Autoantibody Profiles and Neurological Correlations of Thymoma

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ABSTRACT

Purpose: Determine muscle and neuronal autoantibody frequencies in patients with thymoma, with and without paraneoplastic neurological accompaniments.

Experimental Design: Analysis of IgG autoantibodies in stored serum collected between 1985 and 2003 from 201 patients with histologically diagnosed thymoma (including six with thymic carcinoma). Contemporary assays quantitated antibodies reactive with muscle and neuronal cation channels, muscle sarcomeric proteins and neuronal cytoplasmic, and nuclear proteins.

Results: Neurological diagnoses included myasthenia gravis (MG), myositis, encephalitis, neuromuscular hyperexcitability, autonomic neuropathy, and subacute hearing loss, a previously unrecognized accompaniment of thymoma. Muscle acetylcholine receptor (AChR) binding antibodies were found in all patients with a diagnosis of MG. Muscle autoantibodies (AChR-binding, AChR-modulating, or striational) were also found in 59% of patients without any neurological disorder. One or more neuronal autoantibodies were found in 41% of patients without any neurological disorder, 43% of patients with MG only, and 78% of patients with other neurological disorders. Neuronal autoantibody specificities were, in descending order of frequency, as follows: glutamic acid decarboxylase, voltage-gated potassium channel, collapsin response-mediator protein-5, ganglionic AChR, and antineuronal nuclear antibody-type 1 (ANNA-1).

Conclusions: Neuronal autoantibodies complement skeletal muscle autoantibodies as serological markers of thymoma in patients with and without clinical evidence of a neurological disorder. The high prevalence of glutamic acid decarboxylase autoantibody, not previously considered a paraneoplastic marker, justifies its consideration as a marker of thymoma-related neurological autoimmunity. Serological evaluation of a patient's profile of neuronal and muscle autoantibodies may aid in preoperative identification of an indeterminate mediastinal mass.

INTRODUCTION

Thymoma is a relatively rare neoplasm that arises from thymic epithelium and is commonly associated with autoimmune disorders, particularly myasthenia gravis (MG). It is estimated that 15% of patients presenting with adult-onset MG have thymoma and that MG will become manifest in 40% of patients who have thymoma (1–4). Weakness in MG is caused by autoantibodies that interfere with synaptic transmission by binding to the extracellular domain of acetylcholine receptors (AChR) in the postsynaptic membrane of muscle. Other autoimmune neurological disorders are encountered with thymoma, albeit less frequently. These include myositis (3–5), encephalitis (6–8), autonomic neuropathy (9–11), and a spectrum of acquired neuromuscular hyperexcitability disorders (12, 13). The association of thymoma with neurological autoimmunity is thought to be related to this neoplasm's expression of pertinent neuronal and muscle autoantigens in highly immunogenic form (1).

The first autoantibodies recognized with thymoma were specific for sarcomeric ("striational") proteins of skeletal muscle (14). Striational antibody specificities identified to date include titin, myosin, actin, α-actinin, and ryanodine receptors (15–18). Striational antibodies and muscle AChR antibody have both been reported in patients with thymoma without evident MG (14, 19). Striational antibody (20) and a high level of muscle AChR-modulating antibody activity (21) are commonly associated with thymomatous MG.

Antibodies specific for autoantigens expressed in the plasma membrane, cytoplasm, and nucleus of neurons are increasingly recognized as markers of paraneoplastic neurological autoimmunity (22). Several have been reported in patients with thymoma (13, 23–26), but their overall frequency with thymoma has not been evaluated. Here we report the prevalence of neuronal and muscle autoantibodies in 201 patients who had a histologically confirmed thymoma or thymic carcinoma, with and without a paraneoplastic neurological accompaniment.

