

**SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES AND TECHNOLOGY**
THIRUVANANTHAPURAM, KERALA



**CLINICAL PROFILE OF JUVENILE MYASTHENIA GRAVIS
A TERTIARY CARE CENTRE EXPERIENCE**

Thesis submitted in partial fulfilment of the rules and regulations for

PDF Neuromuscular disorders Degree Examination of
Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

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Month and Year of Submission: December 2021

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01/01/2021- 31/12/2021

DECLARATION

I, Dr. Vaibhav Tandon, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, In-charge Neuromuscular and Multiple Sclerosis Divisions, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram,
Date: 14/12/2021

Vaibhav Tandon
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FORWARDED

The candidate, Dr Vaibhav Tandon has completed the project under my guidance.

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ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to **Dr.Sruthi S.Nair**, Associate Professor of Neurology, SCTIMST, my guide for the study, for her expert guidance, constant review, kind help and keen interest at each and every step of the study.

I am thankful to the entire faculty, neuro-technicians, and my colleagues for their valuable input and assistance to the study.

Last but not the least, I extend my gratitude to all my patients and their primary caregivers who participated in this study, without whose cooperation this study would not be possible.

Dr. Vaibhav Tandon

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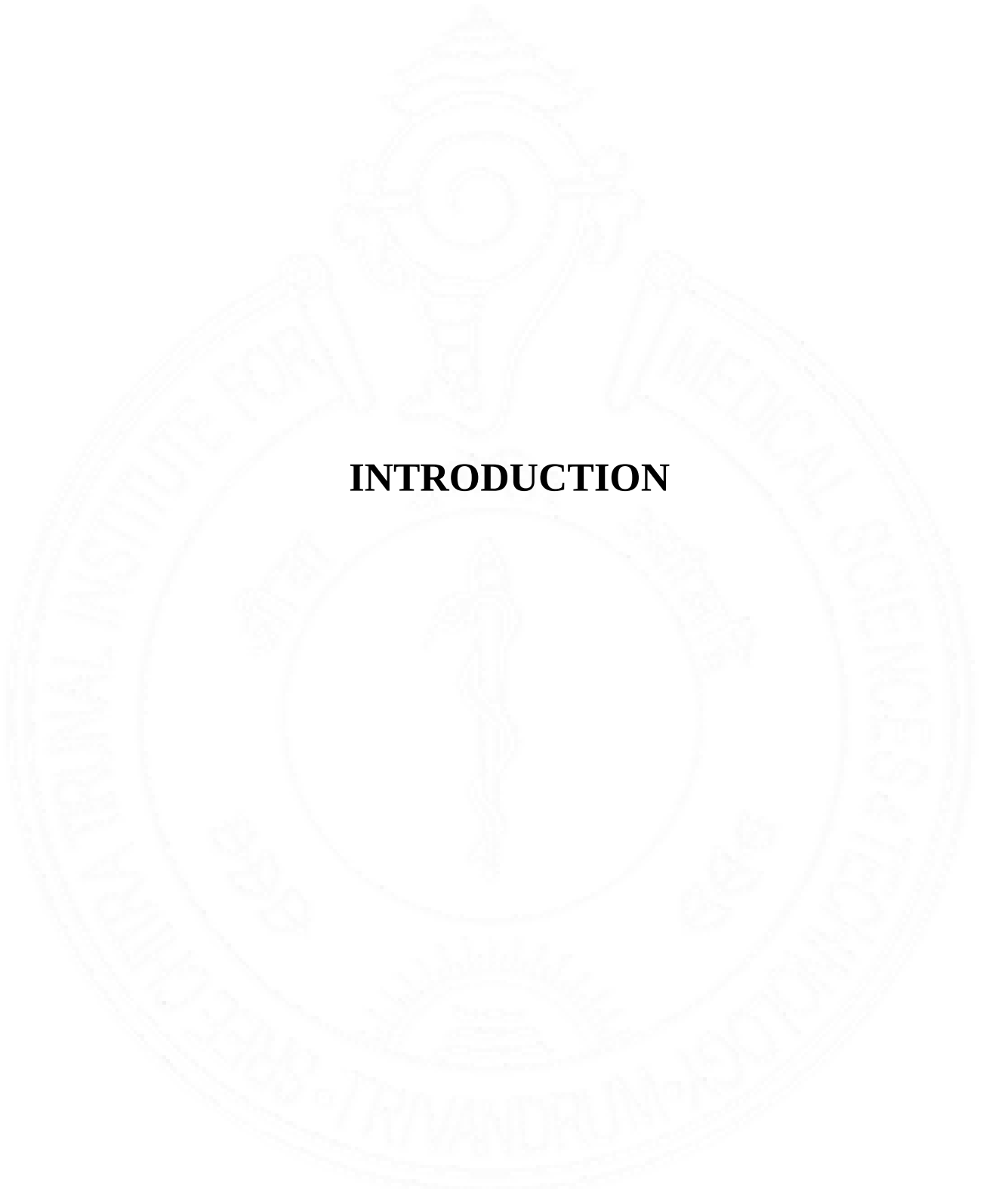
SYNOPSIS

Background: The profile of juvenile myasthenia gravis (JMG) differs from adults. We aimed to study the clinical profile, outcomes and predictors of treatment response of JMG in a tertiary care neurology centre.

Methods: We reviewed the inpatient case records of autoimmune myasthenia gravis with symptom onset ≤ 18 years admitted between 1999 and 2020. Descriptive analysis of their clinico-demographic characteristics and outcomes was performed.

Results: 60 JMG patients (38 females) with mean age of onset of 11.4 years were followed up over a mean period of 7 years (range 1-22). 26 (43.3%) had ocular myasthenia gravis(OMG) and rest had generalized myasthenia gravis(GMG). Anti-acetylcholine receptor and muscle specific kinase antibodies were positive in 37 (68.5%) and 3 (5%) respectively. Immunotherapy was administered in 43(71.6%) patients which included glucocorticoids in all patients and steroid sparing immunotherapy (azathioprine/mycophenolate mofetil) in 23 patients (38.3%). Thymectomy was performed for 19 patients (47.5%) and none had thymoma. 36 patients (60%) achieved optimal outcome; complete stable remission in 6 and minimal manifestation in 30. 14 patients (23.3%) improved on therapy, 9 remained clinically unchanged (15%) and 1 patient expired due to immunosuppressant associated toxicity. It was seen that ocular myasthenia gravis had a pre-pubertal and earlier mean age of onset($p=0.001$) and had higher chances of maintaining well on acetylcholinesterase inhibitors($p=0.036$) alone when compared to generalized myasthenia gravis. However, there was no difference seen in outcome between the ocular and generalized groups. The number of relapses were more in the sub-optimal group of patients($p=0.04$).

Conclusion: Pre-pubertal age group is associated with more patients with ocular onset of disease. OMG is associated with lesser relapses and more chances of remission with acetylcholinesterase inhibitors alone but has similar outcomes as compared to GMG. However, the response to treatment is generally good with majority of patients achieving optimal outcome.

