Increase in Incidence of Elderly-onset Patients with Myasthenia Gravis in Nagano Prefecture, Japan

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Abstract

Objectives **In European countries and the United States the incidence of elderly-onset myasthenia gravis (MG) has recently been increasing. To investigate whether the incidence of the elderly-onset MG has increased in Nagano Prefecture of Japan, we divided the patients into young and elderly groups, and retrospectively examined their incidence.**

Patients and Methods **On the basis of two-step questionnaires sent to hospitals and the patient list of the intractable disease registration system in Nagano Prefecture we studied 213 MG patients diagnosed between 1982 and 2001. This 20-year period was divided into 4 five-year terms, and the incidence of MG in young- (younger than 65) and elderly-onset (65 or older) groups was investigated separately for each term.**

Results **The ratio of the elderly-onset group showed a significantly positive correlation with terms irrespective of associated thymoma ($r=0.98$, $p<0.05$). There was a significant difference in the mean onset age among the 4 terms ($p<0.005$). The standardized incidence of MG gradually increased in both young- and elderly-onset groups as well as in the whole age range. The elderly group showed a particularly high incidence in females (12.01/million/year) and in patients without thymoma (8.78/million/year) in the final five years.**

Conclusions **We confirmed that the incidence of elderly-onset MG has recently been increasing in the Nagano Prefecture. Since the change of the age distribution in this district is almost identical to that of the whole country, the incidence of MG might have been increasing in Japan as a whole, particularly in the elderly population. (Internal Medicine 44: 572–577, 2005)**

Key words: elderly population, incidence, myasthenia gravis

Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by an antibody-mediated attack directed against acetylcholine receptors (AChR) at neuromuscular junctions (1). In various population-based studies, the average annual incidence of MG has been reported to range from two to six per million. Although this disease can develop at any age, two peaks have been recognized in its incidence: the twenties in women and, less consistently, the over-fifties in men (2, 3). In recent decades, however, several reports have noted that the incidence of elderly-onset patients with MG has been increasing in the United States and in European countries (3–7). To investigate whether the incidence of elderly-onset patients with MG has been increasing also in Japan, we retrospectively conducted a population-based epidemiological study on the occurrence of this disease during the years 1982 through 2001 in Nagano Prefecture, Japan. In conjunction with an increase in the ratio and number of elderly-onset MG patients, the standardized incidence of MG gradually increased in this group, particularly in females without thymoma. We postulate a recent increase in the incidence of elderly-onset MG also in Japan, and discuss some possible causes of this change.

Patients and Methods

Study area

The study area was Nagano Prefecture, situated in the center of Honshu, the main island of Japan. This prefecture

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is surrounded by high mountains, and is usually divided into four parts: northern, southern, eastern and western areas. Each of these constitutes a geographically distinct community and medical service area. There were 2.35 million inhabitants in these communities in 2000, and the age and sex distribution of the study population was virtually identical with that of the whole country, although the ratio of the elderly people was slightly higher in the former than in the latter.

Case ascertainment and inclusion criteria

We sent two-stage questionnaires to hospitals for enrollment of MG patients. The first questionnaire was mailed to 98 hospitals in Nagano prefecture, which had a department of internal medicine, neurology, pediatrics, thoracic surgery or ophthalmology. It asked whether MG patients had been treated between 1982 and 2001, and if so, how many. The second was mailed only to doctors who had treated MG patients during this period, in order to obtain patients' clinical profiles, including name, sex, the date and age of onset, disease severity, the residential area and association with thymoma. This questionnaire was carefully handled using a direct mail and a locked computer system for management of data, because it included the personal information. Disease severity was expressed according to the classification of the Myasthenia Gravis Foundation of America (MGFA) (8). For each patient, associated thymoma was surveyed mainly from the medical records and also from reports on the histopathology of the thymus in thymectomized patients. We asked the doctors to critically review each patient record for the accuracy of diagnosis, and the only patients included in the study were residents of Nagano Prefecture with fluctuating weakness in one or more muscle groups and a clearly positive response to the edrophonium chloride test. Anti-AChR antibodies became commercially available in the mid-1980s, and have since been determined in all cases suspected as having MG. An increase in anti-AChR antibodies in serum as well as the waning phenomenon in the repetitive stimulation test at a low frequency also supported the diagnosis of MG.

