

Are multifocal motor neuropathy patients underdiagnosed?

An epidemiological survey in Japan

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Abstract

Objective: Our objective was to do an epidemiologic survey of patients with multifocal motor neuropathy (MMN) in comparison with those with amyotrophic lateral sclerosis (ALS) in Japan.

Methods: In this retrospective study, we examined 46 patients with MMN and 1,051 patients with ALS from major neuromuscular centers in Japan from 2005 to 2009. Diagnosis was based on the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) and the revised El Escorial criteria. The efficacy of intravenous immunoglobulin (IVIg) was also taken into consideration in the diagnosis of MMN.

Results: The ratio of MMN to ALS patients (0-0.10) varied among the centers, but mostly converged to 0.05. The prevalence was estimated to be 0.29 MMN patients and 6.63 ALS patients per 100,000 population.

Conclusions: The frequency of MMN patients was around 1 out of 20 ALS patients, and MMN was possibly underdiagnosed in some centers.

Key words: multifocal motor neuropathy, amyotrophic lateral sclerosis, diagnosis, conduction block, prevalence

Introduction

Multifocal motor neuropathy (MMN) is characterized by predominant involvement of motor nerves presenting with slowly progressive muscle atrophy and weakness, a typical age of onset between the third and fifth decades of life, and a high prevalence in men.¹⁻³ The characteristic diagnostic features of MMN are conduction block (CB) in multiple peripheral nerves and the presence of anti-GM1 IgM antibodies⁴⁻⁷. However, the diagnosis of MMN may be missed in those without overt evidence of CB or elevated anti-GM1 IgM antibody levels⁸⁻¹⁰. CB may not be detected in MMN patients whose demyelinating lesion is located in proximal nerve segments (e.g., plexus, nerve root)¹¹ or when it is associated with significant secondary axonal loss^{8,12}. Several diagnostic criteria for MMN have been proposed¹³⁻¹⁵. The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria may have limited sensitivity due to the possibility of undetected CB^{11, 13, 16}. MMN is treatable with various immunomodulatory therapies, particularly intravenous immunoglobulin (IVIg), and the response may be a feature that distinguishes MMN from lower motor neuron diseases, including amyotrophic lateral sclerosis (ALS)^{17, 18}.

Except for 1 clinic-based study that estimated the prevalence of MMN to be approximately 10% of that of ALS¹⁹, detailed large-scale epidemiological studies of

MMN have been undertaken rarely. The lack of knowledge of the above technical limitations in the diagnosis of MMN, and the rarity of the disease, might lead clinicians to underdiagnose MMN. We therefore conducted an epidemiological survey of MMN in major neuromuscular centers in Japan and compared it with ALS, whose prevalence is known.

A brief preliminary report of this study has been published in Japanese²⁰.

Methods

Patients. This study was based on a retrospective hospital-based survey in Japan. The diagnosis of MMN was based on the 2006 EFNS/PNS criteria and the response to IVIg. The 2006 criteria were used, because the latest criteria were not available at the time of clinical evaluation. We excluded patients with MMN who died during the course of the study because one of those patients might actually have had ALS. The diagnosis of ALS was made by using the revised El Escorial criteria, and patients who fulfilled the “clinically definite,” “clinically probable,” or “laboratory-supported probable” criteria were included for further epidemiological analysis²¹. We excluded those with the “possible” criterion, because it might include MMN and other neuromuscular conditions. First, we sent questionnaires to 46 major neuromuscular

centers in Japan requesting clinical information on patients with MMN and ALS at each site. Twenty-five centers (54.3%) expressed their willingness to cooperate in the survey, but 5 centers did not follow through. Of the 20 centers that responded to the second survey, 1 was excluded because of insufficient data for analysis. We further analyzed the clinical records of patients with MMN and ALS from 2005 to 2009. We also checked the results of electrophysiological studies for MMN. The participating 19 centers were not biased geographically and were located throughout Japan.

