Myasthenia Gravis and Diabetes Mellitus: —A 35-year Retrospective Study—

Nobuo Wakata, Hiroshi Nemoto, Shinngo Konno, Hiroshi Nakazora, Nobuatsu Nomoto,
Hideki Sugimoto and Teruyuki Kurihara

Abstract

Background The most common treatment of myasthenia gravis is high-dose prednisolone administration and thymectomy. A well-known adverse effect of prednisolone is hyperglycemia, however, to date there is no such detailed report.

Patients and Methods We treated 325 myasthenia gravis patients in a recent 35 years period, and found 11 patients with diabetes mellitus. We compared these 11 diabetic patients with previously-reported cases.

Results These 11 patients did not have any antibody against β -cells in the pancreas such as anti-glutamic acid decarboxylase antibody. In 10 of 11 patients diabetes mellitus was controlled with oral medications.

Conclusion Myasthenic patients with diabetes mellitus could be classified into 2 groups, one group with positive organ-specific autoantibodies to many organs (with type 1 diabetes mellitus), and the other group with diabetes mellitus onset during prednisolone administration (with type 2 diabetes mellitus).

Key words: myasthenia gravis, diabetes mellitus, anti-GAD antibody, anti-islet cell antibody, IDDM, NIDDM

(DOI: 10.2169/internalmedicine.46.6237)

Introduction

Myasthenia gravis (MG) is an autoimmune disease which is believed to occur when anti-acetylcholine receptor (AChR) antibody binds to the post synaptic receptor site. Some cases of diabetes mellitus (DM) are also thought to result from an autoimmune mechanism against β -cells in the pancreas such as anti-glutamic acid decarboxylase (GAD) antibody and/or anti-islet cell antibody in insulin-dependent diabetes mellitus (type 1 DM). In one report on neuromuscular disease, anti-GAD antibody was also positive in certain diseases. It is well known that 40-60% of Stiff person syndrome cases have positive anti-GAD antibody (1), and that this antibody was present in MG-associated DM patients (2-5). One of the most important therapeutic strategies for MG is high doses prednisolone administration, though subsequent hyperglycemia is a common adverse effect of prednisolone. We examined whether prednisolone induced hyperglycemia in patients predisposed to DM or whether an autoimmune mechanism was responsible.

Patients

We treated 325 cases of MG from 1968-2004 and encountered 11 cases of DM. Eight male (60-93 years old) and 3 female (64-74 years old) patients were examined, and 7 patients underwent thymectomy. They included 6 hyperplasia and 1 invasive thymoma cases. MG was diagnosed on the basis of typical history and clinical signs, positive responses to i.v. edrophonium chloride, electromyographic examination ($>20\%$ decrement at the 4th stimulus on repetitive nerve stimulation test) and positive value for anti-AChR antibody titer (>0.2 nmol/l). Three cases of sero-negative MG were found (anti-muscle specific tyrosine kinase antibody was not examined), and they were diagnosed on the basis of typical clinical signs, positive edrophonium chloride test or positive waning phenomenon by repetitive nerve stimulation test. DM was defined as over 126 mg/dl fasting blood sugar and over 200 mg/dl blood sugar 2 hours after 75 g oral glucose tolerance test. We studied clinical datum such as MG classification, thymus pathology, dose of PSL and DM treat-

Table 1. Summary of Patients

Case Age/gender	MGFA classification Onset/present	Thymus finding	Prednisolone Max/present/period (alternate day)	DM onset after MG onset	DM therapy	HbA1c (<5.8) (FBS)	C-peptide (0.7~2.2)	Anti-GAD ab (<1.5)	Anti-ACh R ab onset/present (<0.2nmol/l)
1. 63/M	IIa/0	hyperplasia	100mg/0mg/6Y	4Y	Glibenclamide 5mg	6.7 (133)	4.3	0.4	0.2/0.2
2. 64/M	IIa/I	hyperplasia	100/24/6Y	3Y	Nateglinide 30mg diet	7.6 (216)	4.8	0.3	1.4/0.4
3. 60/M	IIIa/0	hyperplasia	100/10/5Y	2Y	diet	5.9 (129)	2.0	0.3	1.5/0.2
4. 54/M	Vb/IIa	invasive thymoma	140/60/5Y	4M	Glibenclamide 10mg Voglibose 0.9mg	5.9 (117)	2.7	0.3	41/30
5. 63/M	IIIb/0	hyperplasia	80/8/12Y	30Y	diet	6.6 (131)	3.4	0.3	8/0.8
6. 67/M	I/0	hyperplasia	100/21/1.5Y	3M	Voglibose 0.9mg Nateglinide 270mg	8.1 (136)	2.6	0.3	2.2/2.1
7. 62/M	IIb/I	hyperplasia	100/0/3.6Y	15Y	diet	5.8 (101)	3.2	0.3	92/580
8. 74/F	IIIa/0	n.e.	60/0/1Y	-6Y	Penfill-30R 22U	9.6 (218)	1.0	0.3	0.2/0.2
9. 66/F	IIa/0	n.e.	60/22.5/15Y	2M	Glibenclamide 10mg Acarbose 200mg	7.8 (154)	2.0	0.3	230/380
10. 64/F	IIIa/IIa	n.e.	30/10/15Y	25Y	diet	5.2 (72)	4.9	0.3	0.2/0.2
11. 93/M	IIIa/I	n.e.	60/5/10Y	8Y	diet	6.7 (111)	6.8	0.3	87.8/37

