

Myasthenia Gravis in Enugu, South East Nigeria - Renewed Management Options

Ndionuka IB^{1*}, Onwuekwe IO² and Ekenze SO³

¹Senior Registrar Neurology Unit, Department of Internal medicine University of Nigeria Teaching Hospital, Enugu, Nigeria

²Professor of Internal Medicine, Neurology Unit, Department of Internal Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

³Consultant Neurologist, Department of Internal Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

***Corresponding Author:** Ndionuka IB, Senior Registrar Neurology Unit, Department of Internal Medicine University of Nigeria Teaching Hospital, Enugu, Nigeria.

Received: August 19, 2017; **Published:** September 25, 2017

Abstract

Background and Objectives: Myasthenia gravis (MG) is an autoimmune neurologic disease that affects postsynaptic portion of the neuromuscular junction. MG poses a diagnostic challenge in resource poor setting, where diagnostic aids are limited. This paper highlights the challenges of managing such cases in southern Nigeria and improved outcome with thymectomy.

Result: In this paper, we report different cases of myasthenia gravis at different stages of the disease and improved outcome with thymectomy. The diagnosis was based only on clinical symptoms and Acetylcholine receptor antibody assay. Other investigative measures like MUSK antibodies and electromyography were not feasible, due to high cost. The patients eventually had rapid improvement with thymectomy.

Conclusion: Thymectomy has proven to be life saving in the management of Myasthenia Gravis in resource poor settings, saving patients from high cost of medications. General outcome of management of MG will greatly improve with diagnostic aids in low resource countries of the world.

Keywords: Myasthenia Gravis; Challenges; Nigeria; Diagnosis

Introduction

Despite advanced diagnostic and treatment techniques, Myasthenia gravis still represents a challenge in resource poor settings, due to unavailability of diagnostic aids and other pharmacologic therapy. Below are clinical vignettes of Myasthenia gravis in a tropical and resource poor setting.

Case 1

A 19 year old single lady who presented in 2015 with a 4 year history of progressive fatigable weakness noted while walking, worse with repeated activity and as the day progressed and improved by rest. At the same time, she noted double vision which was better with closing one eye, and was unable to sustain an upward gaze. Few months later, she found it difficult to climb stairs or raise her hand above her head. She also had occasional falls. There was no difficulty chewing, swallowing or nasal regurgitation. She had no sensory symptoms, sphincteric disturbances or affectation of her consciousness. There was no weight loss, increased bowel motion, bulging of the eyes or tremors. Patient also did not have excessive thirst, polyuria or polyphagia. There were no skin rashes or joint pains.

Key findings on examination were young woman with mild bilateral asymmetric ptosis, and ophthalmoparesis involving both superior rectus muscles. She had fatigable dysarthria and limb weakness affecting proximal more than the distal muscles. Other aspects of the nervous system and systemic examination were normal.

A working diagnosis of Myasthenia gravis Ossermann stage 2A was made.

Investigation results are as follows:

Laboratory Findings

Test	Result	Normal Range
White blood cells	4.5 x 10 ⁹ /L	4.0 - 10.0
Haemoglobin	11.6 g/L	11 - 14
Platelets	254 x 10 ⁹ /L	150 - 350
ESR	3 mm/hr	< 15
AchR antibody	6.36 nmol/L	0 - 0.24
T4	13.8 mmol/L	7.2 - 16.4
T3	5.4 mmol/L	3.8 - 6.0
TSH	1.10 U/L	0.37 - 3.50

FEV1 1.75, FVC 1.89, FEV1/FVC 93%

Chest X-ray - Normal

Thoracic inlet X-ray-Normal

CT Scan Chest – Normal

Treatment –She was placed on Oral Pyridostigmine 120 mg 8am, 90 mg 2pm, 90 mg 8pm.

No history of cholinergic crisis. Though patient still had few episodes of weakness in between doses.

Surgery was recommended. Patient had a Trans-sternal total thymectomy via median sternotomy, done September 2016.

Had an impressive recovery post operatively and received only one dose of Pyridostigmine on day 1. Pyridostigmine was gradually withdrawn. No ptosis or weakness was observed post operatively. Patient was discharged on day 7 post operation.

Muscle strength was increasingly better at first visit post discharge.

