

Oculobulbar Myasthenia Gravis in an Octogenarian

Olayinka A. Ogundipe^{a, b}, Alka Joshi^a, Helen E. Jones^a

Abstract

This case describes an 89-year-old lady presenting with ‘slow progress with rehabilitation’ following the surgical repair of an osteoporotic hip fracture. She was noted to have symptoms and signs of insidious onset and of a progressive nature that were subsequently attributed to oculobulbar myasthenia gravis. The patient was seropositive for the acetylcholine receptor (AChR) antibody and also had features consistent with myasthenia gravis on a single fibre electromyography. She showed good clinical response to oral pyridostigmine and subsequently completed her rehabilitation and discharge planning uneventfully. A discussion on the basic epidemiology, clinical presentation, evaluation and treatment options for myasthenia gravis is presented.

Keywords: Acetylcholine receptors; Antibody; Frail elderly; Myasthenia gravis; Neuromuscular junction; Pyridostigmine bromide; Rehabilitation

Introduction

Myasthenia gravis (MG) is the commonest acquired disorder of the neuromuscular junction. MG is characterised by fluctuating skeletal muscle weakness that worsens with repetitive activity (fatigability), and tends to improve with rest. The condition is often noted to have an autoimmune basis. The onset of MG exhibits a bimodal pattern. Most patients present in the 20 - 40 year age range, but it is also recognised to occur as a late-onset presentation (> 50 years). The major-

ity of cases are seropositive for post-synaptic acetylcholine receptor antibodies or muscle specific kinase antibodies.

We report the rare case of an octogenarian who was diagnosed with oculobulbar MG in the context of slow progression with rehabilitation following major surgery for an osteoporotic hip fracture. With globally increasing life expectancy, this case offers a timely clinical reminder of the need to be aware that MG can present newly in the very elderly (> 85 years) population. Further investigation and treatment can be tailored to the specific patient. The institution of appropriate pharmacological treatment can potentially transform both the functional capabilities and the quality of life of an older patient.

Case Report

An 89-year-old caucasian lady was admitted to hospital following a fall resulting in a fracture to the left femoral neck that required surgical repair. The post-operative period was complicated by delirium. The delirium resolved following treatment of an *Escherichia coli* urinary tract infection with oral trimethoprim, and subsequently a hospital acquired pneumonia that was treated with IV piperacillin/tazobactam.

Her medical history was notable for ischaemic heart disease, hypothyroidism, peptic ulcer disease, iron deficiency anaemia and osteoporosis. She was a non-smoker and teetotal. There was no family history of relevance. Prior to admission she had lived on her own and was independent with activities of daily living.

Her medications (all oral) on admission included aspirin 75 mg daily, levothyroxine sodium 100 µg daily, omeprazole 20 mg daily, ferrous sulphate 200 mg three time daily, Adcal-D₃ 1 tablet twice daily, and alendronate sodium 70 mg weekly. Post-operatively, she was prescribed oral paracetamol 1 g four times daily, oral codeine phosphate 30 mg four times daily and subcutaneous dalteparin sodium 5,000 units daily.

Following recovery from the acute phase of her illness, she was transferred from the trauma orthopaedic unit to an orthopaedic rehabilitation unit. Her progress with rehabilitation was slow on account of ‘easy fatigability’.

About four weeks into her period of rehabilitation (about

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^aDepartment of Medicine of the Elderly, Royal Infirmary of Edinburgh, Edinburgh, Scotland, EH16 4SA, UK

^bCorresponding author: Olayinka A. Ogundipe, Department of Medicine of the Elderly, Royal Infirmary of Edinburgh, Edinburgh, Scotland, EH16 4SA, UK. Email: ola_ayodele@hotmail.com

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eight weeks post-operatively), she complained of difficulty keeping her eyelids open whilst reading her daily newspaper. This was initially difficult to appreciate on bedside assessments but the clinical features evolved progressively over the subsequent four weeks. She was noted to develop partial ptosis with mild bifacial symmetric weakness which worsened towards the end of the day. Her speech was noted to become increasingly dysarthric during conversation, and there was a degree of lisping and hypernasality to the speech. She reported mild dysphagia to solids and required modification to a soft diet. Assessment revealed no dysphasia, muscle wasting, fasciculations, sensory deficits or sphincteric symptoms.