MGFA: myasthenia gravis foundation of America, Max.: maximum, DM: Diabetes mellitus, FBS: fasting blood sugar, HbA_{1c}: hemoglobin A1c, Anti-AChR ab: anti-acetylcholine receptor antibody, Anti-GAD ab: anti-glutamic acid decarboxylase antibody, Y: year, M: month, n.e.: not examined, U: unit.

ment, and defined high-dose PSL as up to 1mg/kg body weight on alternate-days. Then we measured HbA_{1c}, C-peptide, anti-GAD antibody and anti-AChR antibody.

Results

The male/female ratio was 8 : 3, and male was predominant. There was no significant difference between MG type (MGFA classification) and DM severity. There was also no significant difference between thymectomy, thymus pathology and DM occurrence. High-dose prednisolone was administered, except in case 10. DM started during prednisolone administration in 9 cases, but case 7 started 10 years and case 8, 7 years, after prednisolone withdrawal. Injected insulin was administered to cases 4 and 8. Case 4 started prednisolone before thymectomy because of symptom severity. He suffered a post-thymectomy crisis, after which insulin was injected, but he was subsequently controlled with glibenclamide and voglibose. Case 8, who had DM before MG onset, was controlled with glibenclamide; however, after that she was later given injected insulin because she could not maintain diet therapy. The other patients were controlled with diet and oral medication. DM control was relatively satisfactory but 4 patients had HbA_{1c} of over 7.0%. Serum C-peptide was normal or high. All patients were negative for anti-GAD antibody. Anti-AChR antibody was negative in 3 patients throughout the observation period, and became sero-negative in 1 patient (Table 1).

Discussion

DM prevalence varies greatly by nationality. The gender prevalence was reported to be 7.1% in males and 4.5% in females in Japan (6). There appears to be no detailed preva-

lence reports on the association of MG and DM, but it has been calculated to be 2-3% (7). The prevalence in our patients was 3.4%, lower than in the general population. Because MG patients are sometimes checked for their blood sugar level, they subsequently may pay careful attention to their food intake. There are reports of MG accompanied by DM associated with primary biliary cirrhosis (8), pernicious anemia, autoimmune thyroiditis and autoimmune adrenalitis (9), juvenile chronic arthritis (10), and positive autoantibody for islet cells, gastric mucosa and thyroid gland (11). Among MG patients accompanied by DM and anti-GAD antibody; additional complications included thymoma (3), Stiff person syndrome and Hashimoto's thyroiditis (3), thymoma, autoimmune hepatitis and Hashimoto's thyroiditis (4) and one patient who suffered type 2 DM, who was given interleukin-2 because of renal cell carcinoma, developed myositis and type 1 DM (6). All patients were given injected insulin. The former 4 cases may include the latter group, because they were reported before 1990 and, at that time anti-GAD antibody analysis was not common (Table 2).

The present study included 8 males and 3 females, which is an unusual finding as MG prevalence is higher in females. C-peptide has been the most important research tool in the study of the natural course of β -cell destruction in type 1 DM patients (12). Most patients showed normal or high C-peptide levels, meaning their β -cell function was maintained. Anti-GAD antibody was negative in all patients, and their DM onset was not a result of an autoimmune mechanism.

Corticosteroid-induced hyperglycemia or DM is thought to occur because corticosteroid acts on post insulin-receptor mechanisms to induce dose-dependent insensitivity of insulin's target tissues. Dosages equivalent to 30 mg/day or more of prednisolone are particularly likely to raise glucose

Table 2. Myasthenia Gravis and Diabetes Mellitus Associated with Another Auto-immune Disorders

