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A Clinical Audit of Juvenile Myasthenia Gravis at Two Academic Hospitals in Johannesburg

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2025

University of the Witwatersrand, Johannesburg

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Duma, Nolwandle . (2025). A Clinical Audit of Juvenile Myasthenia Gravis at Two Academic Hospitals in Johannesburg [Master`s dissertation, University of the Witwatersrand, Johannesburg]. WIReDSpace. https://hdl.handle.net/10539/48238

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DISSERTATION

A CLINICAL AUDIT OF JUVENILE MYASTHENIA GRAVIS AT TWO ACADEMIC HOSPITALS IN JOHANNESBURG

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DEDICATION

This work is dedicated to my family, Owami and Khanya Assan, Ntokozo and my mother in heaven. Thank you for being the wind beneath my wings.

“I look up to the mountain, from whence cometh my help?...My help cometh from the Lord”
Psalm 121 v 1-2

DECLARATION

I hereby declare that the work on which this research is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being or is to be submitted for another degree at this or any other university.

NN Duma _____ 2025/03/17 _____

N.N Duma (MMed (Paed), FCPaed, MBChB) **Date:**

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LIST OF ABBREVIATIONS

JMG - Juvenile Myasthenia Gravis

AChR - Acetylcholine receptor

AChE - Acetylcholine esterase

Ab - Antibodies

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

CHBAH - Chris Hani Baragwanath Academic Hospital

MGFA - Myasthenia Gravis Foundation of America

Abstract

Myasthenia gravis is an autoimmune disorder affecting the acetylcholine receptor leading to deficits in neuromuscular transmission across the receptor. The disorder although rare, can affect children and in which case it is termed juvenile myasthenia gravis(JMG). This study is a clinical audit to elicit the characteristics of juvenile myasthenia gravis in children diagnosed with JMG who were attending Paediatric Neurology Clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) or Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods

This study was a retrospective audit of all patients with a diagnosis of JMG attending the paediatric neurology clinic at CMJAH or CHBAH. The files of 80 patients were reviewed for presentation, clinical findings, management and the response to treatment. Their clinical findings were classified according to the Myasthenia Gravis Foundation of America (MGFA) classification. Their remission status was also determined in relation to their clinical presentation.

Results

The most common clinical presentation was ocular JMG which translated to MGFA class I. There was a female gender predominance. Sixty one percent of the children who had an AChR antibody test result were seropositive. Treatment was based upon standard treatment guidelines for JMG. The remission rate was 15% with a majority of those who achieved remission being prepubertal.

Conclusion

Most of the children who were treated for JMG were prepubertal, female and MGFA classification I. The remission rate was 15%.

Chapter 1

Introduction

Myasthenia gravis (MG) was initially described in the 1600s when the scientist, Thomas Willis, described a condition where a person became fatigued as the day progressed. The research continued in the 1800s and 1900s when the acetylcholine receptor was described and ascribed to the pathology surrounding MG. Myasthenia gravis in children was soon described thereafter; after being considered rare (1)

A large multicentre trial involving hospitals in Cape Town, Johannesburg and Bloemfontein was previously conducted in 2011(2). This study investigates our local patient profile and since there has been some clinical advances, it was relevant to conduct a clinical audit to ascertain the characteristics of JMG patients and their clinical outcomes.

Chapter 2

Literature analysis:

Pathophysiology

Myasthenia gravis (MG) is an autoimmune condition that results in fatiguability of ocular and/or skeletal muscles (3). The pathophysiology of MG involves the formation of antibodies against the nicotinic acetylcholine receptor (AChR) thus impairing binding of acetylcholine to the AChR and therefore preventing synaptic transmission across the neuromuscular junction leading to muscle weakness and fatiguability (3).

Myasthenia gravis can be classified as seropositive or seronegative depending on the serological status of the patient. Worldwide, in patients with MG, antibodies against the AChR are found in 80 – 85% of patients with generalised MG and in 40 – 60% of patients with ocular myasthenia gravis (4,5). Anti AChR antibodies affect neurotransmission by attaching to the AChR receptor and altering the receptor, they can also accelerate the degradation of acetylcholine and destroy the surface of the postsynaptic membrane (3). The thymus has been implicated in the pathology of myasthenia gravis as thymomas have AChR reactive T cells and B cells that are capable of producing AChR antibodies (3). Rarely, seronegative MG presents with antibodies against the neuromuscular junction protein, muscle-specific kinase (MuSK) which is sometimes associated with severe disease (4)

Epidemiology and Demographics

Myasthenia gravis occurring in the paediatric population includes three disease entities i.e., congenital myasthenic syndromes, transient neonatal MG and juvenile myasthenia gravis (6). Juvenile myasthenia gravis, is an acquired autoimmune

disorder with an incidence of 1 to 5 per million worldwide (3,5) which is similar in South Africa (2,7).

Juvenile myasthenia gravis (JMG) occurs in children between the ages of 0 to 19 years and the presentation varies according to demographics (8-10). Population studies have shown that children of Asian ancestry present much earlier with JMG than those of European ancestry with a mean age of presentation of 5 to 10 years (5,11). In contrast, studies conducted in South Africa indicate that children of African ancestry present earlier than children of European ancestry (2). Prepubertal JMG has an equal male to female ratio, while there is a female predominance post puberty (11)

Clinical presentation and symptoms

The clinical presentation of myasthenia gravis also differs in different population groups with those of Asian or African ancestry presenting with predominantly ocular symptoms which may worsen to a generalised state over time while those of European descent mostly present with generalised symptoms (9,11). Ocular myasthenia is the most common presenting symptom in JMG. The most prominent ocular sign is ptosis which may be associated with strabismus, lid retraction and diplopia (9,12). For MG to be classified as a pure ocular form, the patient must have ocular symptoms for 2 years without generalisation of symptoms (11,12). Children who present with pure ocular symptoms present earlier or prepubertal (12). Generalised MG may present with ocular symptoms, facial weakness, bulbar weakness with drooling and choking as well as limb weakness. In severe cases, there is weakness of the respiratory muscles which may result in respiratory failure (9,11,12). The Myasthenia Gravis Foundation of America Clinical Classification is used to rate the severity of myasthenia (13) and includes 5 classes as follows:

Table 1 Myasthenia gravis classification

Class I	Any ocular weakness
Class II	Mild weakness. May also have ocular muscle weakness of any severity
Class III	Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity
Class IV	Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity
Class V	Defined by intubation, with or without mechanical ventilation

Juvenile myasthenia gravis can coexist with other autoimmune disorders like thyroid disease and polymyositis (14). In a South African cohort, 6% of the study population had coexisting autoimmune disorders such as rheumatoid arthritis, insulin dependent diabetes mellitus and thyroid disease (2).

Clinical diagnosis of Myasthenia Gravis

Myasthenia gravis can be diagnosed clinically by demonstrating muscle fatigability and/or using pharmacological testing with a short-acting acetyl choline receptor antagonist e.g. neostigmine or edrophonium(2,15). Clinically, one can demonstrate fatiguability using the upward gaze test and reversibility or reduction of ptosis using the ice test. This test is conducted by measuring the palpebral fissure height then placing an ice pack over the eye for 1 to 2 minutes and then measuring the height

again, an improvement of the palpebral fissure height by 2mm or more is considered a positive result (9).

Neostigmine is used as one of the pharmacological agents to test for myasthenia gravis as edrophonium is no longer available. It inhibits acetylcholinesterase therefore allowing more acetylcholine availability at the post synaptic muscle membranes. Side effects of acetylcholinesterase inhibition include sweating, fasciculations and bradycardia therefore resuscitative measures should be available when the test is performed, including atropine to prevent cholinergic side effects. The pharmacological agent that is mostly used since the discontinuation of edrophonium is neostigmine which functions as an acetylcholinesterase inhibitor therefore allowing acetylcholine availability (2,15).

Serology:

Serological confirmation of MG entails testing for anti-AChR antibodies in the serum. The presence of these antibodies is highly specific for myasthenia gravis (11,12,15). The optimal level of anti-AChR antibodies that provides a positive predictive value is generally stated as ≥ 0.2nmol/l (3). Generalised myasthenia gravis in children is usually AChR antibody positive and ocular myasthenia gravis mostly yields negative results for AChR antibodies (11). Patients with AChR negative MG may present with antibodies against the neuromuscular junction protein, muscle specific kinase which is rare in children but if detected, may present with worse disease as well as a female predominance.

Imaging

The role of imaging in MG is relevant once the condition has been diagnosed and in treatment resistant cases. CT scan or MRI of the thymus is indicated, (12) to look for

thymic hyperplasia or thymoma. Thymomas are rare in the paediatric population (11). Brain imaging (CT or MRI) may be necessary to exclude brainstem lesions mimicking JMG (2).

Treatment options for myasthenia gravis:

The general approach to treatment would be to classify the patient according to the severity of their symptoms and their MGFA classification. Patients are commenced on acetylcholinesterase inhibitors with or without intermittent steroid therapy however some would require other forms of immunosuppression (11,12,15).

Acetylcholine esterase inhibitors

Acetylcholine esterase inhibitors prevent the degradation of acetylcholine to choline and acetate at the synaptic cleft and therefore helps to facilitate neuromuscular transmission (2,15). In children with JMG the AChE inhibitor of choice is pyridostigmine (Mestinon) at a dose of 0.5 to 1mg/kg every 4 to 6 hours and its effects usually last for 3 to 5 hours (12,15). It is preferred due to its better side effect profile and longer duration of action (2,12).

Immunosuppressive medication:

Immunosuppressive medication helps to decrease mortality in MG and also reduces the use of AChE inhibitors (2,11,12). Corticosteroids work by inhibiting T cells and antibody synthesis (2). There also appears to be a facilitatory presynaptic effect on neurotransmission with the use of steroids. They are mostly utilised for generalised MG not responding to AChE inhibitors (12) however they have been found to also reduce the progression from ocular to generalised MG (2).

Azathioprine is a steroid sparing agent that inhibits purine metabolism. It also affects rapidly dividing cells like lymphocytes (15). Azathioprine can be considered in children

who show a poor response to steroid therapy and AChE inhibitors (12,15). One of the side effects of Azathioprine is hepatotoxicity (12) hence the need for hepatitis B testing and a baseline liver function test prior to its commencement.

Methotrexate has been successfully utilised for the management of myasthenia gravis as an immunosuppressant and a steroid sparing agent and has been proved to be as effective as azathioprine (12).

Immune modulator therapy such as plasmapheresis and intravenous immunoglobulins (IVIG) can be used in the acute management of myasthenia(3). Plasmapheresis helps to clear AChR antibodies from the circulation while IVIG binds AChR antibodies and prevents the binding of the antibodies to the neuromuscular junction (16). Both modes of treatment can be utilised in myasthenic crisis or when there is severe muscle weakness or in preparation for thymectomy (12).

Thymectomy

Thymectomy is a treatment option in children presenting with a thymoma or thymic hyperplasia. Thymectomy has been associated with improved remission rates in children (5, 11,16)

Remission and clinical outcomes

Remission in myasthenia gravis is defined as the absence of MG symptoms without medication for a year (16). The remission rate in children with myasthenia gravis is between 22 to 30%. (3,5,6,8). The outcomes for treatment are classified according to the Millichap and George classification (5) as seen in table 2 below:

Table 2 : Millichap and Dodge Classification

A: remission without medication
B: good response both subjective and objective requiring medication in the same or lower dosage
C: mediocre response (slight improvement subjective and/or objective) with high dosage
D: without changes or worsening
E: death

Predictors of outcome are variable but may include age of symptom onset with children whose disease commenced before the age of 10 years having a better chance of remission. Race also influenced the outcomes of patients with Asians and Caucasians having better remission than other races (11,16,17). In a South African cohort, the remission rate was higher in black patients than whites even though complete remission was not achieved this finding is likely attributed to black children being more predisposed to ocular myasthenia gravis (6,17). An important predictor of outcome is the seropositivity status where remission is more likely in those clustered only to AChR antibodies(5,17). The course of JMG depends on many variables like age, race, type of disease and other comorbidities however early diagnosis and treatment may improve remission rates (17).