PATIENTS AND METHODS

Clinical Material. This study was approved by the Mayo Clinic Institutional Review Board. Patients with a histologic diagnosis of thymoma or thymic carcinoma made between 1985 and 2003 and a serum sample collected at the time of diagnosis were identified from the Mayo Neuroimmunology Laboratory database. Our review of pathology records at our institution for this interval identified 280 patients with a new diagnosis of primary thymic neoplasm. Of these, 175 patients (62%) had serum submitted to the laboratory as part of a clinical neurological or oncological evaluation. Five patients had atypical thymic neoplasms (two thymic lymphoma, three thymic carcinoid) and were excluded from further consideration; none had a paraneoplastic neurological disorder, and no muscle or neuronal autoantibodies were detected. An additional 31 serum samples

from patients in whom a new diagnosis of thymoma had been made elsewhere were added to the 170 Mayo Clinic cases. The serum samples were stored frozen. Clinical data were obtained by retrospective review of clinical records. Forty-five patients had served as control subjects in a previous report (26) or had been reported in other contexts (6, 11, 13, 23, 25). Sera from healthy control subjects were collected over this same period, stored frozen, and tested with identical assay methods.

Antibody Assays. All serological methods were standardized in the Clinical Neuroimmunology Laboratory. Stored samples were coded and tested retrospectively by blinded technicians who used contemporary clinical assay methods. Muscle and neuronal ganglionic AChR binding, muscle AChR blocking, neuronal voltage-gated potassium channel (VGKC, α-dendrotoxin receptor), P/Q- and N-type calcium channel, and glutamic acid decarboxylase (GAD65) antibodies were detected with radioimmunoprecipitation assays (27–30). The normal range for muscle AChR binding, P/Q- and N-type calcium channel and GAD65 antibody was 0.00 to 0.02 nmol/L. For ganglionic AChR and VGKC antibody, the normal range was 0 to 0.05 nmol/L, and for muscle AChR blocking antibody 0 to 25% blockade. Muscle AChR-modulating antibody was sought by bioassay on monolayer cultures of human myogenic cells and quantitated as percent loss of binding sites for ^{125}I-α-bungarotoxin; normal range 0 to 20% loss (27). Striational antibodies were assayed quantitatively by enzyme immunoassay. Normal value is negative at 1:60 (27). Neuronal nuclear [antineuronal nuclear antibody-type 1, -type 2, and -type 3 (ANNA-1, ANNA-2, ANNA-3)] and cytoplasmic autoantibodies other than GAD65 [Purkinje cell antibody-1, Purkinje cell antibody-2, Purkinje cell antibody-Trotter (ref. 30), amphiphysin-IgG, and collapsin response-mediator protein (CRMP-5)-IgG] were sought by an indirect immunofluorescence screening assay (normal value is negative at 1:60) and were confirmed by Western blot with native rat brain proteins (23, 30). All sera were tested additionally by Western blot with recombinant human CRMP-5 protein (normal value is negative at 1:30; ref. 23).

Statistical Analysis. Differences in continuous variables were evaluated with two-tailed t test (for normally distributed data) or Wilcoxon rank-sum test (for antibody titers), and the Fisher exact test was used to evaluate differences in antibody frequency between groups. P values < 0.05 were considered significant. Statistical analysis was done with JMP software (SAS Institute Inc., Cary, NC).

RESULTS

Between 1985 and 2003, we received serum from 201 patients with a new pathologic diagnosis of thymic neoplasm (Table 1). Thymoma of epithelial, mixed lymphoepithelial, or spindle-cell type was diagnosed in 195, and thymic carcinoma was diagnosed in six. Among the 195 patients with thymoma, eight had concurrent evidence of an unrelated second malignancy (lung carcinoma, breast carcinoma, seminoma, renal carcinoma, thyroid carcinoma, melanoma, colonic carcinoma, or uterine carcinoma). In general, the presence of a second malignancy did not correlate with a specific antibody profile or clinical presentation. Of interest, the patient with coexisting breast cancer had the highest GAD65 antibody level in this

Table 1 Demographics of patients with thymoma or thymic carcinoma

Tumor type	Number	Sex (M:F)	Age range (mean)
Thymoma	195		
With MG	124	45:79*	24–87 (52.1)†
Without MG	71	37:34	23–88 (56.6)†
Thymic carcinoma	6‡	2:4	45–66 (57.4)
Total	201	84:117	23–88 (53.8)

* Female predominance was significant ($P < 0.05$).

