NEUROLOGICAL RARITY

Myasthenia gravis w

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Practical Neurology, 2005, 5, 356–359

INTRODUCTION

Antibodies to the muscle acetylcholine receptor (AChR) are present in about 85% of patients with generalized myasthenia gravis, and 50% of patients with just ocular symptoms. However, up to 70% of the myasthenia patients without AChR antbodies, so called 'seronegative' myasthenia gravis, have antibodies to the muscle specific tyrosine kinase (MuSK). MuSK is another protein at the postsynaptic membrane of the neuromuscular junction, and plays a role in agrin-induced AChR clustering (Hoch *et al*. 2001). These patients may be difficult to recognize, and difficult to treat effectively. Here we describe four AChR antibody-negative/MuSK antibody-positive patients as examples.

Table 1 Features of four patients with MuSK-myasthenia gravis, and comparison with AChR positive myasthenia gravis

CASE	SEX	AGE AT ONSET	PRESENTING FEATURES	DIAGNOSIS	TREATMENTS REQUIRED	OUTCOME
1	F	30	Diplopia, dysarthria, dysphagia	EMG positive	Immunoabsorption, steroids, azathioprine, cyclophosphamide, mycophenolate, rituximax (Figure 1)	In remission on pyridostigmine and cyclosporin (reduced dose)
2	F	3	Facial, ocular, bulbar	EMG positive	Plasma exchange, steroids, azathioprine, cyclosporin	Persistent facial and tongue wasting, atrophy and fatty replacement on MRI.
3	F	57	Diplopia, dysphagia, no fatigue, flat affect	EMG negative	Steroids not tolerated, pyridostigmine only	Improved bulbar and respiratory symptoms
4	F	77	Dysphagia, generalized and ocular, neck and respiratory weakness	EMG positive	Azathioprine not tolerated, steroids	Improved bulbar and respiratory symptoms
Typical AChR antibody-positive			May be ocular, limb, respiratory and/or bulbar	EMG positive	Steroids and azathioprine often suffice. Some patients < 40 years may benefit from thymectomy	Usually improve or go into remission. Few are difficult to treat. Muscle atrophy uncommon

ith MuSK antibodies

THE CASES (SEE TABLE 1)

Case 1

This patient had an age at onset and clinical presentation typical of myasthenia gravis but was difficult to treat. She was a 30-year old woman who developed diplopia, dysphagia and dysarthria during the third trimester of her first pregnancy. EMG showed a defect of neuromuscular transmission and she improved transiently on pyridostigmine (180 mg/day). The pregnancy was terminated by Caesarean section after she developed pre-eclampsia. The baby showed only mild transient signs of neonatal myasthenia. The patient was managed with intravenous immunoglobulin for progressive oculopharyngeal myasthenia and started on conventional immunosuppression with prednisolone and azathioprine. However, she suffered a severe myasthenic crisis, which required two courses of immunoadsorption of IgG antibodies (on a Protein-A column) and six courses of intravenous cyclophosphamide to induce a remission. The remission was sustained for several months, and prednisolone was tapered. She developed a rash, attributed to azathioprine which was replaced by mycophenolate. However, she began to deteriorate and 17 months after onset, despite three further courses of cyclophosphamide, she had another crisis that was treated with immunoadsorption and increased steroids. Four weekly treatments were given with anti-CD20 (rituximab), and mycophenolate was replaced with cyclosporin to maintain the remission. The symptoms then stabilized quite quickly and prednisolone was slowly