Chapter 3

STUDY QUESTION AND AIM

Study question:

What is the profile of children with juvenile myasthenia gravis seen at the Paediatric Neurology clinics of 2 major tertiary hospitals in the Greater Johannesburg area and what are their treatment outcomes?

Aim:

To determine the clinical profile and outcomes of children presenting with JMG to the Paediatric Neurology Clinics at 2 tertiary hospitals located in Johannesburg - CMJAH and CHBAH

Objectives:

- To determine the clinical presenting features of juvenile myasthenia gravis at CMJAH and CHBAH i.e. demographics of the children, frequency of ocular vs generalised JMG
- To assess their antibody status - AChR antibody positive or negative
- To document other autoimmune diseases in this cohort
- To review the treatment regimen, need for steroid therapy and immunotherapy
- To establish the clinical outcome of children with JMG in relation to their age of presentation and AChR antibody status
- Duration of treatment and whether remission was achieved.

Chapter 4

METHODOLOGY

Study Population:

Children who have been diagnosed with juvenile myasthenia gravis attending Paediatric Neurology clinic at either Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) or Chris Hani Baragwanath Hospital (CHBAH). These tertiary hospitals serve as referral sites from primary and secondary heath facilities in and around Gauteng province as well as other provinces. Both of the institutions adhere to Myasthenia gravis treatment protocols.

Study Design:

This study was a retrospective clinical audit of all patients from > 1year up to 20 years of age diagnosed with juvenile myasthenia gravis at the Paediatric Neurology clinic in CMJAH and CHBAH from 2008 to 2021. Children with congenital myasthenia gravis were excluded.

Data collection and procedure:

The patient records of all children who had been diagnosed with JMG at CMJAH and CHBAH Paediatric neurology clinics were accessed and audited over a 3 month period. Both hospitals keep records of patients with JMG on clinical spreadsheets in the files. There are 96 patients who have been diagnosed with JMG between both hospitals. Permission from CMJAH and CHBAH authorities was sought prior to accessing the files. The information from the files was captured on a data collection sheet.

The following information was retrieved from the available patient files:

- Demographic data including age at presentation, race, and gender.

The children were classified as prepubertal if they were less than 12 years of age and post pubertal if they were more than 12 years.

- Clinical presentation, symptom duration and symptom severity at the time of diagnosis of the patient with JMG and whether they presented with ocular or generalised myasthenia gravis.

A diagnosis of myasthenia gravis was made if the patient presented with fatigable muscles with a positive response to cholinesterase inhibitors and /or a positive AChR antibody test (>0.2nmol/l).

- Severity of the child's symptoms was classified according to the Myasthenia Gravis Foundation of America Clinical Classification from grade I to grade V (13).

Class	Clinical symptoms
I	Any ocular weakness
II	Mild Weakness. May also have ocular muscle weakness of any severity
II A	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles or both
II B	Predominantly affecting ororpharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles or both
III	Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity
III A	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles or both
III B	Predominantly affecting ororpharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles or both
IV	Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity
IV A	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles or both
IV B	Predominantly affecting ororpharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles or both
V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management

doi:10.1371/journal.pone.0114060.t001

Figure 1. Myasthenia Gravis Foundation Of America Clinical Classification

- Investigations conducted to support the diagnosis – this included the results for the AChR antibodies and other autoimmune studies including thyroid function test results and antinuclear antibody tests. The patients will then be classified as seropositive or seronegative according to the results of the AChR antibody test.

- Xray and CT scan results were analysed to check for radiological evidence of a thymus as shown on x-rays and / or CT scan

- Treatment that was prescribed for JMG and the response to treatment. The treatment for JMG in the two hospitals is usually commenced with acetylcholinesterase inhibitors, pyridostigmine (mestinon), then immunosuppressant therapy like steroids (prednisone) are commonly added followed by azathioprine as a steroid sparing drug. The need for steroid therapy and immunosuppressant therapy was recorded as well as whether or not a thymectomy was performed as a treatment modality.

- Clinical outcomes of the children who have been diagnosed and treated for JMG in relation to their serological status. The Millichap and dodge classification was utilised to assess clinical outcomes and remission was achieved if there were no myasthenia without medication gravis symptoms for a year.

Data analysis

Data capturing and statistical analysis was be done by capturing all the collected data on Excel and then transferred to the Stata version 17 program. Appropriate descriptive statistical analysis using percentages, means, standard deviations, medians and ranges will be used for demographic data. The Fischer test and Chi square test were used to compare observed results and determine association. A biostatistician was consulted to assist with statistical analysis.

Ethical Considerations

The study did not commence before approval from the Wits Research Ethics Committee (M23/09/63). The permission of hospital authorities was obtained prior to data collection. There was no identifiable data from any of the children. This was ensured by having their names omitted from the data sheet and using patient numbers as identifiers. The computer that was used to store the data was password protected and only the primary investigator had access.

