

# *Study on signs and symptoms of myasthenia Gravis disease before and after thymectomy as well as pathology in Myasthenic patients*

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**Introduction:** Thymus gland as a part of immune system can get involved in both malignant and benign conditions. One result of this gland involvement is myasthenia gravis, which causes general weakness of the body especially during activities. In this situation thymus gland produces antibodies that can compete with acetylcholine in neuro muscular junction and inhibits acetylcholine effect on end plate receptors.

In this study, we aimed to identify the clinical condition of myasthenic patients before and after thymectomy. Thymus pathology and the recuperation of patients as well as their age, sex and family history were investigated.

**Methods:** 32 thymectomized myasthenic patients in Day hospital (Tehran) were studied. Information such as medical history and signs before and after operation, type of thymus pathology and their improvement after thymectomy were investigated.

**Results:** Form 32 patients, 59.4% were female and 40.6% were male. 84.4% of patients were more them 20 years old. Pathologic results showed that 18.75% of cases were thymoma, 50% thymus hyperplasia and 31.25% were without any pathologic changes. In clinical signs, ptosis was the most frequent complaint, whereas weakness of masticatory muscles had the least frequency. 36.6% of patients had complete improvement, 40% partial improvement and 20% without any changes in the condition of the disease. Furthermore, in only one case the signs of the disease were deteriorated.

**Conclusion:** Although the myasthenia gravis is a rare disease but early diagnosis and performing of thymectomy even before medical treatment can have better therapeutic effects on myasthenic patients

**Keywords:** Myasthenia gravis, sign, symptom, pathology, Thymectomy.

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## Introduction

Myasthenia Gravis is an autoimmune disease and is shown with skeletal muscle weakness. This weakness is partially treated with rest and increased with activity. In this disease affection of striated muscles produce many symptoms, among these ptosis and diplopia has more incidence and weakness of upper extremity muscles and mastic muscles has less incidence.<sup>(1)</sup> If weakness of respiratory system due to the problems of intercostal muscles are concomitant with the above mentioned findings, it is called myasthenic crisis which is one the urgent conditions of medicine.<sup>(2)</sup>

Accompanied with this disease there may be other diseases such as thyrotoxicosis, rheumatoid arthritis, systemic lupus erythematosus and even MS and probably diabetes.<sup>(1,3,4)</sup>

From etiologic and physiopathologic point of view there is close relation between this disease and thymus gland, so in 10-15% of Myasthenia Gravis patients there is thymoma and in 65% of them there is hyperplasia of thymus with various degrees.<sup>(2,5)</sup>

In this disease, the reason for muscle weakness is the presence of antibody against nicotinic receptors (acetylcholine receptor antibody) of striate muscles, which is produced in patient's thymus and prohibits the effect of acetylcholine on receptor synapse in the place of synapse between neuron and muscle, and cause muscle weakness.<sup>(2,6)</sup> This aforementioned antibody was seen in blood of 85% of patients with

generalized myasthenia and in 60% of patients with local type of the disease.<sup>(2)</sup>

From histology point of view, thymus mainly contains lymphocytes and thymocytes and also myoid and argiophil cells.<sup>(4)</sup> Among these groups of cells, myoids are like cells of striate muscles and these cells have receptors like the receptors of muscle cell which respond to acetylcholine.<sup>(2)</sup> Virus attacks thymus myoid cells and production of antibody against these cells and similarity of myoid cells to skeletal muscle cells may be affected on the pathogenesis of the disease. In this regard, the hyperplastic with tumoral change may be produced in the gland or even the gland with normal appearance may be caused myasthenia.<sup>(2,4)</sup>

One way for treatment of myasthenia gravis is surgery and thymectomy. Many studies on thymectomic patients have been done and nowadays there is belief that this is an effective treatment. Also every effort should be performed for shortening pre-surgery period in myasthenic patients and on-time surgery has the best results.<sup>(7)</sup> Although in some researches, researchers have concluded that treatment value of thymectomy in myasthenia gravis without thymoma is not exactly confirmed<sup>(8)</sup> but the effect of this surgery in patients with hyperplastic thymus or in thymoma have been exact.<sup>(9)</sup>