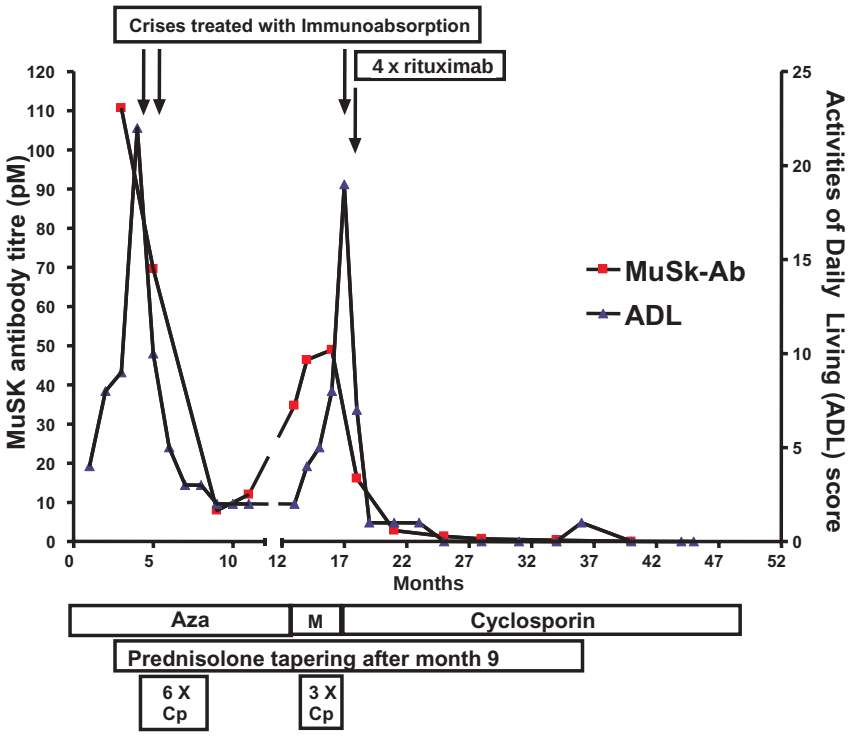

Figure 1 The clinical course and treatments required in case 1 illustrate a particularly difficult case of MuSK-myasthenia gravis in a 30-year-old woman. After treatments with IVIg (not shown), cyclophosphamide, azathioprine, steroids and mycophenolate, she eventually went into a stable remission following treatment with anti-CD20 (rituximab) and cyclosporin, despite discontinuation of prednisolone. The MuSK antibodies, retested using 0.025 µL of each stored serum, generally correlated well with score activities of daily living (Wolfe *et al*. 1999). Unfortunately there was no sample available at the peak of the second crisis. Cp, cyclophosphamide; M, mycophenolate.

tapered again. The patient is still on pyridostigmine and cyclosporin, has been in pharmacological remission for more than 2 years, and has now returned to work. Recently, the dose of cyclosporin was reduced because of raised blood pressure but no other adverse effects have occurred so far. Figure 1 shows her MuSK antibodies and the Activities of Daily Living score over the period of study. MuSK antibody levels were very high at onset and appeared to peak before the second crisis; they have now declined to control values.

Case 2

This patient was unusual in presenting in early childhood and the development of persistent facial muscle and tongue atrophy. She presented with severe facial weakness at the age of 3 years, and subsequently developed a squint and nasal speech. Single fibre EMG when she was 14 years old was positive and to establish whether she had an acquired form of myasthenia, she underwent plasma exchange, resulting in clear clinical improvement, and was started on corticosteroid treatment. As soon as her condition stabilized, she was weaned off steroids but at the age of 15 her symptoms relapsed with profound facial weakness and moderate axial and limb weakness. Steroids were reintroduced and she was started on azathioprine as a steroid-sparing agent, but she failed to respond to the latter so this was switched to cyclosporin to which, together with prednisolone, she responded well. Although her axial and limb problems have been, until recently, in remission, her severe facial weakness persists, and she has marked nasal speech, although no dysphagia for solids or liquids. Strikingly, she has severe wasting of the tongue with a triple furrowed appearance, and MRI of the facial and tongue muscles has confirmed muscle atrophy, with abnormal high signal replacing most of the intrinsic tongue musculature (Fig. 2).

Case 3

This illustrates the diagnostic difficulties in a less severely affected older patient, and the importance of the MuSK antibody assay. She presented at age 57 complaining of diplopia, gait unsteadiness and dysphagia to solids with no regurgitation of fluids, extreme fatigue and loss of weight. She was noted to have a partial gaze palsy to the left with limited upgaze, but there was no ptosis and no features of fatigability. The tensilon test was negative, she did not respond significantly to oral acetylcholinesterase inhibitors, and single fibre EMG studies of both orbicularis oculi and extensor digitorum communis were normal. Thus, there was no objective evidence of myasthenia. Nevertheless, her MuSK antibody titres were clearly elevated. On steroids she developed a severe depressive illness, and she was then managed with pyridostigmine alone. Her symptoms have now resolved and she is off all treatment.

Case 4

This patient presented in later life. She suffered from increasing dysphagia and associated choking episodes at the age of 77 years. This progressed to generalized weakness with dyspnoea, bilateral ptosis, diplopia and moderate neck flexion weakness. She went into type II respiratory failure, at which time single fibre EMG demonstrated increased jitter in both orbicularis oculi and extensor digitorum communis. The patient was treated with a course of intravenous immunoglobulin and started on steroids and azathioprine. She required ventilatory support from which she was later successfully weaned. Unfortunately, she was intolerant of azathioprine because of hepatic enzyme derangement. She was discharged from hospital with her bulbar and respiratory symptoms having improved significantly and she continues to be managed with corticosteroids.