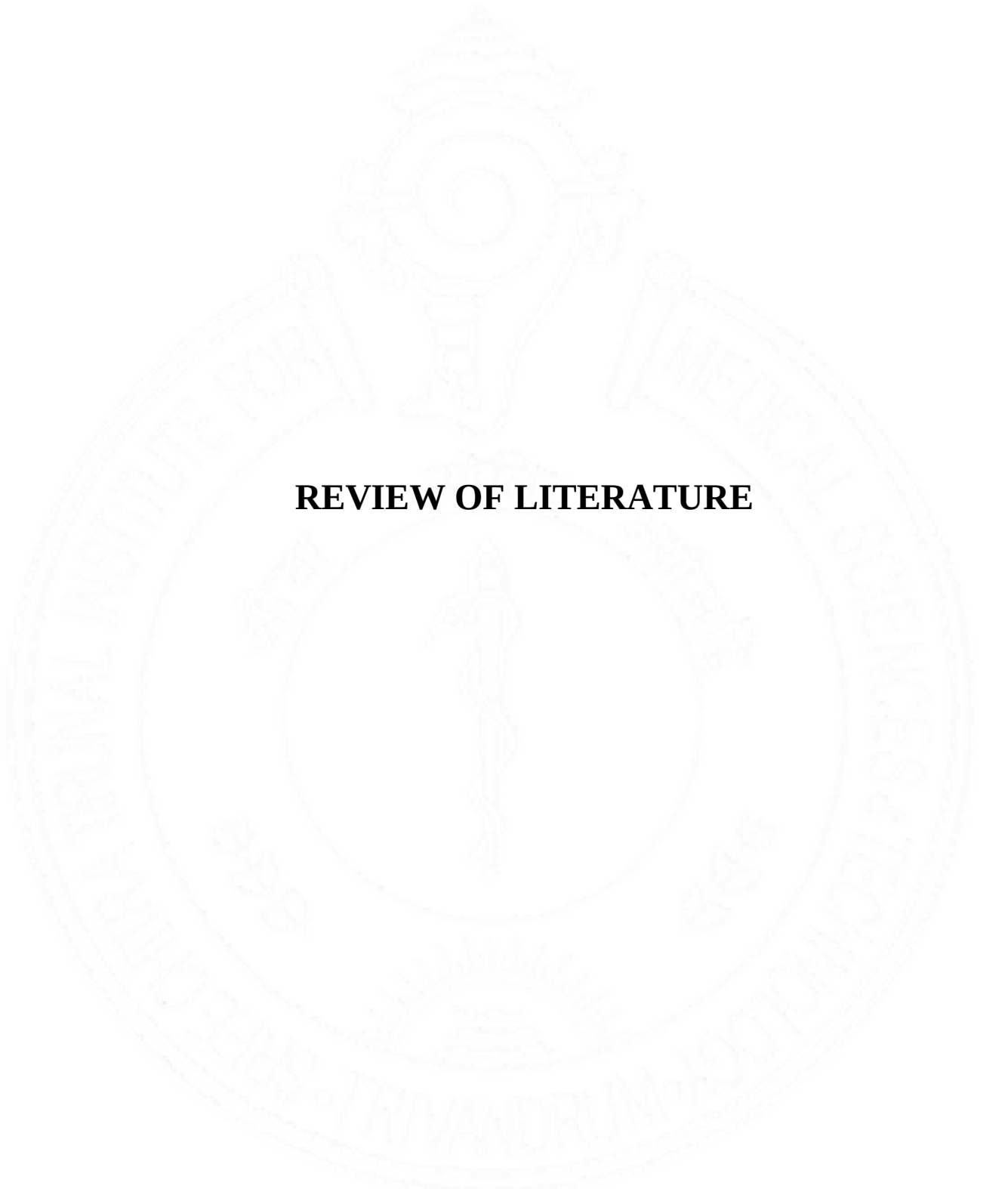


INTRODUCTION

Myasthenia gravis (MG) is an acquired autoimmune disease of the neuromuscular junction and childhood and adolescent onset myasthenia is called juvenile myasthenia gravis. The upper age limit for JMG is 18 years¹. The pathogenesis is autoimmune against the components of the neuromuscular end-plate leading to impaired synaptic transmission². JMG is not just myasthenia gravis occurring at younger age but it differs in severity, treatments used and also response to treatment^{2,3}. This finding stresses the need for large population based studies in JMG.

Epidemiological and clinical studies in JMG are few. There are studies from Asia^{2,4}, South Africa⁵, Europe^{6,7}, UK⁸, USA⁹ that have shown differences in various populations between demographic (sex prevalence, age of onset) and clinical (eg conversion of ocular to generalized, severity, response to treatment, practice of thymectomy) and other aspects of the disease.

There are few retrospective longitudinal studies of JMG from India and our study aimed to address the clinical aspects, long-term course of prepubertal and post pubertal juvenile MG in a tertiary care centre in South India.



REVIEW OF LITERATURE

Both the juvenile and adult forms of acquired autoimmune MG share aspects of pathophysiology and symptomatology. However, it is important to note the differences in epidemiology and prognosis in juvenile MG (JMG).

CLINICAL PRESENTATION, NATURAL HISTORY, AND DEMOGRAPHICS

JMG presented with oculomotor symptoms with or without generalised symptoms.

Percentage of oculomotor onset and generalised myasthenia has been reported to range widely from 9% to 93% in various retrospective analysis. Table 1 summarises few of these studies.

				Presentation				
Study	Year	n	Age at onset	I	IIa	IIb	III/IV	Ocular only
Lindner et al ¹⁰	1997	79		7	36	25	11	9%
Rodriguez et al ¹¹	1983	149	1-16	14	24	108	3	9%
Evoli et al ¹³	1998	133	1.5-20	23	47	38	25	17%
Mullaney et al ¹²	2000	25	0.9-16	14	11			56%
Raksadawan et al ¹³	2002	27	0.25-10	25			2	93%
Xin Huang et al ²⁸	2018	327	1-18	306	17	2	2	19.9%

The variability in presentation seems to be related to ethnicity as studies in Asian population show a higher proportion of patients with ocular myasthenia. Time to correct diagnosis may also influence “symptoms at presentation” in some studies, as the child who is not diagnosed for several months or years may have already progressed to a generalized state.

Generalised onset of disease has been reported in 29-75% of patients which is on contrast to patients with adult myasthenia where 85% of cases are of generalised onset².

JMG has been reported to begin as young as the first year or two of life. There seems to be an effect of pubertal status on presentation with studies showing a greater proportion of pre-pubertal patients with ocular presentation and post-pubertal patients being more likely to present with generalised onset of symptoms. Studies done by Evoli¹⁵ and Buttochi et al¹⁹ show ocular-only presentation rates of between 26% and 31% for prepubescent patients, but rates of 9–16% for pubescent and postpubescent patients.

Studies that cited the gender distribution of JMG patients revealed a female predominance of between 50% and 86%¹⁴⁻¹⁶. However, prepubertal- age patients (<12 years of age) ranged from 53% to 73% female, whereas postpubertal-age patients ranged from 77% to 85% female¹⁴⁻¹⁶.

DIAGNOSIS

The evaluation of JMG is generally the same as it is in adult autoimmune MG. Fatigueable ptosis, nasal speech, nasal regurgitation, fatigueable weakness enable the clinician to diagnose myasthenia clinically. Diagnostic tests support the clinical diagnosis. Four assessments are widely used.

Serology- Serologic testing includes Acetylcholine receptor antibody (AChRAb) and Muscle specific tyrosine kinase (MuSK) antibody. Studies indicate a sensitivity of 80.7% and a specificity of 100% with such tests¹⁷. Not all MG patients test positive for anti-AChR antibodies. Among adults with MG, approximately 80% of generalized adult MG patients and approximately 50% with ocular MG have serum-containing AChR IgG. In prepubertal children, these figures are lower. Although postpubertal adolescents exhibit rates similar to those of adults, only about 68% of peripubertal patients and 50% of JMG cases in prepubertal children were seropositive for anti-AChR antibodies in one study¹⁴. There are conflicting data

regarding seropositivity in ocular JMG. One study suggested a lower rate, and another study documented a higher one¹⁵.

Repetitive nerve stimulation- A child with myasthenia will demonstrate a compound motor action potential amplitude decrement of >10% by the fourth or fifth stimulation

Single fiber electromyography- Single-fiber EMG is especially useful in the diagnosis of seronegative MG and congenital myasthenic syndrome¹⁸. It requires the patient to maintain voluntary contraction of frontalis muscle. So, it is a difficult procedure in children as it requires concentration and co-operation. However, SFEMG can be done by stimulating the muscle with a monopolar needle. Voluntary contraction by the patient is unnecessary, and thus it is a much more useful diagnostic modality in children¹⁹.

Other tests- Other tests include Neostigmine test and Ice pack test which can be used to determine improvement in strength when RNS and serology are negative.

Neostigmine, a rapid-acting, short-duration cholinesterase inhibitor, is administered intravenously as a diagnostic test. A positive result consists of transient resolution of the clinical sign under observation. For the test to be performed, the patient must display a clinical sign that can be easily monitored, such as significant ptosis, ophthalmoplegia, or dysarthria. Extremity strength can be difficult to track objectively.