Chapter 5

Results

A total of 80 patient files were audited in both hospitals over the period April 2022 to June 2022. Sixty-eight (85%) of the files that were audited were from CHBAH and 12 (15%) of the files that were audited were from CMJAH. The gender distribution comprised of 48 (60%) females and 32 (40%) males. At presentation, 44 (91%) of the females and 29 (90%) of the males were prepubertal (<12 years). Seventy-eight of the children were South African (96%) and the remaining 4% (n=2) comprised children from Gabon (Western Africa) and Zimbabwe (Southern Africa). The mean age at presentation was 6.6 years (SD ±3.5 range 9 months to 13.4 years). There were 16 patients who were excluded as their records were incomplete as demonstrated on figure 2.

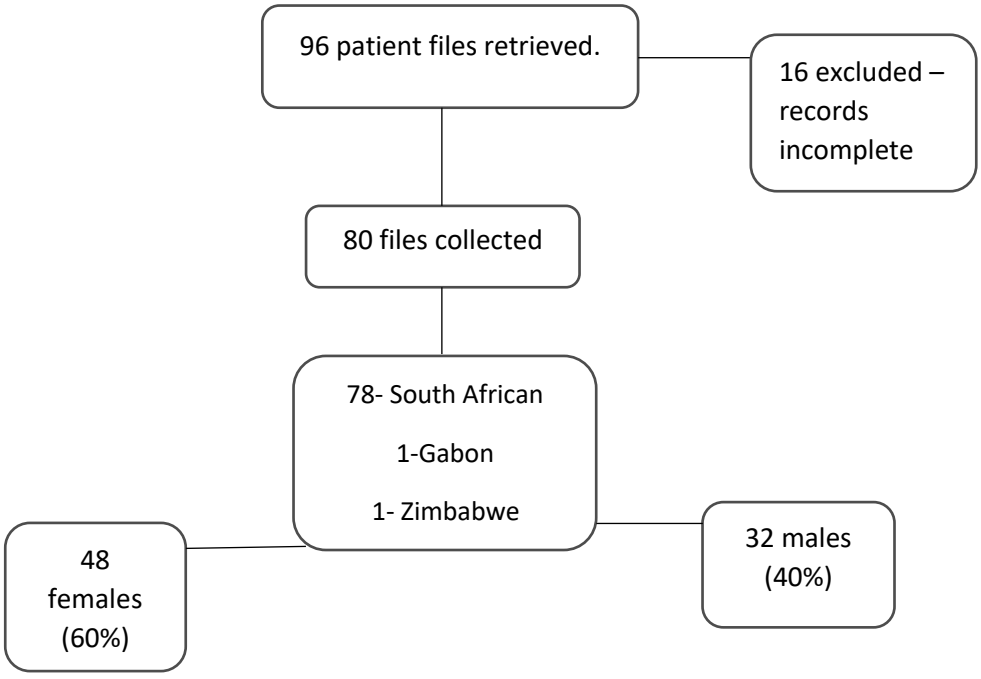


Figure 2. Eligibility and gender distribution

Presentation and Classification

Of the 80 patients, 71 (88%) presented with pure ocular symptoms, these were classified as class I according to the MGFA classification. Of those with ocular symptoms, 49 (69%) had bilateral ptosis while 31(31%) of the children had unilateral ptosis. There were 38 (48%) of children who presented with ophthalmoplegia and 35 (92%) of them were classified as class I, 2 children were class II and one was class V ($p = 0.09$).

There were 5 (6%) children with mild generalized myasthenia gravis of which 2 had predominantly limb weakness and 3 had predominantly oropharyngeal weakness, classified as MGFA class IIa and class IIb respectively. Four of the children (5%) had severe generalized myasthenic symptoms (MGFA class V) and they presented with generalised body weakness and bilateral ptosis. They all needed urgent care and they were hospitalised. Seventy-one children presented with ocular symptoms, 66 (92%) were prepubertal at presentation while only 5 (7%) were postpubertal as demonstrated in table 3.

Table 3. Gender distribution and clinical manifestations relative to pubertal status

Variable	Prepubertal n (%)	Postpubertal n (%)
Gender		
Male (n=32)	29 (90%)	3 (9%)
Female (n=48)	44 (91%)	4 (9%)
Ocular MG	66 (92%)	5 (7%)
Ophthalmoplegia	12 (92%)	1 (8%)
Generalised MG	7 (77%)	2 (28%)
AChR antibody pos	38 (95%)	2 (5%)
MGFA Class		
Class I	62 (77%)	5 (6%)
Class II	4 (5%)	1(1%)
Class III	-	-
Class IV	-	-
Class V	3 (5%).	1(1%)

Values given in numbers of patients (n) and percentages (%)

Testing

The neostigmine test was administerered to 75 children (93%) and 73 (97%) of those tested positive while 2 of the tests were negative. Edrophonium testing was conducted in only 2 (2.5%) children as it subsequently became unavailable; they were both positive. There were 65 (81%) children who had AChR antibody test results, 40 (61%) of those had a positive AChR antibody result while 25 (37%) were negative. Fifteen of the children (18%) did not have recorded results. The ice test was only conducted on 10 (12%) children and they all tested positive.

Table 4. Diagnostic test results

Test	Positive – n (%)	Negative – n (%)	not available
Neostigmine	73 (97%)	2 (3%)	3 (4%)
Edrophonium	2 (100%)	0	0
AChR antibody	40 (50%)	25 (32%)	15 (18%)
Ice test	10 (12%)	0	7 (88%)

Values in numbers of tests (n) and percentages (%)

Co-existing Conditions

With regards to testing for other co-existing autoimmune conditions, 3 children (4%) had antinuclear antibody screening and the results were negative. Only one child was tested for anti-musk antibody and the result was negative. One child was hyperthyroid and 2 had subclinical hypothyroidism. The child who had hyperthyroidism was classified as class IIb and the 2 who had subclinical hypothyroidism was classified as MGFA class I. One of the children with subclinical hypothyroidism had down syndrome as well. Two children were HIV positive on highly active antiretroviral therapy and they were both classified as MGFA class I. One child had vitiligo but no other serological evidence of autoimmune disease. With regard to hepatitis results, 22 of the children (27%) were immune to hepatitis B. Five of the children tested negative for hepatitis b antibodies. The majority (68%) did not have available results.