Histology of thymus- showed thymic hyperplasia

Case 2

A 34 year old woman who presented with a two year history of drooping of the upper eye lid which was worse on the left eye (LE). This was associated with double vision, and progressive fatigable muscle weakness which worsen as the day progressed, on mild exertion, and sunlight and improved by rest. She was commenced on pyridostigmine, based on a diagnosis of myasthenia gravis stage 2A. However, patient defaulted to follow up for 2 years and represented with worsened generalized limb weakness, she was unable to walk about 50meters without resting, occasional falls, had bilateral asymmetric ptosis which was almost complete on the LE and double vision, which improve when the left eye was completely closed. She could hardly make a sentence in one breath, and also had difficulty chewing and swallowing with a feeling of tightness around the chest. There was no excessive sweating or heat intolerance. Her sphincters and consciousness were intact. She is married with 3 children, her last confinement was 18 months ago. All her children are alive and well.

Key examination findings were asymmetric ptosis which was near complete for the left eye, diplopia in all ranges of eye movement, and bifacial weakness. She had fatigable dysarthria and limb weakness affecting proximal more than the distal muscles. Other aspects of the nervous system and systemic examination were normal.

A working diagnosis of myasthenia gravis stage 2B was made.

Laboratory Findings

Test	Result	Normal Range
White blood cells	$7.98 \times 10^9 / L$	4.0 - 10.0
Haemoglobin	12.9 g/L	11 - 14
Platelet	$286 \times 10^9 / L$	150 - 350
AchR antibody	0.34 nmol/L	< 0.40
Fasting blood glucose	5.5 mmol/L	3.5 - 5.6
T3	1.33 mmol/L	0.56 - 14.3
T4	11.3 mmol/L	5.0 - 13.0
TSH	1.1 U/L	0.2 - 5.5
Pre op FEV ₁	1.82	Predicted 3.52
FVC	2.36	Predicted 4.23
FEV ₁ /FVC	77.1%	Predicted 81.1%

Chest CT scan showed asymmetric enlarged thymus gland L > R. Serum electrolytes are normal.

She was commenced on:

Tab Pyridostigmine 60 mg 8am, 120 mg at noon, 120 mg 4pm and 60 mg 8pm.

Tab Azathioprine 25 mg daily

No history of cholinergic crisis. Outcome minimally improved with pharmacologic treatment. Patient had a trans-sternal total thymectomy via median sternotomy, done in October 2016 a week after her second presentation. However recovery was poor and she was placed on ventilatory support. Oral Pyridostigmine was continued at low doses and progressively increased. Post operatively, she made some improvement, - ptosis is better, but she stills has periods of fatigable weakness.

Recovery was slow, patient was weaned off ventilatory support after 8 days. Weakness did not improve markedly even at her first visit post discharge.

However objective assessments of lung function and bulbar muscles have been optimal. Post op spirometry showed FEV₁ 2.53 (predicted 3.01), FVC -2.89 (predicted 3.46), FEV₁/FVC - 87.5% (predicted 82.6%). She was continued on low dose anticholinesterases which have gradually been tailed off. Histology showed thymohemangiolioma.

Case 3

A 40 year old man who first presented to the hospital in 2004 with symptoms of progressive difficulty talking and swallowing and fatigable limb weakness which was worse with exertion and as day progressed and relieved by rest. Was commenced on treatment for MG with Pyridostigmine but patient defaulted to follow up. He however was receiving treatment from a tertiary center in Lagos where tab Prednisolone was added to his treatment. Four years later, patient developed diabetes and is insulin dependent. He also had several episodes of myasthenic crisis during the period. He represented in 2016 with worsening dysphagia, drooling of saliva, inability to speak well especially after eating and as the day progressed, fatigable limb muscle weakness, mild drooling of the upper eyelids and double vision. There was associated weight loss due to his feeding difficulties.

Key findings on examination were young man, mild bilateral asymmetric ptosis which was more demonstrable with unsustained upward gaze and diplopia. He had a nasal speech, fatigable limb weakness particularly in the proximal muscles. Other aspects of the nervous system and systemic examination were normal. A working diagnosis of myasthenia gravis Osserman stage 3 was made.

Investigations showed:

FBG - 120 mg/dl,

Chest CT did not show an enlarged thymus.