Myasthenia gravis was suspected clinically. A serum sample was sent for an Acetylcholine Receptor Antibody (AChR Ab) assay. She was reviewed by neurologists. In addition to the features described earlier, the neurologists noted eye movement fatigue, but no diplopia or nystagmus. There was slowness of abduction of the left eye on saccades. Pupils were normal sized and reactive. Normal reflexes were present to the limbs and jaw jerk reflex was negative. Testing of power to the extremities noted mild proximal upper limb weakness. The distal muscles groups were fatigable. The neurologists entertained a clinical diagnosis of (predominant) oculobulbar myasthenia.

Her haemoglobin level was 83 g/L with a mean corpuscular volume (MCV) of 74 fL. White cell and platelet counts were normal. A chest x-ray was normal. Clinical breast examination was normal. Fasting blood sugar, renal function, thyroid function, sodium, potassium, calcium, magnesium, serum protein electrophoresis, erythrocyte sedimentation rate, creatine kinase, vitamin B₁₂ and folate levels were unremarkable. Alkaline phosphatase was mildly elevated at 284 in keeping with a healing fracture; otherwise the liver function tests were normal. Her serum 25-OH vitamin D level was normal. Electrocardiogram showed sinus rhythm with a left anterior hemi-fascicular block.

The AChR antibodies returned marked elevated at 221 (immunology laboratory reference range 0 - 5 × 10⁻¹⁰M). A computerised tomography scan of her chest revealed the absence of an anterior mediastinal soft tissue mass that would have suggested the presence of a thymoma. An osteoporotic wedge fracture of the 12th thoracic vertebra was noted incidentally. Single fibre electromyography (SFEMG) showed clear increased 'jitter' in the right extensor digitorum communis in keeping with a diagnosis of myasthenia gravis.

Treatment was commenced with oral Pyridostigmine bromide which was titrated from 15 mg up to 60 mg four times daily with good clinical results. She noted marked improvement to the bilateral ptosis, resolution of the dysarthria, improvement in the dysphagia, less levels of fatigue, increased exercise tolerance, and improved mobility. Her Forced Vital Capacity (FVC) was 0.85 L prior to introduction of the oral pyridostigmine. Following institution of

treatment, the FVC progressively improved to 1.56 L, and subsequently to 1.68 L although all the results were potentially influenced by poor technique.

Subsequent progress with rehabilitation was uneventful and progressed rapidly within a short period. She was discharged home mobilising with a wheeled frame, and with some equipment and additional support to supervise aspects of personal care at home.

Discussion

Brief historical background and variants of the myasthenic syndromes

Myasthenia Gravis (MG) is a neuromuscular disorder that often follows a chronic and progressive course, and is essentially caused by a deficiency of acetylcholine at the neuromuscular junction [1-3].

In its commonest form, MG is acquired and characterised by the presence of antibodies against the post-synaptic acetylcholine receptor at the muscle surface.

More rarely, congenital forms of the myasthenic syndromes have also been described and can be inherited. Phenotypic variants vary depending upon which protein mutations are present in the neuromuscular junction [2, 3].

A distinct and also less common disorder, the Lambert-Eaton myasthenic syndrome (LEMS) is an acquired autoimmune myasthenic condition, often characterised by the presence of antibodies against the pre-synaptic voltage-gated calcium channels. LEMS can also be associated with paraneoplastic presentations (for example, small cell lung carcinoma) [2, 3].

Possibly one of the earliest reported cases of MG was around 1664, with reference to the death of the Native American Chief Opechancanough [1]. The English physician, Thomas Willis is often attributed as being the first to describe a female patient with "fatigable weakness" involving the ocular and bulbar muscles in 1672. The term "myasthenia gravis pseudo-paralytica" was first employed by Jolly, who presented two cases at the Berlin Society meeting in 1895 [2]. In 1959 - 1960, Nastuk et al proposed an autoimmune aetiology for MG [3].

