RESEARCH PAPER

Thymus histology and concomitant autoimmune diseases in Japanese patients with MuSK-antibody- positive myasthenia gravis

Ruka Nakata, M.D.1), Masakatsu Motomura, M.D.1), Tomoko Masuda, M.D.1), Hirokazu Shiraishi, M.D.1), Masahiro Tokuda, M.D.1), Taku Fukuda, M.D.1), Takao Ando, M.D.1), Toshiro Yoshimura, M.D.2), Mitsuhiro Tsujihata, M.D.3), Atsushi Kawakami, M.D.1)

1) Department of Clinical Neuroscience and Neurology, Graduate School of Biomedical Sciences, Nagasaki University
2) Nagasaki University School of Health Science
3) Nagasaki Kita Hospital

Words count of text; 1816 words

References:

Corresponding author; Masakatsu Motomura

Department of Clinical Neuroscience and Neurology, Graduate School of Biomedical Sciences, Nagasaki University

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Phone：+81-95-819-7265 (desk) or 7262 (call), FAX：+81-95-849-7270

Email:lems@nagasaki-u.ac.jp

RN and MM contributed equally to this paper.

Key words; MG, MuSK, titin antibodies, thymus, associated autoimmune disease

Abstract

Background: The differences in the characteristics of thymus histology, coexisting autoimmune diseases and related autoantibodies between anti- muscle- specific receptor tyrosine kinase (MuSK)-antibody (Ab) - positive myasthenia gravis (MG), and anti-acetylcholine receptor (AChR)- Ab-positive MG are not clearly defined.

Methods: We investigated the types of thymus histology, coexisting autoimmune diseases and associated antibodies in 83 MuSK- Ab- positive patients nationwide and compared them to those in AChR- Ab- positive patients followed at our institute (n=83). As for the autoantibodies associated with thymoma, titin antibodies were measured.

Results: Thymoma was not present in any of MuSK- Ab- positive patients but presented in 21 patients (25.3%) among the AChR- Ab- positive patients. Titin antibodies were absent in MuSK- Ab- positive patients but positive in 25 patients (30.1%) among the AChR- Ab- positive patients. Concomitant autoimmune diseases were present in 8 MuSK- Ab- positive patients (9.6%) amongst which Hashimoto's thyroiditis and rheumatoid arthritis predominated; whereas 22 AChR- Ab- positive patients (26.5%) had one or more concomitant autoimmune diseases of which Graves' disease predominated.

Conclusions: The differences in frequency of thymoma and thymic hyperplasia, coexisting autoimmune diseases, and autoantibody positivity between MuSK- Ab- positive and AChR- Ab-

positive MG were indicated, suggesting that, in contrast with the AChR-Ab- positive MG, thymus does not seem to be involved in the pathogenic mechanisms of MuSK- Ab- positive MG.

Introduction

Myasthenia gravis (MG) is an autoimmune neurological disorder characterized by impaired neuromuscular transmission due to circulating autoantibodies [1]. In around 80% of cases, immunoglobulin G1 (IgG1) complement-activating autoantibodies are raised against the acetylcholine receptor (AChR) in skeletal muscle [2]. A new population of antibodies (Abs) against muscle-specific receptor tyrosine kinase (MuSK), mainly consists of the non complement-activating IgG4 subclass was found in 2001 [3]. Recently, a third autoantibody to low-density lipoprotein receptor-related protein 4 (LRP 4), the agrin-binding receptor of the MuSK complex, have been found and they are mainly of the IgG1 subclass,[4]. MG is now recognized as a heterogenous disease with regard to autoantibody profiles.

Thymoma has been known as one of the important features of AChR- Ab- positive MG. Thymoma occurs in 10-30% of AChR- Ab- positive MG [5-7] and thymoma- associated MG has specific characteristics, [8] such as more severe disease course with poorer prognosis. The increasing incidence of late-onset MG without thymoma has been reported with an aging society [9, 10]. Early-onset MG, defined as beginning under the age of 50 years [10] often occurs in females and has enlarged thymus exhibiting lymphofollicular hyperplasia [7, 10-12]. These patients tend to have other organ-specific autoantibodies, most commonly autoimmune thyroid diseases [13-15], comprising a unique subgroup of AChR- Ab- positive MG.