Imaging

Twenty one (26%) of children had reports of imaging performed. Seven (33%) had CT scans of the brain, 1 (4%) had MRI of the brain, 1 (4%) with sonar of the neck and 12 (57%) children had chest x-rays conducted. Only two children were found to have a thymoma and one child had thymic hyperplasia. Of the 2 children who had a

thymoma, one was MGFA class V and the other was class I.The child that was found to have thymic hyperplasia was found to be MGFA class I. There were no children with intracranial pathology.

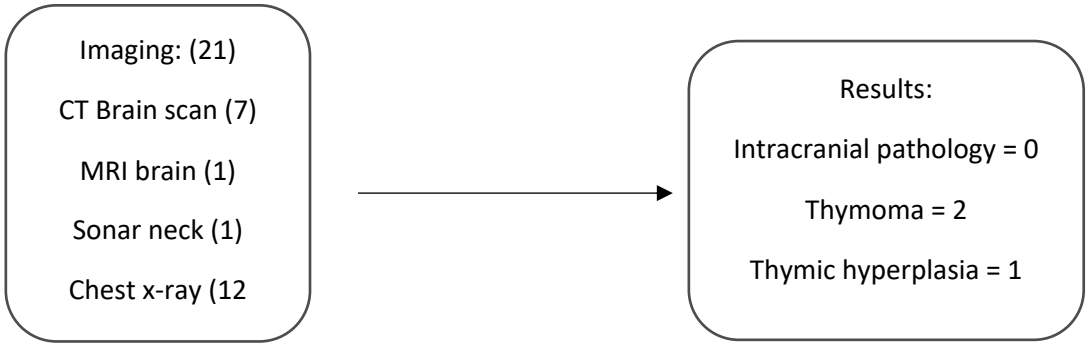


Figure 3: Imaging and Results Result and (n)

Treatment

All the children were commenced on an acetylcholinesterase inhibitor,Mestinon, which was initiated in a hospital setting. The children were started on low dose Mestinon and then increments were made every third day according to the child's therapeutic response. A further 65 (81%) children had steroids added to mestinon when there was a poor response to mestinon alone. Fourteen children (17%) responded to mestinon with no steroid use. Of those who had steroids in addition to mestinon, 58 (89%) were MGFA class I while 2 (3%) were class IIa, 1 (1.5%) child was class IIb and 4 (6%) children were class V. A total of 31 children were commenced on azathioprine in addition to mestinon and steriods; 17 children (22%) received methotrexate. Ten children received both azathioprine and methotrexate in addition to mestinon and steroids. Only 3 children (4%) had a thymectomy, two of them were classified as MGFA class V and the remaining child was class I but had a myasthenic crisis and was reclassified as MGFA class V.

There were 3 children (4%) who received intravenous immunoglobulins and 1 child who received a plasma exchange. Two of the chidren who received intravenous immunoglobulins were MGFA class V and the remaining one was MGFA class I, this was a child who responded poorly to mestinon and immunosuppressants and was given a trial of polygam. The only child who received a plasma exchange was MGFA classification V and was one of the children who had also had a thymectomy, as demonstrated in table 5.

Table 5. Treatment regimen used in relation to MGFA classification

Treatment	Class I	Class II	Class III	Class IV	Class V
Mestinon (n=80)	71 (88%)	5 (6%)	-	-	4 (5%)
Mestinon + Steroid (n=65)	58 (89%)	3 (5%)	-	-	4 (5%)
Mestinon + Steroid + Aza (n=31)	27 (87%)	1 (3%)	-	-	3 (10%)
Mestinon + Steroid + Methotrex (n=17)	14 (82%)	1 (6%)	-	-	2 (12%)
Immunoglobulins (n=3)	1 (34%)	-	-	-	2 (66%)
Plasma Exchange (n=1)					1 (100%)
Thymectomy (n=3)					3(100%)

Values in n and percentage. Aza= azathioprine, methotrex = Methotrexate

With regards to the remission status, 12(15%) children achieved a status of being symptom free with no medication after a year; while 2 (3%) patients were symptom free with minimal medication. This corresponds with Millichap and Dodge staging A

and B, respectively. The majority of children were in the Millichap and Dodge stage C and D. No deaths were noted. The remission rate was therefore 15%. All of the children who achieved remission were under the age of 12 at presentation and commencement of treatment (p=0.7). Nine of those who had clinical remission (75%) were female while 3 (25%) were male (p=0.3).

Of the children who achieved remission, one child (9%) was classified MGFA class V while the other 11 (90%) were class I (p=0.7). The mean time period to remission was 6 years (SD±3.6) with the shortest time period being 1 year while the longest time period was 11 years.

Six (50%) of the children who achieved remission were AChR antibody negative while only 4 (33%) were antibody positive while 2 (17%) children had unavailable results (p=0.4). The neostigmine test was positive for all the children who went into remission (p=0.66). None of the children who went into remission had any thyroid disorders, HIV infection or autoimmune conditions.