In one study on 160 myasthenic patients of myoclinic (all of them were adult) half of them were treated by

drug and half of them were treated by surgery. 7 patients of the first group (8.7%) and 27 patients from second group (33.7%) were completely treated. In the survey, drug treatment was only preferred in the patients with eyes symptoms.<sup>(4)</sup>

In another study on 124 myasthenic patients (with average age of 29.2 years) 82.2% of patients were cured after surgery, 13.7% of them had no cure and the remainder were aggravated. Among 104 of them which had a follow up of 40-54 months after surgery, it was shown that in patients with shorter period of disease before surgery, better response was obtained.

In another survey on 35 patients with myasthenia who underwent surgery, pathology of thymus in 15 patients was hyperplasia, in 12 was thymoma and in 8 patients was atrophic or normal. After 96 months of follow up, significant improvement was seen in 26 patients.<sup>(10)</sup>

In one study which was done in Kerman on 52 individuals who have undergone surgery, the results of pathology were as follow: 32(61.5%) individuals with follicular hyperplasia, 8(15.4%) with thymoma and 12 individuals with pathologic atrophy or normal.<sup>(11)</sup> In this study nothing was mentioned about symptoms of patients at the time of refer and treatment conditions of the patients.

Since there is no exact statistics in Iran regarding the symptoms before surgery, pathologic shape of thymus and clinical status after surgery, we decided to evaluate thymectomic

patients in Day hospital in Tehran, in order to investigate reasons of refer of the patients, pathology of the gland and their condition after surgery.

### Methods

This was a retrospective and non-probable study. 32 patients who underwent thymectomy due to myasthenia gravis in Day hospital from 1993 to 2002 were evaluated for the symptoms at the time of refer and hospitalization, pathology of the tumor and patients' status after surgery. Patient's history and their status after surgery and also the result of their pathology were evaluated. In this survey, pathologic results after thymectomy were classified into three categories: thymoma, thymus hyperplasia and thymus without histological abnormality concomitant with lipid tissue increase. Status of patients was evaluated after thymectomy by periodic follow ups using their address or phone number in their files. The base for evaluation of patients were: gender, age of the onset of the disease, positive symptoms before surgery, result of pathology of thymus gland (after operation) and the effect of surgery on the condition of the patient considering pathology of thymus gland. Regarding the symptoms before and after surgery, nine symptoms were considered which are as follow respectively: 1) diplopia, 2) ptosis, 3) disorder in speech, 4) weakness of lower extremities, 5) general weakness feeling, 6) disorder in swallow, 7) weakness in upper

extremities, 8) weakness in masticatory muscles, 9) disorder in breathing. It is worth to mention that in evaluation of patients' files, access to two files was not possible. To evaluate the result of treatment, we divided the patients (who underwent surgery) at the period of about 8 years, to the following categories: complete cure, partial cure, without change, aggravated symptoms. In this study the first and second categories were considered as treated groups.

The gathered information was analyzed by SPSS software and Chi2 and fisher tests were used.

### Results

From 32 patients with myasthenia gravis who underwent thymectomy, 19(59.4%) individuals were female and 13(40.6%) individuals were male with no positive family history of disease.

5 individuals (15.6%) were under 20 years old, 9(28.1%) between 20 to 29 years old, 8(25%) between 30 to 39 years old, 9(28.1%) between 40 to 49

years old and 1 individual was more than 50 years old.

The incidence of symptoms in the above patients before and after surgery is shown in table 1. Regarding the initial symptoms which made patients to go to the physician office, no one mentioned only one symptom and no one had all nine symptoms. Only in one case 8 symptoms was reported. The most frequent symptom was ptosis and the least one was weakness in masticatory muscles. Pathologic studies shown that in 6(18.75%) individual there was thymoma, in 16(50%) there was follicular hyperplasia of thymus and in 10(31.25%) individuals there was no pathologic change of thymus.

