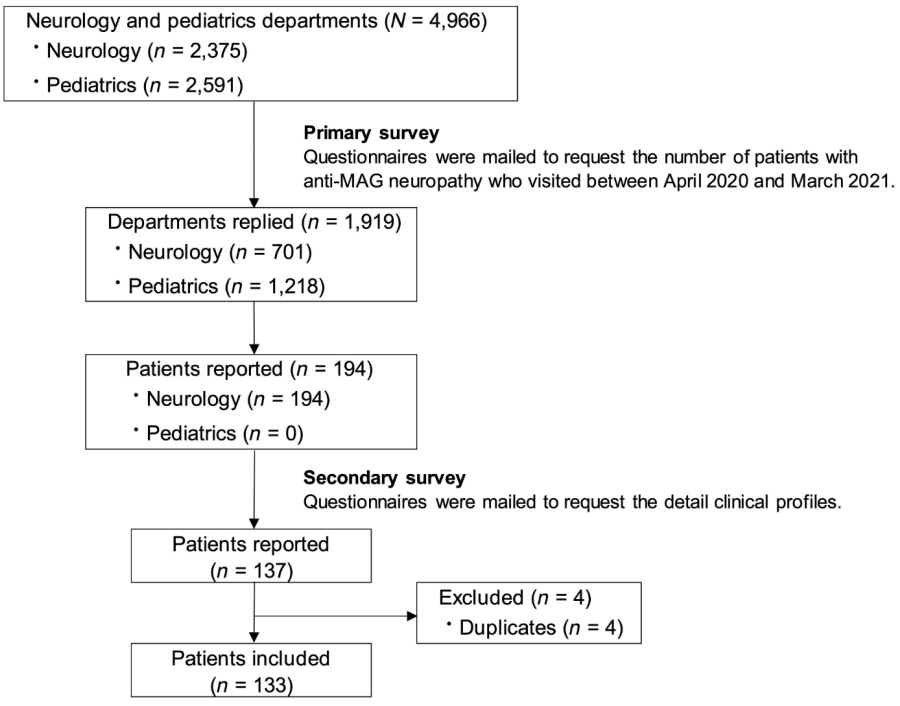

FIGURE 1 Survey profiles, number of responding hospital departments and number of cases.

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TABLE 1 Clinical profiles of anti-myelin-associated glycoprotein neuropathy patients.

	Patient ($n=133$)
Male, %	78
Age at onset, median (range) years	67 (30–87)
Disease duration at the first visit, median (range) months	22 (0–241)
Follow-up period, median (range) months	62 (2–254)
Hematologic tumor comorbidity, %	18
Waldenström macroglobulinemia, %	95
Multiple myeloma, %	5
Overall Neuropathy Limitation Score	
Arm	1 (0–4)
Leg	2 (0–6)
Total	2 (0–9)
Walking independently before the first treatment, %	83
Walking independently at the last visit, %	73
Symptoms at diagnosis, %	
Cranial nerve involvement	2
Muscle weakness	60
Muscle atrophy	25
Areflexia	92
Sensory deficits	74
Ataxia	42
Tremor	18
Neuropathic pain	50

TABLE 2 Laboratory findings of anti-myelin-associated glycoprotein neuropathy patients.

		Patients ($n=133$)
Electrophysiological findings[a], mean ± SD ($n=98$)		
Median nerve	Distal latency, ms	9.7 ± 5.3
	Motor conduction velocity, m/s	36.2 ± 11.2
	CMAP amplitude, mV	5.8 ± 4.1
	Terminal latency index	0.21 ± 0.09
	Sensory conduction velocity, m/s	36.0 ± 11.5
	SNAP amplitude, μV	3.3 ± 6.3
Tibial nerve	Distal latency, ms	13.1 ± 7.1
	Motor conduction velocity, m/s	23.5 ± 9.9
	CMAP amplitude, mV	1.8 ± 3.2
	Terminal latency index	0.36 ± 0.15
Sural nerve	Sensory conduction velocity, m/s	39.0 ± 8.8
	SNAP amplitude, μV	2.2 ± 3.8
IgM monoclonal gammopathy at diagnosis ($n=129$), %		95
Antibodies, %		
MAG+/SGPG+		94
MAG+/SGPG-		3
MAG-/SGPG+		4
MAG titer, median (range)		102,400 (1600–3,276,800)
SGPG titer, median (range)		819,200 (3200–819,200)
CSF proteins		
Mean mg/dL		111.6 (20–1224)
CSF proteins over 80 mg/dL, %		57
Nerve enlargement on neuroimaging abnormality, *n*/*N* (%)		
Ultrasonography		15/15 (100)
MRI		16/54 (30)