Due to the cholinergic effects of anticholinesterases, neostigmine testing in children must be conducted in a monitored setting with atropine and a staff skilled in cardiac resuscitation available to counteract side effects such as bradycardia, nausea, diarrhoea, and excess salivation, should they occur.

Ultimately, MG remains a clinical diagnosis, but positive results on one or more of these tests will support the clinical impression.

Treatment

Treatment of MG may be divided into four broad categories¹:

- acetylcholinesterase inhibitors
- medical immunomodulation
- surgical immunomodulation;
- Supportive respiratory therapy during myasthenic crisis

Acetylcholinesterase inhibitors—

Anticholinesterase inhibitors (anti-AChEs), especially pyridostigmine, are the first line of therapy in JMG, as they are in adult MG. Initial pyridostigmine therapy is typically 0.5–1 mg/kg every 4–6 hours. For older children and adults, the typical starting dose is 30 or 60 mg every 4–6 hours. The maximum starting dose is 60 mg. The maximum total dose is 7 mg/kg/day, with an absolute maximum of 300 mg/day for older children and adults. The liquid form is generally dispensed at 60 mg per 5 ml.¹

Medical immunomodulation—

For patients who remain symptomatic with anti-AChE medication, a form of immunomodulation is often added to the treatment regimen. There are four basic therapeutic options in this category:

- (1) Steroids
- (2) Steroid-sparing immunosuppressants
- (3) IVIg
- (4) Plasmapheresis

Steroids—

Systemic steroids, including prednisone, are efficacious and cost-effective. Some patients get worse in the first week or two of a steroid course, but responses to immunosuppressive therapies often reach 80%.²⁰

For ambulatory patients in a non-urgent setting, prednisone should be started at a low dose, as patients are at risk of worsening in the first several weeks of therapy. A suggested starting dose would be approximately 0.5 mg/kg/day, with a maximum starting dose of 30 mg/day for older children and adults. The dose may be increased gradually as tolerated, but the patient should be maintained on the lowest efficacious dose¹.

The chronic side effects of prednisone, however, are numerous and significant, and they have a long-term impact in children. These include growth-stunting, weight gain, mood alteration, hyperglycemia, hypertension, susceptibility to infection, and cushingoid features. Thus, steroids should be used with caution in children.

In view of these side effects, steroid sparing immunomodulatory agents are started in patients who relapse on tapering the dose of steroids.

Steroid sparing immunomodulatory agents—

Cytotoxic drugs are an alternative to steroids. They have been used on a limited basis in children in the past several decades. Published reports have for the most part only discussed the use of azathioprine^{2,10,15}.

The use of cyclosporine and cyclophosphamide in JMG has been reported^{14,15}, and newer agents, such as rituximab and mycophenolate mofetil, could be considered in severe refractory cases.

Azathioprine and other cytotoxic medications should be considered as adjunctive medications to assist in the weaning of steroids, and they may also be used alone to supplement other types of therapy.

Thymectomy—

There is a paucity of data regarding the efficacy of thymectomy in the pediatric population. Retrospective studies, however, do provide some guidance. A recent, thorough review of the literature of thymectomy in patients with juvenile MG suggested that thymectomy within 2 years of diagnosis results in a higher rate of remission in Caucasian children²¹.

The histological status of the thymus is associated with long-term outcomes following thymectomy. In a retrospective analysis of 147 juvenile and adult patients who had T3-thymectomies, the patients with thymoma had a 27.7% remission rate after 10 years, whereas those without thymoma had a 45.2% rate²². The prognosis of non-thymomatous patients seems to depend on age of onset and immunosuppressive therapy, whereas prognosis of thymomatous patients depends on immunosuppressive therapy only²³.

Thymectomy does not appear to impair the immune status of the majority of childhood patients, but it should be undertaken with caution in very young children due to the occurrence of some immunological abnormalities in this group post thymectomy¹⁴.

Treatment during myasthenic crisis—

As in adult autoimmune MG, the standard immunomodulatory therapy for myasthenic crisis in JMG appears to be plasmapheresis, based on the limited reports available.^{24,15} In this acute setting, plasmapheresis is most effectively and safely administered via central access rather than peripheral lines at any age. If plasmapheresis is not available or is contraindicated, IVIg or pulse intravenous

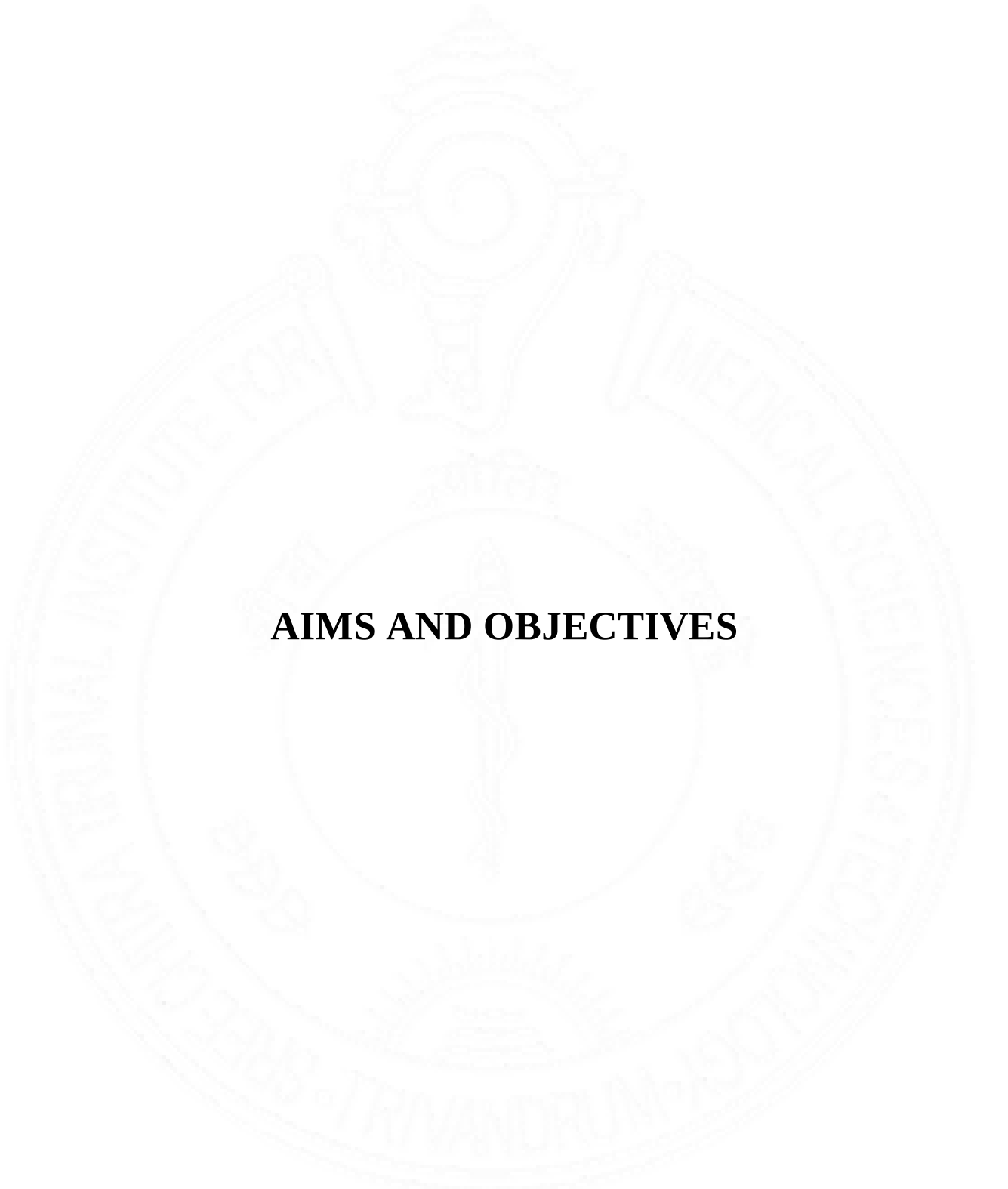
steroids may be considered. A Cochrane database review of IVIg in MG found insufficient evidence to conclude that doubling IVIg treatments leads to systematic improvement²⁵

All children in myasthenic crisis should be observed in an intensive care unit until their respiratory status has stabilized, regardless of whether they actually require mechanical ventilation.