† Age difference was not statistically significant ($P = 0.06$, two-tailed t test).

‡ Two had MG.

series (490 nmol/L) but no signs or symptoms of stiff-man syndrome.

Although a broad spectrum of paraneoplastic disorders was represented (Table 2), the inherent bias in referral of neurological patients to this institution, and of sera to this laboratory, precludes an accurate determination of the frequency of autoimmune neurological disorders in patients with thymoma. Patients with MG were predominantly female (63%), but there was no sex predominance among thymoma patients without MG. Thirteen patients had non-neurological paraneoplastic disorders, including autoimmune hematologic and dermatological syndromes. To circumvent the effect of neurological referral bias, we analyzed the frequency of neuronal and muscle autoantibodies after assigning patients to four subgroups based on neurological diagnoses (Table 3): MG only, MG plus another neurologic diagnosis, neurologic diagnosis other than MG, and no neurologic disorder.

Serological Findings: Muscle Autoantibodies. Muscle AChR antibodies were the most common serological finding overall and were significantly more frequent in patients with clinical evidence of MG than in those without MG (Table 3). All patients with a clinical diagnosis of MG had muscle AChR-binding antibody and all but one had AChR-modulating antibodies. Additionally, values for muscle AChR-binding antibody among patients with MG ($n = 126$; mean 16.3 nmol/L) were higher than values among seropositive patients without a diagnosis of MG ($n = 25$; mean 4.6 nmol/L, $P < 0.0001$, rank sum test). Muscle AChR-modulating antibody values exceeded 90% loss of AChR in 93 of 126 patients with a diagnosis of MG (74%), but in only 13 of 75 patients without MG (17%; $P < 0.0001$). Striational antibodies were detected in 77% of all patients with a diagnosis of MG but in only 23% of patients without clinical evidence of MG. However, the titers of striational antibody in seropositive patients with MG were not significantly different from those of seropositive patients without MG.

Serological Findings: Neuronal Autoantibodies. Neuron-specific autoantibodies were less frequent than muscle-specific autoantibodies, but their frequency was elevated compared with age-matched healthy control subjects tested during the same time period using identical techniques (Table 4). The highest prevalence of neuronal autoantibodies was among patients with neurological disorders other than MG, but the frequency of neuronal antibodies was increased even among thymoma pa-

Table 2 Autoimmune disorders identified in 145 patients with thymoma or thymic carcinoma *

Disorder	Mayo patients (*N* = 170)	Non-Mayo patients (*N* = 31)
Myasthenia gravis	103 (61%)	23 (74%)
Other neurological disorders †	18 (11%)	19 (61%)
Encephalopathy	7	5
Dysautonomia or GI motility disorder	4	6
Myositis	3	5
Neuromuscular hyperexcitability	4	4
Subacute hearing loss (c.n. VIII)	2	0
Stiff-man syndrome	0	1
Non-neurological disorders	13 (8%)‡	
Pemphigus	4	
Hematologic abnormalities	4	
2 pure red cell aplasia, 1 agranulocytosis/hypogammaglobulinemia, 1 thrombocytopenia		
Lupus or sicca syndrome	3	
Alopecia and/or vitiligo	2	

Abbreviations: GI, gastrointestinal; c.n., cranial nerve.

* 56 patients had no autoimmune diagnosis.

† 24 of 37 (65%) had one or more other neurological diagnosis coexisting with MG.

‡ 8 of 13 (62%) had coexisting MG.