Basic epidemiology

Myasthenia gravis (MG) has an estimated prevalence varying widely between 25 and 142 per million, and is the most common disorder of the neuromuscular junction [2, 4]. MG is described as having a bimodal curve for its age of onset. Approximately 60% of the patients develop MG between the ages of 20 and 40, and a further age peak for late-onset (> 50 years) cases of MG occurs between the ages of 70 and 80 years [5]. In addition to age, another epidemiological asso-

ciation in the prevalence of MG appears to be gender. Below 40 years of age, the female:male ratio is about 3:1; however over 50 years of age, it occurs more commonly in males [6].

However, over the last few years there has been an increasing incidence of MG being diagnosed in patients over the age of 60. This increase is thought to be most likely due to both improved diagnosis and a longer life expectancy. However, a recent study demonstrated that despite this perceived increase, MG may still be substantially underdiagnosed in the very elderly. This could be partly due to it being misdiagnosed as another neurological condition (such as delayed stroke related disease presentations), or due to its being overlooked altogether. In particular, the ocular symptoms can be difficult to appreciate or not readily detected clinically, or they might be inappropriately attributed to being features of ageing [7, 8]. A similar experience was noted in relation to the initial subtle ocular symptoms in this index case, with the evolution of the patient's symptom profile ultimately facilitating diagnosis.

MG has been described in association with other autoimmune conditions, for example, Hypo-/Hyperthyroidism, Rheumatoid Arthritis, Type 1 Diabetes Mellitus [2]. This index case was on treatment for pre-existing hypothyroidism, but this appeared to be optimally treated (both clinically and biochemically).

Pathophysiology

Autoimmune MG is a multifactorial disease and even though it shows limited heritability, it appears to be significantly influenced by some identified genetic factors [9]. MG has been associated with some human leucocyte antigens including HLA-DQB1*05:02 and DRB1*16 [10].

Two antibodies have classically been associated with the pathogenesis of MG: the post-synaptic acetylcholine receptor (AChR) antibodies and the muscle specific kinase (MuSK-MG) antibodies. AChR antibodies are harboured in about 85% of patients with MG [11] and the remaining patients are referred to as being 'seronegative' for AChR antibodies; of which about 40-70% possess antibodies against MuSK-MG [12]. The MuSK-MG positive patients can present with predominantly bulbar muscle weakness and some patients may be refractory to conventional treatments [12]. In general, seronegative forms of MG are less common in the older age ranges. This index case in an 89-year-old lady was positive for AChR antibodies.

The thymus represents a central organ in the human immune system, and plays a key role in the initiation of the autoimmune cascade response to AChR. The thymus gland may be hyperplastic with a germinal centre in about 85% of MG cases, and may harbour a thymoma in a further 10% of MG cases. Thymic atrophy might be found in some patients, and particularly in late-onset MG [13]. It has been postulated that some cases of MG can be induced by infections

(for example, Herpes simplex, Hepatitis C), and some drugs (notably the anti-rheumatic agent D-Penicillamine) have also been implicated in the pathogenesis of a variant of the disease [14].

Clinical presentation

Clinically, MG is characterised by fluctuating skeletal muscle weakness that is worsened with repetitive activities (namely, fatigable), and improved with rest.

Ocular muscle weakness manifesting as diplopia and ptosis is by far the most common initial presentation. Fifteen percent of patients have purely ocular involvement, whilst the remaining 85% may progress into generalised muscle weakness predominantly affecting the proximal muscle groups. In Bulbar MG, there is involvement of the facial muscles, muscles of mastication and swallowing. Furthermore, involvement of the diaphragmatic muscles can be life threatening (myasthenia crisis), sometimes necessitating tracheal intubation and naso-gastric (NG) tube feeding [14].