DISCUSSION

These four cases illustrate the main features of MuSK-myasthenia gravis. Typically patients are young females presenting between 10 and 40 years of age. However, about one in eight pa-

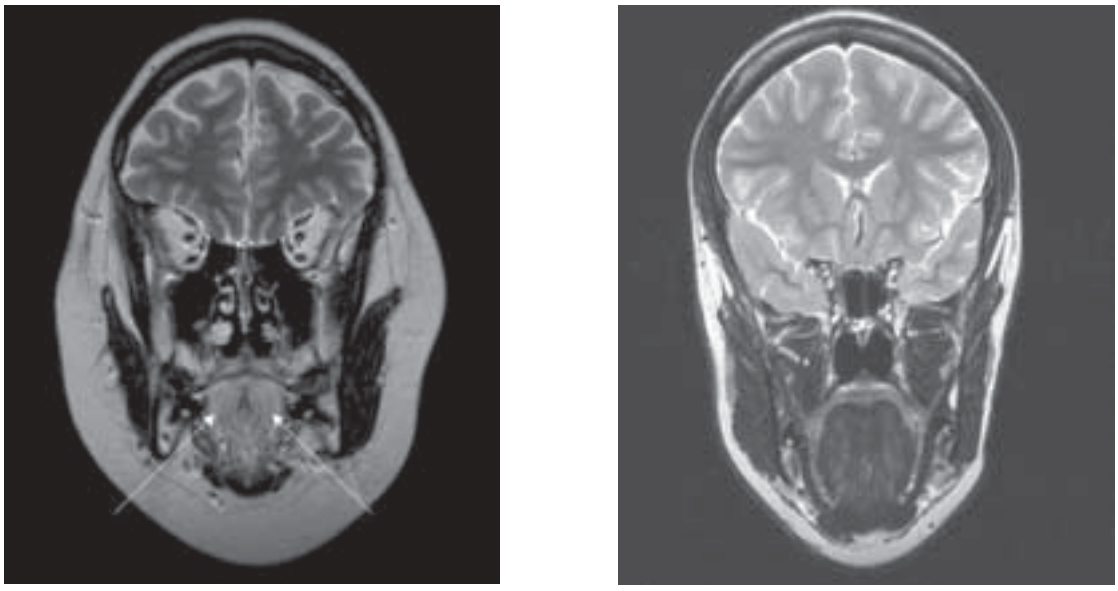

Figure 2 MR T2-weighted coronal sequences showing atrophy and fatty infiltration (high signal) in the tongue of case 2 (left), compared with normal appearance of healthy individual (right).

tients are male (Vincent, unpublished data) and, with increased awareness of the disorder by neurologists, older cases are now being identified (cases 3, 4). The patients often present with bulbar and ocular symptoms, but profound neck or respiratory weakness without other signs may occur (Sanders *et al*. 2003; Zhou *et al*. 2004; Melms A, unpublished). Limb and axial muscle involvement may be present in the acute phase of disease, but is seldom severe and usually responds readily to treatment. These patients can deteriorate rapidly (as in case 1 and 4), relatively frequently requiring ventilatory and nutritional support. Dysphagia and weight loss may at first suggest motor neuron disease (Case 4), and some patients may not complain of typical myasthenic fatigue (Case 3).

It is important to note that, in contrast to AChR antibody-positive patients, the tensilon test may be only weakly positive. Also, single fibre EMG studies on limb muscles may be normal at presentation, as in case 3, and this has been noted frequently in patients studied following treatment (Nemoto *et al*. 2005; Farrugia *et al*. in preparation). Muscle atrophy, particularly of the facial and bulbar muscles, seems to be a relatively common long-term consequence of the disease (Evoli *et al*. 2003; Sanders *et al*. 2003; Fig. 2), perhaps because the condition can be relatively difficult to treat effectively, frequently responding poorly to steroids and azathioprine and sometimes requiring other immunosuppressive agents (cases 1 and 2). It has also been noted that the patients may not respond well to acetylcholinesterase inhibitiors (Evoli *et al*. 2003; Sanders *et al*. 2003); ambenonium chloride (mytelase) may be tolerated better and can be helpful in some patients (A Melms, unpublished observations). None of these four patients were treated with thymectomy, which is of doubtful benefit in MuSK antibody-positive cases. In fact, two recent studies have shown that the histology of the MuSK-MG thymus is normal or near normal (Lauriola *et al*. 2005; Leite *et al*. 2005).