Table 6. Remission status in relation to demographic and clinical symptoms

	Remission (n= 12)
Gender	
Female	3 (25%)
Male	9 (75%)
Age at onset	
Prepubertal	12 (100%)
Postpubertal	0
AChR Antibody	
Positive	4 (33%)
Negative	6 (50%)
No result.	2 (17%)
MGFA	
Class I	11 (90%)
Class II	0
Class III	0
Class IV	0
Class V	1 (10%)
Mean years to remission	6 years

Values in n and percentage

Eight (66%) of the children who achieved remission were given steroids while 4 (34%) were not on steroids and responded solely to mestinon. Additionally, from the group who achieved remission only 2 (16%) children received methotrexate in addition to the normal regimen of AChR inhibitor and a steroid. None of the children who had a thymectomy went into remission(p=0.8). None of the children who went into remission had received intravenous immunoglobulins or plasma exchange (p=0.7)

Table 7. Treatment regimen relation to remission status

Treatment used	Remission (n=12)
Mestinon only	3 (25%)
Mestinon + Steroid	8 (67%)
Mestinon + Steroid + Aza	0 (0%)
Mestinon + Steroid + Methotrexate	1(8 %)

Values in n and percentage. Aza = Azathioprine

The outcome of the children who did not achieve clinical remission in the study was as follows and demonstrated in Table 7:

10 (12%) were transferred to adult clinic to continue their monitoring and treatment. Of those, 5 were male and 5 were female. They were all on Mestinon and a steroid. Five of them were on azathioprine and 5 were on methotrexate upon transfer to adult clinic.28 (35%) were lost to follow up, one was transferred to Steve Biko Academic hospital.

Table 8. Outcome

Outcome Category	n (%)
Remission (no treatment)	12 (15%)
Adult Clinic transfer	10 (13%)
Transfer to another facility	1 (1%)
Lost to follow up	28 (35%)
Still on treatment	29 (36%)

Values in n and percentage

There are 29 (36%) children who are currently being treated between the two academic institutions, including two who are on minimal medication pending stoppage. Of those that are still on treatment (n=29), 19 (68%) of the children are females and 9 (32%) are male. All of them are on still on Mestinon, 27 (96%) of them are still on steroids, 17 (60%) are on azathioprine and 5 (17%) are on methotrexate. From the non remission group, only 1 child (4%) had a thymectomy. One child (4%) received immunoglobulin therapy.

Table 9. Current clinic statistics – Non-remission category

Category	No remission (n =29)
Gender	
Male	9 (32%)
Female	20 (68%)
Treatment	
Mestinon	29(100%)
Mestinon + Steroid	27 (96%)
Mestinon + Steroid + Azathioprine	17 (60%)
Mestinon + Steroid + Methotrexate	5 (17%)

Values in n and percentage

Chapter 6

Discussion

The study was conducted to ascertain the characteristics of juvenile myasthenia gravis in a cohort of eighty children who attended the Paediatric neurology clinic at two tertiary hospitals in South Africa. Their democraphics, clinical presentation, diagnostic markers, treatment given and treatment response were investigated.

The average age of presentation with juvenile myasthenia gravis was 6.6 years and the majority of the children (77%) were prepubertal at diagnosis and commencement of treatment. The findings in this current study involving predominantly black South African children were similar to the multi-institutional South African study that was published in 2012 by Heckmann et al where the average age of presentation was 7 years (2). An international study by Finnis also indicated a peak age of presentation at 5 – 10 years for black and chinese children however in the Caucasian population there was a postpubertal presentation (12). In a a study by O'Connell et al, the peak age of presentation was 0-4 years in a Taiwanese study (18) This current study is therefore consistent with previous studies with regards to the age of presentation and also racial variance in the presentation of JMG. It must be noted, however that this current study had a ratio of 91% to 9% of prebubertal vs postpubertal JMG respectively and all the children were of African descent.

In this study there was a female gender predominance that was found for prepubertal JMG. Sixty percent of the children who were diagnosed and treated with JMG in our population were female. In a review by Della Marina et al, it was observed that African and Asian populations showed female predominance in all age groups irrespective of their puberta statusl (15) and this finding was supported by a study conducted in the

United Kingdom (16). In contrast, a study conducted China did not find a gender differences in the presentation of JMG (19). Most studies do report a postpubertal gender distribution with a female dominance in the presentation of JMG (12, 19, 20).

The majority of children diagnosed with JMG in this study had ocular mysthenia gravis. In a study by Heckmann, it was shown that children of African ancestry were more prone to develop ocular JMG (2). This is true for this current population group as they were all of African ancestry. The prepubertal presentation of JMG is commonly ocular (6,12,20) which is consistent with our findings as a majority of the children in the current study presented with ocular myasthenia gravis and were also prepubertal. The proportion of children with geneneralised JMG was low in this study which could be due to the fact that a large proportion of our patient population was prepubertal. Several studies have indicated that generalised JMG presentation is more prevalent in postpubertal children (12,19,22).

Ophthalmoplegia at presentation was a common finding (48%) in this population group. In the multinational study that was published by Heckmann et al in 2012, 75% of the children under study had ophthalmoplegia which was higher than in our current population (2). The patients that presented with opthalmoplegia in the Heckmann study were predominantly of African ancestry. All the subjects in this current study were of African descent so it is difficult to make an association since the 2012 was a multinational study with children from various ethnic and genetic backgrounds. In the 2012 study severe ophthalmoplegia was seen in children with generalised myasthenia gravis but this is not true for this current study which had a predominance of children with ocular myasthenia gravis.

The diagnosis of juvenile myasthenia is based upon clinical, pharmacological and serological testing. Although the ice test was conducted in some of the children who were referred to the clinic to demonstrate reversibility of fatigability, it is an option (12) but it remains underutilized in the paediatric setting. Pharmacological testing for JMG was common practice in our population as neostigmine (acetylcholinesterase) was used to assist in the diagnosis of JMG in 93% of the patients. Neostigmine has become the preferred pharmacological test in our population. The use of both edrophonium and neostigmine is advocated for depending on the availability (2,15).

Serological testing for myasthenia gravis revealed that the AChR antibody positivity rate was 61%. Studies have indicated a 30 to 60% seropositivity rate in JMG which is less than in adults and is influenced by pubertal status whereby children who are prepubertal would commonly have a negative AChR antibody titre (2,19). O'Connell et al further explained that children with generalised mysthenia gravis were more likely to have seropositive myasthenia gravis (18). The South African study conducted in 2012 by Heckman et al also showed that seropositive JMG was more prevalent in postpubertal children with generalised symptoms (2).The population in this study had predominantly ocular JMG and a prepubertal presentation which may explain the positivity rates (2,15,19).