Electrophysiological study. Electrophysiological studies were performed at each center using conventional techniques. CB was defined as a >50% reduction in compound muscle action potential (CMAP) amplitude/area from distal to proximal stimulation (i.e., median, ulnar, radial, and deep fibular nerves)^{14, 22}. Other electrophysiological features of peripheral nerve demyelination included reduced motor conduction velocity (motor conduction velocity; <75% of the lower limit of normal), prolonged distal motor latency, or prolonged minimal F-wave latency (>130% of the upper limit of normal), and activity-dependent conduction block (ADCB).^{9, 22, 23} To detect ADCB, CMAPs from the abductor pollicis brevis (APB) were determined with magnetic stimulation of low-cervical nerve roots. One-minute voluntary maximal

exercise of the APB was performed, and CMAPs were compared before and after exercise. ADCB was defined by a >50% drop in the CMAP amplitude after exercise.⁹

Epidemiological study. The Japanese Ministry of Health, Labour, and Welfare has a nationwide registry system for ALS patients, and the number of patients registered in 2009 was 8,492. First, we calculated the ratio of MMN to ALS patients in each center and in the whole study cohort. The number of patients with MMN in 2009 was then estimated based on the ratio of MMN to ALS patients. The population of Japan was based on data from the national population census in 2009. We estimated the prevalence of MMN and ALS (number of cases/100,000 persons), and the 95% confidence interval (CI) in 2009 by assuming a binomial distribution. The number of patients with MMN in Japan (Z) was estimated by $X*Y/N_y$, where X denotes the total number of patients with ALS in Japan, and Y and N_y denote the number of patients with MMN and ALS, respectively, registered at 19 neuromuscular centers. The variance of Z (V_z) was estimated by the following equation, assuming that X and Y are independent: $V_z = [E(Y)*E(Y)*V_x + E(X)*E(X)*V_y + V_x*V_y] / (N_y*N_y)$, where $E(X)$ and $E(Y)$ denote the expected value (mean) of X and Y , respectively, and V_x and V_y denote the variance of X and Y , respectively.

We conducted the McNemar test to determine whether the prevalence differed significantly between MMN and ALS. Two epidemiologists (SH and KA) conducted the overall analysis.

Clinical characteristics of MMN and ALS. Basic data, such as gender, age of onset, and diagnosis, were collected from patients with MMN and ALS.

Standard protocol approval, registration, and patient consent. All investigations were approved by the institutional ethics committee of the University of Tokushima.

Statistical analysis. The acquired data were processed and analyzed using SPSS software (version 11.0, SPSS Inc., Chicago). Differences in patient characteristics between MMN and ALS were tested using the Mann-Whitney U test. Two-tailed *P* values <0.05 were considered significant.

Results

Forty-six patients with MMN and 1,051 patients with ALS were analyzed (Table 1). The onset age of MMN was younger (mean, 42.5 ± 15.0 years; range, 16-74 years) than that of ALS (mean, 62.2 ± 36.5 years; range, 33-87 years) (*P*<0.001, Table 1, Figure 1). There was no significant difference in the male:female ratio between MMN

(71.7%) and ALS (60.4%) ($P=0.12$).

The ratio of MMN to ALS patients (range: 0-0.10; average: 0.044) varied among centers (Table 2, Figure 2). There were no MMN patients in 3 centers in the past 5 years (centers A-C). On the other hand, 4 centers showed ratios of approximately 0.10. These centers were not close geographically (centers P-S) and were staffed by board-certified electromyographers with more than 10 years' experience in nerve conduction studies. Some centers had a large number of ALS patients compared to the number of MMN patients (e.g., centers D, E, and M). The number of ALS patients in the national registry in 2009 was 8,492. Based on the ratio of MMN to ALS patients reported in the whole survey (0.044), the number of MMN patients in Japan was estimated to be 372 (95% CI = 266-477). Overall, the prevalence of MMN in Japan was estimated to be 0.29 patients per 100,000 population (95% CI = 0.21-0.37), whereas that of ALS was 6.63 patients per 100,000 population (95% CI = 6.49-6.77) ($P<0.001$).

Discussion

We conducted an epidemiological survey of patients from multiple neuromuscular centers throughout Japan. The estimated prevalence of MMN in Japan