MuSK- Ab- positive MG is another subtype of MG, distinct from the AChR- Ab- positive group, characteristically exhibits an oculobulbar form with more frequent respiratory crisis [16]. The prevalence of MuSK- Ab- positive MG among seronegative MG varies among geographic regions and reported in 20-40% in the United States [17, 18] and 27-41% in Japan [19-21]. Thymus histology usually appears to be normal in MuSK- Ab- positive MG [22], and there has been no report of concomitant autoimmune diseases MuSK- Ab- positive MG patients. Therefore, we investigated the thymus histology and concomitant autoimmune diseases in a large cohort of MuSK- Ab- positive MG patients in comparison with AChR- Ab- positive MG patients.

Methods

Patients

Demographic data and clinical information from patients are summarized in Table 1. The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with reductions in symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli and the presence of autoantibodies, either MuSK or AChR Abs [23]. The onset age was classified as early-onset $\leq$ 49 years old or late onset $\geq$ 50 years old. The Myasthenia Gravis Foundation of America (MGFA) clinical classification was used to grade disease severity [24].

Nagasaki University Hospital is a center for serological test of MuSK- Ab in Japan. Sera and

clinical information from MuSK- Ab- positive MG patients (n=83) were collected upon requests for serological diagnosis from 2005 until 2009. For comparison, sera and clinical information from AChR- Ab- positive MG patients (n=83) were included. To avoid potential bias, we enrolled consecutive patients with various stages of disease attended at Nagasaki University Hospital over the 18 months between January 2009 and June 2011. We assessed concomitant autoimmune diseases of all cases by studying the medical records and thymus histology of surgical cases including surgery records.

This study was approved by the Medical Ethical Committee of Nagasaki University Hospital. All patients gave informed consent before inclusion.

Antibody assay

MuSK Abs were measured by a standard radioimmunoassay method with iodine I^{125}-labeled rat recombinant MuSK [25]. AChR Abs were measured by a standard radioimmunoassay method with human I^{125}-labeled AChR as the antigen [26]. Titin Abs were measured utilizing commercially available standard enzyme-linked immunosorbent assay (ELISA) kit (DLD Diagnostika GmbH company) [27]. Titin Abs were considered as positive with the titer levels greater than 1.0.

Statistical analysis

Differences between two groups of patients were evaluated using the Student's t-test for continuous variables. The category variables were compared by the chi squared test to determine the significant

differences between two groups. Statistical analysis was performed using the Statmate program ver4.01. Values of $p < 0.05$ were considered statistically significant.

Results

Demographic and clinical characteristics (Table 1):

The mean age at MG onset was not different between MuSK- Ab- positive patients and AChR- Ab- positive patients. Both MuSK- Ab and AChR- Ab- positive MG patients showed female dominancy. The MGFA clinical classification at maximum severity is listed in Table 1. Ocular MG (MGFA Ⅰ) was significantly rarer in MuSK- Ab- positive group ($p<0.001$*). By grouping MGFA Ⅱa, Ⅲa, and Ⅳa categories and comparing them with Ⅱb, Ⅲb, and Ⅳb categories, we were able to show that bulbar (b) categories were more frequently recorded in MuSK- ab- positive patients than in AChR- ab- positive patients. Myasthenic crisis was more frequent in MuSK- Ab- positive patients (28.9%), compared to that in the AChR- Ab- positive patients (15.7%) ($p<0.05$*).

Thymus histology (Table 2):

Twenty-four patients in the MuSK- Ab- positive MG and 43 patients in the AChR- Ab- positive MG had received thymectomy. Among the thymectomized patients in MuSK- Ab- positive MG, only 3 patients (12.5%) had thymic hyperplasia. Notably, no patient presented thymoma.

On the contrary, thymus histology was abnormal in the majority of AChR- Ab- positive patients with thymectomy; 21 patients (48.8%) had thymoma and 14 patients (32.6%) had thymic hyperplasia,

whereas only 8 patients (18.6%) had normal or atrophic thymus.

Thymoma- associated Abs (titin Abs):

Titin Abs were not detected in MuSK- Ab- positive patients. On the contrary, titin Abs were positive in 25 patients (30.1%) with AChR- Ab- positive patients (p<0.001*). The titin Ab positivity was similarly high in thymoma-associated patients and late-onset MG, 10 out of 21 patients (47.6%) and 13 out of 26 patients (50%), respectively.

