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PROJECT REPORT

NAME : DR.LALLY ALEXANDER

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MONTH & YEAR OF SUBMISSION : NOVEMBER 1998

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TITLE

NATURAL HISTORY OF NON-THYMECTOMISED MYASTHENIA GRAVIS

NAME : **DR. LALLY ALEXANDER**

PROGRAMME : **D.M. NEUROLOGY**

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Name	
Page	of
Date	

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CERTIFICATE

I, Dr. LALLY ALEXANDER hereby declare that I have actually performed all the procedures listed/carried out the project under report.

Signature Lally Alexander

Place : **Trivandrum**

Date : 14.11.98

Name in capital letters

LALLY ALEXANDER

Forwarded. She has carried out the project under report.

Signature
Head of the Department

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM 695 011	Name	
	Page	of
	Date	

SREE CHITHRA THIRUNAL INSTITUTE FOR
MEDICAL SCIENCES & TECHNOLOGY

NATURAL HISTORY OF NON-THYMECTOMISED MYASTHENIA GRAVIS

LALLY ALEXANDER

CONTENTS

INTRODUCTION

Myasthenia gravis was first described clinically 300 years earlier by the great physiologist Thomas Willis.[1] Myasthenia gravis is not rare with a prevalence of 50 to 125 cases per million population[4] . The incidence is age and sex related, with one peak in 2nd and 3rd decade affecting mostly women and a peak in the 6th and 7th decade affecting mostly men. The cardinal features are weakness and fatiguability of skeletal muscles, usually occurring in a characteristic distribution. The weakness tends to increase with repeated activity and improve with rest. Ptosis and diplopia occur early in the majority of patients. Studies show weakness remains localised to the extraocular and eyelid muscles in about 15% of patients.

Generalised weakness develops in approximately 85% of patients[2]. It affects the limb muscles often in a proximal distribution, as well as the diaphragm and the neck extensors. If weakness of respiration becomes severe enough to require mechanical ventilation, the patient is said to be in crises. On physical examination the findings are limited

I also place on record my most sincere thanks to all my teachers in the department of Neurology for their valuable guidance and assistance in this study.

Last but not least I register my indebtedness to the unfortunate victims of myasthenia gravis who teach us maximum about this disease and to whose service we have to dedicate our lives.

to the motor system without loss of reflexes or alteration of sensation or coordination.

Twenty years back the discovery of a deficit of acetylcholine receptors at the neuro muscular junction of patients with Myasthenia gravis[3] and the development of an animal model of the disease shed new light to this disorder.

Myasthenia gravis is undoubtedly the most thoroughly understood of all human autoimmune diseases and has served as a model for the elucidation of mechanisms underlying other autoimmune disorders.

The muscular weakness and fatiguability that are hallmarks of Myasthenia gravis are known to be due to an antibody mediated autoimmune attack directed against acetyl choline receptors at neuromuscular junctions.

With the use of modern immunotherapy the prognosis of the disease has improved dramatically. Formerly fatal or disabling in most patients Myasthenia gravis can now be treated effectively so that nearly all patients are able to lead full productive lives. One of the unsolved problems in Myasthenia gravis as in the other human autoimmune disease concerns the origin of the autoimmune response. The thymus has been implicated as a possible site of origin because approximately 75% of patients have thymic abnormalities[5] . The hypothesis that Myasthenia gravis may be triggered by molecular mimicry that is an immune response to an

infectious agent that resembles the acetyl choline receptor has acquired some support. Cross reactivity between certain bacteria and the acetyl choline receptor has been reported.

Genetic factors and abnormalities of immune regulation may increase the likelihood of Myasthenia gravis. There is a moderate association of Myasthenia gravis with the HLA antigens B8 and DRw 3 a stronger association of Myasthenia gravis with HLA DQw2 is still controversial[6,7].

Paradoxically about 10-20% of patients with acquired Myasthenia gravis do not have acetyl choline receptor antibodies detectable by radioimmunoassay. These subgroup of patients have generalised weakness whose disease corresponds to conventional Myasthenia gravis with respect to other clinical diagnostic and therapeutic features. actually these patients have circulating acetyl choline receptor antibodies that are not detected by radio immunoassay[8,9,10].

IMMUNO AND NEURO BIOLOGY OF MG.

ACHR is a trans membrane glycoprotein with a molecular weight of apparently 2,50,000 daltons, the molecule being composed of four subunits arranged in a pentamer(2 alpha chains and one each of beta, gamma and delta), which is highly conserved phylogenetically. The acetyl choline receptors is synthesised within the muscle cell at its myotube stage and is inserted into the membrane. The antibodies measured in Myasthenia gravis EAMG serum are produced by plasma cells, which derive from further differentiation of B cells.

The thymic abnormality in the form of thymic hyperplasia or thymoma is seen in most Myasthenia gravis patients. In hyperplasia the thymic medullary epithelium is frequently hyperplastic and even in the atrophied thymus associated with Myasthenia gravis, lymphoid follicles with active germinal centres occur in the thymic medulla. These cells have been shown to secrete antibodies.

The thymus gland of most patients with Myasthenia gravis shows obvious pathology. The presence of hyperplasia (lymphoid follicles containing germinal centres) in the glands of most young patients as well as the presence of

thymoma in 20-30% of myasthenia gravis, has suggested a major role for the thymus in the induction of the disease.

The normal turnover of acetyl choline receptor at motor end plates is low, with the estimated half life of about 13 days. Synthesis of new junctional acetyl choline receptors must occur. Extra junctional ACHRs are replenished every few days, their life span ranging from 6-35 hours, depending on the cells of origin.

Over 75% of ACHR must be blocked to observe a decrease in the muscle action potential. almost 92% must be blocked to reduce the twitch tension to a level where muscle contractions would be insignificant. The excess of quanta released by nerve impulses and excess of ACHR available both contribute to the safety factor of neuro muscular transmission. In Myasthenia gravis ACHR in the intercostal muscles are reduced by about 50%. Since there is no change in the release of quanta, weakness is related to loss of ACHR as well as to the markedly abnormal geometry of the post junction membrane and the abnormal related positions of residual receptors and nerve terminal active zone transmitter release sites. The function of the acetyl cholinesterases in Myasthenia gravis is to prolong the time for acetyl choline molecules to find the residual ACHR, but even this will not be of much value at severely damaged end plates.