To enroll all the patients who had developed MG between 1982 and 2001, we obtained information also from the intractable disease registration system in Nagano Prefecture. Clinical profiles of the patients, particularly their names, were carefully checked in order to avoid duplicate enrollment.

Data analysis and statistical methods

The patients were classified into young (younger than 65) and elderly (65 or older) groups according to the age of onset. In cases with uncertain date of onset, the age at time of diagnosis was used for classification. To investigate whether the incidence of MG has recently been increasing among the elderly population, the 20-year period was divided into the following 4 terms of 5 years each: 1982–1986, 1987–1991, 1992–1996 and 1997–2001. The average annual incidence rates, including sex- and associated thymoma-specific rates, were calculated for each of the 5-year periods using the mid-point year population of Nagano Prefecture as denominator, and standardized with the population of Japan in 1985. For each incidence ninety-five percent confidence intervals were calculated using a binomial approximation of the Poisson distribution.

The age of onset represented the mean ± standard deviation, and the Kruskal-Wallis test was employed for evaluating a statistical difference among the 4 terms. A relationship between the standardized incidence and terms was statistically evaluated by a single regression test. In all analyses the level of significance was $p<0.05$. Commercially available statistics software was used for data analysis (Microsoft Excel, Microsoft Corporation, Redmond, USA).

Results

We received replies to the first questionnaire from 90 hospitals (93.8%), and of these only ten had 205 MG patients in total who had been diagnosed and treated between 1982 and 2001. The main data source was the Departments of Medicine and Pediatrics in Shinshu University School of Medicine, and 168 of the 205 cases were identified through the medical record system of this hospital. Primary data for the remaining 37 cases were obtained from in- and outpatient charts from 9 other hospitals. In the intractable disease registration data in Nagano Prefecture we found an additional 8 patients who had developed MG during this period. By critical review of medical records these patients were also confirmed as having MG. In total 213 MG patients were enrolled in the study. In all of the patients anti-AChR antibody in serum was determined by radioimmunoassay, and positive results were seen in 178 patients (83.6%). Repetitive stimulation tests were performed in 188 patients, and of these only 101 (53.7%) showed a clear waning phenomenon.

Clinical profiles and distribution of the patients according to the age of onset are shown in Table 1 and Fig. 1, respectively. The age of onset, the number of all patients in each term, and the percentage of the elderly in each term were as follows: 35.1±16.7 years, n=48, and 2.1% in 1982–1986, 41.4±20.0 years, n=39, and 12.8% in 1987–1991, 43.0±21.7 years, n=49, and 16.3% in 1992–1996, and 49.4±22.0 years, n=77, and 31.2% in 1997–2001. There was a statistically significant difference in the age of onset among the four terms ($p<0.005$). The number of patients newly developing MG had gradually increased in both young- and elderly-onset groups, but no significant correlation was found between terms and the number of each of these. In the ratios of young- and elderly-onset groups there was a significantly negative ($r=-0.975$, $p<0.05$) and positive correlation ($r=0.978$, $p<0.05$) with terms, respectively (Fig. 2). It was also noted that the number of patients without thymoma was obviously increased in the elderly-onset group, particularly in the last term (Fig. 1).

The standardized incidence of MG in each term is demonstrated in Table 2. In the young-onset group and total MG

Table 1. Profile of the Patients Enrolled in this Study

	Number of patients		Onset age (years)	MGFA* classification								Associated thymoma	
	Total	Male/Female		I	IIa	IIb	IIIa	IIIb	IVa	IVb	V	+	–
1982–1986	48	18/30	35.1±16.7	6	22	8	10	0	0	1	1	19	29
1987–1991	39	16/23	41.4±20.0	9	10	12	6	1	1	0	0	15	24
1992–1996	49	15/34	43.0±21.7	14	20	9	1	1	0	1	3	14	35
1997–2001	77	26/51	49.4±22.0	13	30	12	9	7	1	2	3	23	54

*MGFA: Myasthenia Gravis Foundation of America.