was 0.29 patients per 100,000 population or approximately 1/20 that of ALS. The gender distribution was similar to that reported previously^{19, 24}. The mean age of onset of MMN was slightly older than that of a previous study¹⁹. The prevalence in our study was lower than those in prior studies conducted in Europe.^{19, 25} One clinic-based study in Italy estimated the prevalence of MMN to be approximately 10% that of ALS¹⁹. A study in the Netherlands reported the prevalence of MMN to be 0.6 patients per 100,000 population.²⁵ The exact reason for the difference is unknown. Given the similar prevalence of ALS worldwide, a possibility why MMN is less common in Japan would be that it is underdiagnosed, particularly in the centers that showed very low prevalence. Another possibility is that the patients visiting neuromuscular centers were skewed to the elderly population in Japan, and this might have contributed to the lower estimate of MMN than that of ALS. We compared the ratios of MMN to ALS patients among the centers and found considerable variation (0-0.10). The ratios were around 0.10 in the top 4 centers that were widely distributed in Japan and staffed by electromyography experts. It is therefore unlikely that the prevalence of MMN is higher in some parts of Japan than it is in others. Interestingly, 2 of the top 4 centers adopted activity-dependent CB as a criterion for diagnosis of proximal CB. Although activity-dependent CB was not widely performed and might not be observed in some

patients with MMN,²⁶ it appeared to increase the diagnostic sensitivity in this study.

Our study has a few limitations. One of the reasons why some cases of MMN were underdiagnosed is that MMN was often misdiagnosed as other motor neuron diseases, such as ALS. Another reason is that only 19 of the 46 centers provided data for the study. The 46 centers include various neurological facilities that treat neurologic subspecialty or general neurological ones. The low response rate means that we did not intentionally select neurological centers in the first survey. Further diagnostic tests, such as imaging, would further increase the prevalence of MMN, and such efforts would enable us to provide the appropriate immunological treatment. Although MMN is considered to be rare, its accurate diagnosis should rely heavily on clinical suspicion and electrodiagnostic investigations.

Abbreviations:

ADCB: activity-dependent conduction block

ALS: amyotrophic lateral sclerosis

APB: abductor pollicis brevis

CB: conduction block

CI: confidence interval

CMAP: compound muscle action potential

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society

IVIg: intravenous immunoglobulin

MMN: multifocal motor neuropathy

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Figure Legends

Figure 1. Distribution of age of onset. Proportion is defined by the ratio of the number of patients according to age of onset to the total number of MMN or ALS patients.

MMN, multifocal motor neuropathy; ALS, amyotrophic lateral sclerosis.

Figure 2. Geographical distribution of the ratios of MMN to ALS patients among centers. Crosses: non-participating centers; triangle: center that provided inappropriate data; squares: participating centers (open squares: 0; gray squares: 0.019-0.081; black squares: 0.085-0.10). Open circles indicate the highly-populated cities (government-ordinance-designated cities with populations exceeding 0.7 million).

Table 1. Demographic data of registered patients

Characteristic	MMN (n=46)	ALS (n=1051)	<i>P value</i>
Onset age, range (mean±SD), y	16-74 (42.5±15.0)	33-87 (62.2±36.5)	<0.001
Proportion of men (%)	71.7	60.4	0.12

Table 2. Ratios and estimated numbers of patients.

Center	MMN	ALS	Ratio
	n [^a age, proportion of men (%)]	n [^a age, proportion of men (%)]	MMN/ALS
A	0	58 (60.0±13.6, 53.4)	0
B	0	26 (68.2±7.2, 53.8)	0
C	0	26 (60.9±12.0, 61.5)	0
D	3 (41.3±7.59, 66.7)	154 (62.8±1.10, 62.3)	0.019
E	2 (57.0±16.0, 50.0)	101 (56.5±12.6, 62.3)	0.020
F	1 (24.0, 100)	43 (63.5±9.41, 60.5)	0.023
G	1 (30.0, 100)	34 (63.2±13.4, 50)	0.029
H	2 (42.0±1.00, 50.0)	58 (62.5±9.40, 41.4)	0.034
I	1 (62.0, 100)	28 (60.5±11.0, 64.3)	0.036
J	1 (23.0, 100)	28 (59.2±12.2, 46.4)	0.036
K	4 (43.0±17.0, 75.0)	94 (64.6±9.42, 54.3)	0.043
L	1 (37.0, 100)	18 (56.2±12.1, 38.9)	0.056
M	2 (45.5±0.50, 50.0)	36 (64.3±9.67, 66.7)	0.056
N	7 (36.0±15.3, 71.4)	113 (64.1±10.4, 58.4)	0.062

O	3 (38.0±8.52, 100)	37 (58.8±12.9, 73.0)	0.081
P	3 (51.3±16.4, 33.3)	35 (63.9±11.6, 65.7)	0.086
Q	9 (42.8±16.3, 77.8)	99 (61.0±11.4, 57.6)	0.091
R	4 (55.3±8.93, 75.0)	43 (67.8±10.6, 33.0)	0.093
S	2 (34.0±17.0, 100)	20 (67.6±8.74, 50.0)	0.10
^b total	46	1,051	0.044
Japan	^c 372	^d 8,492	0.044

^aage range: range of onset age (mean±SD).