Abbreviations: CMAP, compound muscle action potential; CSF, cerebrospinal fluid; MAG, myelin-associated glycoprotein; MRI, magnetic resonance imaging; SD, standard deviation; SGPG, sulfated glucuronyl paragloboside; SNAP, sensory nerve action potential.
[a]Nerve conduction study findings before initial treatment.

was used as the first-line therapy in 43% of patients who received it, and 54% of these patients responded to the treatment. The overall response rate was highest in the rituximab-treated group (64%) and <50% in the other treatment groups.

We compared clinical characteristics based on the responsiveness to IVIg treatment, which was the most commonly used therapy. Sensory nerve action potential (SNAP) amplitudes of the median and sural nerves were significantly lower in the nonresponding group (Table S3).

DISCUSSION

This was the first nationwide epidemiological study focusing on anti-MAG neuropathy and showed a prevalence rate of 0.28 per 100,000 people and an incidence of 0.05 per 100,000 in Japan. Clinical and laboratory data were collected from 133 patients. This is the largest study of anti-MAG neuropathy, providing an updated status of current treatments and outcomes. Patients with anti-MAG neuropathy who do not have monoclonal gammopathy are rare, but this cohort included six such patients. These patients' median anti-MAG titer was sufficiently high. In addition, some patients had low anti-MAG titers. However, their characteristics were consistent with those of patients with anti-MAG neuropathy. Although there is the possibility of misdiagnosis, it is important to recognize the presence of anti-MAG neuropathy in patients without monoclonal gammopathy or with low anti-MAG antibody titers. Moreover, our results showed that 32% of the patients received rituximab therapy; the response was generally favorable

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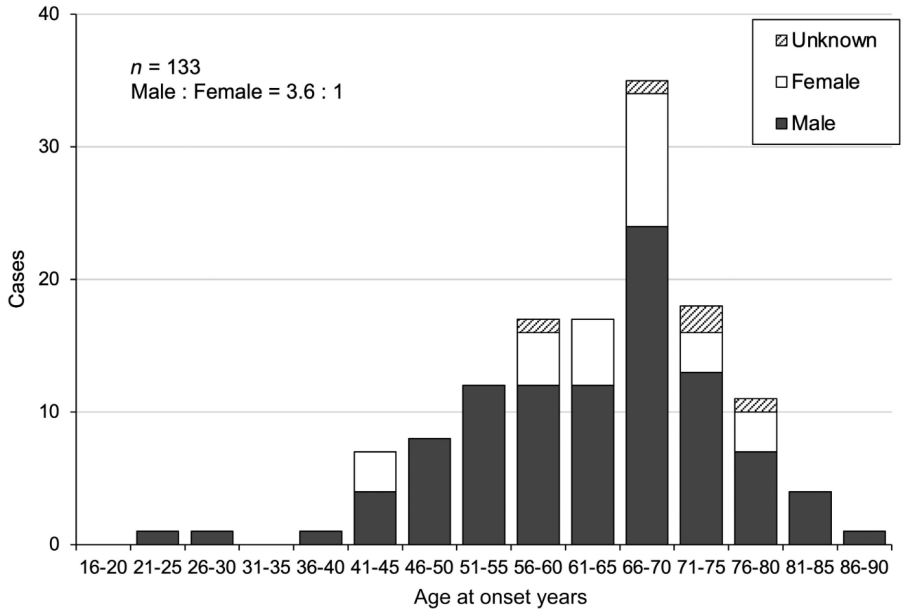

FIGURE 2 Age at onset and gender distribution of anti-myelin-associated glycoprotein neuropathy patients.

TABLE 3 Treatment and response rate of anti-myelin-associated glycoprotein neuropathy patients.

	Patients ($n = 133$)	Response rate[a]
Duration to first treatment, median (range) months	25 (2–317)	
Treatment		
Immunoglobulin	86 (65%)	49%
Corticosteroids	30 (23%)	47%
Plasma pheresis	15 (11%)	27%
Rituximab	42 (32%)	64%
Chemotherapy/fludarabine	10 (8%)	20%

Abbreviation: MAG, myelin associated glycoprotein.

[a]Improvement of 1 point or more on the Overall Neuropathy Limitations Scale.

but 27% of 133 patients could not walk independently at the last visit, suggesting that the disorder is still serious and more intensive treatment is required to improve the prognosis.