REVIEW OF LITERATURE

Ocular Myasthenia gravis is a subtype of Myasthenia gravis that causes relatively mild disability but may convert into severe generalised muscle weakness. A universal management plan for ocular Myasthenia gravis has not been established. Particularly there is no clear cut guidelines as to the need for thymectomy.

Ocular Myasthenia gravis generally has a good prognosis In a recent retrospective study of 78 patients with ocular Myasthenia gravis with mean duration of 8.3 years showed that in 69% of patients the disease remained confined to the extraocular muscles[11]. Of these 54% were in remission 33% improved and 13% patients remained unchanged state at the end of the study.

In the study published in 1983 by Bever et al , 53 of 108 patients (diagnosed 1957-69 in New York city) 49% later generalised[12].

Grob et al in his large collection of patients found that among 202 patients 34% with initial ocular Myasthenia gravis remained ocular[13].

Oosterhuis reviewed an even earlier series of patients who were first documented between 1926 and 1965 in

Amsterdam were managed without steroid or other immuno suppressive treatment[24]. In this group 24 of 35 (69%) developed generalised Myasthenia gravis, probably reflecting the natural course of the disease.

Common to all studies including the study by Somar and Sigg is the finding that the risk of generalisation is greatest soon after onset gradually declining with time. Generalised Myasthenia gravis developed in 88%in the Oosterhuis and 83% in the Bever study group within 2 years of onset[12,24].

Different treatment modalities such as steroids, azathioprine and thymectomy clearly improve auto immune Myasthenia gravis. Evoli et al reports a series of 48 patients with ocular Myasthenia gravis[85]. They state that corticosteroids are effective in most cases. Thymectomy is now a standard treatment for patients with Myasthenia gravis with suspected thymoma and in young onset patients on whom thymic hyperplasia with germinal centres can be expected[26,27]. However most neurologists do not consider thymectomy as a standard treatment for ocular Myasthenia gravis. In Sommer Sigg series thymectomy for ocular Myasthenia was only performed when chest CT indicated thymoma. Thymoma associated with ocular Myasthenia had a tendency to become generalised. However all patients without thymoma remained ocular. In 1985 Sahuma et al reported a series of 18 mainly

young patients with ocular Myasthenia who seemed to benefit from thymectomy and 13 of whom showed thymic hyperplasia. Although immunosuppressants were used in partial and a clear criteria for an expected therapeutic effect could not be identified. Sommar and sigg et al concluded that thymectomy should be considered in ocular Myasthenia[11].

In a retrospective study by Grob et al in 1987 who studied 108 patients with ocular myasthenia was carried out to identify factors influencing prognosis[13]. Increasing duration of pure ocular Myasthenia was associated with a decreasing risk of late generalised symptoms. Only15% of the observed generalisation occurred after more than 2 years of solely ocular symptoms. Increasing age at onset was associated with greater risk of respiratory crises or death caused by Myasthenia gravis. Whereas patients younger at onset had greater chance of benign outcome. Neither systemic curare tests nor responses to repetitive nerve stimulation had prognostic value. This study was comparable in many respects to others[14,15,16,17,18].

Age at onset appeared to have prognostic significance. Patients older than 50 years at onset were at significantly greater risk of generalisation complicated by respiratory crises or death, and younger age at onset was associated with a more benign outcome.

NATURAL COURSE OF MYASTHENIA GRAVIS

A model clinical study traced the natural of 1036 patients observed between 1940 and 1980[19]. The disease was initially purely ocular in 40% but remained confined to the ocular muscles in only 16% and 7%of generalisation occurred within 13 months of onset. In patients with generalised disease the interval from onset to the first episode of maximal weakness was less than 36 months in 83% and more than 50% of deaths resulting from the disease took place in that period. Tracing the course of 382 patients between 1940 and 1960 and of 476 patients between 1960 & 1980 who had generalised disease revealed that significantly more patients improved (36% versus 20%)or were unchanged (42% versus 29%) and significantly fewer became worse (2% versus 7%)or died (12% versus 33%) in the 1980 to1960 group. The improvement was primarily due to improved management of severely ill patients and especially to improved respiratory care during the first 3 years of the disease. The mortality in crises fell from 30% between 1940 and 1960 to only 3% between 1970 and 1980. Even within severe generalised disease more than 40% of patients can now attain an improved or steady state.

The natural course of Myasthenia gravis is not well known. In the earlier series the diagnosis was probably limited to the more severely affected patients with

mortality rates of 30-40%. Since the introduction of anticholinesterases in 1934 the diagnosis was facilitated in less prominent cases although a response may be absent in ocular cases

Thymectomy is generally thought to have improved the natural course in early onset cases without thymoma but some doubt has been expressed because of the lack of randomised prospective studies. Improved intensive care facilities and the use of prednisolone, immunosuppressive drugs and plasma exchange are of benefit especially to the 20%severely affected patients with intermittent respiratory insufficiency. The use of new diagnostic tools such as single fibre EMG,EMG with ischemia and the determination of antibodies to acetyl choline receptor proteins allows a more accurate diagnosis in mild cases and exclude other myesthenic syndromes and pseudomyesthenias. As a result these procedures include mild cases which probably remained undiagnosed in earlier series, thereby improving the prognosis.

Between 1961-65 Hans J Oosterhuis studied 53 patients with Myasthenia gravis living in Amsterdam. This epidemiologically defined cohort was followed until 1985.

Thymectomy in non thymoma patient was not used before 1965 while prednisolone and azathioprine were only used after 1970 in some patients and affected the final outcome

only a few. In his observation which included ocular in 35 patients, oculobulbar in 16, bulbar in 11, limb weakness in 9 and generalised in 12/53 patients purely ocular. 21 became generalised within 2 years in 3 patients generalisation occurred between 10-22 years.