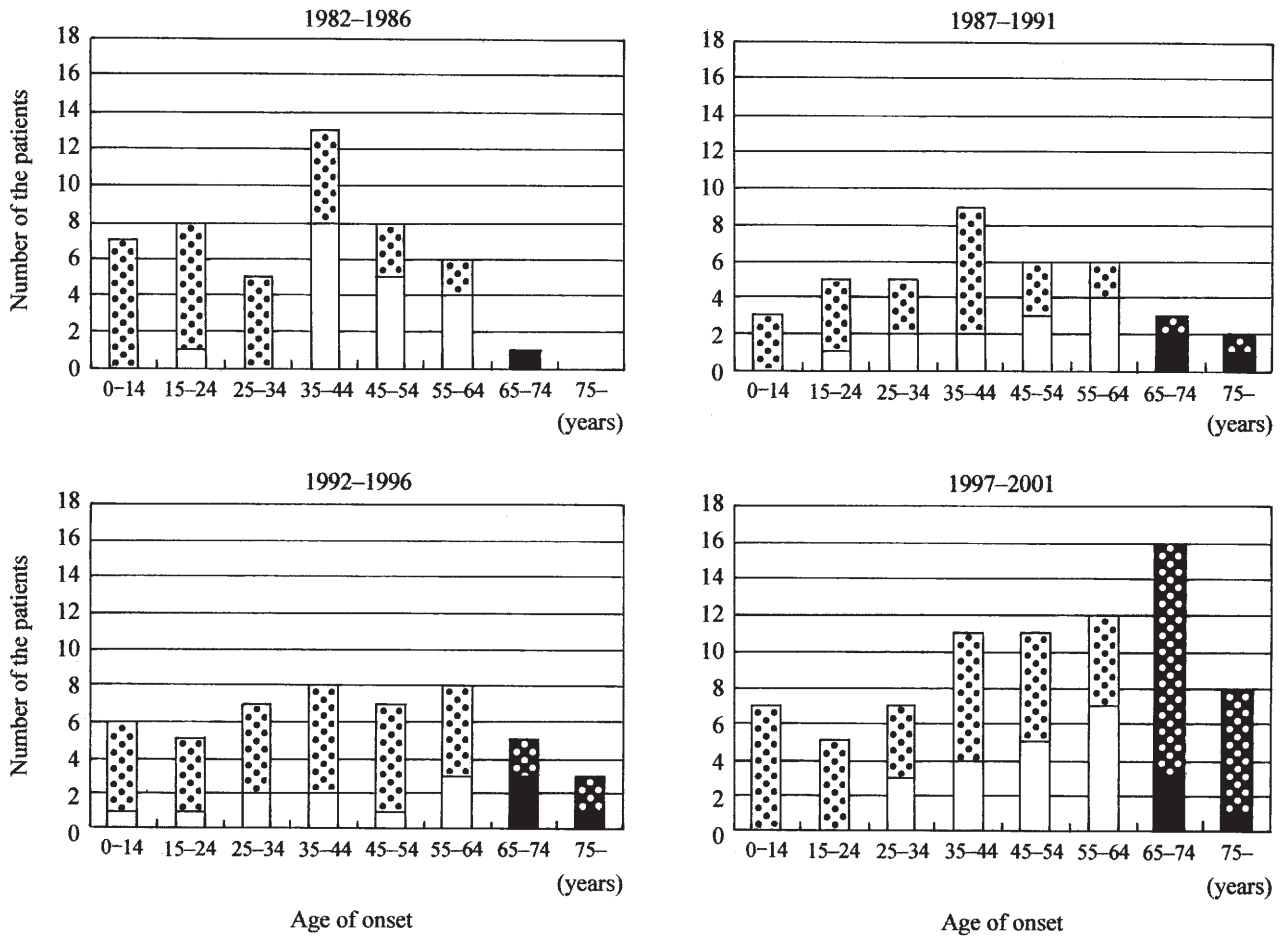

Figure 1. The period of 20 years was divided into 4 terms of 5 years each: 1982–1986, 1987–1991, 1992–1996 and 1997–2001. In each term the number of patients with myasthenia gravis (MG) is shown according to the age of onset and the presence of thymoma. Multiple dots in columns indicate the absence of thymoma, and white and black backgrounds of the columns represent young (younger than 65) and elderly (65 or older) groups, respectively. It is noted that the number of elderly-onset MG patients was gradually increased with terms, particularly in those without thymoma.

patients the incidence showed no change or a slight increase, while that of the elderly-onset group has recently been increasing, particularly among females. In the last term the elderly-onset group showed 12.01/million/year in females and 10.57/million/year in the total patients, and these incidences were ten- to fifteen-fold those in 1982–1986. There was a positive correlation between the standardized incidence and terms in young- and elderly-onset groups as well as in the whole age-range, but the relationship was statistically insignificant. From the viewpoint of the histopathology of thymic

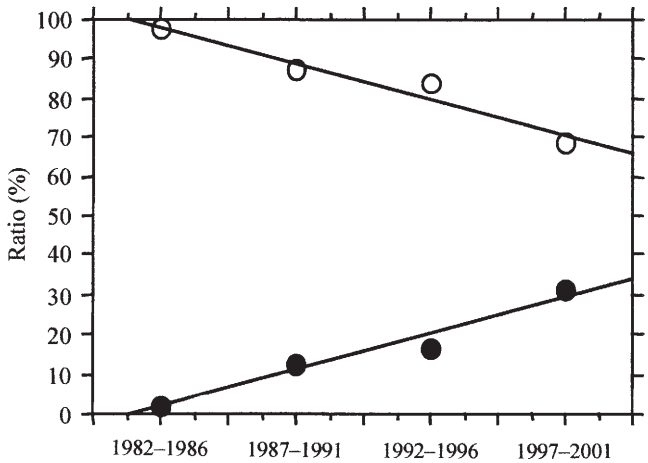

Figure 2. There was a significantly negative and positive correlation between the ratio and terms in the young- ($p<0.05$) and elderly-onset groups ($p<0.05$), respectively. Open circles: the young-onset group, closed circles: the elderly-onset group.

tissues (Table 3) the standardized incidence in elderly-onset patients with thymoma was 1.80/million/year in the last term, while those without thymoma in this group showed an incidence of 8.78/million/year. In the last term, therefore, the elderly-onset group with and without thymoma showed a 4.1-fold increase in incidence over 1982–1986 and a remarkable increase from 0 to 