Outcome

Children tend to exhibit higher rates of spontaneous remission than adults. Several studies of children of various ethnicities have demonstrated spontaneous remission rates ranging from 15% to 34.7% following a variety of nonsurgical treatments^{2,11,15,26}.

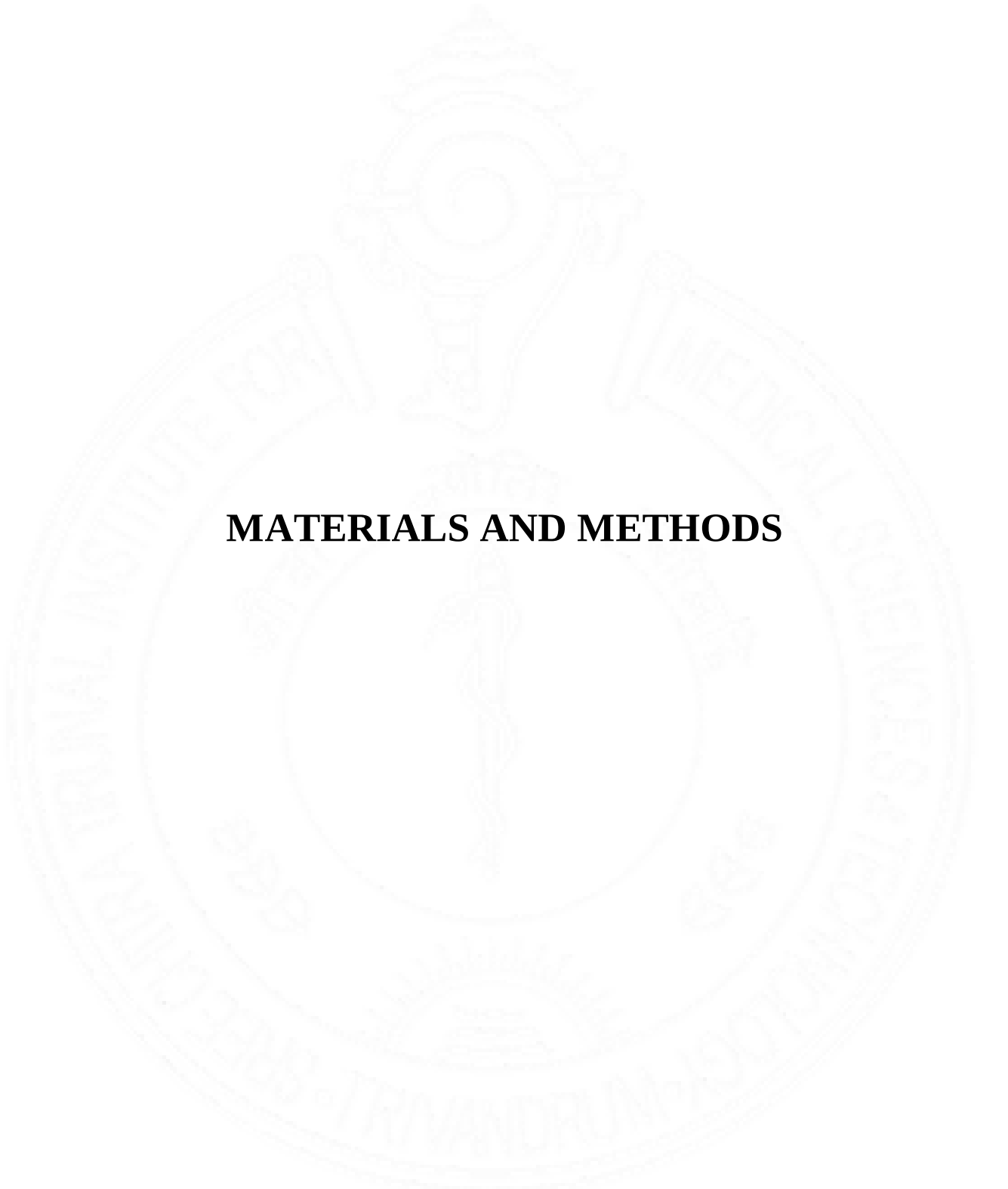
One study suggested that patients of African descent, however, have lower rates of remission. It also showed a significant difference in outcome based on age of onset, with 44% of those with prepubertal onset achieving a spontaneous remission¹⁴.



AIMS AND OBJECTIVES

- To describe the clinical profile and clinical outcomes in patients with JMG.
- To describe factors that may affect the outcome of juvenile myasthenia gravis patients.





MATERIALS AND METHODS

Patient acquisition

Stored electronic records of inpatients as well as outpatients visiting Sree Chitra Tirunal Institute of Medical Sciences and Technology from January 1990 to December 2020 were retrieved. The records of 62 patients were reviewed. The diagnosis of JMG was based on clinical symptoms of fatiguable weakness and confirmation by more than 10% decrement on supramaximal stimulus at repetitive stimulation at 2-3 Hz or positive result of Anti-Acetylcholinesterase (AChE), MusK antibodies, positive ice pack test or a positive neostigmine test. AChR antibody test was done by enzyme linked immunosorbent assay. Titres of antibodies were not available for patients in earlier years as the test was initially expensive. The patients were divided into pre and post-pubertal age group with patients <12 years of age belonging to the former. Cases of congenital myasthenic syndrome were excluded.

Data collection

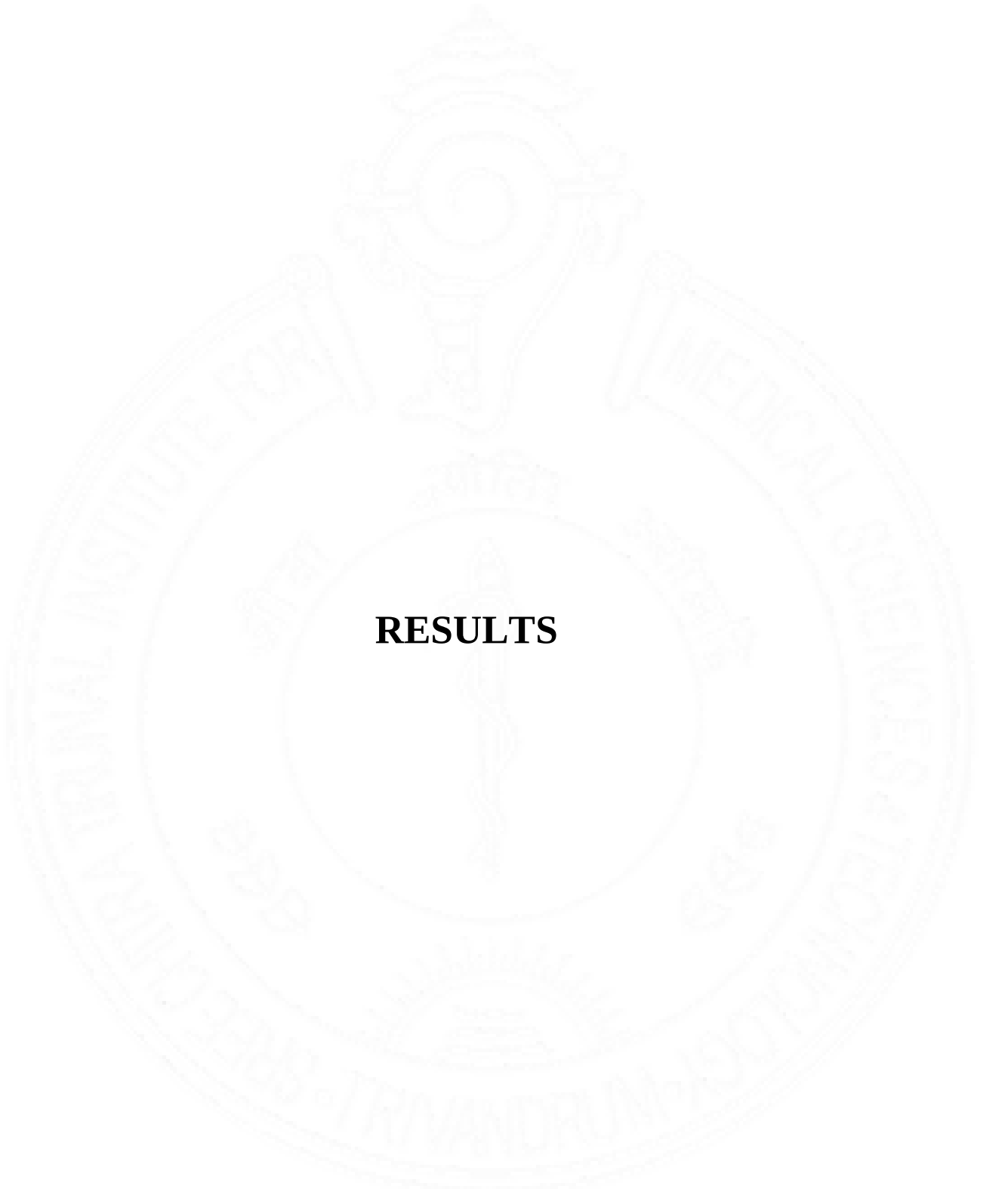
Myasthenia gravis symptoms were classified according to Myasthenia gravis foundation of America (MGFA) clinical classification scale with Class I, pure ocular weakness; Class II, mild generalized weakness; Class III, moderate generalized weakness; Class IV, severe generalized weakness; and Class V, intubation. Class II, III and IV were designated “a” if weakness was predominantly limb weakness, and “b” if predominately oropharyngeal weakness was present. Therapy given was divided into anti-cholinesterase alone, cholinesterase inhibitors with steroids or steroids with immunomodulatory therapy. Thymectomy if done was documented and histopathology records were also reviewed. Response to therapy was classified according to the MGFA Post intervention Status Scale (PIS): complete stable remission (CSR), pharmacological remission (PR), minimal manifestation 0-3 (MM0-3), improved (I), unchanged (U), worse (W), or died of MG (D).