Spontaneous remission in the first year of disease occurred in 16/53 and in 8/53 the interval to relapse was 3-12 months. These early remissions were not related to the ultimate severity of the disease. In this study it was noted that the worst period including death occurred in 50 patients (87%). Within the first seven years while in 12 patients the clinical condition did not change. In 5 patients of whom 3 had only ocular signs, an exacerbation took place 10-25 years after onset. Thymomas were detected in 9 men and 5 women 5 were present in the early onset group. In all patients with thymomas Myasthenia gravis was generalised. In this study 18 patients died in a myaesthenic crises , 13 within 3 years after onset (3 in the period before prostigmine)in a crises precipitated by an operation and an airway infection. 18/58 patients died in a myasthenia crises, 13 within 3 years after onset (3 in the period before prostigmine), 3 in the 6^{th} year after onset, 8 of 14 thymoma patients died, 4 of these shortly after thymectomy.

It was found that the incidence and prevalence of Myasthenia gravis in this study is comparable with data from

other studies[20,21,22,23]. The natural history that emerges from this above study by Oosterhuis comprising of 53 patients is as follows. After an uncertain onset with spontaneous transitory remission in about 20% of patients, the disease gradually develops a maximum intensity in the first 7 years, although about 15% may have their worst period later.

In a another large series of Myasthenia gravis patients studied by Oosterhuis which constituted 374 patients with onset between 1965-84, the frequency of thymoma was 19%, the detection rate is likely to increase if all patients with anti-SM are examined with CT scanning of the mediastinum[24]. About 25% of patients will die mainly in this first period. Spontaneous clinical remission and substantial improvement may be expected from the 2nd year after onset and may occur at any time thereafter but the clinical course is unpredictable in the individual patient. The general trend in the survivors is that of a gradual improvement in the long term a complete clinical remission (without medication) occurring in more than 20% approximately 15%, usually with mild symptoms, do not change.

The impact of new therapies such as thymectomy in early onset patient and prednosolone or immunosuppressive treatment in late onset patients and in patients with thymomas is reflected in a large series by Oosterhuis consisting of 328 patients with generalised Myasthenia

gravis with onset between 1965-84 and a mean follow up of 12 years[24].Complete clinical remission with or without therapy occurred in 37% and death in 9%. The latter was due to Myasthenia gravis in 52% of the patients who were not treated with PDN in 1.8% due to the side effects prednisolone or azathioprine, and in 2% due to the invasiveness of their thymoma or thymomas associated myocarditis.

In another study by Oosterhuis of interest he has reviewed retrospectively all patients diagnosed as having Myasthenia gravis at the University department of neurology in Amsterdam from 1926-65[24]. Thymectomy was not used before 1965 for patients who did not have a thymoma. If we assume that anticholinesterase drugs do not influence the outcome of the disease then the outcome in the early patients reflects the natural course of Myasthenia gravis . A quarter of the patients had died by 1965. In 1985, 22% of the original cohort were in complete remission, 34% had improved, 16% were unchanged and 3% had deteriorated.

Similar large series by Grob et al who studied patients with Myasthenia gravis between 1940-60 with a mean follow up of 12 years showed that 11% had complete clinical remission, 21% had improved, 36% had not improved but had worsened and 32% had died[13].

Other older series by Simpson et al studied 87 patients with an onset between 1934-56 with a mean follow up of 14 years. It was found that 19% had remission, 22% had improved, 22% had not improved with death in 37%[33].

Associated diseases of probable autoimmune origin were present in 3 of 11 patients with thymomas and in 12 of 47 patients without thymomas. This frequency (25%) is probably higher than expected for the whole population although the prevalence of autoimmune diseases in a population studied over a long period in not known. Only rheumatoid arthritis in women had a definitely higher prevalence than expected from a population study which yielded about the same prevalence as that in the Netherlands (expected age adjusted prevalence 3.25% means 15% in the study by Oosterhuis[24,18].

Antibodies to acetyl choline receptors were found in 18 of 21 patients with generalised Myasthenia gravis and in 3 of 6 patients with ocular Myasthenia gravis. The 2 patients with onset in early infancy was seronegative and those whose clinical course and favourable reaction to prostigmine indicated that they had an acquired and not a congenital Myasthenia gravis in one patient . In one patient in this study had a remission. These findings also confirm data that the antibodies to acetyl choline receptors remain present even if patient is in a clinical remission. Anti smooth muscles were present in all thymoma patients and in 5 of 40

patients without detectable thymoma. The titre in the latter were definitely lower than in patients with a confirmed thymoma.

The natural history of Myasthenia gravis is uncertain. Acetylcholinesterase preparations were introduced in1934 and now a therapeutic response to part of the definition of the disease. Historical evidence of outcome is unreliable as in the early series before the advent of thymectomy, the less severe form of the disease were almost certainly missed. The combination of EMG,SFEMG and the measurement of acetyl choline receptor antibodies now allows the detection of milder cases and the exclusion of other myaesthenic syndromes. yet despite advances on our understanding of the pathophysiology of Myasthenia gravis its treatment is still controversial because of the lack of data from controlled clinical trials[29]. Such trials are difficult to carry out because of the long duration of treatment required before benefit may be obtained and the fluctuation in the natural course of the disease. Indeed these trials may now be unethical as large uncontrolled studies have shown the beneficial effects of various treatments used.

A retrospective comparison of medical treatment (without corticosteroids) with surgical treatment showed that patients treated by thymectomy were more likely to achieve remission and less likely to die of their disease[30].

As Myasthenia gravis is well established to be an autoimmune disorder, what is the therapeutic contribution of immunosuppression? Corticosteroids & plasma exchange seem to be particularly useful in patients who are too weak to undergo thymectomy and in those who remain severely disabled after thymectomy. Corticosteroids induce remission too early, however for this to be the result of immunosuppression they probably act by protecting the acetyl choline receptors from immunological attack. Corticosteroids may be expected to cause remission in 80% of patients[31].

Survival was also substantially improved by the recognition of cholinergic crises and by the introduction of positive pressure ventilation in 1953. Although thymectomy is less effective in patients with a thymoma it should still be undertaken to decrease the risk of local invasion by the tumor.

