Proceedings S. Z. P. G. M. I. Vol. 1 (1987), pp. 54–59

A Young Female with Progressive Muscular Weakness

A Case of Myasthesia Gravis

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HISTORY

Mrs. K S. a 28 year old house wife from Wazirabad was admitted in medical ward of Sheikh Zayed Hospital through outpatient department on 4-11-86 with the complaint of

"Progressive weakness for the last 5 months"

She was alright 5 months before admission when she under went a normal vaginal delivery, assisted by forceps, gave birth to normal baby but after puerperium, she started feeling weakness and tiredness more so after exertion. She would feel normal in the morning but became more tired and weak as the day passed and would be maximally troubled with these complaints during evening. She would recover after a night's sleep and follow the same pattern the next day.

Three months ago she started feeling difficulty in opening her eyes at times more so on right side.She felt that her right eye had become smaller. There was also history of blurring of vision and diplopia in the evening which persisted even after correction with glasses.

These complaints were progressive in the sense that they started interfering in her daily activities. First to be involved were the acts consisting of repititive movements, like using a sewing machine.

20 days prior to admission she found herself unable to get up from the sitting position without the help of others. She would walk but was unable to go upstairs. A few days later she was unable to comb her hair as her arms felt tired and weak without any pain. She had no difficulty in writing. She became unable to chew solid foods so was forced to take liquid or semisolid foods. No history of chocking, or nasal regurgitation of food. No history of numbness, paraesthesia, involuntary movements, fever, fits, unconsciousness, body aches and pains. No bowel or urinary complaints. Appetite, sleep and interpersonal relationships remained normal and satisfactory to the patient.

She consulted various doctors for these complaints and received various tablets and injections including Neurobion & Calcium but no improvement.

In the past there was nothing significant, No history of diabetes, hypertension or allergy. She was married for 4 years having two healthy daughters. Family history was not contributory. All family members were quite healthy. She was non smoker, having normal menstrual periods.

On Examination:

A young lady of average built and nutrition, not dyspnoeic, fully conscious and cooperative.

Pulse 88/m regular & normal
B.P. 140/95 mm Hg Temp: 37 ^{o}C RR 18/min.

General physical examination and examination of respiratory system, cardiovascular system and abdomen revealed nothing significant. Her speech was normal. Though most of the time she spoke short sentences and in low intensity voice.

Cranial nerves were intact but there was drooping of eye lids. When she was asked to see upwards, she could not hold her eyes open for more than 30 seconds and in the end drooping occured spontaneously which improved after closing her eyes for few minutes. Drooping also progressed when she was asked to blink continuously for sometime. Pupils were normal. Motor system examination showed no wasting, or fasciculation. Muscle power was equal on both sides but reduced symmeterically grade 3 to 4/5. She could raise the hands above the head but could not hold them even for 15 seconds. Gait was normal but she was unable to stand from squatting position Reflexes were normal. No sensory deficit was noted.

In short this is a young married lady complaining of progressive weakness for the last 5 months which varied

during the day more in the evening with droping of eyelids, blurring of vision, diplopia and difficulty in performing repititive movements for longer time. On examination showing some weakness of all the limbs more marked in proximal parts with normal reflexes and no sensory loss.

Provisional diagnosis:–

Myasthenia gravis

Differential diagnosis:–

1. Myopathy (Thyrotoxic)
2. Eaton Lambort Syndrome
3. Polymyositis

(1) Patient with Myopathy especially limb girdle type or thyrotoxic may present like this but usually proximal muscles are involved and ocular and muscles of mastication are spared. Serum CPK levels and anticholinestrase tests are quite helpful to differentiate. In thyrotoxicosis there are two possibilities.

(a) Patient having simple thyrotoxic myopathy
(b) Patient having thyrotoxicosis and myaesthenia gravis together. Anticholinestrase test is again decisive.

(2) In Eaton Lambort Syndrome patient feels tiredness and weakness during early part of activities and improve with repititive movements.

Anticholinestrase test has little effect while patients show good response to Guanethidine.