Concurrent autoimmune diseases (Table 3):

Other autoimmune disorders occurred concomitantly in 7 of 83 MuSK- Ab- positive patients (8.4%), amongst which Hashimoto's thyroiditis (3 patients) and rheumatoid arthritis (3 patients) were predominant. One patient had MuSK- Ab- positive MG and two other autoimmune diseases; Hashomoto's thyroiditis and Sjögren's syndrome concomitantly.

Other autoimmune disorders occurred concomitantly in 20 out of 83 AChR- Ab- positive patients (24.1%), amongst which autoimmune thyroid diseases were predominant. Two patients had AChR- Ab- positive MG and two other autoimmune diseases concomitantly; one patient with Graves' disease and systemic lupus erythematosus, and another patient with Hashimoto's thyroiditis and systemic lupus erythematosus.

Among MuSK- Ab- positive patients with other autoimmune diseases (n=7), the mean age of MG onset (44 years) was similar to that of the overall average of 83 patients with MuSK- Ab (44 years).

The disease severity of MG did not differ with or without other autoimmune diseases in MuSK- Ab-positive patients. Among AChR- Ab- positive patients with other autoimmune diseases (n=20), the mean age of MG onset (37 years) was younger than the overall average of 83 patients (43 years). They demonstrated a less severe MG disease. The MG patients associated with Graves' disease (n=7) were younger (median age 26 years) and demonstrated a less severe disease, without myasthenic crisis or thymoma.

Discussion

The most common immunocondition associated with MG has been considered as thymus abnormalities (thymoma/thymic hyperplasia), followed by autoimmune thyroid disease. In this study, we characterized the differences between the two major subgroups of MG, MuSK- Ab- positive MG and AChR- Ab- positive MG regarding the associated thymus histology and concomitant autoimmune diseases, as these issues have yet to be elucidated.

It has been reported that the thymuses from MuSK- Ab- positive MG patients do not differ from those in normal aging, because thymuses from these patients do not contain thymus lymphoid follicles and contain less lymphoid cells in the perivascular space than thymuses from AChR- Ab positive patients [17, 18, 22, 28, 29]. Consistently in the present study, we demonstrated that abnormal thymus findings are infrequent in MuSK- Ab- positive MG, and thymoma has not been diagnosed [17, 22, 28].

Thymoma associated MG patients are well known to be frequently titin ab positive [30-32]. Titin abs

specific for the main immunogenic region are found in 95% of thymoma-associated MG, and is a very strong diagnostic indicator for thymoma among MG patients [32]. Titin antibodies also have been shown to be found in 50% of late-onset MG patients without thymoma [33], thus the similarity in serological profile between paraneoplastic MG and late-onset MG has been indicated despite different thymus pathologies [34]. In our analysis, titin abs were frequently found in MG patients with thymoma and late-onset MG among AChR- Ab- positive patients [30, 35, 36]. There were no titin Ab-positive patients in the MuSK- Ab- positive MG group, which is consistent with the thymus findings.

Concomitant autoimmune diseases are frequent in MG, with an activated immune system as a general background. In previous reports, MG and associated autoimmune diseases have been reported to coexist in 8-26% of patients [15, 37, 38]. In our analysis, AChR- Ab- positive MG patients showed similar frequency. It has been reported that MG with associated autoimmune diseases are significantly more correlated with thymic hyperplasia than thymoma [39, 40] and their pathology show notable formation of germinal centers. The recent report of patients with MG and neuromyelitis optica spectrum disorder also suggested that they were more frequently associated with thymic hyperplasia and often achieved remission with rare MG relapses [41]. Thymic hyperplasia also is a common and reversible feature in Graves' disease [42-44]. In MuSK- ab- positive MG, titin abs are negative and thymus histology appears normal in majority of cases, which suggests distinct immunopathogenic mechanisms of MuSK- Ab- positive MG in comparison with the MG associated with AChR- Abs,

either with normal or hyperplastic thymus, or thymoma.