Corticosteroids and plasma exchange seem to be particularly useful in patients who are too weak to undergo thymectomy and in those who remain severely disabled after thymectomy. Corticosteroids induce remission too early, however for this to be the result of immunosuppression they probably act by protecting the acetyl choline receptor from immunological attack. Corticosteroids may be expected to cause remission in 80% of patients, and the remission can be

maintained by relatively small doses given an alternate days.

It has been argued that corticosteroids and immunosuppressants do not diminish the already low mortality from Myasthenia gravis, but there is little doubt that they improve the quality of life.

Reviewing the epidemiology of myasthenia gravis in Denmark- it was a longitudinal and comprehensive population survey[32].The mean annual incidence rate was 4.4 million population. Age and sex specific incidence rates disclosed a bimodel appearance for both sexes with a peak age at onset located in early onset group and another peak for late onset of Myasthenia gravis.

Factors causing increased mortality are bulbar and respiratory involvement of disease. Maximum mortality seen in first 2 years of onset. In the course of Myasthenia gravis, 70% of patients experienced generalised muscular weakness and 30-40% also suffered from respiratory problems. But the highest point prevalence was seen in Norway where it was 100/1 million population, annual incidence rate was 4/year[33].

Simpson et al observed a bimodal pattern for male patients with a peak age at onset at 25-35 years and 60-70 years and peak for females in the 3rd decade. Kurtizke

estimated the peak incidence rates at 6.2 and 10.8 per million population for woman and men respectively.

Evoli et al studied 360 myesthenic patients in clinic between 1968-1986, of this 132 cases the onset of disease occur strictly confined to extrinsic ocular muscles[28]. Afterwards generalised disease occurred in 84 on these patients (64%) mostly within 1 yeat of onset while the remaining 48 patients continued to have purely ocular Myasthenia gravis during the whole period of observation.

The review of literature from 1950-89 discloses that observed point prevalence rates differ widely ranging from 25-100 per million population.

The observed rapid progression of the disease to a plateau phase in most cases is in accordance with Oosterhuis and Grob et al[34].

It is essential to note that in the course of disease 70% of all patients experience moderate to severe generalised muscular weakness and 30-40% suffer from respiratory problems.

In an epidemiologic study done in Norway a number of patients with Myasthenia gravis diagnosed and registered in Norway from 1912-1981 has been collected representing essentially all diagnosed cases during these 70 years.

The incidence rate by diagnosis per million population 1951-1981 is 2.6 for male and 5.3 for females and 4 for both sexes.

The prevalence/million 52 for males & 27 for females and 90 for both. The mortality in this population seen in males is 14.4% and females 15.3%

The excess mortality is much greater in patients less than 60 years of age especially in females. The underlying cause of death was pneumonia, malignant tumors thymomas, tuberculosis, respiratory insufficiency, stroke and myocardial infarction.

In a study done by Ian Andrew and Donald B Sanders, assessed the influence of race, sex and puberty upon clinical features and outcome in 115 patients with autoimmune juvenile Myasthenia gravis[35], the demographic variables influenced not only disease incidence but also disease severity, response to therapy and outcome despite comparable therapeutic strategies. Among white patients those with pre pubertal onset had low incidence and equal sex ratio, the incidence in females increased during and after puberty, males had lesser severity than females during and after puberty, spontaneous remission were most frequent and persistence of active juvenile Myasthenia gravis for more than 10 years was less frequent in patients with pubertal onset, remissions were more frequent after early

than late thymectomy, and final disease severity was less after early than late thymectomy. Black patients had similar incidence disease severity and sex ratio (F:M=2:1) with pre, peri or post pubertal disease onset infrequent spontaneous or treatment induced remissions and the same final disease severity after early or late thymectomy. These observations imply that race and sex hormones modify the clinical features and outcome of juvenile Myasthenia gravis, spontaneous remissions are common in white patients with prepubertal disease onset, early thymectomy may be more beneficial than late thymectomy in white patients, and the role of thymectomy in the youngest patients is uncertain.

Childhood or adolescent onset Myasthenia gravis accounts for 11 to 24% of all patients with Myasthenia gravis.

The natural course Myasthenia gravis in children remain largely undetermined. Three forms of Myasthenia gravis occur in childhood juvenile Myasthenia gravis congenital Myasthenia gravis (genetic Myasthenia gravis) & transient neonatal Myasthenia gravis, juveile Myasthenia gravis is an acquired, sporadic, autoimmune disorder in which circulating antibodies against the acetyl choline receptor together with compliment, reduce the number of functional acetyl choline receptors or motor end plates & interfere with normal neuromuscular transmission. These pathogenic antibodies are

not measurably elevated in all patients with autoimmune Myasthenia gravis, yet seronegative and seropositive patients have similar clinical features and similar responses to thymectomy, immunosuppression and plasmapheresis[36]. Host factors, including sex, and race, play an important role in the pathogenesis and clinical features of autoimmune disorders. the influence of sex hormones upon Myasthenia gravis is evidenced by their effects on incidence of Myasthenia gravis. The variation of disease severity with the menstrual cycle in one third of woman with Myasthenia gravis and the increased number of estrogen receptors on lymphocytes and thymocytes in patients with Myasthenia gravis[35,37]. Race also influences the incidence of Myasthenia gravis (compared with older children onset before puberty is infrequent in European patients but relatively frequent in Japanese patients[38,39]).

These factors not only influence the disease incedence but also outcome in juvenile Myasthenia gravis.

Spontaneous remissions only occurred in white patients with prepubertal onset and all occurred within 40 months of first symptoms. The frequent persistence of acute juvenile Myasthenia gravis for more than 10 years in white patients with prepubertal disease onset also indicates that this subgroup has a better outcome. Similarly there was a higher spontaneous remission rate in patients with onset before 11

years than after 11 years in the large Mayo clinic series collected[40]. These authors followed up 149 children with juvenile Myasthenia gravis from onset of disease for as long as 40 years. Median follow up was 17 years, minimum was 4 years of the juvenile Myasthenia gravis patients, 85 (57%) underwent thymectomy because of disease severity. In juvenile Myasthenia gravis a spontaneous remission rate of 22.4 per 1000 persons years was observed regardless of disease duration. A remission rate of 260 per 1000 person years was seen during the first year after thymectomy with a rate of 95 per 1000 person year during the next 2 years. Early surgery, presence of bulbar symptoms, absence of ocular signs or generalised symptoms, onset of symptoms between ages 12&16, and presence of other immune disease were associated with increased post operative severity.

