ORIGINAL RESEARCH PAPER

Cardiology

KEY WORDS: statins, rosuvastatin, myasthenia gravis, acetylcholine receptor antibody, coronary artery disease

STATIN INDUCED DE-NOVO LATE ONSET MYASTHENIA GRAVIS AFTER CORONARY BYPASS SURGERY

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ABSTRACT

Drug induced myasthenia gravis is a rare clinical presentation of late onset myasthenia gravis. We report a case of a 58-year-old gentleman who was prescribed high dose rosuvastatin after undergoing coronary artery bypass graft for acute coronary syndrome. He developed fluctuating oculobulbar weakness within one month of initiation of statin and was diagnosed as having myasthenia gravis. Remission was achieved after rosuvastatin was stopped along with immunomodulation. This case highlights that use of statins can induce or aggravate myasthenia gravis in susceptible patients.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction.[1] Drug induced MG is a well-documented phenomenon.[2] Statins, used worldwide for the treatment of hyperlipidemia and routinely given in patients of acute coronary syndrome, is known to adversely cause myalgia and myopathy.[3-5]However, a clinician rarely sees the development of frank MG after the use of statins.[6-15]We report a rare case of drug induced MG in a patient of coronary artery disease after coronary artery bypass graft. The case highlights that a high index of clinical suspicion is required for early diagnosis of drug induced MG.

CASE REPORT

A 58-year-old male with well controlled diabetes mellitus type 2 and dyslipidemia for the previous 5 years,on DPP4 inhibitors, metformin, atorvastatin 10 mg, metoprolol 25mg was apparently asymptomatic till 4 months prior to presentation when he noticed chest discomfort on exertion. He underwent treadmill test which was positive for inducible myocardial ischemia. After one and half months, he experienced severe chest pain at rest and was diagnosed as a case of acute coronary syndrome. He underwent coronary angiography which revealed left main with triple vessel disease.Coronary artery bypass graft (CABG) was done with good revascularization. The patient was put on dual antiplatelet therapy (aspirin and clopidogrel) and metoprolol was continued. The statin was changed to rosuvastatin(20 mg). He resumed his work after 4 weeks without evidence of dyspnoea or angina on exertion and was able to walk on the treadmill for 15 minutes daily.

However, a month later he noticed slight breathlessness on exertion which gradually progressed. He was admitted and evaluated for cardiac and pulmonary causes.All baseline investigations including contrast enhanced CT chest showed no significant abnormality and he was discharged after 3 days.His symptoms gradually worsened and he noticed hoarseness of voice followed by difficulty in swallowing solid food, drooping of eyelids,difficulty in swallowing liquids,nasal regurgitation and double vision, in that order, over the next 15 days.

He was again admitted and neurological evaluation was done.This revealed ptosis, lateral gaze restriction of extraocular movements and proximal weakness of upper limbs, neck flexors and facial muscles. MRI Brain and MR angiography of intracranial and neck vessels was normal. The nerve conduction studies were normal. However, repetitive nerve stimulation test (RNST) was positive (Figure 1A). Electromyography of the limb muscles revealed small amplitude, short duration polyphasic potentials suggesting additional myopathic involvement of the proximal upper limb and distal lower limb muscles patchily (Figure 1B). Acetylcholine receptor autoantibody levels were strongly positive-39.67 nmol/L (normal < 0.4).Patient was started on pyridostigmine with partial improvement. Statin was stopped due to possible etiological link with neuromuscular transmission defect. Additionally, patient was put on corticosteroids and azathioprine (after TPMT gene testing) with which he improved. On follow up after 2 months, there was improvement in overall muscle power. There was no diplopia, ptosis, nasal regurgitation, dysphagia or dyspnoea on exertion with minimal dysphonia.

DISCUSSION

Myasthenia gravis (MG) is an autoimmune disease causing fatiguable muscle weakness due to impaired transmission at the neuromuscular junction.[1] It is mainly caused by either antibodies to acetylcholine receptor (AchR) or muscle specific tyrosine kinase (MuSK). MG may affect any skeletal muscle group such as ocular, bulbar, limb or become generalized (80%). A number of drugs may interfere with the neuromuscular transmission through several mechanisms, either by affecting pre- or postsynaptic ion channels or by affecting acetylcholinesterase.[2] MG may be triggered or exacerbated by several drugs used in cardiovascular medicine such as statins and beta blockers.