Patients with MGFA-PIS of CSR,PR and MM were grouped into optimal outcome and remaining were classified as sub-optimal outcome and the characteristics of two groups were analysed.

Patients of ocular myasthenia gravis progressing to generalised MG were also seen.

Statistical Analysis

Descriptive analysis including was expressed using mean and percentages. Comparison between groups was done with Independent sampled t-test, Chi-square test were used. P-value <0.05 was considered as significant.



RESULTS

Demographic and clinical characteristics

The study involved 60 cases of Juvenile myasthenia gravis. The mean age was 11.4 years. There were 38 females and 22 males. There was no significant difference between mean age of onset between males (12 years) and females(11.1years). Patients were divided into pre-pubertal and post-pubertal age groups based on the onset of the disease before or after 12 years of age.28 patients had pre-pubertal onset and the remaining were post-pubertal. The number of female cases dominated in both age groups with 17/28 in pre-pubertal group and 21/32 in the post-pubertal group. (Table 1)

Table-1.Demographic characteristics of patients of JMG

Parameter	Number(%)
Gender	
Male	38 (63%)
Female	22 (37%)
Mean age	11.4 ±4.31 years
Age at onset	
Pre-pubertal	28 (46.7%)
Post-pubertal	32 (53.3%)

Patients with ocular onset had younger mean age of onset(8.8years) as compared to patients with generalised onset of disease.(**p-0.001**)

3.2 Symptom onset and severity

In total, 26 patients (43.3%) had only ocular symptoms and 34 patients (56.7%) had generalised onset of disease. Limb weakness without ocular symptoms was found in 1 patient and bulbar weakness alone was present in 1 patient.1 patient had presented with respiratory weakness at onset but it had associated ocular, bulbar and limb weakness. (Table 2)

Table 2. Table showing the symptoms onset in study group

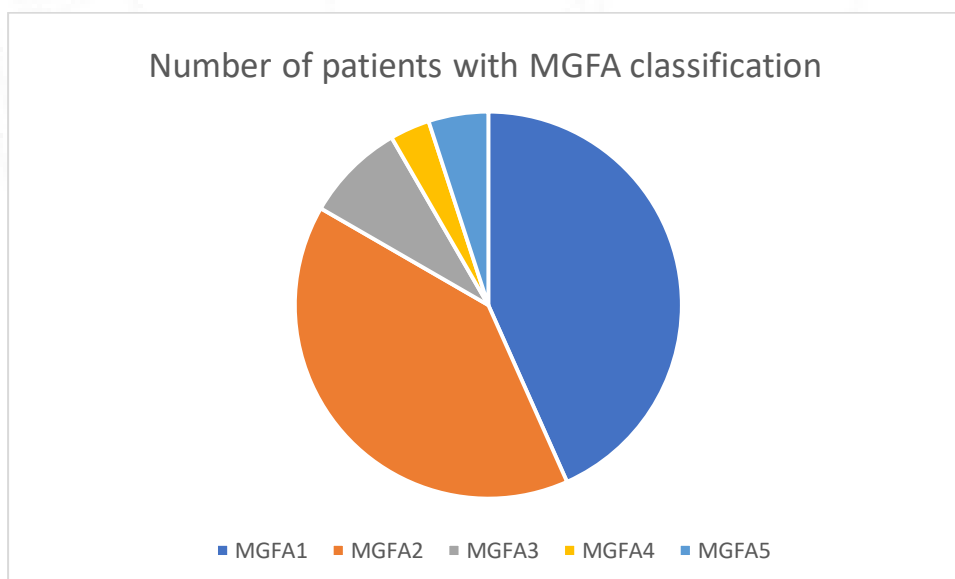
Symptoms	
Ocular	26 (43.3%)
Bulbar	1 (1.7%)
Ocular and bulbar	5 (8.3%)
Limb	1 (1.7%)
Ocular, bulbar and limb	13 (21.7%)
Ocular and limb	10 (16.7%)
Crisis	3 (5%)

In the pre-pubertal age group, 20 patients had disease onset as OMG whereas only 5 patients had onset as OMG in post-pubertal group.(**p-0.001**)

3.3 Myasthenia Gravis Foundation of America (MGFA) functional classification at onset

26 patients had presented with ocular symptoms(MGFA I). Among the 34 patients with generalised symptom onset, 24 patients (40%) had presented with mild symptoms(MGFAII), 6(10%) had moderate symptoms(MGFAIII) and 2 patients(3.3%) had severe symptoms. 3 patients (5%) had presented in myasthenic crisis.(Figure 1)

Figure 1. Pie chart showing number of patients in different MGFA categories



3.4 Serological studies

Information of AChRAb testing was available for 54 patients and 37 (61.7%) patients were positive and 17(28.3%) were negative. MusK antibody testing was available in only 12 patients. It was positive for 3 patients(25%) and negative in 9(75%). Proportion of patients with AChRAb positivity was similar in ocular and generalised myasthenia gravis subgroups. MusK antibody positivity was seen in 3 patients.(Table 3) All patients had presented with generalised onset disease. 1 had presented in myasthenic crisis. Second patient had ocular bulbar as well as limb weakness and one had ocular and limb weakness without bulbar weakness.

61.2% of prepubertal age group had AChR antibody positivity whereas 78.2% of patients were positive in post-pubertal group(p=0.18).(Table 4)

Table 3. Various diagnostic modalities used in the diagnosis

Diagnosis	
Repetitive nerve stimulation	43 (71.7%)
AChRAb+	9 (15%)
Ice pack test	1(1.7%)
Neostigmine test	6 (10%)
Clinical	1 (1.7%)
Serology	
AchRAb+	37/54 (68.5%)
Musk+	3/12 (25%)

3.5 Treatment

All patients were initially treated with pyridostigmine and additional steroids were given in 26 patients(43.3%) and additional immunomodulation was required in 9 patients(15%). At the end of follow-up, it was seen that 17 patients could maintain on pyridostigmine alone and 20 patients(33.3%) patients required addition of steroids and 23 patients (38.3%) required additional immunomodulation. In addition, 20/60(33.33%) patients could not be tapered off steroids and became steroid dependent.(Table 4) All MusK antibody positive patients required immunosuppression at the onset of disease.