	MG	DM	Thymoma	Stiff person syndrome	Hashimoto thyroiditis	Autoimmune hepatitis	Pernicious anemia	Anti-GAD ab	Anti-IC ab	Others
Taillan 1989	+	+	-	-	-	-	-	n.e.	n.e.	PBC
Green 1988	+	+	-	-	+	-	+	n.e.	n.e.	autoimmune adrenalitis
Jenkins 1989	+	+	-	-	-	-	-	n.e.	n.e.	arthritis
Paolisso 1990	+	+	-	-	-	-	-	n.e.	n.e.	
Aso 1997	+	+	-	+	+	-	-	+	+	
Kitae 2001	+	+	+	+	-	-	-	+	+	
Asakawa 2002	+	+	+	-	+	+	-	+	+	
			invasive							
Fraenkel 2002	+	+	-	-	-	-	-	+	n.e.	renal cancer, myositis

MG: myasthenia gravis, DM: diabetes mellitus, Anti-GAD ab: anti-glutamic acid decarboxylase antibody, Anti-IC ab: anti-islet cell antibody, PBC: primary biliary cirrhosis, n.e.: not examined

levels in diabetic patients, and can induce glucose intolerance or diabetes in previously normoglycemic subjects (13).

These findings suggest that MG-associated DM can be classified into 2 groups: 1) those that sometimes have accompanying thymoma and have positive organ-specific autoantibody to neuro-muscular junction (anti-AChR antibody), pancreas β -cell (anti-GAD antibody and anti-islet cell antibody), thyroid (antithyroglobin antibody, antithyroid peroxidase antibody), liver (histological findings) and stomach (antibodies to gastric parietal cells). 2) the so-called type 2

DM patients; DM appears during prednisolone administration, with evidence of hyperglycemia or DM.

In the present study, 9 out of 11 patients with MG developed DM during prednisolone administration, however, 3 patients remained diabetic after prednisolone withdrawal and 2 patients had DM onset 7-10 years after prednisolone withdrawal. Therefore, it remains unclear whether prednisolone administration directly induced DM, or if it merely accelerated disease onset.

References

- Vincent A, Grimaldi LME, Martino G, et al. Antibodies to 125I-glutamic acid decarboxylase in patients with stiff man syndrome. *J Neurol Neurosurg Psychiatry* **62**: 395-397, 1997.
- Kitae S, Kawakami H, Matsuoka N, Etoh R, Nakamura S. A case of myasthenia gravis accompanied by large thymoma and anti-GAD antibody. *Rinsho Shinkeigaku* **41**: 818-821, 2001.
- Aso Y, Sato A, Narimatsu M, et al. Stiff-man syndrome associated with antecedent myasthenia gravis and organ-specific autoimmune pathology. *Intern Med* **36**: 308-311, 1997.
- Asakawa H, Kashiwara T, Fukuda H, Yamamoto M. A patient with thymoma and four different organ-specific autoimmune diseases. *Neth J Med* **60**: 292-295, 2002.
- Fraenkel PG, Rutkove SB, Matheson JK, et al. Induction of myasthenia gravis, myositis, and insulin-dependent diabetes mellitus by high-dose interleukin-2 in a patient with renal cell cancer. *J Immunother* **25**: 373-378, 2002.
- Sasaki Y, Tominaga M, Eguchi H, et al. Comparison of the prevalence of diabetes mellitus and impaired glucose tolerance in Japan and other countries. *Diabetes* **41**: 355-362, 1998 (in Japanese).
- Simpson JA. Immunological disturbances in myasthenia gravis with a report of Hashimoto's disease developing after thymectomy. *J Neurol Neurosurg Psychiatry* **27**: 485-492, 1964.
- Taillan B, Hastier P, Vinti H, et al. The association of myasthenia gravis, primary biliary cirrhosis and insulin-dependent diabetes. *Presse Med* **18**: 493, 1989 (in French).
- Green ST, Ng JP, Chan-Lam D. Insulin-dependent diabetes mellitus, myasthenia gravis, pernicious anaemia, autoimmune thyroiditis and autoimmune adrenalitis in single patient. *Scot Med J* **33**: 213-214, 1988.
- Jenkins EA, Hull RG, Gray RES, et al. Diabetes mellitus and myasthenia gravis in a patient with systemic onset juvenile chronic arthritis. *J R Soc Med* **82**: 368-369, 1989.
- Paolisso G, Varricchio M, Donofrio F. Thymectomy and azathioprine in the treatment of type 1 (insulin-dependent) diabetes mellitus. *Diabetes Metab* **16**: 524-525, 1990.
- Bennett PH, Knowler WC. Definition, diagnosis, and classification of diabetes mellitus and glucose homeostasis. In: Joslin's Diabetes Mellitus, 14th ed. Kahn CR, Weir GC, King GL, Jacobson AM, Smith RJ, Eds. Lippincott Williams & Wilkins, Philadelphia, 2004: 333-334.
- Gittoes NJL, Kendall MJ, Ferner RE. Drugs and diabetes mellitus. In: Pickup J, Williams G, Eds. Textbook of Diabetes. 2nd ed. Blackwell Science, Massachusetts, 1997: 69.1-69.10.