ACHR ab 1.945 (> 1.10 Positive)
 Serum electrolytes - Normal.
 Hb = 14.8g/dl
 WBC Total = 6.04 x 10⁹/L
 Platelet = 154, 000/L
 Urinalysis: pale yellow and slightly cloudy, sugar 4++++, WBC 1-2/hpf
 He was commenced on:
 Tab Pyridostigmine 120mg 8am, 120mg 2pm, 60mg 8pm.
 SC Humulin R 10: 12: 8
 Patient thereafter had thymectomy.

He made remarkable improvement on the first day post op. Speech became clearer and audible. The doses of Pyridostigmine was reduced to 15 mg 8am, 15 mg 2pm, 15 mg 8 pm. On day 3 post op, patient could swallow solid food. Ptosis improved and he also could walk longer distances. Was discharged on day 8 post op. Patient progressively improved even at the first visit op and has been tailed off Pyridostigmine. Histology showed - Thymic hyperplasia.

Discussion

Myasthenia Gravis (MG) is a chronic autoimmune disease that usually manifests in young adults or in the elderly, being characterized by weakness and fatigue of skeletal muscles due to repetitive use [1-6].

It is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscle. The underlying defect is a decrease in the number of available acetylcholine receptors at neuromuscular junctions due to an antibody mediated autoimmune attack.

MG is a rare disorder. World incidence has increased in the last decades going from 2 - 5 /1, 000,000 to 9 - 21/1,000,000 but without proportional increase in mentality. Attacks mainly women in the third and fourth decades of life in the proportion of 3:2 [7]. It is a rare disease among Africans but the prevalence among Caucasian adults vary from 1 in 10, 000 to 50, 000. Has a male predilection after 50 years of age.

Aetiology is related to environmental and microbial agents e.g. HSV, Hepatitis C and other viruses. There is also genetic predisposition. Pregnancy, emotional stress, surgeries, trauma, use of antibiotics suggested as some predisposition factors.

Ocular and palpebral muscle involvement is at times the only manifestation of MG with symptoms of diplopia and palpebral ptosis. These muscles have particularities: They have high blood flow motor units and high mitochondrial content, therefore, have high metabolic rate. With repetitive action of these muscles they are susceptible to fatigue.

Muscle	Percentage of involvement
Ocular	17%
Ocular and bulbar	13%
Mild/moderate	2%
Moderate/severe	11%
Ocular and limbs	20%
Generalized	50%
Mild	2%
Moderate	14%
Severe	15%
Requiring ventilatory assistance	11%
Death despite ventilatory assistance	8%

Table 1: Percentage of Muscle involvement in MG.

Although many aspects of MG still has no convincing explanation, there is no doubt about the immunologic character of the disease, proven by the substantial improvement of patients with plasmapheresis [8,9]. Antibodies usually IgG1 and IgG3 are capable of activating the complement system [10]. The nature of these immunoglobulins indicate that they are T lymphocyte dependent and that Thymic cells type ED4 help B cells in their production [11,12]. Thus in an expressive percentage of patients mainly young ones, the thymus is abnormal [2]. Despite a significant number of patients with thymic involvement, the presence of other sites of formation of these antibodies has been suggested, since patients are clinically improved after thymectomy but not cured [13].

The main focus of these antibodies is without any doubt the neuromuscular junction, site of many drug interactions and intoxications because in this region there is no hematologic barrier [14,15]. Thus similar to MG other autoimmune diseases that also interfere with muscle contraction have been identified, among them we could mention the reaction against calcium channels in Lambert Eaton myasthenic syndrome and against potassium channels in congenital neuromyotonia [10].

Most patients have anti-muscular nicotinic receptor antibodies, and there are those been considered a special group of MG. In such patients antibodies against muscle specific kinase, a molecule in the proximity of the muscular nicotinic receptors that maintains the anatomic integrity of the neuromuscular junction are detected [13]. Note that antibodies in MG do not attack subunits of the nicotinic receptors, explaining the absence of autonomic and central nervous system symptoms [16]. Finally in 10% of patients antibodies are not detected ; however they have satisfactory response to plasmapheresis and injection of plasma from these patients induces MG in animals, suggesting that even though antibodies are not detected by traditional methods, there must be an antibody producing mechanism involved in this type of MG. Clinical evolution, age, involvement of human leukocyte antigen, antibodies against nicotinic, and ryanodine receptors, besides the presence of thymic disease, help classify and predict the evolution of the disease.