Table 4. Table showing the initial and final treatment in the study population

Initial Treatment	
Anti-acetylcholinesterases	25 (41.7%)
AChEIs+Steroids	26 (43.3%)
AChEIs+Steroids+Immunomodulators	9 (15%)
Final treatment	
Anti-acetylcholinesterases	17(28.3%)
AChEIs+Steroids	20(33.3%)
AChEIs+Steroids+Immunomodulators	23(38.3%)

Thymectomy was performed in 19 patients(31.7%).13 thymectomy specimens showed thymic hyperplasia and the rest were normal. Pre and post pubertal subgroups had similar proportion of patients receiving immunosuppressive therapy.(71.3% vs 71.8% respectively). Out of 17 patients, 11 patients (64.7%) had ocular symptoms at onset whereas only 6 patients of generalised myasthenia at onset could be managed with pyridostigmine alone. **(p-0.036)**.

It was seen that 10 patients with OMG had relapses compared to 22 patients in GMG group **(p-0.043)**

Acetylcholine receptor antibody positivity did not predict additional treatment requirement with 30% antibody negative patients requiring immunosuppressive therapy.

Various clinical characteristics and their comparison in ocular and generalised myasthenia gravis patients is illustrated in the following table.

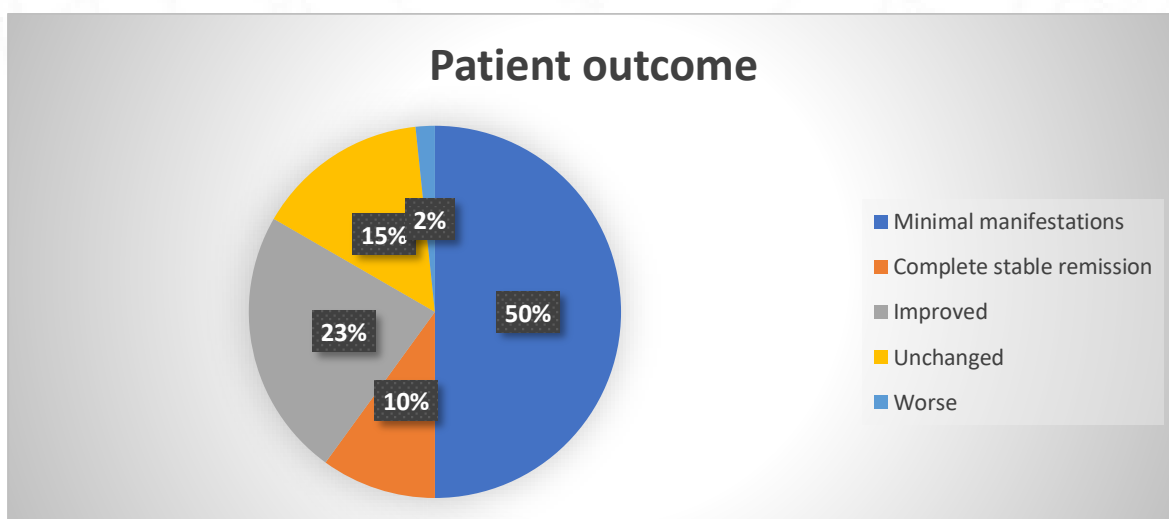
Table 5. Table showing the comparison in clinical characteristics of patients in ocular and generalised myasthenia subgroups

Parameter	Ocular myasthenia gravis	Generalised myasthenia gravis	p-value
Mean age at onset	8.78±3.97 years	13.52±3.35 years	0.001
Gender			
Male	10	12	
Female	16	22	
Relapses	10	22	0.043
AChRAb+	18	19	0.914
Final treatment			
AchEI	11	6	0.036
AChEi+Immunosuppressant	15	28	

3.6 Outcomes

Minimal manifestations could be achieved in 30(50%) patients and complete stable remission was achieved in 6 patients (10%).14 patients (23.3%) improved by at least one MGFA class. 9 patients (15%) remained unchanged and 1 patient died. 4 out of 26(15.3%) patients in OMG subgroup attained CSR compared to 2 out of 34(5.8%) patients in GMG subgroup(p=0.38).(Figure 2)

Figure 2. Pie chart showing proportion of patients between various treatment outcome categories



Proportion of patients achieving minimal manifestations was similar in OMG and GMG subgroups (53.4 and 50% respectively). Proportion of patients achieving CSR and MM was similar between gender and pre and post-pubertal age groups.

MGFA I and II were grouped together as mild disease and MGFA III,IV and V were grouped into severe disease as the number of patients in individual subgroups were low. All 6 patients who achieved CSR had mild disease (MGFA I&II) however the association was not statistically significant.(p=0.58). The severity of the disease at onset did not appear to influence outcome.(p=0.30)

Acetylcholine receptor antibody positivity did not seem to influence the outcome with 22(59.4%) out of 37 antibody positive patients achieving CSR and MM. 58% patients in antibody negative subgroup achieved CSR and MM.

Patients with MusK antibody positivity presented with moderate to severe disease activity and 2 of 3 remained unchanged while 1 patient achieved minimal manifestation status.

32 patients(53.3%) had relapses. Mean number of relapses were 1.94(Range 1-6). Only 43% of patients achieving CSR and MM had relapses whereas 69.5% of patients with sub-optimal outcome experienced relapses.(p=0.04).

Thymectomy was done in 19 patients. The procedure was not found to significantly affect the outcome with 6 out of 19 patients achieving MM and 1 patient achieving CSR. The outcomes were found similar between the patients with normal thymus histology and thymic hyperplasia patients.(p=0.14).

Table showing association of various factors with the outcome is shown in the table.(Table 6)

Table 6. Table showing factors influencing outcome

Parameter	Optimal outcome	Sub-optimal outcome	p-value
Age at onset			
Pre-pubertal	18	10	0.696
Post-pubertal	19	13	
Gender			
Males	16	6	0.271
Females	21	17	
Symptom at onset			
Ocular	18	8	0.292
Generalised	19	15	
Severity at onset			
Mild	32	17	0.221
Severe	5	6	
Relapses			
Present	16	16	0.04
Absent	21	7	
Thymectomy			
Done	9	10	0.121
Not done	28	13	

3.7 OMG progressing to GMG

4 patients with OMG progressed to GMG. All patients were pre-pubertal in age of onset with mean age of 7.7 years. AChRAb was positive in 2 patients and negative in the other 2. MusK antibodies were negative in one and not available in the remaining 3 patients. 2 patients required steroids and 2 patients were on immunomodulation. Two patients had a relapse with myasthenic crisis and these patients were negative for AChR antibodies. All patients had mild disease at last follow up. 2 patients were on azathioprine and one on mycophenolate mofetil and one on steroids alone.



DISCUSSION

JMG is a rare disorder of childhood. Our study showed a female preponderance of disease overall and also in the pre and post-pubertal age groups with female:male ratio of 1:1.5 and 1:1.9 respectively. This is consistent with literature^{4,7}. There is heterogeneity in sex distribution in pre-pubertal and post-pubertal age group with studies showing equal distribution⁹ or female predominance in post-pubertal group¹⁵. Castro and Evoli et al^{9,15} showed equal ratio in pre-pubertal age group. A Indian study, by Singhal et al²⁷, has identified a male:female ratio of 2.70:1. Thus, there is a heterogeneity in the sex distribution in JMG.

In our study population, the onset of the disease with GMG(56.7%) was more common than OMG(43.3%) which is consistent with some studies⁹ and contrasts with some^{2,28}. OMG patients had younger mean age of onset as compared to GMG which was consistent with literature.

Differences in pre and post-pubertal age group has been defined in various studies. Our study was consistent with OMG more common in pre-pubertal as compared to post-pubertal age group^{1,15,16,29}. Equal proportion of patients in both groups required immunosuppressive medications. The proportion of patients achieving CSR and MM was however similar between the two groups and we did not find a higher rate of remission in pre-pubertal as compared to post-pubertal group as is described in some studies^{29,30}.

Features of patients with MusK antibody positivity showed features described in previous studies^{31,32}. Female predominance (2/3), severe disease at onset with predominantly generalised and bulbar symptoms, all required additional immunosuppression. 2 out of the 3 patients received rituximab and one achieved MM status but continues to require steroids to maintain remission and one patient did not improve. Rituximab has shown to be an efficacious treatment for MusK positive myasthenia gravis in some studies^{33,24} and needs further studies with large patient number to establish efficacy.