8.78/million/year, respectively. In the young-onset group the standardized incidence of MG in the last term was at most 1.0 to 1.2-fold that in 1982–1986 irrespective of associated thymoma. In statistical analyses, however, there was no significant correlation between terms and an increase in the standardized incidence in any of the young- and elderly-onset groups and total MG patients.

Discussion

Although MG has in general been considered to often develop before the age of 60 (9–11), the percentage of elderly-onset patients with this disease has gradually increased and reached around 30–60% in European countries and the United States according to several recent reports (4, 7, 12). There is much difference in the age distribution of MG among races, and it is well known that the number of elderly-onset MG patients is far fewer among the Chinese than among Caucasian people (13). In the present study we showed that the percentage of MG patients with onset-age of 65 or higher was approximately 30% in the last 5 years, and this result is very similar to that in Denmark (12). The ratio of elderly patients newly developing MG was found to have a significantly positive correlation with terms irrespective of associated thymoma, and there was a significant difference in the mean onset age among the 4 terms. In addition to this, the standardized incidence of MG has been gradually increasing in both young- and elderly-onset groups as well as in the whole age-range. Although there was no significantly positive correlation between terms and incidence, the increase was most remarkable in the elderly-onset group, as also seen in reports from the United States (4, 5), Denmark (6) and the United Kingdom (3, 7). The elderly-onset group showed a particularly high incidence in females (12.01/million/year) and in patients without thymoma (8.78/million/year) in the last five years.

