SHORT REPORT

Epidemiology of myasthenia gravis with anti-muscle specific kinase antibodies in the Netherlands

Erik H Niks, Jan B M Kuks, Jan J G M Verschuuren

J Neurol Neurosurg Psychiatry 2007;**78**:417–418. doi: 10.1136/jnnp.2006.102517

The epidemiology of myasthenia gravis subtypes and the frequency of antibodies to muscle-specific kinase (MuSK) was studied in patients with generalised myasthenia gravis without anti-acetylcholine receptor antibodies who had an onset of symptoms between 1990 and 2004 in a well-defined region in the Netherlands. The nationwide prevalence and incidence of myasthenia gravis with anti-MuSK antibodies were also studied. MuSK antibodies were found in 22% of patients with generalised myasthenia gravis without anti-acetylcholine receptor antibodies. Nationwide, 35 patients with MuSK myasthenia gravis were identified, yielding a prevalence of 1.9 per million (95% confidence interval (CI) 1.22 to 2.59) and an annual incidence 0.10 per million person-years (95% CI 0.06 to 0.14).

In North American and European cohorts, 38–47% of patients with generalised myasthenia gravis without anti-acetylcholine receptor antibodies (AChR Ab– MG) have antibodies to muscle-specific kinase (MuSK).^{1–3} By contrast, this proportion is only 4% in Taiwan, and myasthenia gravis with anti-muscle-specific kinase antibodies (MuSK Ab+ MG) seems to be absent in Norway, suggesting large regional differences.^{4,5} We studied the epidemiology of myasthenia gravis subtypes, the proportion of MuSK Ab+ MG in patients with generalised AChR Ab– MG in a well-defined region in the Netherlands, and the nationwide prevalence and incidence of MuSK Ab+ MG.

METHODS

Patients

Patients diagnosed with any form of myasthenia gravis in the densely populated northern part of the province of South Holland have been followed up by our centre since 1 January 1990 as described previously.⁶ All patients with myasthenia gravis, with an onset of symptoms up to 1 January 2004 while living in this region were included in the regional study. In addition, all eight university medical centres and five larger general hospitals included patients with generalised AChR Ab– MG in the nationwide study up to 1 January 2006 by listing patients under current treatment, searching computerised diagnosis registrations, and the use of patients identified in an earlier study.⁷

Inclusion criteria for AChR Ab– MG

The diagnosis was based on clinically confirmed fluctuating weakness of voluntary muscles acquired after the age of 2 years and the absence of anti-acetylcholine receptor (AChR) antibodies. Ocular myasthenia gravis was diagnosed when only diplopia or ptosis had been present throughout the course of the disease. The presence of mild weakness of lid closure was allowed for the diagnosis. Generalised myasthenia gravis was defined as the involvement of muscles other than external eye muscles, the levator palpebrae or the orbicularis oculi. The diagnosis was considered to be confirmed electrophysiologically

if a decrement of the compound muscle action potential of >10% had been found during repetitive nerve stimulation or if single-fibre electromyography (EMG) had shown an increased jitter or blocking.

Data collection

The month in which the initial symptoms of myasthenia gravis had occurred was noted according to the patient's chart. Patients with AChR Ab– MG were asked for informed consent by their attending neurologist. Serum was tested for the presence of anti-MuSK, anti-AChR and anti-voltage-gated calcium channel antibodies using standardised immunoprecipitation assays (RSR Ltd, Pentwyn, Cardiff, UK) and patients were re-examined by EHN for confirmation of the clinical criteria and the time of onset. Population figures were provided by Statistics Netherlands.

Statistics

Incidences were computed using the number of patients with the onset of symptoms between 1 January 1990 and 1 January 2004 and the total observed person-years. Prevalences were calculated on 1 January 2004. Poisson distribution was used for 95% confidence intervals (CI).

RESULTS

Regional patients

We identified 288 patients in whom myasthenia gravis had been considered. After reviewing their charts, 35 were excluded because of a revised diagnosis ($n = 30$), congenital myasthenia gravis ($n = 2$) or lack of sufficient data to confirm the diagnosis ($n = 3$). Of the remaining 253 patients with clinical myasthenia gravis, 189 tested AChR Ab+. On 1 January 2004, 160 patients were alive and 111 had an onset between 1990 and 2004. Information on the antibody status of eight patients was not available, leaving 56 patients with AChR Ab– MG. In this group, 30 had ocular myasthenia gravis (45% of all patients with ocular myasthenia gravis), in whom no anti-MuSK antibodies were found. In 26 patients with generalised AChR Ab– MG (14.5% of all patients with generalised myasthenia gravis), diagnosis had been confirmed electrophysiologically in 16 and by a positive response to acetylcholinesterase inhibitors in 8. In the other two patients the diagnosis had been based on clinical symptoms. Three patients died before the onset of the study. Among the remaining 23 patients, anti-MuSK antibodies were present in 5 (22%; 3 women and 2 men). All five were alive on 1 January 2004, and four had an onset between 1990 and 2004. During this period, the regional population increased from 1 641 227 to 1 778 564, yielding a total of 23 926 703.5 observed person-years. Table 1 shows the prevalences on 1 January 2004 and the average annual incidence of myasthenia gravis subtypes.