Acetylcholinesterase inhibitors are the first line therapy in JMG, especially in OMG^{35,36}. Our study also showed similar results 64.7% of patients being in OMG subgroup who responded to acetylcholinesterase inhibitors alone. Corticosteroids usually improve symptoms in patients of JMG and in addition immunomodulatory treatment with azathioprine/mycophenolate mofetil can be added. In our study 71.6% patients required addition of additional immunosuppressive treatment which is similar to another study done by Ashraf et al where immunosuppressive treatment was administered in 67% of patients. Other studies^{9,15} show immunosuppressive administration in 54-58% of cases.

We observed that 50% patients achieved MM stage and an additional 10% patients achieved CSR. However, the proportion of patients with this good outcome were similar in OMG and GMG groups. This was similar to study done by Lee et al⁴ which showed that time to treat and remission rates didn't differ between OMG and GMG. This is in contrast to previous studies^{30,37,38} which have shown better outcome with OMG as compared to GMG. This might be explained by the small sample size and is contributed in addition by referral bias as ours is a tertiary care referral hospital and patients not responding to acetylcholinesterase inhibitors alone are referred for further treatment.

The number of relapses were shown to influence outcome in our study with optimal outcome subgroup having lesser relapses. In addition, ocular myasthenia gravis patients were noted to have lesser relapses than generalised myasthenia gravis subgroups.

Limitations of the study

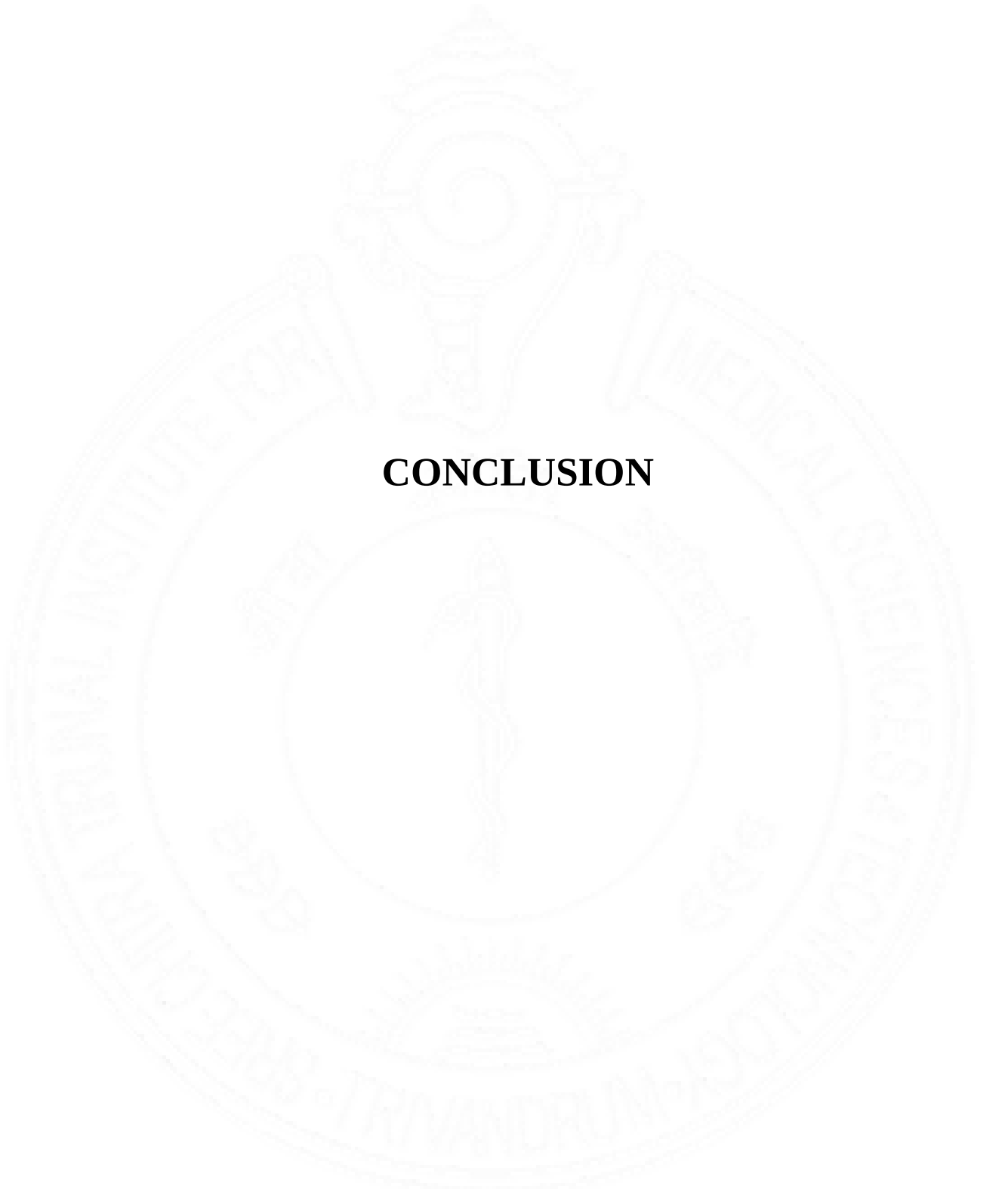
The retrospective study design is bound to have limitations which include missing data for patients which included AChRab and MusK antibody positivity and small sample size. This is also an open, uncontrolled longitudinal study with varying number of observers.

Strengths of the study

The study was done using MGFA class for severity determination and response to therapy was documented as MGFA-PIS scale which makes the data more objective.

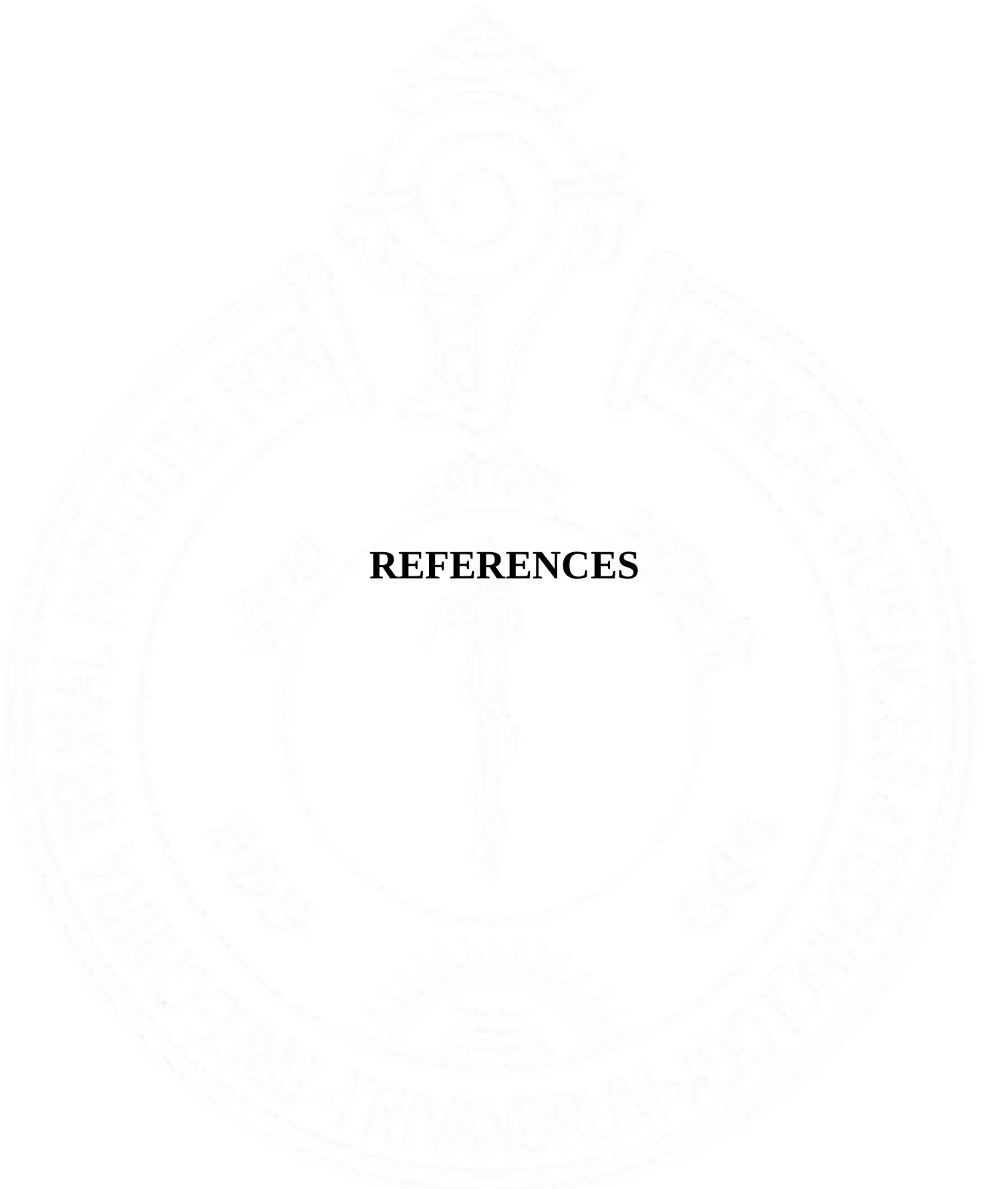
It is one of the few studies from India which describe the clinical profile of patients with JMG