The precise cause of the recent increase in the incidence of MG, particularly in the elderly-onset group, remains unclear, but there are three possible factors worth consideration: an increase in the elderly population, increased reliability in the diagnosis of MG, and an immunological background different from that of young patients. According to Japanese government statistics, life expectancy was 73.57 years for men and 79.00 years for women in 1980, and 76.70 years for men and 83.22 years for women in 1995 (14). In parallel with the lengthening of life expectancy the percentage of the population over 65 has increased from 12.0% to 18.0% in the past 10 years (15). Nagano Prefecture, where this study was conducted, belongs to the highest group in Japan with respect to both life expectancy and the percentage of population over 65 (14, 15). To exclude the influence of a recent expansion in the elderly population (7, 16, 17), the standardized incidence was calculated in this study using the population of Japan in 1985, and showed a gradual increase with terms. These findings support the idea that the incidence of elderly-onset MG patients has truly been increasing in Nagano Prefecture irrespective of the rapid growth in the elderly population.

The second possible factor is increased reliability in the diagnosis of MG. Until the early 1980s muscular and/or ocular symptoms due to MG sometimes led to a misdiagnosis of other neurological diseases, particularly cerebrovascular attack, or were overlooked in elderly people (15). Following the establishment of the fellowship system in the Japanese Neurological Society, the opportunity for neurologists to examine MG patients has been consistently increasing, with the result that the rate of misdiagnosis or overlooking the disease in elderly patients is very low, particularly after the anti-AChR antibody became commercially detectable in the middle of the 1980s. These changes and progress in the diagnosis of MG might have contributed to the increase in the number of MG patients with clinically mild phenotypes (I or IIa in MGFA classification) in this study (8).

Another possible factor related to the increase in the incidence of elderly-onset MG patients is an immunological background different from the young group. According to several reports the serum level of circulating anti-AChR antibodies is often lower in elderly-onset MG patients than in the young group (18, 19), antibodies to titin can be found in around a half of elderly patients (while the young group rarely shows a positive result for this antibody) (17), and the development of MG is frequently associated with HLA-DRw3 in the young group and with DRw2 in elderly patients (20), suggesting that there is some difference in the immuno-

Table 2. Average Incidence of MG in Each Term in Nagano Prefecture

		1982–1986				1987–1991			
		Number of residents	Number of patients	Incidence (/million/year)	Standardized incidence* (/million/year)	Number of residents	Number of patients	Incidence (/million/year)	Standardized incidence* (/million/year)
Young group	Male	909,937	18	3.96 (1.47–10.67)	3.87	912,546	12	2.63 (0.80–8.68)	2.48
	Female	928,409	29	6.25 (2.83–13.80)	6.47	911,399	22	4.83 (1.96–11.91)	4.88
	Total	1,838,346	47	5.11 (2.73–9.59)	5.19	1,823,945	34	3.73 (1.79–7.77)	3.58
Elderly group	Male	116,387	0	0 (0–33.00)	0	136,640	4	5.85 (0.88–38.94)	5.77
	Female	163,480	1	1.22 (0.06–25.88)	1.24	198,067	1	1.01 (0.05–21.36)	1.07
	Total	279,867	1	0.71 (0.03–15.12)	0.72	334,707	5	2.99 (0.53–16.92)	2.99
Total	Male	1,026,324	18	3.51 (1.30–9.46)	3.56	1,049,186	16	3.05 (1.07–8.69)	2.75
	Female	1,091,889	30	5.5 (2.52–11.99)	5.85	1,109,466	23	4.15 (1.71–10.04)	4.43
	Total	2,118,213	48	4.53 (2.43–8.45)	4.73	2,158,652	39	3.61 (1.82–7.19)	3.52