The interpretation of our data is limited by its retrospective design. Also, selection bias is inevitable, since MuSK- Ab- patients were recruited nationwide from Japan, and AChR- Ab- positive patients were all from our institute. To minimize the selection bias, we included consecutive AChR- Ab- positive patients from our institute, and their characteristics were consistent with the past data. The information from MuSK- Ab- positive patients is mostly limited to that up to serological diagnosis, but that from AChR- Ab- positive patients includes more longitudinal data. We could not expand our assay to include autoantibodies for other autoimmune diseases, which is also a limitation.

We have shown the heterogeneity of MG with the differences in thymus abnormality and autoanibodies, indicating the possible role of thymic hyperplasia as an immunological trigger for the onset of MG and some of other autoimmune diseases. Another subgroup is paraneoplastic MG patients with thymoma, the elder onset MG patients with no thymoma who tend to have increased titin antibodies, and they are speculated to share, in part, similar immunological background. We also confirmed the less association of thymus in MuSK- Ab- positive MG, suggested a further distinction between the two major subtypes of MG. Further studies to search for the relationship between thymus changes in MG and the onset of other autoimmune diseases would offer more precise classification of MG subgroups.

Table 1. Patient characteristics

Clinical factors	MuSK MG, n=83	AChR MG, n=83	*P* Value
Female (%)	75.9	68.7	0.30
Mean onset age ± SD (y/o)	43.5±16.1	42.5±20.7	0.73#
Thymoma (%)	0	25.3	0.00000094**
EOMG (≤ 49y/o) (%)	60.2	43.4	0.03*#
LOMG (≥ 50y/o) (%)	39.8	31.3	0.26#
MGFA classification at maximum severity (%)			
Ⅰ	2.4	25.3	0.00002**
Ⅱa, Ⅲa, Ⅳa	20.5	32.5	0.11
Ⅱb, Ⅲb, Ⅳb	48.2	26.5	0.0039**
Ⅴ	28.9	15.7	0.04*

(Statistics by: x^2 test or #Student's t-test, *<0.05, **<0.001**)**

Abbreviations: MuSK; muscle-specific receptor tyrosine kinase, AChR; acetylcholine receptor, MG; myasthenia gravis, EOMG; early onset myasthenia gravis, LOMG; late onset myasthenia gravis, MGFA; myasthenia gravis foundation of America.

Table 2. Thymus histology in MuSK- and AChR- Ab- positive MG

Thymectomized	MuSK MG, n=24	AChR MG, n=43	*P* Value
Thymoma (%)	0	48.8	0.000036**
Hyperplasia (%)	12.5	32.6	0.07
Normal/atrophy (%)	87.5	18.6	0.000000048**

(Statistics by: x^2 test, ** <0.001**)**

Abbreviations: MuSK; muscle-specific receptor tyrosine kinase, AChR; acetylcholine receptor, MG; myasthenia gravis.

Table 3. Concomitant autoimmune diseases in MuSK- and AChR- Ab- positive MG

	MuSK MG, n=83	AChR MG, n=83	*P* Value
Total autoimmune diseases, n (%)	8 (9.6%)	22 (26.5%)	0.0048*
Graves' disease	0 (0%)	7 (8.4%)	0.0069*
Hashimoto's thyroiditis	3 (3.6%)	5 (6.0%)	0.47
Systemic lupus erythematosus	1 (1.2%)	5 (6.0%)	0.10
Rheumatoid arthritis	3 (3.6%)	1 (1.2%)	0.31
Polymyositis	0 (0%)	2 (2.4%)	0.15
Sjögren's syndrome	1 (1.2%)	0 (0%)	0.32
Idiopathic thrombocytopenic purpura	0 (0%)	1 (1.2%)	0.32
Neuromyelitis optica	0 (0%)	1 (1.2%)	0.32

(Statistics by: x^2 test, *<0.05**)**

Abbreviations: MuSK; muscle-specific receptor tyrosine kinase, AChR; acetylcholine receptor, MG; myasthenia gravis.

Acknowledgments: The authors thank Ms Yuko Ohyama, Ms Michiko Morita, and Mr Mitsuyoshi Motomura for technical assistance and the patients who participated in this study.