The number of patients in pre and post-pubertal age group as well as OMG and GMG subgroup are balanced.



CONCLUSION

JMG is a chronic disease with variable clinical profile. Pre-pubertal age group is associated with more patients with ocular onset of disease. OMG is associated with lesser relapses but has similar outcomes as compared to GMG. However, the response to treatment is generally good with majority of patients achieving optimal outcome. Further multicenter prospective studies are required to clarify this disease and its features in children.



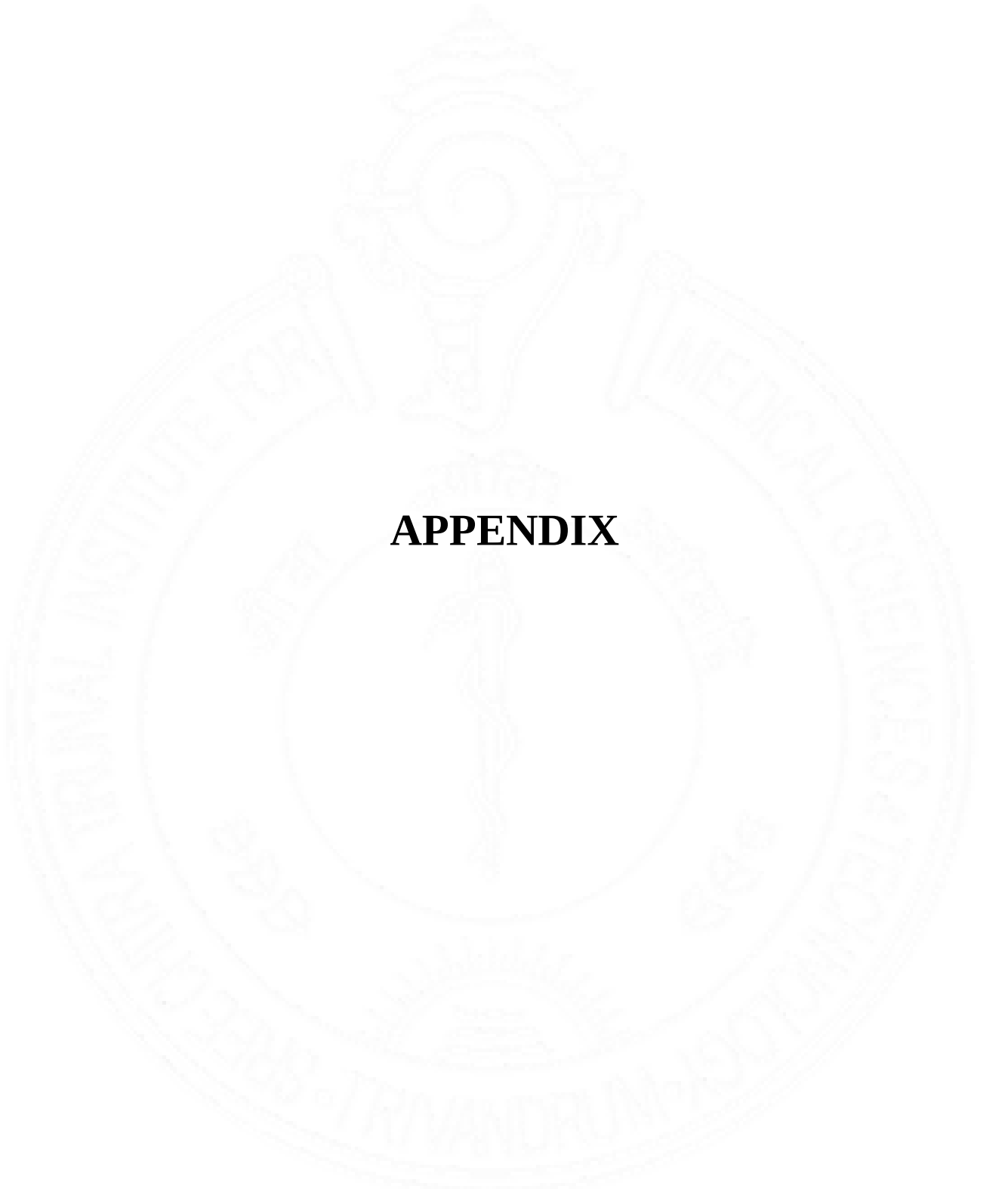
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APPENDIX

LIST OF ABBREVIATIONS

JMG	Juvenile myasthenia gravis
GMG	Generalised myasthenia gravis
RNS	Repetitive nerve stimulation
SFEMG	Single fibre electromyography
AChRAb	Acetylcholine receptor antibody
MGFA	Myasthenia Gravis foundation of America
CSR	Complete stable remission
PR	Pharmacological remission
MM	Minimal manifestations
OMG	Ocular myasthenia gravis
GMG	Generalised myasthenia gravis
IVIG	Intravenous immunoglobulin
MuSK	Muscle specific tyrosine kinase



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Institutional Ethics Committee (IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SC/IEC/1483/NOVEMBER-2019

03.09.2020

Dr. Harikrishnan R
Resident
Department of Neurology
SC/IMST, Thiruvananthapuram

Dear Dr. Harikrishnan,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "A STUDY ON THE CLINICAL PROFILE AND OUTCOME OF JUVENILE MYASTHENIA GRAVIS (IEC/1483)" on 5th November, 2019.

The following documents were reviewed:

Original submission

1. Covering Letter addressed to the Chairperson, IEC, with checklist
2. TAC Approval Letter
3. IEC Application Form
4. Forwarding Letter from the Co-Principal Investigator
5. Project Proposal
6. Proforma
7. CV of Principal Investigator and Co-Principal Investigators

Revised submission

1. Covering Letter addressed to the Chairperson, IEC, with checklist
2. Copy of IEC Recommendation Letter dated 07.11.2019
3. TAC Approval Letter
4. IEC Application Form
5. Forwarding Letter from the Co-Principal Investigator
6. Project Proposal
7. Revised Proforma
8. CV of Principal Investigator and Co-Principal Investigators

Page

The following members of the Ethics Committee were present at the meeting held on 5th November, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL No.	Member Name	Highest Degree	Gender	Scientific / Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Kale Kesavan, P	MBBS, MD	Female	Basic Medical Scientist	No
3.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
4.	Dr. Harkrishna Vanna PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
5.	Dr. S S Giri Sankar	LL.M, Ph.D.	Male	Legal Expert	No
6.	Dr. V. Raman Kutty	M.D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
7.	Dr. Aneesh V Pillai	BA, LLB (Hons.), LL.M, Ph.D, SET (Law)	Male	Legal Expert	No
8.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
9.	Dr. P. Manickam	BSMS, MSc (Epid), PhD	Male	Health Science Expert/ Social Scientist	No
10.	Dr. Harkrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
11.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
12.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
13.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

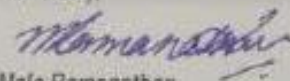
The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



Mala Ramanathan
Member Secretary, IEC