The over all prognosis for survival and remission or improvement in the young patient with Myasthenia gravis is fairly good. In this study 80% of patients with juvenile were estimated to be alive at 40 years of age. In those patients who did not undergo thymectomy, 22 remissions and 18 improvements occurred (62% of 64). In a matched study of adults, 27 of 78 (6%) thymectomy patients were in remission compared with 6 (7.7%) of 78 non thymectomy patients. Improvement was noted in 26 (3%) of 78 surgically treated patients and in 13 (16.6%) of 78 receiving medical treatment

alone of the total adult group, 46% were in remission or were improved at last follow up.

Myaesthenic symptoms recognised at birth or shortly thereafter in infants who are not born to myaesthenic mothers may be caused by any of a variety of inherited neuromuscular transmission defects. Seybold and Lindstrom have emphasised the resemblance of these disorders of neuromuscular transmission to myasthenia acquired in the first 2 years of life[41]. Measurement of the acetyl choline receptor antibodies is necessary to establish the proper diagnosis because these antibodies are often present in patients with juvenile autoimmune Myasthenia gravis but absent in those with juvenile autoimmune Myasthenia gravis? In those with congenital Myasthenia gravis diplopia and ptosis were the most persistent and disabling features; and therapy with acetylcholinesterases, steroids or thymectomy had no beneficial effect. Favorable response has been noted in young children with presumed autoimmune Myasthenia gravis after therapy with prednisolone or thymectomy or both.

In another series by Linburg & Oosterhuis et al wherein they examined the significance of the presence or absence of anti acetyl choline receptor antibodies in 250 Myasthenia gravis patients and the relatives between clinical features and anti acetyl choline receptors levels[42]. They found high anti acetyl choline receptors levels in 2 out of 11 thymoma

patients. 37 out of 250 Myasthenia gravis patients had no detectable anti acetyl choline receptor antibody. The absence of these antibodies was related to purely ocular disease and to steroid therapy or thymectomy. The level of anti acetyl choline receptors levels did not correspond significantly to differences in disease activity when single measurements in patients were analysed. The results were influenced by both the presence or absence of a thymoma, the age at onset of disease and by steroid therapy. The thymic pathology and age at onset seemed to act independently. Early onset of disease was associated with high anti acetyl choline receptor levels and absence of antibodies to striated muscle (anti SM), whereas late onset was associated with low anti acetyl choline receptor and presence of anti SM. Thymomas both have high anti acetyl choline receptor and high anti SM. The effect of steroid therapy as antibody level was seen in all patient groups but strongest in thymoma with early onset of disease.

Patients with autoimmune diseases often have circulating antibodies to a variety of different autoantigens other than the n-acetyl choline receptor protein and even manifestations of autoimmune disease in more than one organ (autoimmune overlap). It is often stated that Myasthenia gravis patients frequently have manifestations of autoimmune diseases other than Myasthenia

gravis. In a study of 48 patients by S Thorlacius the occurrence of autoimmune thyroiditis (5 patients,0.4%) & systemic lupus erythematosis (4 patients,8.3%) in the Myasthenia gravis patients was clearly higher than that reported in the general population. Rheumatoid arthritis was found in 2 patients (4.2%)[43]. The autoimmune diseases were mainly recorded among the non thymectomised Myasthenia gravis patients. In addition to those with definite diseases of autoimmune nature, 3 other Myasthenia gravis patients had thyroid antibodies and had anti nuclear antibody without evidence of autoimmune diseases, 7 patients (14.6%) had unspecific arthralgia during active periods of Myasthenia gravis,2 Myasthenia gravis patients had ankylosing spondilitis.

These findings were similar to the results of Scherbaun et al who found that 16 out of 81 Myasthenia gravis patients had other immune disorders

In the above study, 7 of our Myasthenia gravis patients had elevated titres of antinuclear antibodies and thyroid antibodies. Myasthenia gravis, Systemic lupus erethematosis, rhematoid arthritis and thyroiditis are all diseases with autoimmune features. The associated autoimmune diseases were mainly found among patients with generalised Myasthenia gravis. Autoimmune features and ocular Myasthenia gravis are

less prominent than those with generalised Myasthenia gravis.

A retrospective study of 108 patients with Myasthenia gravis who had solely ocular symptoms at onset were carried out to identify factors influencing prognosis[44]. Duration of pure ocular Myasthenia gravis was associated with a decreasing risk of late generalised symptoms, only a (15%) of the observed generalisations occurred after more than 2 years of solely ocular symptoms. Being age at onset was associated with greater risk of respiratory crises or death, caused by Myasthenia gravis, whereas patients younger at onset had a greater chances of a benign outcome. Neither systemic curare tests nor responses to repetitive nerve stimulation had prognostic value.

The diagnosis of ocular Myasthenia gravis relies mainly on clinical data, typical history and signs of incomplete opthalmoplegia and spontaneous and provoked fluctuations.

In a study done by A. Evoli et al 48 patients with purely ocular Myasthenia gravis were studied. Tensilon tests were positive in 46 patients(95%), decremental response from limb muscular was present in 24 patients (50%); anti acetyl choline receptor antibodies were detected in 20 of 44(45.5%). 22 patients underwent thymectomy, 18 were given corticosteroids, 42 received anticholinesterases. At the end of the observation period 8% of patients were in remission,

67% were improved, 25% were unchanged. Anticholinesterases were found not very effective in extrinsic ocular muscles. Thymectomy should be indicated for cases in the early stages of the disease within first year of onset, corticosteroids are effective in most cases, but relapses after withdrawal are not uncommon.

INDIAN STUDIES

Not many Indian series are available studying the natural history on Myasthenia gravis.