(3) Polymyositis e.g. limb girdle syndrome. Patient has muscular cramps, myalgia, raised CPK. Anticholinestrase test helpful. Skin leasions may accompany.

Keeping in view these possibilities patient was investigated.

INVESTIGATIONS

HB% 13.9% E.S.R. 20 mm after Ist hour TLC $6900/mm^3$ P=60% L=32% M=4% E=2% urine examination.

Sp. Gravity 1030
PH = 5
Sugar = Nil
Albumin = Nil
Microscopy = Few WBC/HPF
Blood Urea = 39 mg%
Serum creatine = 0.7 mg%
S.Na^+ = 134 mEq/l
Serum K^+ = 3.4 mEq/l
CPK = 49 U/L (N 10 – 80 U/L)
LDH = 224 U/L (N 230 – 460 U/L)
E.C.G. = Normal

X-rays chest PA and Lateral view showed normal heart size and shape. No pulmonary, mediastinal or pleural leasion seen.

In view of history, clinical features and above mentioned investigations most probable diagnosis came out to be

Myasthenia gravis

To confirm our diagnosis Antiacetylcholine strase test with injection Prostigmine was performed as Edrophonium (Tensilon) was not available. Patient showed very good response and after ½ hr of giving injection she felt quite significant improvement in her muscular strength. Subjectively she also showed positive response. She could hold her hand above head for more than three minutes.

To see the extent of respiratory muscular involvement pulmonary functions test were performed. Following results were obtained before and after giving the treatment i.e. Tab. Pyridostigmine

	Pre treatment	Post treatment
Vital Capacity	1.87 L	2.38 L
Predicted vital capaciaty	3.10 L	3.10 L
% Vital Capacity	60.3 L	76.7 L
FEV_1	1.30 L	1.67 L
FVC	2.05 L	2.80 L
FEV_1/FVC	63.4%	62.8%
PEFR	1.38 L/Sec	1.80 L/Sec

With repeated pulmonary function test before treatment patient showed progressive deterioration in her pulmonary functions.

Myasthenia gravis

It is characterized by progressive weakness of voluntary muscles, more so after exertion and showing recovery after rest. It is an autoimmune disease in which antibodies are formed against motor end plates, causing antigen antibody reaction complement fixation and destruction of cholinergic receptors.

It is of four types:

Type 1 Only occular muscles are involved.
Type 2 Occular and skeletal muscles are involved
Type 3 Along with above respiratory muscles also

affected
Type 4 Myasthenic crisis

It does not involve the smooth muscles so in patients with myasthenia gravis incidence of uterine inertia is same as that of normal population. Myasthenia gravis does not effect pregnancy but pregnancy has some effect on disease process and pt. may require increased dose of drugs during early period of pregnancy and puerperium. During pregnancy patient may show remission of disease process and dose has to be adjusted.

Other investigations which may be done in patient with myasthenia gravis are

(1) Antiacetylcholine receptor antibody detection. These are present in 80% of patients with myathenia gravis but titre does not correlate with severity of the disease.

(2) Anti striatal antibodies may be present in more than 66% of patients with Thymoma but in patient without thymoma incidence is only 10%.

(3) Electromyography: After repeated stimuli patient shows marked decrease in the amplitude of graphs while in Eaten Lambert Syndrome patient show increase in the amplitude of graphs after repeated stimuli.

(4) To rule out thymoma

X-ray chest PA and Leteral view
Radio isotop scan
CAT scan

Among patients with myasthenia gravis only 10% show thymoma and most of them are elderly males.

(5) Investigations to rule out other associated diseases.

(6) Muscle biopsy but electron microscopy is needed.

MANAGEMENT

(1) Avoid precipitating factors e.g.

(a) infections espically respiratory tract.
(b) Drugs e.g. Aminoglycosides
Quinidine
Procainamide
Beta blockers
Curare like drugs
(c) Stress, loss of sleep or any debilitating disease.