There are many unanswered questions about MuSK antibody-associated myasthenia gravis. It is not clear what role MuSK plays at the mature neuromuscular junction, or even whether MuSK antibodies cause disease. AChR numbers at the neuromuscular junction appear normal (Selcen *et al*. 2004; Shiraishi *et al*. 2005), and there is little complement deposition, probably because the MuSK antibodies are predominantly IgG4 which does not activate complement (McConville *et al*. 2004). Although originally reported in 70% of AChR antibody-negative patients, in a prevalence study performed in Oxford, the proportion of MuSK antibody-positive sera within AChR antibody-negative sera from different populations worldwide varies between 0 and 50%, perhaps reflecting an environmental or genetic susceptibility factor (Vincent *et al*. in preparation). All these observations have led to some concerns about the relevance of MuSK antibodies. Nevertheless, they are very rare (< 1 : 700) in community controls, and have not been found in any of > 200 AChR antibody-positive patients studied in Oxford (Galati and Vincent unpublished results). Moreover, as in AchR antibody-positive cases, MuSK antibodies correlate well with clinical severity (Fig. 1). Thus the antibody is highly specific for a form of myasthenia gravis that, although quite rare, has no other diagnostic serum marker and needs to be considered in the differential diagnosis of patients with unexplained weakness at all ages.

CONCLUSIONS

- MuSK-myasthenia gravis often presents with predominantly bulbar and ocular symptoms.
- Facial muscle atrophy is relatively common in long-standing MuSK-myasthenia gravis
- The age range at onset is wide although to date most patients are young adult females.
- There is no substantial thymus pathology
- Limb symptoms may remit with treatment while facial and bulbar weakness persists
- Neurophysiological studies usually show evidence of transmission defect in facial muscles but may be normal in the limb muscles
- Response to plasma exchange is usually very good. Response to conventional treatments with prednisolone and azathioprine can be poor, and additional immunosuppressive drugs may be required.

ACKNOWLEDGEMENTS

We are most grateful to Prof J Newsom-Davis and Dr D Hilton-Jones for permission to study their patients and for their helpful comments on the manuscript. MEF was supported by the Myasthenia Gravis Association/Muscular Dystrophy Campaign.

REFERENCES

Evoli A, Tonali PA, Padua L *et al*. (2003) Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain*, **126**, 2304–11.

Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A & Vincent A (2001) Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nature Medicine*, **7**, 365–8.

Lauriola L, Ranelletti F, Maggiano N *et al*. (2005) Thymus changes in anti-MuSK-positive and – negative myasthenia gravis. *Neurology*, **64**, 536–8.

Leite MI, Ströbel P, Jones M *et al*. (2005) Fewer thymic changes in MuSK-antibody positive than in MuSK-antibody negative MG. *Annals of Neurology*, **57**, 444–8.

McConville J, Forrugia ME, Beeson D et al. (2004) Detection and characterization of MuSK antibodies in seronegative myosthenia gravis. Annals of Neurology, **55**, 580–4.

Nemoto Y, Kuwabara S, Misawa S *et al*. (2005) Patterns and severity of neuromuscular transmission failure in seronegative myasthenia gravis. *Journal of Neurology, Neurosurgery and Psychiatry*, 76, 714–80.

Sanders DB, El-Salem K, Massey JM, McConville J & Vincent A (2003) Clinical. aspects of MuSK antibody positive seronegative MG. *Neurology*, **60**, 1978–80.

Selcen D, Fukuda T, Shen XM & Engel AG (2004) Are MuSK antibodies the primary cause of myasthenic symptoms? *Neurology*, **62**, 1945–50.

Shiraishi H, Motomura M, Yoshimura T *et al*. (2005) Acetylcholine receptors loss and postsynaptic damage in MuSK antibody-positive myasthenia gravis. *Annals of Neurology*, **57**, 289–93.

Wolfe GI, Herbelin L, Nations SP *et al*. (1999) Myasthenia gravis activities of daily living profile. *Neurology*, **52**, 1487–9.

Zhou L, McConville J, Chaudhry V *et al*. (2004) Clinical comparison of muscle-specific tyrosine kinase (MuSK) antibody-positive and – negative myasthenic patients. *Muscle Nerve*, **30**, 55–60.