Contributors: NR designed and conducted the antibody experiments, and conducted the statistical processing and wrote the paper. NR and MM diagnosed the patients, MT, SH, TM, FT and TA diagnosed the patients and conducted the antibody experiments. TM and AK conceived the study and designed the experiments. MM conceived the study, designed the experiments and wrote the paper.

Funding: This work was supported in part by the Health and Labour Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labour and Welfare of Japan.

Competing interests: None.

Ethics approval: The ethics committees from Nagasaki University approved the study.

Provenance and peer review: Not commissioned; externally peer reviewed.

References

1. Lang B, Vincent A. Autoimmune disorders of the neuromuscular junction. *Curr Opin Pharmacol* 2009;9:336-40.

2. Leite MI, Waters P, Vincent A. Diagnostic use of autoantibodies in myasthenia gravis. *Autoimmunity* 2010;43:371-9.

3. Hoch W, McConville J, Helms S, et al. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001;7:365-68.

4. Higuchi O, Hamuro J, Motomura M, et al. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. *Ann Neurol* 2011;69 2:418-22

5. Skeie GO, Romi F. Paraneoplastic myasthenia gravis: immunological and clinical aspects. *Eur J Neurol* 2008;15:1029-33.

6. Evoli A, Minisci C, Di Schino C, et al. Thymoma in patients with MG: characteristics and long-term outcome. *Neurology* 2002;59:1844-50.

7. Murai H, Yamashita N, Watanabe M, et al. Characteristics of myasthenia gravis according to onset-age: Japanese nationwide survey. *J Neurol Sci* 2011;305(1-2):97-102.

8. Meriggioli M.N, Sanders D. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol* 2009;8:475-90.

9. Aarli JA. Myasthenia gravis in the elderly: Is it different? *Ann N Y Acad Sci* 2008;1132:238-43.

10. Suzuki S, Utsugisawa K, Nagane Y, et al. Clinical and immunological differences between early and late-onset myasthenia gravis in Japan. *J Neuroimmunol* 2011;230:148-52.

11. Leite MI, Jones M, Ströbel P, et al. Myasthenia gravis thymus. *Am J Pathol* 2007;171:893-905.

12. Schluep M, Willcox N, Vincent A, et al. Acetylcholine receptors in human thymic myoid cells in situ: an immunohistochemical study. *Ann Neurol* 1987;22:212-22.

13. Oosterhuis H.J.G. Myasthenia Gravis. *Clin Neurol Neurosurg* 1981;83-3:105-35.

14. Tola MR, Caniatti LM, Granieri E, et al. Immunogenetic heterogeneity and associated autoimmune disorders in myasthenia gravis: a population-based survey in the province of Ferrara, northern Italy. *Acta Neurol Scand* 1994;90:318-23.

15. Christensen PB, Jensen TS, Tsiropoulos I, et al. Associated autoimmune diseases in myasthenia gravis; A population-based study. *Acta Neurol Scand* 1995;91:192-95.

16. Guptill J, Sanders D. Update on musle-specific tyrosine kinase antibody positive myasthenia gravis. *Curr Opin Neurol* 2010; 21:530-35.

17. Sanders DB, El-Salem K, Massey, et al. Clinical aspects of MuSK antibody positive seronegative MG. *Neurology* 2003;60(12):1978-80.

18. Zhou L, McConville J, Chaudhry V, et al. Clinical comparison of muscle specific tyrosine kinase(MuSK) antibody-positive and negative myasthenic patients. *Muscle Nerve* 2004;30:55-60.

19. Nemoto Y, Kuwabara S, Misawa S, et al. Patterns and severity of neuromuscular transmission

failure in seronegative myasthenia gravis. *J Neurol Neurosurg Pshychiatry* 2005; 76:714-18.