Predominantly oculobulbar features were noted in this index case report, but her breathing was not comprised. She required a period of revision to the texture of oral food on account of mild dysphagia, and this subsequently improved with pharmacological treatment for the myasthenia.

The muscular weakness of MG has a fluctuating pattern and is often aggravated by exposure to heat, infection, and stress [6]. This index case had recently undergone major surgery with general anaesthesia, and had recovered from post-operative urinary and respiratory tract infections. These could be considered potential triggers or aggravating factors in the onset of the MG. 'Easy fatigability' had been noted as a possible reason for her 'slow progression with rehabilitation', but this had initially been attributed to the iron deficiency anaemia and to ongoing convalescence from the post-operative medical complications. In retrospect, it became clearer that MG was contributory to the initial slow progress with rehabilitation; particularly when judged in the context of her subsequent good progress following institution of treatment with Pyridostigmine.

In ladies of child-bearing age, flare ups of MG symptoms are more likely during the first trimester of pregnancy and in the first month postpartum. In 20-40% of patients, an improvement in symptoms has been seen in the second and third trimester [15].

In addition to the earlier mentioned D-Penicillamine, further examples of drugs which are known to aggravate MG symptoms include antibiotics like the aminoglycosides (for example, Gentamicin and Neomycin) and macrolides (Clarithromycin and Erythromycin), antimalarial agents (for example, Chloroquine, Quinine and Mefloquine), beta blockers, lithium carbonate, other rheumatological agents (Hydroxychloroquine and Colchicine), magnesium containing antacids and laxatives [14, 16].

Investigations and diagnosis

Immunology

Around 50-60% of patients with ocular symptoms, and 85% to 90% of those with widespread symptoms have antibodies directed against AChR, making it a reasonably specific serologic test [17]. Titres tend to be highest in those with a thymoma; however high levels do not show a direct positive correlation with disease severity.

Antibodies to muscle-specific tyrosine kinase (MuSK) can be identified in over 40% of patients who are negative for AChR antibodies. MuSK-positive disease can occur at any age but it seems to be more common in younger patients [8, 18].

Neurophysiology tests

Electromyography (EMG) may elicit a decremental response at low frequency, with nerve stimuli falling > 10% being considered abnormal on repetitive stimulation [19]. Single fibre EMG tends to be more sensitive, with an increase in 'jitter' response particularly in the weak muscles [19]. However, SFEMG is described as being technically more difficult to perform, requires highly trained personnel and has the potential to give some false positive results with other neuromuscular conditions (for example, motor neurone disease) [20-22]. The SFEMG in this index case showed a result consistent with myasthenia gravis.

Edrophonium test

The Tensilon (Edrophonium Chloride) test is performed by intravenously injecting Edrophonium, a short acting cholinesterase inhibitor that prolongs the action of acetylcholine at the neuromuscular junction by inhibiting its breakdown [20, 21]. Following administration, those with MG should have a noticeable improvement in muscle power which lasts for about 2 minutes. Resuscitation equipment and atropine should be easily accessible as there could potentially be over activity of the cardiac muscarinic receptors leading to life threatening bradycardias, especially in the elderly [21]. To help prevent this, oral acetylcholinesterases should be withheld. Due to some of the highlighted safety concerns, some do not favour this test being performed routinely. The index case was not tested with Edrophonium due to her background history of ischaemic heart disease.

Ice pack testing

Unlike some of the other investigations, the 'ice pack test' can be undertaken at the bedside and performed in a couple of minutes. It consists of applying 'covered' ice (to prevent sticking onto the skin) to the eyelids for 2 - 5 minutes. The

test is considered positive if the characteristic ptosis resolves or if the patient's diplopia improves [23]. It is thought that by cooling the muscle fibres acetylcholinesterases are inhibited, and thereby increasing the availability of the neurotransmitter acetylcholine [23].

Radiology

All patients with suspected myasthenia gravis should have a thoracic imaging study (for example, a CT or MRI scanning of the mediastinum) to exclude the presence a thymoma, as this can easily be missed on a plain radiograph [19, 21]. The index case had a normal CXR, and she did not have a thymoma on CT scanning.