Table 3 Muscle autoantibody frequency in 201 patients with thymoma or thymic carcinoma

Patients		Muscle AChR antibodies (%)				Any muscle
Clinical subgroup	No.	Binding	Modulating	Blocking	Striational (%)	antibody (%)*
MG only†	103	100‡	99‡	61‡	76‡	100‡
Other neurological disorder with MG	23	100§	100§	50§	87§	100§
Other neurological disorder without MG	14	50	57	14	29	64
No neurological diagnosis	61	30	44	7	21	59

* Prevalence of any muscle AChR or striational antibody in healthy age-similar control subjects is <2% (V. A. Lennon, unpublished observation).

† No other neurological disorder. Includes four patients with pemphigus, one with lupus, one with idiopathic thrombocytopenia, and one with pure red cell aplasia.

‡ Seroprevalence significantly higher than patients without MG; *P* < 0.0001.

§ Seroprevalence significantly higher than neurological disorders without MG; *P* < 0.001.

tients with no neurological diagnoses. Among seropositive patients, the levels of VGKC and ganglionic AChR antibodies were not different among the clinical subgroups. Voltage-gated calcium channel antibodies were not detected in any patient.

GAD65 antibody was the most frequently encountered neuronal autoantibody (22% positive overall). Its frequency and serum level were significantly higher in patients with neurological disorders other than MG (Fig. 1). In eight patients, the serum level of GAD65 exceeded 20 nmol/L, a value that generally distinguishes patients with stiff-man syndrome from those with type 1 diabetes (29). One patient among those eight, in fact, had stiff-man syndrome (without MG), and four others had neurological disorders other than MG. Only five patients with GAD65 antibody had a diagnosis of diabetes or fasting hyperglycemia (16% of the 31 with adequate clinical information available).

Twenty-nine patients (14%) had antibody specific for CRMP-5, which is a divergent member of the collapsin response-

Table 4 Neuronal autoantibody frequency in 201 patients with thymoma or thymic carcinoma

Patients		Ganglionic AChR	VGKC	GAD65	CRMP-5-IgG or	Any neuronal
Clinical subgroup	No.	antibody (%)	antibody (%)	antibody (%)	ANNA-1 (%)	antibody (%)
MG only	103	8*	13*	15*	18*	43*
Other neurological disorder (± MG)§	37	19*	32†	54‡	30†	78‡
No neurological diagnosis	61	8	13	21	7	41
Healthy subjects		0	2	8	0	
		(refs. 26, 31)	(ref. 33)	(ref. 29)	(refs. 23, 34)	

* No difference in seroprevalence compared with patients without a neurological diagnosis.

† Seroprevalence significantly higher than patients without another neurological disorder; *P* < 0.05.

‡ Seroprevalence significantly higher than patients without any neurological disorder; *P* < 0.0001.
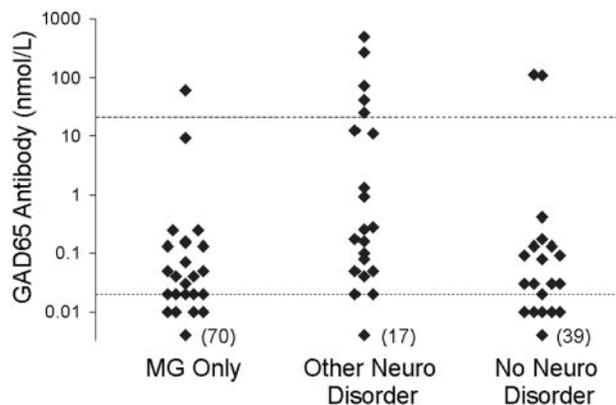
§ Twenty-three had MG.

Fig. 1 GAD65 antibody in patients with thymoma. Individual GAD65 antibody values are plotted on a logarithmic scale for three clinical subgroups of patients with thymoma. The line at 0.02 nmol/L represents the cutoff for normal values. Numbers in parentheses represent the number of individuals with undetectable GAD65 antibody in each group. Patients with neurological disorders other than MG had a significantly higher frequency and level of GAD65 antibody ($P < 0.01$) compared with the other clinical subgroups. The line at 20 nmol/L represents the level that generally distinguishes patients with stiff-man syndrome.

mediator protein family that is expressed in adult neurons. CRMP-5 antibody is recognized clinically as a marker of both thymoma and small–cell-lung carcinoma (23).