(2) Specific Treatment

Pyriodostigmine 60 mg 6 or 8 hourly
or Neostigmine 15 mg 6 or 8 hourly

Dose may be increased according to the response and it is safer to increase the dose after performing anticholine-strase test. If it is positive, increase the dose otherwise not as the weakness in patient with myasthenia gravis may be because of myasthenic crisis or cholinergic crisis.

15 – 20% patient show remission but more than 50-60% show large improvement after proper treatment.

If no response occurs other modalities may be tried e.g.

(1) Corticosteroids
(2) Thymectomy
(3) Immunosuppressive drugs
(4) Plasmapheresis

Corticosteroids
indications are:

(1) Post thymectomy
(2) Patient more than 50 years age and not responding to cholinergics
(3) Patient not fit for surgery
(4) Only occular type as it does not respond to thymectomy

But steriods may increase the weakness in the begining so if we want to start steriods with larger doses patient should be hospitalized, otherwise start with low dose and then increasing gradually till maximum results are obtained then it should be switched on to alternate day. Then it should be decreased very gradually till maximum effect with minimum dosage is achieved.

Thymectomy:
Indications

1. Thymoma — Radiation
Thymectomy

Disease does not show improvement but it may be malignant.
2. Young patient not responding to drugs
3. Repeated episodes of crisis

50 – 80% of patients show improvement after thymectomy usually after 4 – 6 weeks or months

Causes of lack of response to thymectomy are

(a) irreversible damage at myoneural junction
(b) improper surgery
(c) ectopic thymus

Role of Thymus in the causation of disease is not clear perhaps some accetylecholine receptor like material, on its calls, especially thymphocytes, provoking antibody production against acetylcholine receptors at motor end plate.

Immunosuppressive like azathioprine

Plasmapheresis : for transient relief for 6 months to year.
If the patients comes with *myasthenic crisis.*

- admit in ICU.
- Artificially assited respiration may be needed.
- Differentiate between cholinergic or myasthenic crisis.
- Repeated doses of neostigmine with repeated anticholinestrase test
- Antibiotics
- Corticosteroids
- General care of the patient

Pregnancy

Dose of drugs to be adjusted patient may need low or high doses. During labour laocal analgesia should be used and drugs like tranquillizer narcotics should be avoided.

If preeclampsia occurs magnesium sulphate must not be used as it may precipitate myasthenia.

Heart & Myasthenia Gravis

As it is an autoimmune disorder and affecting only skeletal muscles but microscopic involvment of cardiac muscle has been noted. Pt. may have dysarrhythmia, heart failure and non specific ST changes. In patients with crisis transient E.C.G. changes of acute infraction may occur which revert after treatment. Quinidine, procainamide and lidocaine should be avoided. Treatment of choice for dysarrhythmia in patient with myasthenia gravis is cardioversion.

In short this disease is easy to diagnose as we have a test which can be performed first at the bed side but only if it is kept in mind otherwise the patient may be just labelled as functional. As far as management is concerned we will have to manipulate different drugs and avoid unnecessary medication as far as it is possible.

During discussion period following question were raised by FCPS students

DR. ZIA *(FCPS II Std.)* Generally action potential follows the all and none law and its height remains the same where as the end plate potential varies but in myathenia gravis you said that height of action potential is reduced after repeated stimuli. Would you please comment on this controversy?

DR NADEEM: Large number of recepters present at motor end plate are destroyed and reduced so in the beginning available accetylchole stimulate the receptors very well and a strong muscular contraction is obtained in that muscle, but later on only few recepters are available so action potential spreads to less number of muscle fibers and less powerful contraction is obtained. So all the recepters are not producing action potential at the same time.

DR. ZUBAIR QAYUM *(FCPS II Std)* What we are recording on EMG paper is the sum of all the action potentials in different motor units. So action potential does follow the all and non law but what we are recording on the paper is not the action patient but the sum of electrical activity going on in that muscle at that times which decreases with repeated stimuli because of less number of available motor units.

DR. PERVAIZ *(FCPS II Std.)* why urine urobilinogen was advised in this patients?

DR. NADEEM: you are right it was not indicated in this patient but it is done routinely.

