PREVALENCE OF ECTOPIC THYMIC TISSUE IN MYASTHENIA GRAVIS AND ITS CLINICAL SIGNIFICANCE

Forty patients with myasthenia gravis underwent maximal thymectomy. Complete histologic study findings were available for 38 patients. The prevalence of ectopic thymic tissue was 39.5% (15 of 38). On the basis of the presence or absence of ectopic thymic tissue, patients were divided into two groups: group I had ectopic thymic tissue and group II had no ectopic thymic tissue. Male/female ratio was almost equal (1.1:1) in group I, whereas in group II the ratio was 1:2.8. The duration of the disease was less than 1 year in 80% of group I and 47.8% of group II patients ($p = 0.05$). Furthermore, ectopic thymic tissue (group I) was associated with poor outcome of operation ($p = 0.003$). Only 2 (13.3%) of 15 patients in group I had complete remission as compared with 11 (47.8%) of 23 patients in group II. Thus it appears that the presence of ectopic thymic tissue not only modifies some of the clinical parameters of myasthenia gravis, but also could serve as a prognostic factor in predicting the outcome of operation. (J THORAC CARDIOVASC SURG 1995;109:632-5)

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There are ample data now to suggest that the thymus gland plays a major role in the pathogenesis of myasthenia gravis (MG).¹⁻³ Thymectomy is increasingly being accepted as a treatment modality for MG.⁴⁻⁸ However, thymectomy does not achieve complete remission rates consistently in all patients. In some of these cases, foci of thymic tissue have been left behind at various locations.^{8,9} Some of these ectopic locations are accessible through various approaches used for thymectomy. On the other hand, ectopic thymic tissue in the retrocarinal area is not accessible through even the most aggressive approach.¹⁰ The significance of ectopic thymic tissue with regard to clinical characteristics of MG and outcome of operation, to my knowledge, has not been studied before. In this report I present the pattern of MG in patients with ectopic tissue and compare it with the pattern in those without ectopic thymic tissue.

Patients and methods

The cases of 40 patients with MG who were operated on consecutively between July 1987 and June 1993 at King Khalid University Hospital, Riyadh, Saudi Arabia, were

reviewed retrospectively. MG was diagnosed in the patients on the basis of clinical presentation and edrophonium chloride (Tensilon) test results. All were receiving anticholinesterase inhibitors. Fifteen patients were receiving steroids and three were also receiving azathioprine. Most were having uncontrolled myasthenic symptoms with medical treatment. Any attempt to taper off medications resulted in increased disability.

Before operation all patients had a mean of three sessions of plasmapheresis. This protocol was adopted with the aim of not only improving patient status before operation, but also decreasing the incidence of morbidity after operation. Patients underwent transcervical-transsternal "maximal" thymectomy according to technique described by Jaretzki and Wolff.¹¹ During the first phase of operation via transcervical incision, upper poles of thymus were isolated carefully. A thorough search was made to locate any suspicious thymic rests in the retro-thyroid area and in the pretracheal adipose tissue. Most of the adipose tissue in these areas was carefully removed and sent for histologic examination in separate containers. The second phase of operation was done via the transsternal approach. All visible thymus gland was excised en bloc with anterior mediastinal adipose tissue. The left phrenic nerve was lifted off the pericardium to facilitate gland dissection in the hilar region. Adipose tissues in the retro-innominate-vein area, aortocaval window, aortopulmonary window, and both cardiophrenic angles were sent separately for histopathologic examination.

Multiple microscopic sections were taken from each specimen and stained with hematoxylin and eosin. These were examined for thymic tissues. Thymic tissue was identified by the presence of Hassall's corpuscles. If the identification of thymic tissues was in doubt, staining with T-cell markers and immunohistochemical staining with cytokeratin were done for the identification of thymocytes and epithelial cells, respectively. On the first day after operation all patients were started on half the amount of

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Table I. Age and sex distribution

Age group (yr)	Male patients	Female patients	Total	Percent
Up to 20	3	11	14	36.8
21-40	8	12	20	52.6
40+	3	1	4	10.5

Table II. Details of ectopic thymic tissue

Patient no.	No. of ectopic sites	Site of ectopic thymic tissue
1	1	Right cardiophrenic angle
2	2	Left retrothyroid lobe and left cardiophrenic angle
3	1	Retro-innominate vein
4	1	Below thyroid isthmus
5	1	Pretracheal tissue
6	1	Left retrothyroid lobe
7	1	Left carotid sheath
8	1	Aortopulmonary window
9	4	Right and left cardiophrenic angles, adjacent to left thyroid lobe, and retro-innominate vein.
10	1	Left retrothyroid lobe
11	1	Adjacent to left thyroid lobe
12	1	Left retrothyroid lobe
13	1	Adjacent to left thyroid lobe
14	1	Below thyroid isthmus
15	1	Below thyroid isthmus

their preoperative medications. The outcome of operation was judged according to the following criteria: (1) complete remission was achieved when the patient had no symptoms and received no drugs, (2) pharmacologic remission occurred when the patient had no symptoms with half or less of the amount of preoperative drugs, (3) improved condition occurred in patients who had no symptoms with the same preoperative drugs, and (4) no change occurred when the patient had symptoms with medical therapy.

Statistical analysis was done by Mann-Whitney rank-sum test with use of BMDP statistical package version 7.01, 1994 (University of California Press, Berkeley, Calif.).