Neurological Accompaniments. Neuronal autoantibodies were most common in patients with a paraneoplastic neurological disorder other than MG (Table 5). Twelve of these 37 patients had encephalitis, and 11 of those had one or more neuronal autoantibodies; 50% had VGKC antibodies. Nine presented as typical limbic encephalitis with subacute memory impairment, psychiatric manifestations, seizures, electroencephalogram abnormalities, and magnetic resonance imaging signal change in mesial temporal lobes. The other three patients presented clinically with diffuse involvement of the cerebral cortex and magnetic resonance imaging evidence of multifocal inflammatory lesions in the cerebral cortex (6, 25).

Ten patients had gastrointestinal dysmotility (seven gastroparesis or intestinal pseudo-obstruction, and three esophageal achalasia). Three presented with intestinal pseudo-obstruction in the context of a severe panautonomic neuropathy coexisting with MG (11). Neuronal ganglionic AChR-specific antibodies

were found in high titer in three patients, consistent with their diagnosis of subacute autoimmune autonomic neuropathy (31).

Eight patients had inflammatory myopathy (myositis) defined by electromyography and muscle biopsy. Four (50%) additionally had clinical evidence of myocarditis. All had concurrent generalized MG, elevated serum creatine kinase, high levels of striational antibody (exceeding 1:15,360) and muscle AChR-modulating antibody (exceeding 90% loss of AChR). This group also showed a high frequency of GAD65 and VGKC antibodies (Table 5).

Eight patients had an acquired disorder of neuromuscular hyperexcitability characterized by muscle cramps, stiffness, rippling, and fasciculations (13, 32, 33). Six of these patients had concurrent MG, and VGKC antibody was detected in five (Table 5). Three patients with VGKC antibody had a combination of encephalitis and neuromuscular hyperexcitability (Morvan syndrome; ref. 33).

Two patients had subacute and profound hearing loss. One became deaf within 2 weeks of developing symptoms of MG. The other did not have MG but had clinical and laboratory evidence of subacute hearing loss and profound peripheral vestibular failure consistent with a bilateral disorder of cranial nerve VIII.

DISCUSSION

Thymoma has long been recognized in the company of autoimmune syndromes and serum autoantibodies, particularly skeletal muscle and antinuclear antibodies. Our study highlights the diverse neurological paraneoplastic syndromes associated with thymoma and defines autoantibody profiles that aid the diagnosis of thymoma. We found that both neuronal and muscle autoantibodies are frequent accompaniments of thymoma, even among patients who lack any clinical evidence of a paraneoplastic neurological disorder. Autoantibody profiles did not distinguish benign thymoma from metastatic or invasive thymoma, or from thymic carcinoma.

It has been estimated that MG occurs in 35 to 40% of patients in whom thymoma is diagnosed (3, 4). Published case reports have established myositis, limbic encephalitis, autonomic neuropathy, and neuromuscular hyperexcitability as additional neurological associations of thymoma. These disorders are thought to have an autoimmune pathogenesis based on pathologic findings and responses to immunomodulatory therapy in individual cases (6, 11, 12). Our present study has

Table 5 Neuronal autoantibody frequency in 37 patients with neurological disorders

Patients		Ganglionic AChR antibody	VGKC antibody	GAD65 antibody	CRMP-5-IgG or ANNA-1	Any neuronal antibody
Neurological diagnosis	No.*					
Encephalopathy	12	2	6 (50%)‡	5 (42%)‡	4	11 (92%)†
Autonomic/GI dysmotility	10	3 (30%)§	1	5 (50%)‡	3	5 (50%)
Myositis	8	0	3	5 (62%)‡	2	6 (75%)
Neuromuscular hyperexcitability	8	1	5 (62%)†	3	2	8 (100%)†
Hearing loss	2	1	1	1	0	2