DR. ZUBAIR QAYYUM *(FCPS II Std.)* Before performing Anticholinestrase test do you think pt. should be intubated or facilities for intubation must be present at bed side?

DR. NADEEM: He shoud not be intubated but facilities should be present.

DR. PERVAIZ *(FCPS II Std.)* Acetylecholine receptors are present in smooth muscles why they are not affected in myasthenia gravis?

DR. NADEEM: These antibodies are specific against receptors at motor end plate and in case of smooth muscles no motor end plate is present.

PROF. ABDUL HAMEED: *(Prof. Pharmac.)* How cortisone helps in this disease?

DR. NADEEM: Exact machanism is unknown but as it also helps in other autoimmune diseases so does here but it is not evident why it causes the increase in the weakness during early therapy.

DR. NAJAM *(FCPS II Std.)* Myasthenia does not affect the pregnancy but does it effect the foetus and does the antibodies cross placenta?

DR. NADEEM: antiacetylecholine recepter antibodies cross the placenta and thus affect foetus and in about 15% babies of myasthenic mothers neonatal myasthenia gravis is found because of passive antibodies and babies recover after 3–4 weeks.

DR. AWAIS *((FCPS I Std.))* Is Rhumetoid arthritis associated with myasthenia gravis as such or the immune modulating drugs used in rheumatoid afrthritis cause myasthenia gravis?

DR. NADEEM: Like other auto immune disroders rheumetoid arthritis has increased incidence in patient with myasthenia gravis but as far as immune modulating drugs like penicillarnine are concerned they do not causes myasthenia gravis they can precipitate myasthenia gravis.

DR. MAHMOOD: *(Prof. Surg.)* As this disease has increased incidence of association with other auto immune disorder why other tests like LE cell or ANA were not performed in this patient?

DR' NADEEM: Clinically we were not suspecting SLE, Rheumetoid artharities, Thyrotoxicosis or other disorders in this patient. So I think these tests were not required but because of academic purpose these can be done.

QUESTIONS

DR. ZIA *(FCPS II Std.)* What is the incidence of myasthenia gravis in general patients in Pakistan?

DR. NADEEM: Prevalence 2 – 10/10,000 population but exact incidence is not known. Prof. Ashfaq clearified that in Lahore General Hospital which is a 1000 bedded hospital incidence reported is 20 – 30 per year.

DR. ABDUL RAUF (Anaesthesia) We usually use Tubocurare in anaethesia so if it is used in an undiagnosed patient what should be our line of management.

DR. NADEEM: Patient should be treated in the sameline as myaesthenic crisis as minor dose of curare like drugs can cause complete paralysis in such patients.

DR. ABDUL RAUF: Is there any effect of suxamethonium

DR. NADEEM: I do not think so.

PROF. ABDUL HAMEED: Suxamethonium has different mechanism of action it is ultrashort acting muscle relaxant and it can further aggravate the condition.

COMMENTS OF PROFESSORS

DR. ANWAAR *(Gastroenterologist)* In patients with mysthenia gravis upper part of oesophagus may be involved causing dysphagia and in older patient aspiration pneumonia so while manging the patient this should be kept in mind.

PROF. G. A. SHAH *(Prof. Ortho)* "Do you mean pharyngeal muscles or oesophagus?

DR. ANWAAR: "Upper part of oesophagus is also voluntary muslce"

DR. IFTIKHAR UL HAQ QURESHI *(Cons. Opth.)* Eye involvements is an essential feature of myasthenia gravis and most often the ophthalmologist pick up the case and we train our residents to do tensilon test to confirm it. As far as the management of occular side is concerned, the ptosis gets better with treatment but other extra ocular muscle may not respond so well and involvement is also assymmetrical. Intraocular are spared. If diplopia persists we may offer just covering the one eye later see the recovery. Steroids may be used. Children may present with ptosis.