Results

Complete histologic study findings were available for 38 of 40 patients. The two patients with incomplete data shall not be considered further. There were 14 male and 24 female patients with ages ranging from 10 to 61 years and a mean age of 26.8 years (Table I). Duration of disease ranged from 1 month to 20 years with mean of 34.9 months. Fifteen patients (39.5%) had ectopic thymic tissue at 19 locations (Table II). Ectopic locations were in the neck in 63.2% of cases (12 of 19) and in the cardiophrenic angles in 21% (4 of 19). Eight (57%)

Table III. Ectopic and nonectopic group characteristics

Characteristics	No. of patients	
	Group I	Group II
Sex		
Male	8	6
Female	7	17
Age		
Up to 20 yr	5	9
21-40 yr	9	11
40+ yr	1	3
Duration of symptoms		
Up to 1 yr	12	11
>1 yr	3	12
Osserman class		
I	3	3
II	7	8
III	5	9
IV	0	3
Anti-acetylcholine receptor antibodies		
Positive	5	10
Negative	3	10
Not done	7	3
Histologic type of thymus		
Hyperplasia	14	19
Atrophic	1	4
Outcome of thymectomy		
Complete remission	2 (13.3%)	11 (47.8%)
Pharmacologic remission	8 (53.3%)	12 (52.2%)
Improved	5 (33.35%)	0 (0%)

of 14 male patients and 7 (29.2%) of 24 female patients had ectopic thymic tissue. Fourteen (41.2%) of 34 patients with ectopic thymic tissue were younger than 40 years old as compared with only 1 of 5 patients older than 40 years. Fourteen (42.4%) of 33 patients with thymic hyperplasia had ectopic thymic tissue whereas only 1 of 5 with atrophic thymus had ectopic thymic tissue.

On the basis of the presence or absence of ectopic thymic tissue, 38 patients were divided into two groups: group I patients had ectopic thymic tissue and group II patients had no ectopic thymic tissue. The various characteristics of the two groups are depicted in Table III. Male:female ratio was almost equal (1.1:1) in group I whereas in group II the ratio was 1:2.8. Of group I patients 80% (12 of 15) had duration of disease up to 1 year whereas in group II only 47.8% (11 of 23) had duration of disease up to 1 year ($p = 0.05$). There was no significant difference in Osserman class in the two groups.

The follow-up period ranged from 4 months to 6 years with a mean of 14.5 months. All patients in

both groups benefited from thymectomy. However, the complete remission rate in group I was only 13.3% (2 of 15) compared with 47.8% (11 of 23) in group II. All the remaining patients in group II achieved pharmacologic remission whereas in group I only 53.3% (8 of 15) achieved pharmacologic remission and 33.3% (5 of 15) had improved conditions ($p = 0.003$).

Discussion

Thymus gland develops as two separate lobes from the third pharyngeal pouch along with inferior parathyroid glands. During subsequent growth it descends into the anterior mediastinum to a variable extent and two lobes join at a variable distance for variable length. This complicated development provides ample scope for ectopic and abnormal position of thymus gland as was seen in two patients in this series in whom one lobe or the whole of the thymus was seen passing behind the left innominate vein. Jaretzki and Wolff¹¹ noted 98% of patients with MG had anatomic variability in the distribution of thymic tissue in the mediastinum. Goldstein and Mackay¹² reported 20% of normal subjects had ectopic thymic tissue.

In an autopsy study on subjects without myasthenia gravis, 44.4% had ectopic thymic tissue in anterior mediastinal fat and 7.4% had ectopic thymic tissue in the retrocarinal area.¹⁰ In patients with myasthenia gravis, 72.2% had ectopic thymic tissue in anterior mediastinal fat.¹³ In the present series, I found ectopic thymic tissue in 39.5% of patients at variable locations (Table II). Twelve (63.2%) of 19 ectopic sites were in the neck close to the thyroid gland. This is understandable because embryologically the development of thyroid and thymus glands is closely related. On several occasions, I have found one or both inferior parathyroid glands embedded in the substance of thymus gland near the upper poles. Four (21%) of 19 ectopic sites were in cardiophrenic angles.

Although most patients had a single ectopic site, two patients had ectopic thymic tissue at multiple locations. One of these two had ectopic thymic tissue at four different locations. This raises the question of multiple ectopic sites in at least some patients at hitherto unknown sites. Ectopic thymic tissue was found in 57% of male patients and 29.2% of female patients. This indicates a relative preponderance of ectopic tissue in the male population. Ectopic thymic tissue was seen more frequently in patients younger than 40 years old compared with

those older than 40 years (41.2% versus 25%). On the basis of the high prevalence of ectopic thymic tissue in the neck and cardiophrenic angles, I recommend that dissection in these areas should form an integral part of operation for MG, particularly in male patients younger than age 40 years.

The clinical characteristics of group I and group II patients are shown (Table II). Some of these were surprisingly different between groups. Male:female ratio was almost equal in group I whereas women outnumbered men by a factor of 2.8 in group II. The duration of disease was less than 1 year in 80% of group I patients and 47.8% of group II patients ($p = 0.05$). In group I, the presence of ectopic thymic tissue not only modified some of the clinical pattern of MG, but also altered the outcome of operation. The complete remission rate was 13.3% in group I and 47.8% in group II. Furthermore, all the remaining patients in group II had pharmacologic remission whereas in group I, 53.3% (8 of 15) had pharmacologic remission and 33.3% (5 of 15) had improved conditions ($p = 0.003$). When the complete remission rate is taken as the only parameter to judge the outcome of operation, it is apparent that patients with ectopic thymic tissue had less favorable outcomes as compared with the outcomes of those without ectopic thymic tissue. The presence of ectopic thymic tissue, thus, could have prognostic value in determining the outcome of operation. Poor outcome of operation in these patients might be a result of still more ectopic sites that are inaccessible by the present radical techniques of thymectomy.

In conclusion, it seems that the presence of ectopic thymic tissue altered some of the clinical parameters of MG and was also associated with poor outcome of operation.

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