* Total exceeds 37 because three patients had more than one accompanying neurological disorder.
† Seroprevalence greater than patients with MG only or with no neurological disorder; $P = 0.001$.
‡ Seroprevalence greater than patients with MG only or with no neurological disorder; $P < 0.01$.
§ Seroprevalence greater than patients with MG only or with no neurological disorder; $P = 0.05$.

identified subacute hearing loss as a novel accompaniment of thymoma (two patients). Subacute hearing loss is recognized as a paraneoplastic manifestation of small–cell-lung carcinoma (34) and as an idiopathic autoimmune disorder (35), but it has not to our knowledge been reported previously with thymoma.

We confirmed that muscle AChR-binding, AChR-modulating, and striational antibodies are the most common serological markers of thymoma. Fifty-two percent of patients without evidence of any neurological disorder had one or more muscle autoantibodies. We did not identify any case of "seronegative MG" with thymoma. The most characteristic profile of MG associated with thymoma was a high level of AChR-modulating antibody (AChR loss 90% or greater) accompanied by striational antibody.

This study is the first to comprehensively evaluate the frequency of neuronal autoantibodies in patients with thymoma and to present data from an important control group of 61 patients with thymoma who had no neurological disorder. More than 40% of patients in that control group had autoantibodies reactive with antigens expressed in the plasma membrane, nucleus or cytoplasm of neurons. These antibodies were found in 78% of patients with neurological disorders other than MG. As expected, ganglionic AChR antibody was detected in patients with autonomic neuropathy (31), and VGKC antibody was detected in patients with neuromuscular hyperexcitability or encephalitis (33). However, neither antibody was restricted to patients with a specific neurological syndrome, and both were found in thymoma patients without a neurological diagnosis. The CRMP-5 autoantibody (also known as anti-CV2) has been reported previously in association with paraneoplastic MG (23, 36) and with other neurological accompaniments of thymoma (6, 23). This study revealed CRMP-5-IgG in thymoma patients without neurological diagnoses (7%), with MG alone (17%), and with neurological syndromes other than MG (30%).

There is considerable overlap in the autoantibody accompaniments of small-cell carcinoma and thymoma (muscle and ganglionic AChR, VGKC, striational, CRMP-5, and ANNA-1 antibodies). However, we did not encounter neuronal calcium channel antibodies (N-type or P/Q-type) in any patient with thymoma. Because these autoantibodies are a frequent accompaniment of small–cell-lung carcinoma (37, 38), their detection in the serological evaluation of an indeterminate mediastinal mass would favor the diagnosis of lung cancer, usually small-cell carcinoma (38).

The 50% seroprevalence of GAD65 autoantibody in patients with neurological complications of thymoma other than MG suggests that GAD65 antibody production in this context may be a paraneoplastic phenomenon. GAD65 antibody is the principal specificity of the pancreatic islet cell antibody marker of type 1 diabetes (39). It is detectable in 80% of patients with that diagnosis, usually in low titer (<20 nmol/L) and in 8% of healthy subjects aged 50 or older (29). This antibody was first identified as a serological marker in 90% of patients with stiff-man syndrome (40), usually in very high titer (>20 nmol/L; ref. 29). A high titer of GAD65 antibody also is recognized as a serological marker of nonparaneoplastic autoimmune cerebellar ataxia (41) and idiopathic epilepsy (42). GAD65 autoantibody has been reported in individual patients with MG and thymoma (11, 43), and our laboratory has reported

its detection in 18% of patients with neurological autoimmunity related to lung carcinoma or breast carcinoma (44, 45). Serological testing for muscle autoantibodies, GAD65 antibody, and other neuronal autoantibodies (VGKC, ganglionic AChR, CRMP-5, and ANNA-1) is a valuable adjunct to chest imaging for raising or supporting a clinical suspicion of thymoma. Serial serological testing can also prove useful in the early detection of thymoma recurrence (20).

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