^btotal: the total number of patients in the 19 centers (A-S).

^cNumber of MMN patients in Japan was estimated on the basis of the number of ALS patients (8,492) and the ratio (0.044).

^dNumber of ALS patients was obtained from the national registry in 2009.

Figure 1.

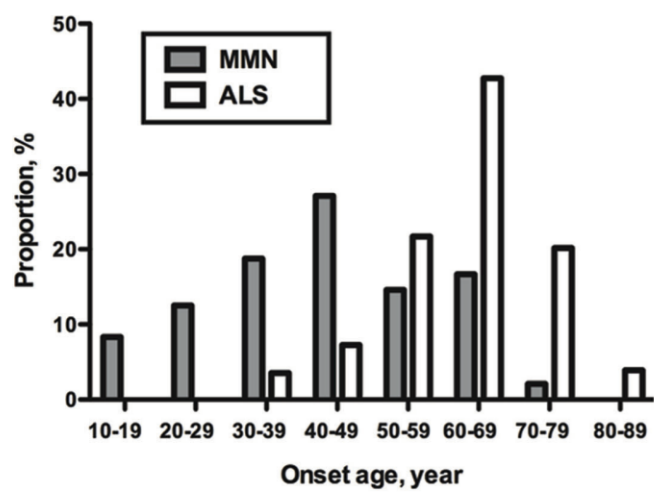
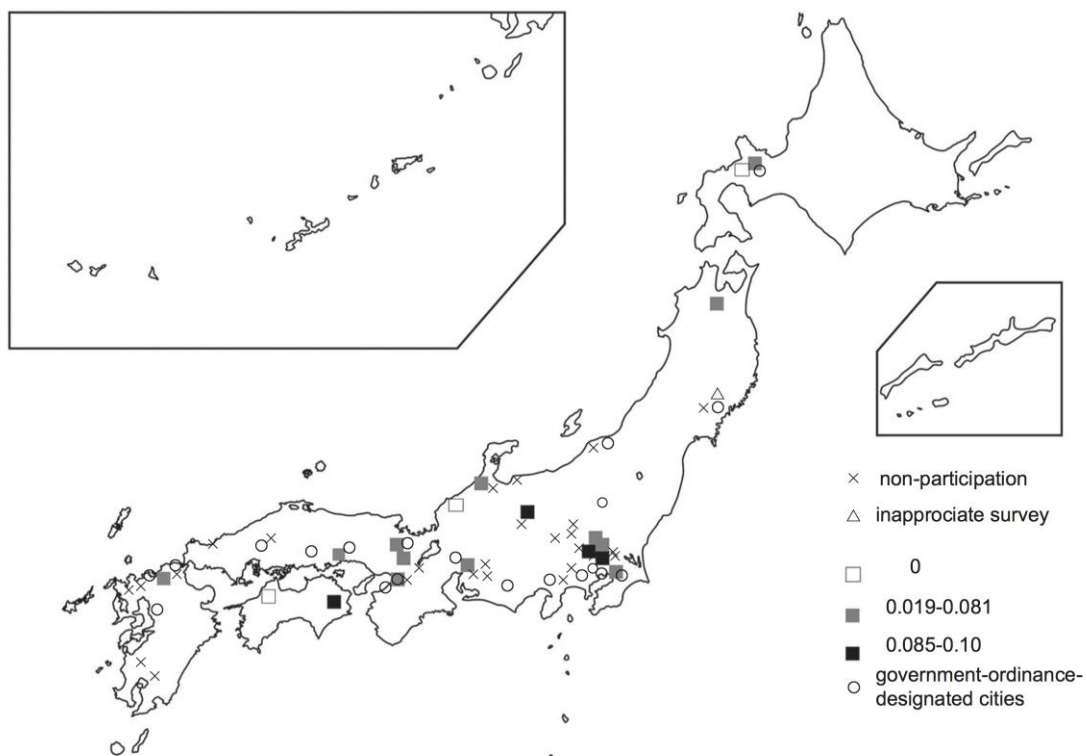


Figure 2.



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