Statins are 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors which reduce the serum cholesterol and have shown to decrease cardiovascular and cerebrovascular morbidity. Despite their popularity, statins have had their share of adverse effects specially over the neuromuscular system.[3,4]The myotoxic effects include myalgia, myositis (muscle involvement with elevation of creatine kinase and transaminases), rhabdomyolysis (muscle involvement with raised creatine kinase>10 times), unmasking or worsening of MG, myotonic dystrophy, McArdle's disease, rippling myopathy, acid maltase deficiency, Kennedy's disease, mitochondrial myopathy and necrotizing myopathy.[5,6] As per the study by Oh et al,[6]myasthenic symptoms were considered to be statin-induced if symptoms developed within 4 months after statin treatment, no other possible cause was found and clinical improvement occurred either with or without modification of treatment after discontinuation of statin. Out of 54 MG patients on statins, 13% developed a myalgic syndrome while 11% had worsening of MG independent of myalgia and involved predominantly the oculobulbar muscles.[6]

Till date, 19 patients have been reported to have developed MG de-novo or had worsening of MG after being initiated on statins (Table 1).[6-15]Most of these patients were elderly with age >55 years and with or without thymoma as in our patient. Late onset myasthenia is less likely to be associated with thymoma and tend to have autoimmune basis with ocular and bulbar presentation.[16] No particular brand of statin had lack of association with MG. The intervening period from start of statin use to the development of first symptoms of myasthenia is usually within 4 weeks, though it may occur upto 4 months. Majority of reported cases describe the

worsening of pre-existing MG after statin use.[6,10,14,15] Oh et al[6] reported worsening of MG in patients without regard to type of MG or brand of statin. MG worsening involved predominantly oculobulbar symptoms within 1-16 weeks of statin treatment.On the other hand, 6 other reported cases suggest that statin unmasked MG in their patients.[9-11,13,14] Our case exemplifies that MG may occur de-novo after statin acts as an immune trigger leading to formation of antibodies against the neuromuscular junction as in 3 previously reported cases.[7,8,12] Most of these cases report high levels of AchR antibodies and show rapid resolution within 1-10 weeks after cessation of statins along with other immunomodulators.

The proposed mechanisms of neuromuscular injury by statins is either direct myotoxicity or by immunomodulation. Statin induced myotoxicity may contribute to worsening of MG by causing a myalgic syndrome. This may be due to mitochondrial dysfunction and/or muscle membrane dysfunction.[3,6] Statins may additionally modify the immune responses as evidenced by the documented induction of other autoimmune diseases and the production of pathogenic autoantibodies including anti-HMG CoA reductase antibodies.[4,15]This is supported by the increase in acetylcholine receptor antibodies, as in our case.The additional presence of myopathic changes on EMG in the proximal muscles support the contention that these neuromuscular defects were linked to statins as observed in 1.5-3% to 33% in clinical trials.[17] Our case exemplifies the occurrence of de-novo late onset myasthenia gravis with associated myopathy, both of which are statin induced, suggestive of the "double-hit". The subsequent rapid response to cessation of statin therapy with additional immunomodulation substantiates the etiological link.

Conclusion

Statins are an indispensible part of the medical armamentarium to reduce cardiovascular and cerebrovascular morbidity and mortality. However, one should have a high index of suspicion of statin induced MG and myopathy in the presence of worsening or de-novo neuromuscular symptoms. Cessation of statins and changing the group of cholesterol lowering agent such as bile acid sequestrants, ezetimibe etc may have a place specially in patients with new onset or deterioration of pre-existing neuromuscular disorders.

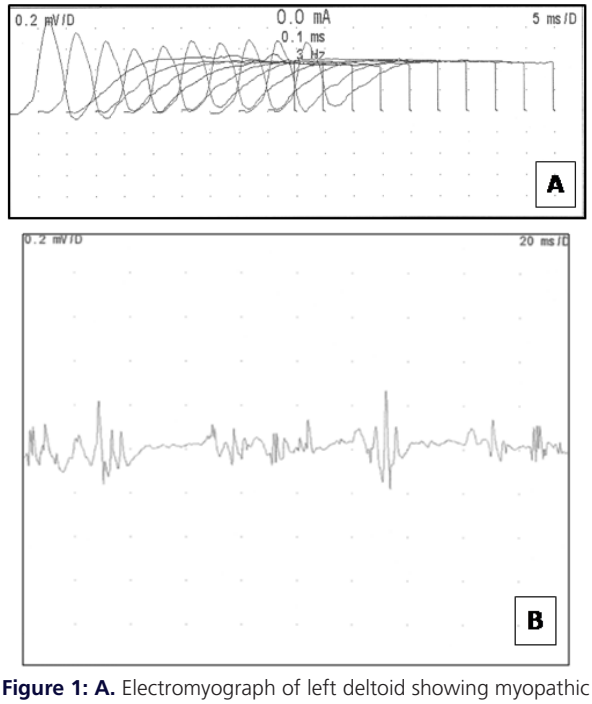

Figure 1: A. Electromyograph of left deltoid showing myopathic potentials.