DR. GHAZALA *(Cons. Gynae & Obs.)* During the second stage of labour one must be careful and forceps delivery may be needed and regarding first stage of labour it is advisable not to use sedatives. As far as forceps delivery is concerned I think it is because of weakness of accessary muscle (abdominal) not because of uterine muscular weakness.

DR. SAJID MAQBOOL *(Paediatritian)* Neonate may present with myaesthenia (transient) because of passive disease which recover after 4 – 6 weeks. In older children we may get it but process is not exactly the same.

DR. MUHAMMAD IQBAL *(Pulmonologist)* Like any neuromuscular disease, myasthenia gravis also affects the respiratory muscles and patient suffer from type II respiratory failure i.e. they cannot blow out their carbon dixide and CO_2 retension occur.

On bed side clinician should diagnose it by counting the number in a single breath. Normal healthy person can count up to 50 but if it starts decreasing and is near 20 it is indicative of grave signs and show involvement of respiratory muscle especially diapharagm.

Second test is vital capacity, if it decreases successively and is 1.5 L it is again a grave's sign. And if facilities for blood gasees are there, that should be done and if there is CO_2 retension especially with thymoma artifical respiration should be started.

DR. DURRANI *(Ophthalmologist)* 10 – 15% of myasthenia gravis patient present to ophthalmologist and trasient diplopia may be the presenting symptom. Other 40–50% patient may show features of other skeletal muscle involvement. In younger patients females are preponderant and over that age no sex difference. Before tensilon test another coinical test is done by the ophthalmologist. It is to keep the finger in front of patient and ask him to follow it, you can see the weakness coming there. After that tensilan test may be performed to cofirm it and some people inject Atropine before it, others just keep it ready and tensilon is given in gradually increasing doses. Side effects may be bradycardia. G.I. T symptoms and respiratory distress.

PROF TAHIR SHAFI *(Neprologist)* Haemodialysis has shown good effect on myaesthenia gravis as those patients who suffer from renal failure with myasthenia gravis when haemodialysis is done they show improvement in myasthenia also which is longer than the tensilon test.

Plasmapheresis is also effective especially in patient who do not show good response with other drugs like corticosteroids and even after thymectomy..

PROF. ASHFAQUE A. KHAN *(Cardiologist)* Effect on Heart was mentioned. As far as I know microsscopic involvement of the heart muscle per se is very rare but secondary involvement because of respiratory involvement and chronic hypoxia corpulmonale like syndrome the heart may show E.C.G. changes.

FINAL COMMENTS

PROF. M.A.Z. MOHYDIN *(Prof. Med.)* I think this case has been so well discussed that actually nothing has been left for me to discuss but it shows the magnitude of this illness that you could have each and every specialist to take part in it. But the basic lesson which we have learnt from it is that this is a patient who developed weakness after delivery. Then finally when ptosis and diplopia appears the case is easily diagnosed even by young doctor. Point of importance is that when a patient comes with history of undue weakness, we should keep myasthenia gravis at the top of list and subject the patient to tensilon test. Because if we do not consider we are likely to miss the diagnosis and if we over do it, it will cause unnecessary tensilon test and increasing failure. So while considering the diagnosis, history, patient's personality, & patients general health should be considered.

Second point is that drugs like Quinine for malaria may precipitate it. Other drugs like quinidine, procainamide and aminoglycosides must be given cautiously.

Regarding use of steroids basic principle is that they suppress immunity like in other auto immune disorders and sterorids also cause myopathy and muscular weakness. Patient in crisis or resistant case require much larger dose of steroids.

As far as primary cardiomypathy is concerned, auto immune diseases are described as a group causing primary cardiomyopathy. Though specifically myasthenia gravis has not been mentioned in literature but this comes under the wide range of auto immune diseases.

I agree with Dr. Mahmmod that certain other tests like ANF LE cell must have been done in this patient.

Thymus gland has got a funny factory and at times it causes antibody production against specific cells like RBC and pt. may improve with thymectomy. Regarding the further management of this lady she is suffering from an auto immune disorder which is precipitated by pregnancy We must look into her general health, care for infection and follow her up. In other words there is no cure and it is just supportive treatment.