Singhal, C.V. Savanth et al from JJ Hospital and Bombay hospital reported 249 cases of Myasthenia gravis in their 25 years of experience[45]. Male to Female ratio was 2.8:1. Mean age of onset was 41.7 in male with peak in the 6th decade and 33.5 in female with one peak in 3rd decade and second small peak in the 5th decade. Commonest clinical presentation was severe generalised Myasthenia gravis (grade 2 B). In this group, a selective oculobulbar form was commoner in those above 50 years. Thymoma was seen in 14%.Mean age of onset of this group was 34.3 years. Male to female ratio of 4:1. Those receiving steroids or azathioprine in this group fared significantly better in the non thymoma group[103].

Thymectomised patients did significantly better than patients managed conservatively.

Gurshani and Singhal et al also studied the elderly non thymoma Myasthenia gravis patients separately with age of onset > 50 years. Among the 249 cases of Myasthenia gravis, 75(30%) belonged to this group of whom adequate follow up was obtained for 30. Among these cases (a) 10 underwent

thymectomy. 4 went into remission and 6 benefitted. All had atrophic thymuses. (b) 12 were treated with steroids, and 11 benefitted. (c) 8 patients could be treated with anticholinesterases only. 3 improved, 5 did not and 3 died[46].

Thus steroids were found to be as useful or more useful than thymectomy in this category of patients.

The same authors studied 29 patients with Myasthenia gravis associated with thymoma treated by transternal thymectomy over a mean follow up time was 2 to 34 years.

(A) 18 received postoperative steroids, azathioprine or both. Of these 14(77.8%) benefited including 7 in full remission, 3 did not benefit and 1 died in myaesthenic crises.

(B) 11 did not receive any steroids or azathioprine. Both locally invasive (malignant) and benign thymomas showed a similar trend. All deaths occurred on 3 years of onset of onset of Myasthenia gravis and within one year after surgery.

Long term outcome does not differ much from that of nonthymoma Myasthenia gravis. Data suggest significant improvement in prognosis after thymectomy by the use of steroids or azathioprine.

Ahuja and Venugopal et al have presented 10 years of experience of Myasthenia gravis treated with thymectomy[47]. Among 82 patients subjected to thymectomy, 3 had ocular

Myasthenia gravis and 79 patients had generalised disease. Mean duration of follow up was 4 years. 72 (87.8%) showed early improvement out of 76 patients with long term follow up 70(92%) got total remission or significant improvement. Females with early surgery improved maximum.

Improvement was not related to a) histology of thymus b) age c) sex d) duration of symptoms. Age and long duration are not contra indications. Study confirms that thymectomy is safe and effective mode of treatment of Myasthenia gravis.

Zaheer et al reported a study based at Madras. The clinical status and drug requirement of 27 patients of Myasthenia gravis well stabilised assessed on a modified form of Scadding's categorisations. Thymectomy singularly resulted in reducing disability and amount on medications the patients required for stabilisations to do a full days work[48].

Zaheer emphasised that this effect of thymectomy should prove particularly useful to overcome the limitations prevalent in a developing country, which could be applicable to the situation in developed countries as well.

Narayanan et al retrospectively evaluated the outcome of 71 south Indian Myasthenia gravis patients who were thymectomised between 1987 to 1993 and analysed the relationship between clinical and histopathological features

and post thymectomy outcome[49]. It was found that the clinical severity of the disease did not differ between the 29 patients with and 42 patients without a thymoma.

79% of patients responded favourably to thymectomy, without additional immunosuppressive treatment.

52% achieved a near complete remission. A younger age and milder disease correlated with good outcome. Patients with thymoma responded as favourably as without a thymoma. In conclusion the post thymectomy response of South Indian Myasthenia gravis patients in general did not differ from that of western and oriental patients.

AIMS

1. To determine the natural history of nonthymectomised Myasthenia gravis.

and

2. To compare the factors helpful in predicting the natural course of patients with Myasthenia gravis.

MATERIALS AND METHODS

This was a retrospective study analysis of 190 patients with newly detected Myasthenia gravis between the years 1978-1996. The patient's age were in the range of 1- 70 years.

The diagnosis of Myasthenia gravis was confirmed in each of these cases by the following al of the three criteria given below

1. Clinical history typical of Myasthenia gravis with fluctuating weakness of skeletal muscles with definite evidence of fatiguability by standard clinical test for fatiguability and progress of muscle weakness by 2 grade of MRC classification on repetitive exercised

2. Positive neostigmine test >50% recovery of power of tested skeletal muscle or >50%recovery of ocular muscle function subsequent to intramuscular administration of 1-1.5 mg of prostigmine preceded by 0.6 mg of atropine intramuscularly 15 minutes prior.

3. Positive decremental response on RNS test - A normal amplitude of CMAP on supramaximal stimulus and a >10% decrement between first and fourth CMAPs of the orbicularis

oculi, deltoid, trapezius and hypothenar muscles obtained by repetitive supramaximal stimulation of concerned motor nerve.

The clinical characteristics regarding age, sex, duration of illness, type of onset of symptoms the associated diseases were studied using a preabstracted proforma.. The repetitive nerve stimulation, neostigmine test, CT thorax and acetyl choline receptor antibody (if possible) were done. The medication that the patient was on and the Kaynes clinical class that the patient was in at the time of diagnosis and on follow up with medication.

The follow up period ranged from a 3 months to 7 years, and the functional scale was assessed each time.

They were classified into 1 of the 7 defined group according to Kaynes modified criteria.

1. Drug free remission
2. Drug free remission with residual ocular palsy
3. Remission on anticholinesterases alone.
4. Remission on steroid alone.
5. Remission on anticholinesterases and steroids
6. Poor control or worsening
7. Death

RESULTS

Out of the 190 patients charactesistics that were analysed

1. It was found that only 45 patients (23%) remained unthymectomised.
2. Sex distribution showed that males were more affected 30 (66%) than females 15(33%)
3. Age distribution showed 9 (20%) were below 20 years, 3 were below 6 years and diagnosed to have possibly congenital myaesthenic syndrome with age group ranged from 1-6 years.