The results of this study according to the change in the patients' complaint before and after surgery shows that in one case the disease was aggravated, in 11 cases (36.3%) there was complete cure, in 12 cases (40%) there was partial cure and in 6 individuals there was no change in clinical symptoms.

**Table 1: Incidence of positive symptoms before & after Thymectomy in 30 patients under study**

Disorder in breathing	Weakness in mastic muscles	Weakness of upper extremities	Disphagia	General weakness	Weakness of lower extremities	Disorder in speech	Petosis	Diplopia	Type of symptom No&percent
9(30%)	5(7/16%)	10(3/33%)	14(6/46%)	28(3/93%)	10(3/33%)	15(50%)	29(7/96%)	18 (60%)	Before surgery
1(1/11%)	2(40%)	3(30%)	21(34%)	4(2/14%)	2(20%)	5(3/33%)	15(7/51%)	5(7/27%)	After surgery

## Discussion

In this study the result of under-investigation patients shows that the incidence of thymoma is 18.75%, incidence of follicular hyperplasia of thymus is 50% and incidence of no pathologic change is 31.25%. In comparison with 55 cases of operated patients in 1991 which the results of their pathologies were 29.1%, 41.8% and 29.1%, respectively<sup>(4)</sup> the incidence of thymoma in our study was less.

In the 27 year study of Venute on 217 patients with myasthenia gravis who underwent surgery, the incidence of thymoma was 28.45(12). In one study by Klein on 51 patients, 25.5% thymoma, 41.1% hyperplasia of thymus and 33.4% without pathologic changes were reported.

In this study the incidence of thymoma was less but the incidence of hyperplasia and normal condition of thymus with replacement of lipid tissue was more. Maybe the low number of sample in under-survey group of our study was the reason for the difference. Nevertheless, for access to the more exact percent of thymoma in patients we need vast studies. Comparison of our patients' pathology with the study which was done on 52 patients in Kerman, have reported the amount of the thymoma, thymus hyperplasia and normal thymus, is as follow respectively: 15.4%, 61.5%, 23%; and have more correlation. According to these studies it can be concluded that thymoma in comparison with two other shapes (hyperplasia and normal

Thymus) had worse prognosis after thymectomy<sup>(7,9,12)</sup> and it has been confirmed in our study.

Regarding treatment process of patients in this study the following results were obtained: 33% complete cure, 40% partial cure, 20% without changes and 7% with aggravated symptoms. In Yao et al. study on 124 patients with surgery, follow up was done in 40-54 months and 102 patients (82.2%) responded to treatment, 17 patients (13.7%) had no response, and 5 patients (4%) were aggravated<sup>13</sup>. In one follow up with the average time of 42.8 months in 114 thymactomic patients, the amount of complete cure was 27.2%, partial cure was 67.5% and the remainder (5.3%) had no satisfaction from treatment.<sup>(14)</sup> In other study in 217 patients with surgery for their myasthenia gravis after about 119 months of follow up, 54 patients (25%) had complete cure, 100 patients (46%) had better clinical symptoms, 24 patients (11%) had aggravated symptoms and the remainder had no change.<sup>(12)</sup> Despite the close similarity of these statistics according to the explanation of differences in various researches different reasons were introduced.<sup>(12)</sup> Although in our study according to the statistical tests there was no relationship between age and surgery according to the cure ( $p < 0.005$ ), among other reasons for the mentioned difference, is the time between detection of disease and the time of surgery. Shorter time has been explained as a better prognosis.<sup>(7,12,13)</sup>

As mentioned previously, in most researches type of thymus pathology is related with the result of treatment, thymoma had worse prognosis and other types had better prognosis. In this study, we obtained the same results; that is in the complete cure 80% of pathologies were hyperplasia and normal, and 20% were thymoma. But in the aggravated condition of the symptoms, 100% of pathologies were thymoma. According to gender in this research 59.4% of cases were female and 40.6% were male. In some researches gender has been shown as an unimportant variable<sup>(7,9,12)</sup> but it is believed in some articles that this disease has affected more females than males.<sup>(1,4)</sup> We couldn't find out the main reason for patients referral in our investigations, but an interesting point was that among the nine common symptoms, no one had only one symptom, no one had all nine symptoms and more than 40% of patients in the period of disease had only three symptoms, that is ptosis with 96.7% was the most prevalent symptom and weakness of mastic muscles with 16.7% was the less prevalent one. After surgery the symptoms with complete treatment

were related to breathing disorders and general weakness, and the symptoms with least treatment were ptosis and weakness of muscles. Nevertheless, in some articles ptosis and diplopia have been mentioned as the most common symptoms.<sup>(15)</sup>