Abbreviations: AChR, acetylcholine receptor; AChR Ab– MG, myasthenia gravis without anti-acetylcholine receptor antibodies; EMG, electromyography; MuSK, muscle-specific kinase; MuSK Ab+ MG, myasthenia gravis with anti-muscle specific kinase antibodies

Table 1 Prevalence and incidence of myasthenia gravis subtypes

	Prevalence per million inhabitants	Incidence per million person-years
Regional MuSK Ab+ MG	2.8* (0.30 to 5.33)	0.17* (0.00 to 0.33)
Nationwide MuSK Ab+ MG	1.9* (1.22 to 2.59)	0.10* (0.06 to 0.14)
AChR Ab+ MG	90.0 (75.8 to 104.2)	4.64 (3.76 to 5.52)
Generalised AChR Ab- /MuSK Ab- MG	10.1 (5.3 to 14.9)	0.38 (0.13 to 0.63)

AChR Ab+ MG, myasthenia gravis with anti-acetylcholine receptor antibodies; AChR Ab- MG, myasthenia gravis without acetylcholine receptor antibodies; MuSK Ab- MG, myasthenia gravis without anti-muscle-specific kinase antibodies.

Values are n (95% CI)

*Differences between regional and nationwide data are not statistically significant.

Nationwide patients

We identified 130 patients diagnosed with generalised AChR Ab- MG. After clinical re-examination, 21 were excluded because of low anti-AChR titres in newly acquired serum (n = 14) or not meeting clinical criteria (n = 7). Anti-voltage-gated calcium channel antibodies were found in one patient. MuSK antibodies could not be determined in 11 patients because of a lack of informed consent (n = 4), loss to follow-up (n = 3) or death (n = 4). Among the remaining 97 patients, anti-MuSK antibodies were found in 35 (36%), of whom 2 died before the onset of the study. Thirty three patients were clinically re-examined. There was a female predominance (27 v 8). Median age at onset was 30.5 (range 2–74.6) years. We identified 30 white patients, two Creoles, one Persian, one Iraqi and one of Balkan origin. Median time from the onset of symptoms to a diagnosis of myasthenia gravis (not MuSK Ab+ MG) was 9 months (range 1 month–33 years). The neuromuscular transmission defect had been confirmed by EMG in 31 patients although no single-fibre EMG had been performed in the other 4. Three of these four had shown a positive response to intravenous acetylcholinesterase inhibitors.

On 1 January 2004, 31 patients were alive, and 22 had an onset between 1990 and 2004. The annual incidence fluctuated between 0 and 4 patients per year without a trend to increase. From 1 January 1990 to 1 January 2004, the population increased from 14 892 574 to 16 258 032 inhabitants. Nationwide prevalence and incidence rate of MuSK Ab+ MG are shown in table 1.

DISCUSSION

MuSK Ab+ MG is found only in a minority of patients with generalised AChR Ab- MG in The Netherlands. The difference between the regional and non-regional proportion of MuSK Ab+ MG is not statistically significant (odds ratio 0.41, 95% CI 0.14 to 1.22). The lower regional proportion of 22% seems a more accurate estimate coming from a population-based registration of all myasthenia gravis subtypes. Regional prevalence and incidence rate of AChR Ab+ MG are comparable to those found in other European countries, varying between 77 and 105 per million and between 3.8 and 7.4 per million per year.⁸ The proportions of patients with AChR Ab- in the groups with ocular and generalised myasthenia gravis are comparable to historical data indicating that no large referral bias towards AChR Ab- MG occurred. Nationwide, not all patients with generalised AChR Ab- MG who have often only mild weakness,² may have been referred to one of the tertiary centres involved, increasing the proportion of patients with MuSK Ab+ MG. The higher proportion of 36% with MuSK Ab+ MG nationwide is comparable to 38% in North American, 41% in British and 47% in Italian cohorts, and selection or referral bias may well cause this variation. By contrast, the low prevalence of MuSK Ab+ MG in Taiwanese and Danish patients (F Somnier, oral communication) and its absence in Norway also suggest a genetic or environmental susceptibility, which was previously proposed in other autoimmune diseases. T helper cell 1-mediated diseases

such as type-1 diabetes mellitus and multiple sclerosis have increased prevalences at higher latitudes, whereas pemphigus vulgaris, thought to be T helper cell 2 mediated, has lower prevalences at higher latitudes.⁹ MuSK Ab+ MG is comparable to pemphigus vulgaris with regard to a predominance of IgG4 in active disease and an association with the HLA-DR14-DQ5 haplotype.^{3–10} Epidemiological data from other countries may help to confirm regional differences in the prevalence of MuSK Ab+ MG and to identify possible aetiological mechanisms.

ACKNOWLEDGEMENTS

We thank the following neurologists for allowing the inclusion of their patients: MH de Baets, R Beekman, PE Briët, SFTM de Bruijn, MH Christiaans, JL van Doorn, PA van Doorn, BGM van Engelen, CG Faber, RJ Groen, WJHM Grosveld, J Haan, PJ Koehler, AJ van der Kooi, PCLA Lambregts, NC Notermans, MJJ Prick, AL Strikwerda, JPM Stroy, CC Tijssen, ChJ Vecht, GAM Verheul, A Verrips, LH Visser, M de Visser and A van der Zwart.

Authors' affiliations

Erik H Niks, Jan J G M Verschuuren, Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

Jan B M Kuks, Department of Neurology, University Medical Centre Groningen, Groningen, The Netherlands

Funding: EHN was supported by the Prinses Beatrix Fonds. This project was supported by the Foundation "De Drie Lichten" in The Netherlands.

Competing interests: None.

Correspondence to: Erik H Niks, Department of Neurology, J3-R 166, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands; ehniks@lumc.nl

Accepted 13 October 2006

Published Online First 20 October 2006

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