Pulmonary function testing

Serial spirometry testing (especially vital capacity) might prove useful in the assessment and monitoring of breathing and respiratory reserve in patients with MG. The spirometry in this index case was noted to improve progressively following introduction of treatment with pyridostigmine.

Treatment

Pharmacotherapy

1) Acetylcholinesterase (AChE) inhibitors

The first-line treatment option for the symptomatic management and maintenance therapy of MG are acetylcholinesterase inhibitors. Pyridostigmine bromide is the most commonly used drug due to its better pharmacodynamic profile and tolerability compared to other acetylcholinesterase inhibitors such as Neostigmine [24]. The index case responded well to treatment to a titrated dose of oral Pyridostigmine.

2) Immunosuppression/Immunomodulation

Immunosuppressants like corticosteroids (oral prednisolone) are used on a short-term basis in the treatment of MG. Corticosteroids act by interfering with the activation of T-cells [25]. Drugs like Azathioprine, Cyclosporine and Methotrexate are used for longer term immunosuppression [21, 24]. Intravenous immunoglobulins (IVIg) and Plasmapheresis are used in myasthenia crisis; or when temporary improvement is required, or as a method of stabilising MG before surgery [26, 27]. Steroids were not used in this index case due to the recent osteoporotic fracture, and immunosuppressive therapy was not deemed to be clinically indicated.

Surgery (Thymectomy)

Thymectomy plays a significant role in the management of

patients with MG at all stages of the progressive disease. It is associated with high improvement rates, and has low surgical mortality and morbidity [28].

The surgical approaches are generally trans-sternal (commonest), trans-cervical (minimally invasive option) or trans-thoracic. However despite removing the thymus gland there have been cases of individuals developing serum antibody against AChR and symptoms of MG [29].

In general, the benefits of thymectomy might be more significant in younger patients < 50 years, and possibly in those with symptom duration of less than 2 years [21, 28].

Somewhat more controversial is the debate around the benefit(s) of potentially improving upon the clinical status of patients, versus the potential risk(s) of exacerbating the condition, when thymectomies are performed in patients without a thymoma. Although the underlying mechanism is not completely understood, it may involve the disruption of B-cells producing AChR antibodies. It has also been suggested that thymectomy is beneficial for cases of ocular MG [24].

In malignant thymoma, radiotherapy with or without chemotherapy has also been well recognised as adjuvant therapy to thymectomy [30].

Prognosis

Due to advances in medical care, surgical techniques and pharmacological developments, the prognosis of MG has been dramatically improved. However, spontaneous remission is still relatively uncommon and possibly in the region of < 10% in the autoimmune variants [6, 21, 31].

MG can show a fluctuating symptom profile, which along with some potential side-effects of the various treatment options, can translate to variations in both quality of life and functional capabilities, particularly in (frail) older patients.

Key points

1). Myasthenia gravis is the commonest autoimmune disorder of the neuromuscular junction [32, 33]; 2). MG can be newly diagnosed even in the very old patient (> 85 yrs); 3). Fifteen percent of patients have purely ocular involvement; with the remaining 85% variably progressing into more generalised muscle weakness patterns that predominantly affect the proximal muscle groups [32, 33]; 4). Two antibodies in particular have been associated with pathogenesis of MG; the post-synaptic nicotinic acetylcholine receptor (AChR) antibodies, and the muscle specific kinase (MuSK-MG) antibodies [21, 34, 35]; 5). The acetylcholinesterase (AChE) inhibitors (for example, oral Pyridostigmine) [36] are the first-line treatment option for the symptomatic management and maintenance therapy of MG. They are often well tolerated and tend to have good clinical effect. There may be a role for the selective avoidance of potential trigger medica-

tions, immunosuppression/immunomodulation and thymectomy.

Author Contributions

OAO conceived the idea for the article. OAO, AJ and HEJ contributed to the preparation, critically review and editing of the manuscript. All authors approved the final version.

Conflicts of Interest and Source of Funding

None.

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