   18 (41%) were between 20-39 years

   12 (27%) between 40-59 years

   4 (9%) above 60 years

4. Out of the 45 patients who remained nonthymectomised, it was found that the ocular muscles were most commonly involved 41 of 45 (91%) than

   appendicular 26 (58%)

   bulbar in 17(37%)

   axial in 8 (18%)

   respiratory in 1 (2.2%)

5. At the time of diagnosis -majority in Osserman stage 2
6. Duration of illness
7. Co-morbidities found were diabetes mellitus 4 (8.9%), Thyrotoxicosis 1 (2.2%), bronchial asthma 3 (6.7%), anaemia 2 (4.4%) and associated infection in 2 (4.4%)
8. CT thorax was done in 21 out of 45 patients out of which 19 (42.2%) was found to be normal. In one patient (2.2%) had a thymoma and another one (2.2%) had a thymic hyperplascia. Chest X ray was normal in 38 (84.4%), widened mediastinum in 2 (4.4%)
9. Repetitive nerve stimulation test was done in 38 patients showed that it was positive in 20/38 (52%), negative in 17/38 (44%)
10. A neostigmine test was done in 39 patients and it was positive in 31/39 (87%), negative in 4 (10%) and not done in 6 (15%)
11. Acetyl choline receptor antibody was estimated in 3 patients being positive in one (2.2%)
12. Other tests done showed associated hyperthyroidism in one (2.2%)
13. At the rime of diagnosis 33 out of 45 (73%) were in modified Kaynes class 3, 7 (15%) were in class4 and 3 (6.6%) in class 2 and 2 in class 1.

14. Medications taken 34 (75%) were on anticholinesterases alone, 10 (22%) were on steroids & anticholinesterases and one (2.2%) on steroids alone. None were exhibited to other treatment modalities like IV Ig, plasma exchange or azathioprine.

15. Follow up was available for only 35 out of 45 patients (77%) or a mean period of 4.4 years (1.5-13 years) and found that 27 out of 35 (77%) were in class 3, one out of 35 (2.8%) worsened to class 5 and 7 out of 35 (20%) remitted to class [redacted]. These had only ocular Myasthenia gravis.

DISCUSSION

This study has shown to be similar in comparison with other studies done earlier by Norbeat Sommer, Barbara Sigg et al where in a retrospective study, 5/78 patients with ocular Myasthenia gravis showed a good remission rate[11]. This study also showed that those with ocular Myasthenia gravis were in remission. Grob et al similarly noted that in his large collection of ocular Myasthenia gravis, only 35% or less will ultimately remain ocular[2,13,16]. Similarly it was found that the longer the patients remained to be confined to the extraocular muscles they had less chance of generalisation.

In a large series of 328 patients reviewed by Oosterhuis with generalised Myasthenia gravis with a mean follow up of 12 years showed complete clinical remission occurred in 37%[24]. But our series also showed better in the ocular Myasthenia gravis. Out of the 7 who had remitted 4 had ocular Myasthenia gravis (57%).

Other studies show a larger incidence of associated thymomas (25%) in the Oosterhuis series[7,34]. In our series those who remained unthymectomised had a low incidence of thymoma (2.2%)

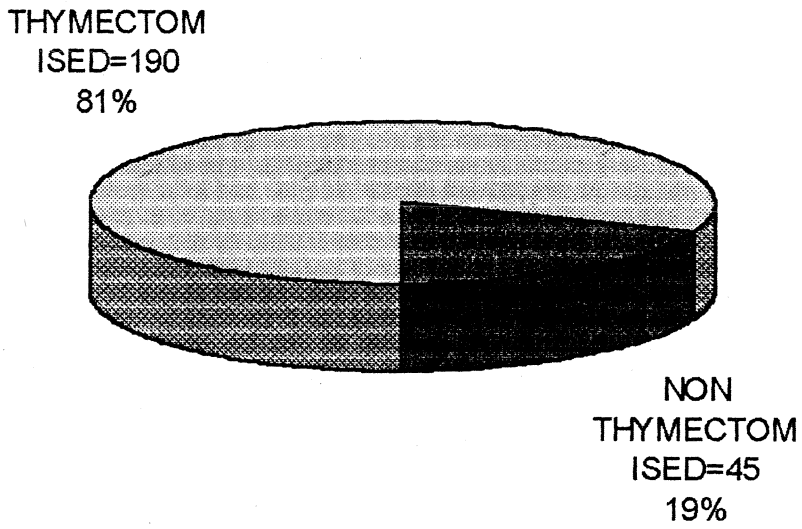
When comparing series, young onset Myasthenia gravis had a better prognosis.In our study all the 5 who had remitted were in age group less than 20 years. With associated disorders in Myasthenia gravis, other studies showed that there was an associated incidence of thyroiditis (0.4%), SLE (8.3%), rhematoid arthritis (4.2%)[43]. In our series these associated disorders also had similar incidence, though SLE was not seen .

CONCLUSION

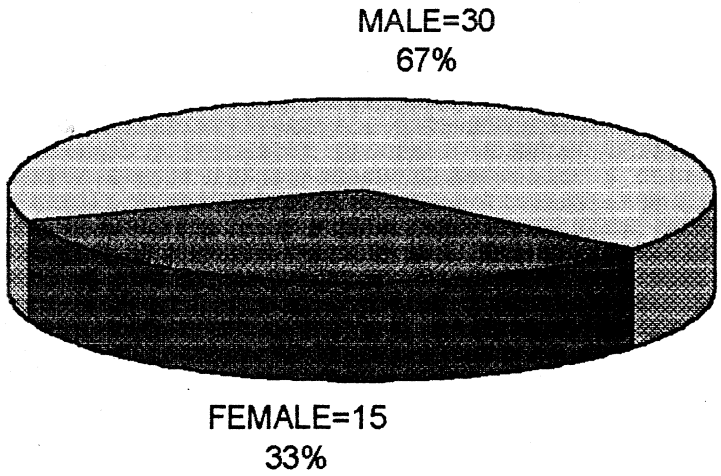
1. This study of unthymectomised Myasthenia gravis patients showed that the overall prognosis of ocular Myasthenia gravis was good. Of the 7 patients who had total remission, 4 had purely ocular Myasthenia gravis.

2.All the unthymectomised patients were predominantly treated with anticholinesterases alone. Majority remained in modified Kaynes class 3, both at the time of diagnosis and during follow up.