		1992–1996				1997–2001			
		Number of residents	Number of patients	Incidence (/million/year)	Standardized incidence* (/million/year)	Number of residents	Number of patients	Incidence (/million/year)	Standardized incidence* (/million/year)
Young group	Male	898,349	12	2.67 (0.81–8.81)	2.55	888,252	18	4.05 (1.50–10.93)	3.78
	Female	883,607	29	6.56 (2.97–14.50)	6.55	865,335	35	8.09 (3.92–16.70)	8.00
	Total	1,781,956	41	4.60 (2.35–9.01)	4.53	1,753,587	53	6.04 (3.34–10.94)	5.86
Elderly group	Male	167,293	3	3.59 (0.43–29.70)	3.58	194,433	8	8.23 (1.98–34.23)	8.39
	Female	236,237	5	4.23 (0.75–23.98)	4.40	269,675	16	11.87 (4.16–33.81)	12.01
	Total	403,530	8	3.97 (0.95–16.50)	3.97	464,108	24	10.34 (4.34–24.62)	10.57
Total	Male	1,065,642	15	2.82 (0.96–8.28)	2.64	1,082,685	26	4.80 (2.08–11.07)	4.18
	Female	1,119,844	34	6.07 (2.91–12.66)	6.19	1,135,010	51	8.99 (4.91–16.45)	8.48
	Total	2,185,486	49	4.48 (2.42–8.30)	4.49	2,217,695	77	6.94 (4.24–11.38)	6.36

*The incidence was standardized using the population of Japan in 1985. Ninety-five percent confidence intervals in parentheses.

logical background underlying MG between the young- and elderly-onset patients. Immunological changes developing with aging might play an important role in the pathogenesis of elderly-onset MG, leading to an increase in incidence in elderly people.

In conclusion, the incidence of MG has recently been increasing particularly in the elderly-onset group in Nagano Prefecture. Since the change of the age distribution in this prefecture is almost identical to that of the whole country, the incidence of MG may have been increasing also in Japan as a whole. As the number of elderly-onset patients with MG increases, the strategy for the treatment of this disease should

Table 3. Associated Thymoma-Specific Incidence of MG in Each Term in Nagano Prefecture

		1982–1986			1987–1991		
		Number of Patients	Incidence (/million/year)	Standardized incidence (/million/year)	Number of patients	Incidence (/million/year)	Standardized incidence (/million/year)
Young group	With thymoma	18	1.96 (0.73–5.28)	1.92	12	1.32 (0.40–4.34)	1.22
	Without thymoma	29	3.16 (1.43–6.97)	3.26	22	2.41 (0.98–5.95)	2.46
Elderly group	With thymoma	1	0.71 (0.03–15.12)	0.44	3	1.79 (0.22–14.84)	1.81
	Without thymoma	0	0 (0–13.72)	0	2	1.20 (0.10–13.76)	1.18
Total	With thymoma	19	1.79 (0.68–4.72)	1.80	15	1.39 (0.47–4.09)	1.42
	Without thymoma	29	2.74 (1.24–6.05)	2.93	24	2.22 (0.93–5.29)	2.33

		1992–1996			1997–2001		
		Number of Patients	Incidence (/million/year)	Standardized incidence (/million/year)	Number of patients	Incidence (/million/year)	Standardized incidence (/million/year)
Young group	With thymoma	10	1.12 (0.31–4.09)	1.10	19	2.17 (0.82–5.70)	1.90
	Without thymoma	31	3.48 (1.61–7.49)	3.45	34	3.88 (1.86–8.09)	3.96
Elderly group	With thymoma	4	1.98 (0.30–13.21)	2.01	4	1.72 (0.26–11.46)	1.80
	Without thymoma	4	1.98 (0.30–13.21)	1.97	20	8.62 (3.35–22.16)	8.78
Total	With thymoma	14	1.28 (0.42–3.90)	1.18	23	2.07 (0.86–5.02)	1.90
	Without thymoma	35	3.20 (1.55–6.61)	3.31	54	4.87 (2.71–8.77)	4.46

Ninety-five percent confidence intervals in parentheses.

be reconsidered in the future from the viewpoint of procedural safety and complications.

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