To date, there has been only one epidemiological study on anti-MAG neuropathy, a population-based epidemiological study conducted in Ireland that reported the prevalence of many major neuromuscular diseases and described a prevalence of 0.06 per 100,000 for anti-MAG neuropathy; this figure is lower than that identified in our study [11]. It is unclear whether the difference suggests regional differences in Europe and Asia or differences in epidemiological methodology. Nevertheless, both studies suggest that anti-MAG neuropathy is a rare disease.

Anti-MAG neuropathy predominantly affects older males, causing chronic progressive sensorimotor polyneuropathy, frequently associated with neuropathic pain and sensory ataxia [12–15]. The clinical features observed in this study were consistent with those of previous reports. This study also revealed a male-to-female ratio of 4:1 and a median age of onset of 67 years. In terms of neurological disability, 80% of patients experienced a progressive disease course, and even after treatment, 27% of patients could not walk independently at the last visit.

Electrodiagnostic studies have confirmed a marked prolongation of distal latencies and a moderate decrease in motor nerve conduction velocities, as shown in previous studies [16, 17]. These findings suggest that distal nerve terminals, where the blood–nerve barrier is anatomically deficient, are preferentially affected by anti-MAG neuropathy. This tendency is more prominent than in other immune-mediated neuropathies, such as Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy, presumably because the pathogenic antibodies are of the IgM class. IgM is a pentamer; therefore, the molecular weight is five times greater than that of IgG/A, which would be responsible for more prominent nerve terminal demyelination in anti-MAG neuropathy [18].

The treatment for anti-MAG neuropathy has not yet been established. Although cladribine, cyclophosphamide with prednisone, and IVIg offer transient benefits to some patients, most remain treatment-resistant. Recently, rituximab has been administered. Open-label studies and a recent randomized controlled trial suggested that rituximab is emerging as a better available agent, providing long-term benefits to almost half of patients [6, 7, 19, 20].

In this study, many Japanese patients were initially treated with IVIg or corticosteroids. Almost half of the patients were responsive to IVIg, and SNAP amplitudes of the median and sural nerves were significantly lower in nonresponding patients, possibly indicating severe demyelination or axonal loss in refractory patients. Rituximab therapy was performed in only 32% of patients. However, its efficacy appeared to be higher than that of IVIg and corticosteroids. We agree that rituximab could be the best available agent and could be more intensively used as a first-line treatment for anti-MAG

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neuropathy [21, 22]. More recently, novel drugs such as obinutuzumab (anti-CD20 antibody), PPSGG (antibody-specific therapy: HNK-1 decoys), and ibrutinib for MYD88 gene mutation-positive cases have been suggested as potential future treatment [23–26].

This study had some limitations. There may be selection bias because this study was retrospective, and the response rate to the survey was not sufficiently high (39%). However, 1919 institutes responded to the survey, collecting data from 133 patients. We believe that this large number of patients minimized selection bias. Secondly, evaluation of the treatment response was made at variable timing without specific quantitative methods, and therefore the response rate might not reflect true response. Separately, in 2023, we will establish a disease registry for anti-MAG neuropathy in Japan [27]. In the future, we plan to collect more accurate prospective data.

In conclusion, using a nationwide survey in Japan, this study was the first to report the prevalence and incidence of anti-MAG neuropathy and the current status of treatment and outcomes. The results showed that anti-MAG neuropathy is still a serious disorder; 27% of patients were unable to walk independently at the last visit. Further studies are required to optimize the management of this rare and intractable disorder.

AUTHOR CONTRIBUTIONS

Yuya Aotsuka: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; writing – original draft. **Sonoko Misawa:** Conceptualization; writing – review and editing. **Tomoki Suichi:** Investigation. **Kazumoto Shibuya:** Investigation. **Keigo Nakamura:** Investigation. **Hiroki Kano:** Investigation. **Ryo Otani:** Investigation. **Marie Morooka:** Investigation. **Moeko OgishiOgishi:** Investigation. **Kengo Nagashima:** Formal analysis; writing – review and editing. **Yasunori Sato:** Formal analysis; writing – review and editing. **Nagato Kuriyama:** Methodology; writing – review and editing. **Satoshi Kuwabara:** Writing – review and editing; funding acquisition; conceptualization.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data not provided in the article because of space limitations may be shared (anonymized) at any qualified investigator's request to replicate procedures and results.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Chiba University School of Medicine.

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