PATIENT DISTRIBUTION



SEX DISTRIBUTION



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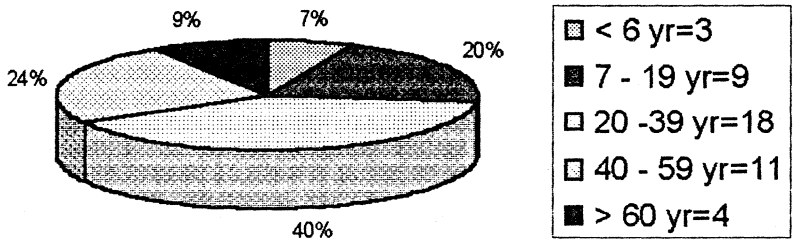


COMORBIDITIES

	NUMBER	PERCENTAGE(%)
BRONCHIAL ASTHMA	3	6.7
INFECTION	2	4.4
ANAEMIA	2	4.4
THYROTOXICOSIS	1	2.2
DIABETES MELLITUS	4	8.4
ALCOHOLISM	3	6.7
ARTHRITIS	0	0
HIV	0	0

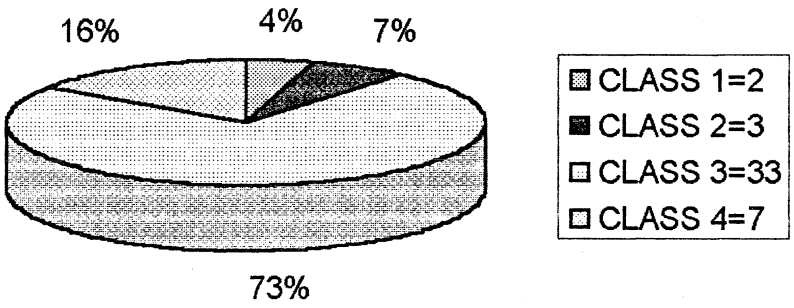
DISTRIBUTION OF WEAKNESS

	NUMBER	PERCENTAGE(%)
OCULAR	41	91
APPENDICUALR	26	58
BULBAR	17	37
AXIAL	8	18
RESPIRATORY	1	2.2

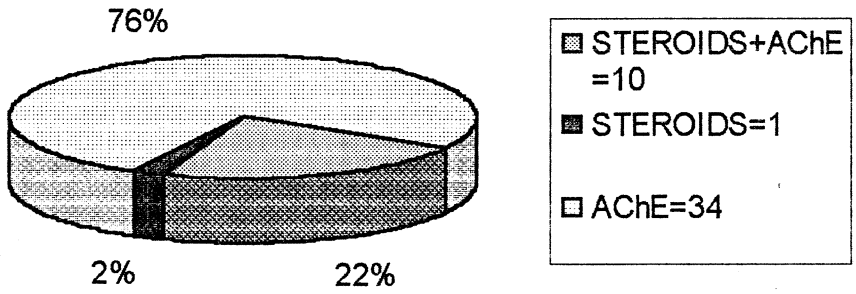
CT THORAX

	NUMBER	PERCENTAGE(%)
NORMAL	19	42.2
THYMOMA	1	2.2
THYMIC HYPERPLASCIA	1	2.2
NOT DONE	24	53.3

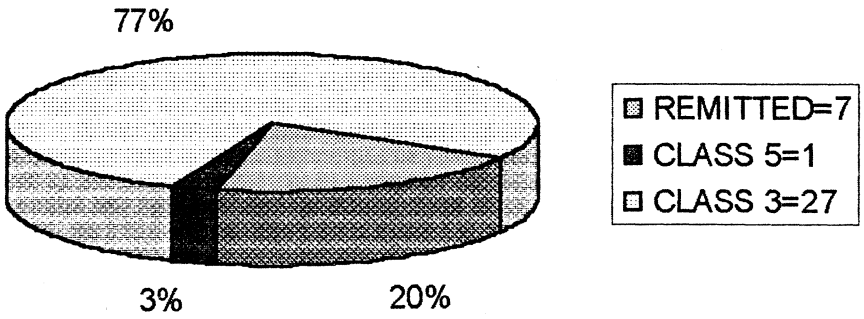
DIAGNOSIS- MODIFIED KAYNES CLASS



TREATMENT



FOLLOW UP STATUS



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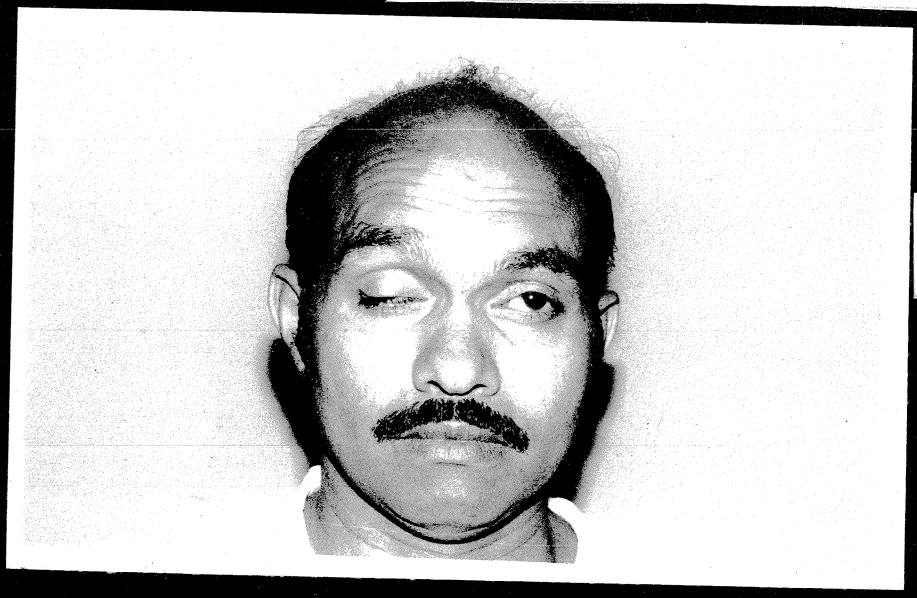
Clinical photographs of a 34 yr old patient with generalised MYASTHENIA GRAVIS.



Asymmetric binocular ptosis

Demonstration of weakness & fatiguability of proximal muscles of upper limbs