B. Repetitive nerve stimulation test of right facial nerve showing significant decremental response in right orbicularis oculi.

Table 1: Cases of statin related myasthenia gravis reported in literature

S.No.	Authors	No. of cases	Age	Gender	Statin used	Time to myasthenic symptoms	Pre-existing myasthenia	Site of myasthenic involvement	Auto-antibodies	EDX%	Thymectomy	Resolution	Recurrence with other statin used
1	Negvesky GJ (2000)[7]	1	60	F	Atorvastatin	10 weeks	No	Ocular	AchR* +	RNST# -	NA	+ in 10 weeks	NA
2	Parmar B (2002)[8]	1	67	F	Atorvastatin	12 weeks	No	Ocular + limb	AchR-	NA	No thymoma	+ in 6 weeks	+ (fluvastatin, simvastatin, benzafibrate)
3	Cartwright MS (2004)[9]	1	55	M	Atorvastatin	1 week	+/-	Bulbar	AchR+	RNST +	No thymoma	+ in 1 week Pyridostigmine +	+ (lovastatin, pravastatin, simvastatin)
4	Purvin V (2006)[10]	4	55 70 71 56	M M M F	Rosuvastatin Rosuvastatin Simvastatin Pravastatin	1 week 1 week 2 weeks 1 week	+/- +/- +/- +	Ocular + bulbar Ocular Ocular + bulbar Ocular + limb	AchR+ AchR+ AchR - AchR+	SFEMG@ + NA SFEMG + NA	No thymoma No thymoma NA No thymoma	Improved with pyridostigmine, steroid in 8 months Partial improvement with pyridostigminein 7 months + in 2 months Partial improvement with pyridostigmine, IVIg, steroids	- - + (Pravastatin) -
5	Oh SJ (2008)[6]	6	41 58 59 51 67	M M M F M	Simvastatin Rosuvastatin Simvastatin Rosuvastatin Simvastatin	6 weeks 2 weeks 1 week 2 months 2 weeks	+ + + + +	Ocular Ocular + bulbar Bulbar + limb Bulbar + limb + crisis Bulbar + limb	AchR - AchR+ AchR+ MuSK$ + AchR-	SFEMG + RNST +, SFEMG + RNST +, SFEMG + RNST +, SFEMG + RNST +, SFEMG +	No thymoma Thymectomy No thymoma Thymoma No thymoma	+ in 1 week Partial improvement with azathioprine, steroids in 22 mths + in 4 weeks Partial improvement with IVIg, cyclophosphamide in 16 mths Partial improvement with azathioprine, IVIg in 2 mths	- + (Simvastatin) - + (Atorvastatin) + (Fluvastain, pravastatin)
			45	M	Lovastatin	4 months	+	Bulbar	AchR+	NA	Thymectomy	Partial improvement with azathioprine, steroids in 2 mths	- + (Pravastatin)
5	Keogh MJ (2010)[11]	1	60	M	Atorvastatin	1 week	+/-	Ocular + bulbar + limb	AchR +	NA	NA	Partial improvement with pyridostigmine, IVIg, steroids	+ (Simvastatin)
6	Bhatti AB (2014)[12]	1	60	M	Simvastatin	2 weeks	No	Ocular + bulbar	AchR +	RNST +	NA	+ in 1 week with pyridostigmine	-
7	Gale J (2014)[13]	2	48 69	M F	Atorvastatin Atorvastatin	4 weeks 4 weeks	+/- +/-	Ocular Ocular	AchR + AchR +	NA NA	No thymoma NA	Partial improvement with pyridostigmine, steroids Improvement with azathioprine, steroids	- -
8	Ragbourne SC (2015)[14]	1	62	F	Ezetimibe	Within 1 week	+	Ocular + limb	AchR -	RNST +	No thymoma	Partial improvement	+ (Simvastatin)
9	Watanabe Y (2015)[15]	1	68	F	Atorvastatin	4 weeks	+	Ocular	AchR +	NA	NA	Improvement withsteroids	-

% EDX- Electrodiagnostic test
***AchR- Acetylcholine receptor antibodies**
$MuSK- Muscle specific kinase antibodies
 # RNST- Repetitive nerve conduction test
@- SFEMG- Single fibre electromyography

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