JMG can be associated with autoimmune disorders such as thyroid disease, rheumatoid arthritis and polymyositis (2,14). However in this study the presence of coexisting autoimmune disorders was low, with only 3 (3.7%) children having been diagnosed with thyroid disease. The multinational sudy conducted in 2012 (2) showed more variability in relation to the types of autoimmune conditions detected and also a

higher rate of autoimmune conditions than this current study i.e. 6% vs 3.7% respectively.

Thymoma and thymic hyperplasia was rare in this paediatric population . Studies have indicated that thymoma is indeed a rare finding in JMG, however, imaging is necessary in all children who have been diagnosed with JMG as the thymus plays a role in the pathophysiology of myasthenia gravis (12,15). Thymoma and thymic hyperplasia is mostly seen in postpubertal children with myasthenia gravis (15).

The standard of care for JMG in the two academic hospital under review is to initiate treatment with acetylcholinesterase inhibitors, pyridostigmine (Mestinon).The second line of treatment that is utilised is immunosuppressant therapy with steroids initially (prednisone) then azathioprine is used as add-on steroid-sparing immunosuppressant drug. Azathioprine can also be substituted into the treatment regimen if the patient has severe steroids side effects. Methotraxate is used if further immunossupresant medication is required or if there is failure to control the symptoms of myasthenia gravis on azithioprine. Methotraxate is also a cost effective alternative in lower income countries(2). Most of the studies advocate for the use of pyridostigmine and steroids plus add on azithioprine but the fourth drug of choice differs from institution to institution(9,12,18).

The use of intraveous immunoglobulins and plasma exchange was low in our study however it was used only for those who had severe generalized JMG according to MGFA classification as well as for myasthenic crisis. This is consistent with the indications for use of immunomodulators worldwide as they are used for acute exacerbations in myasthenic crisis and also for severe disease (11,15,18).

In our setting, thymectomy is utilised in treatment resistant cases who have thymus pathology. Although the rate of diagnosis of thymus pathology was low in this current study, thymectomy was utilised as a treatment modality in 2 of the children with severe generalised JMG. According to O'Connell et al, thymectomy should be considered in generalised JMG with positive AChR antibodies and in mild disease where there is treatment failure (18) however in a contrasting review, it was concluded that the presentation of JMG in African American population differs and that this particular population shows a poorer response to thymectomy (15). In a South African study, there was a trend showing children who had received a thymectomy having higher remission rates however when a sub-analysis of just the Cape town cohort was done, they showed no difference with regards to remission in those that did vs those that did not haave a thymectomy (2).

The remission rate in our study was 15% which is in keeping with the range of 12 to 57% which has been proposed by multinational studies (2,16,22). In a population study in Norway the remission rates were as high as high as 51% (20) which is similar to the South African study comprising of a multi-institutional cohort which showed remission rates of 45% (2). It is valuable to note that the studies that are indicated above were large multicentre, national trials and this current study is a study comprising of 2 hospitals in the Gauteng province of South Africa.

Although a larger proportion of children (75%) who went into remission were female, this finding was not statistically significant and is possibly associated with the female predominance in our study. None of the studies or reviews have found an association between female gender and higher remission rates (16,22).

All the children who achieved clinical remission (1 year treatment free period) were prepubertal however this finding was not statistically significant. Children who were prepubertal at the age of onset of JMG have been seen to have a higher chance of remission (4,10,11). In a study by Vecchio the study did suggest that the remission rates of those <10yrs was better but the results were also not statistically significant (16). The children who achieved remission and were weaned off treatment were predominantly MGFA class 1, ocular JGM. This correlates with the study done in South African which also concluded that higher remissions were seen with ocular disease (16). In Asian and European studies there was a pattern of spontaneous remission in ocular disease (11,18,19).

The majority of children who went into clinical remission were predominantly AChR antibody negative. The studies relating to antibody status and remission in JMG are conflicting. A study conducted in China showed no difference in the remission rate between AchR positive and negative patients while the one conducted in Taiwan indicated that the AChR antibody titre was a good predictor of clinical outcome with children who are antibody negative achieving higher rates of clinical remission (18,22). Although this finding in our current study was not statistically significant, this could be an area of interest in future studies.

None of the children who achieved clinical remission received intravenous immunoglobulins or had a plasma exchange. This is consistent with the notion that ocular myasthenia gravis has higher spontaneous and clinical rates of remission without the need for acute immunemodulator therapy (11,18). In the multicenter South African trial, it was concluded that immunosuppressants and immunomodulating therapy was mostly used in postpubertal children with severe

generalised myasthenia gravis (2). The cohort of this current study consisted predominantly of prepubertal children with ocular myasthenia gravis.

None of the children who achieved clinical remission had a thymectomy in our study. There was also no correlation between thymectomy and remission in this study. According to Ionita et al, the role of thymectomy in prepubertal children with myasthenia gravis remains controversial but is necessary if there is poor response to pharmacological treatment (12). Thymectomy has been found to improve remisssion rates in children with seropositive JMG (95) however in children with prepubertal ocular JMG the chances of remission are good with medical therapy alone (15). The majority of the children in this current study were prepubertal and had ocular disease.

Approximately a third of the children in this current study were lost to follow up. This is a staggering number. A study conducted in the United Kingdom, with appoximately the same number of of subjects, only had a lost to folllow up figure of 4% (16). This discrepancy is most likely related the socioeconomic challenges that exist in lower income countries.

Chapter 7

Conclusion

This study in two South African tertiary institutions was conducted as a clinical audit to contribute to knowledge regarding JMG. This is a smaller follow up study from the study conducted by Heckman et al. in 2012 which was a major national and multi-institution study. A large proportion of the data from the multi-institutional study in 2012 were from this CHBAH cohort. Some of the findings like race, gender and clinical dynamics definitely differ since our population was smaller and homogenous.