### **Recommendations**

Although myasthenia gravis have no high prevalence (43-84/million) but it is a benign and weakening disease. So it is worth to educate and instruct physicians for on-time diagnosis of the disease and with early diagnosis it is recommended that even before drug treatment, surgery takes place. In addition, this research can not respond to the main questions regarding the etiology of the disease and the reason for differences in reactions of patients to the surgery and the probability of aggravation in patients' condition after treatment. Responding these questions need dynamic, sustained and purposeful research.

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## بررسی علائم قبل و بعد از عمل جراحی تیمکتومی و پاتولوژی تیموس در بیماران مبتلا به میاستنی گراو

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### چکیده

زمینه و هدف: غده تیموس با توجه به اینکه بخشی از ایمنی بدن را تامین می نماید می تواند منشا نئوپلاسم های خوش خیم یا بد خیم باشد و با تغییرات فوق یا حتی بدون تغییر پاتولوژیک واضح باعث بیماری میاستنی گراو گردد این بیماری منجر به ضعف عمومی به خصوص در هنگام فعالیت می گردد. در چنین وضعیتی تیموس مولد آنتی بادی هایی می شود که قابلیت رقابت با استیل کولین را داشته و رسپتورهای نیکوتینیک سیناپس عصب به عضله را اشغال کرده و منجر به اختلال کار استیل کولین می شوند. این مطالعه به منظور تعیین وضعیت بیماران مبتلا به میاستنی گراو قبل از تیمکتومی و پاتولوژی غده تیموس این بیماران و وضعیت بهبودی آنها پس از عمل جراحی انجام گرفت. در این راستا ارتباط بیماری با سن و جنس و سابقه فامیلی ارزیابی گردید.

**روش بررسی:** ۳۲ بیمار مبتلا به میاستنی گراو که طی سال های ۷۲-۸۱ در بیمارستان دی تهران مورد عمل جراحی قرار گرفته بودند با بررسی محتویات پرونده بیمارستانی و شرح حال موجود، علائم قبل از عمل جراحی، نوع پاتولوژی غده تیموس و وضعیت بهبود آنها پس از عمل جراحی مورد ارزیابی قرار گرفت.

**یافته‌ها:** از بیماران مورد بررسی ۵۹/۴٪ زن و ۴۰/۶٪ مرد بودند و ۸۴/۴٪ آنها سن بیش از ۲۰ سال داشتند. نتیجه پاتولوژی حاصل از تیمکتومی ۱۸/۷۵٪ تیموما، ۵۰٪ هیپرپلازی تیموس و ۳۱/۲۵٪ بدون تغییرات پاتولوژیک در تیموس گزارش گردید. از نظر وفور علائم قبل از عمل جراحی بیشترین شکایت بیماران افتادگی پلک و کمترین آن ضعف عضلات جونده بوده است و از نظر بهبود پس از عمل جراحی ۳۶/۶٪ بهبودی کامل، ۴۰٪ بهبودی نسبی، ۲۰٪ بدون تغییر در وضعیت بیماری و تنها یک مورد از تشدید علائم شکایات داشت.

**نتیجه‌گیری:** گرچه میاستنی گراو بیماری نادری است ولی تشخیص به موقع و زود هنگام آن و انجام عمل جراحی تیمکتومی حتی قبل از درمان دارویی کمک بسیار زیادی به بهبود بیماری تا حد عدم نیاز به دارو می نماید.

**واژگان کلیدی:** میاستنی گراو، تیموس، استیل کولین، عمل جراحی تیمکتومی.

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