20. Ohta K, Shigemoto K, Fujinami A, et al. Clinical and experimental features of MuSK antibody positive MG in Japan. *Eur J Neurol* 2007;14:1029-34.
21. Shiraishi H, Motomura M, Yoshimura T, et al. Acetylcholine receptors loss and postsynaptic damage in MuSK antibody-positive myasthenia gravis. *Ann Neurol* 2005;57:289-93.
22. Leite, MI, Ströbel P, Jones M, et al. Fewer thymic changes in MuSK antibody-positive MG than in MuSK antibody-negative MG. *Ann Neurol* 2005;57:444-48.
23. Masuda T, Motomura M, Utsugisawa K, et al. Antibodies against the main immunogenic region of the acetylcholine receptor correlate with disease severity in myasthenia gravis. *J Neurol Neurosurg Psychiatry* 2012;83(9):935-40.
24. Jaretzki A [3rd], Barohn RJ, Ernstoff RM, et al, Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;55(1):16-23.
25. Matthews I, Chen S, Hewer R, et al. Muscle-specific receptor tyrosine kinase autoantibodies; a new immunoprecipitation assay. *Clin Chim Acta* 2004;348(1-2):95-9.
26. Lindstrom JM, Seybold ME, Lennon VA, et al. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. *Neurology* 1976;26(11):1054-9.

27. Lübke E, Freiburg A, Skeie GO, et al. Striational autoantibodies in myasthenia gravis patients recognize I-band titin epitopes. *J Neuroimmunol* 1998;81(1-2):98-108.

28. Saka E, Topcuoglu MA, Akkaya B, et al. Thymus changes in anti-MuSK-positive and –negative myasthenia gravis. *Neurology* 2005;65(5):782-83.

29. Lauriola L, Ranelleti F, Maggiano N, et al. Thymus changes in anti-MuSK-positive and –negative myasthenia gravis. *Neurology* 2005;64(3):536-38.

30. Granzier H, Labeit S. Structure-function relations of the giant elastic protein titin in striated and smooth muscle cells. *Muscle and Nerve* 2007;36:740-55.

31. Aarli JA, Stefansson K, Marton LS, et al. Patients with myasthenia gravis and thymoma have in their sera IgG autoantibodies against titin. *Clin Exp Immunol* 1990;82:284-88.

32. Voltz RD, Albrich WC, Nagele A, et al. Paraneoplastic myasthenia gravis: detection of anti-MGT 30(titin) antibodies predicts thymic epithelial tumor. *Neurology* 1997;49:1454-57.

33. Skeie GO, Mygland A, Aarli JA, et al. Titin antibodies in patients with late onset myasthenia gravis: clinical correlations. *Autoimmunity* 1995;20:99-104.

34. Skie G.O, Romi F. Paraneoplastic myasthenia gravis: immunological and clinical aspects. *Eur J Neurol* 2008;15(10):1029-33.

35. Lanska DJ. Diagnosis of thymoma in myasthenics using anti-striated muscle antibodies: predictive value and gain in diagnostic certainty. *Neurology* 1991;41(4):520-24.

36. Yamamoto AM, Gajdos P, Eymard B. Anti-Titin Antibodies in Myasthenia Gravis; Tight association With Thymoma and Heterogeneity of Nonthymoma Patients. *Arc Neurol* 2001;58:885-90.

37. Yagi K. MG and associated diseases. *Clinical Neuroscience* 2005;23(4):408-9.

38. Takamori M. Myasthenia gravis epidemiological survey report 1987 Japan, The Health and Labour Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases). 1988;227-45.

39. Monden Y, Uyama T, Nakahara K, et al. Clinical characteristics and prognosis of myasthenia gravis with other autoimmune diseases. *Ann Thorac Surg* 1986;41: 189-92.

40. Kanazawa M, Shimohata T, Tanaka K, et al. Clinical features of patients with myasthenia gravis associated with autoimmune diseases. *Eur J Neurol* 2007;14:1403-4.

41. Leite MI, Coutinho E, Lana-Peixoto M, et al. Myasthenia gravis and neuromyelitis optica spectrum disorder: A multicenter study of 16 patients. *Neurology* 2012;78(20):1601-7.

42. Yamanaka K, Nakayama H, Watanabe K, et al. Anterior Mediastinal Mass in a Patient With Graves' Disease. *Ann Thorac Surg* 2006;81:1904-6.

43. Tsuda E, Imai T, Matsumura A, et al. Thyrotoxic Myopathy Mimicking Myasthenic syndrome Associated with Thymic Hyperplasia. *Inter Med* 2008;47:445-47.

44. Popoveniuc G, Sharma M, Devdhar M, et al. Graves' disease and thymic hyperplasia: the

relationship of thymic volume to thyroid function. *Thyroid* 2010;20(9):1015-8.