Osserman Classification

- Grade I - Focal Disease(restricted to ocular muscle).
- Grade IIA - Mild generalized disease, prominent limb involvement.
- Grade IIB - Moderate generalized disease, prominent bulbar involvement.
- Grade III - Acute severe generalized disease with respiratory symptoms.
- Grade IV - Severe generalized disease with respiratory symptoms.

Challenges

In spite numerous challenges encountered in managing these cases at different stages of Myasthenia gravis, some level of success is achieved. High cost of antibody assays, unavailability of electromyography, paucity of skilled cardiothoracic surgeons, poorly equipped intensive care units and trained intensive care unit anaesthetists; are some of the bottle necks in the management of these patients. All these are part of the problems in a poor political system in these resource poor areas. Immune modulators like azathioprine and mycophenolate mofetil were also employed at some point in the management but could not be sustained, due to high cost. Plasmapheresis and IV immune globulin were not easily accessible in management.

However these patients benefited markedly from thymectomy despite challenges in diagnosis and other modes of treatment.

Conclusion

General outcome of management of Myasthenia gravis will greatly improve with diagnostic aids in low resource countries of the world. Expressive percentage of these patients have thymic abnormality. Early management with thymectomy is helpful.

Bibliography

1. Vincent A. "Autoimmune disorders of the neuromuscular junction". *Neurology India* 56.3 (2008): 305-313.
2. Lang B and Vincent A. "Autoimmune disorders of the neuromuscular junction". *Current Opinion in Pharmacology* 9.3 (2009): 336-340.

3. Lang B and Vincent A. "Autoantibodies to ion channels at the neuromuscular junction". *Autoimmunity Reviews* 2.2 (2003): 94-100.
4. Mann R, *et al.* "Preanaesthetic train of - four fade predicts the atacurium requirement of myasthenia gravis patients". *Anaesthesiology* 93.2 (2000): 346-350.
5. Romi F, *et al.* "Myasthenia gravis: clinical, immunological, and therapeutic advances". *Acta Neurologica Scandinavica* 111.2 (2005): 134-141.
6. Meriggiol MN. "Myasthenia gravis with anti acetylcholine receptor antibodies". *Frontiers of Neurology and Neuroscience* 26 (2009): 94-108.
7. Meyer A and Levy Y. "Geoepidemiology of myasthenia gravis". *Autoimmunity Reviews* 9.5 (2009): A383-A386.
8. Lennon VA and Lambert EH. "Myasthenia gravis induced by monoclonal antibodies to acetylcholine receptors". *Nature* 285.5762 (1980): 238-240.
9. Newsom- David J, *et al.* "Function of circulatory antibody to acetylcholine receptor in myasthenia gravis: investigation by plasma exchange". *Neurology* 28 (1978): 266-272.
10. Meriggiol MN and Sanders DB. "Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity". *Lancet Neurology* 8.5 (2009): 475-490.
11. Protti MP, *et al.* "Immuno-dominant regions for T helper - cell sensitization on the human nicotinic receptor alpha subunit in myasthenia gravis". *Proceedings of the National Academy of Sciences of the United States of America* 8.197 (1990): 7792-7796.
12. Nang, *et al.* "T-cell recognition of muscle acetylcholine receptor subunits in generalized and ocular myasthenia gravis". *Neurology* 50.4 (1998): 1045-1054.
13. Naguib M and Brull SJ. "Update on neuromuscular pharmacology". *Current Opinion in Anaesthesiology* 22.4 (2009): 483-490.
14. Ellison M, *et al.* "Alpha 9 alpha 10 nAChR: structure and identification of key receptor binding residues". *Journal of Molecular Biology* 377.4 (2008): 1216-1227.
15. Saez Briones P, *et al.* "How do acetylcholine receptor Ligands reach their binding sites?" *European Journal of Biochemistry* 265.3 (1999): 902-910.
16. Vernino S, *et al.* "Neuronal nicotinic Ach receptor antibody in subacute autonomic Neuropathy and cancer related syndromes". *Neurology* 50.6 (1998): 1806-1813.

Volume 8 Issue 2 September 2017

©All rights reserved by Ndionuka IB., *et al.*