Our cohort consisted mainly of prepurbertal African children who presented with ocular myasthenia gravis. The proportion of children with generalised myasthenia gravis was very also low, this can also be due to the higher numbers of prepubertal children in the study. There was a female predominance of JMG in this current study irrespective of prepubertal or postpubertal presentation.

There was a low seropositivity rate in this study however this result could have been impacted by the fact that most of the children were prepubertal and also had ocular myasthenia gravis. Some of the antibody test results (18%) were not available in the files and this could have additionally impacted on the seropositivity rate. The neostigmine test proved to be a useful adjunct in the diagnosis of JMG but the ice test was hugely unpopular in this paediatric population.

The presence of additional autoimmune disease and comorbidities was low in our paediatric population. Thymomas and thymic hyperplasia was also rare.

The standard of care and treatment for JMG is according to international guidelines and practices. The current use of pyridostigmine followed by a steroid then a steroid

sparing agents is the standard treatment pathway and the two institutions under study are aligned with international practice. The use of intravenous immunoglobulins and plasma exchange is practised as per protocol with severe JMG or exacerbations. The use of thymectomy as a treatment modality was uncommon and is reserved for confirmed thymoma and treatment refractory cases in our setting.

The clinical remisssion rate in our study was 15% which is lower when compared to other studies however, it may have been influenced by some patients who were lost to follow-up while they were on treatment. The children who achieved clinical remission were predominantly prepubertal, MGFA class I and were on minimal medication.

Study strengths and limitations

One of the key strengths of this study is its contribution to the scarce reseaerch of juvenile myasthenia gravis in South Africa, addressing a critical knowledge gap in the region.

There are certain limitations and drawbacks that were encountered in this study. Our study group was a homogenous group which rendered it impossible to make any interracial comparisons. The vast majority of children who formed part of the cohort under study were prepubertal. This made it difficult to make definite associations between the prepubertal and postpubertal groups. The small number of children with generalized myasthenia gravis limited our ability to draw comparative insights.

There were children who were on treatment but were lost to follow up and it was therefore not possible to determine their outcomes. Eighteen percent of children did

not have AChR antibody test results and this finding could potentially have an impact on the current study.

Recommendations:

There is a definite need for more research into juvenile myasthenia gravis. Myasthenia gravis in children differs from adult myasthenia gravis in demographic pattern and clinical presentation, it is therefore mandatory to conduct more research on myasthenia gravis in the paediatric population.

Remission in JMG is related to age and the clinical type of MG (ocular vs generalised). Early diagnosis and treatment is therefore imperative to optimise clinical outcomes.

A concerted needs to be made to improve the follow up rate and reduce the number of patients who who are lost to follow up in our units by possibly having community workers who may assist in tracking patients who have been lost to follow up.

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Appendices

A.

Data collection sheet

A CLINICAL AUDIT OF JUVENILE MYASTHENIA GRAVIS AT TWO ACADEMIC HOSPITALS IN JOHANNESBURG

Data Sheet

Study Number:

Date:

Gender:

Age:

Race:

Clinical data

Weight	
Height	
Age at presentation	
Clinical symptoms at presentation	Ocular symptoms only – degree of ptosis: Generalised symptoms- Ocular: axial muscles: oropharyngeal or respiratory:

	Mild:
	Moderate:
	Severe: Need for hospitalisation and intubation: Duration of hospital stay Treatment regimen in hospital:
Examination:	Fatigability and which muscles: Ice Test: positive or negative Neostigmine test: positive or negative
Antibody results	AChR: Positive (titre) Negative:
Other Test Results	Thyroid function test: HIV: Hepatitis studies: Autoimmune studies: Imaging: Thymectomy:
MGFA clinical classification	

Treatment Protocol	Acetylcholinesterase inhibitor dose: initial dose Subsequent dose of AChR inhibitor Response to AChR inhibitor: Steroid dose: min max: Length of steroid use: Steroid response: Immune modulators: Azithioprine: Intravenous immunoglobulins: Response to thymectomy:
Remission status according to Millichap and Dodge	Symptom free without medication for 2 years Symptom free with minimal medication

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26th February 2022

Dear Dr Duma

Master of Science in Medicine (Child Health Neurodevelopmental)

A CLINICAL AUDIT OF JUVENILE MYASTHENIA GRAVIS AT TWO ACADEMIC HOSPITALS IN JOHANNESBURG

As chair of the assessor group held for the Department of Paediatrics on the 23rd November 2022, who requested review of your protocol after making changes, I approve the changes you have made and wish you a successful journey ahead with your project.

Yours sincerely

Karl Technau, MBBCh, Dip HIV Man, DCH, MSc (Med), PhD
Associate Professor, Deputy Director Empilweni Services and Research Unit (ESRU)
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr N Duma

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230963

NAME: Dr N Duma **DEGREE:** MSc (Med)
(Principal and Co-Investigators)

DEPARTMENT: School of Clinical Medicine
Department of Paediatrics and Child Health
Medical School
University

PROJECT TITLE: *A clinical audit of juvenile myasthenia gravis at two academic hospitals in Johannesburg*

DATE CONSIDERED: 29 September 2023

DECISION: Approved unconditionally

CONDITIONS: This clearance covers Chris Hani Baragwanath Academic Hospital only; further sites may be added on presentation to the HREC (Med) of CEO approval

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Professor LG Scher

APPROVED BY: _____
Professor P Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 23 February 2024 **EXPIRY DATE:** 22 February 2029

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report** in the format available at https://wits.ac.za/research/researcher-support/research-ethics/ethics-committees/. This report is due annually, for the duration of the Clearance Certificate, beginning on the first anniversary of Date of Approval above. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

_____ _____
Signature of Principal Investigator Date