Case Report

Statin-Associated Myasthenic Weakness

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Background: *Statin-associated myasthenic weakness is uncommonly recognized. Since 2002, there have been 14 cases described in literatures. However, the underlying mechanism is still unknown.*
Case Report: *In 2007, a 50-year-old woman with generalized, limb predominated, myasthenia gravis (MG), whose MG status has been "minimal manifestation" for several years, developed moderately severe fluctuating bulbar weakness a few weeks after starting simvastatin 20 mg/day. Simvastatin was discontinued and dosage of cholinesterase inhibitor was temporarily increased. The symptoms resolved and she was back to her previous status in one month. In 2008, two weeks after re-challenge with simvastatin 10 mg/day, bulbar weakness re-occurred. Antibody to acetylcholine receptors was measured 4.25 nmole/L. Serum creatine phosphokinase was normal. Electrophysiologic tests showed evidences of postsynaptic neuromuscular junction disorder without evidence of myopathy. The symptoms were again resolved after discontinuation of statin and temporarily increased dosage of cholinesterase inhibitor. She was back to previous status in two months. Hypercholesterolemia was then controlled with ezetimibe without any worsening in MG status.*
Conclusion: *Because of the wide use of statins in clinical practice, physicians should be aware of this potential adverse effect. The incidence of statin-associated myasthenic weakness should be clearly investigated. Challenge with other brands of statin or with reduced dosage is not beneficial in these patients. Non-pharmacological treatment and non-statin medication may be considered.*

Keywords: *Statin, Myasthenia gravis, Statin-associated myasthenic weakness*

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Myasthenia gravis (MG) could be aggravated by several medications due to their ability to interfere with the neuromuscular junction transmission. Statin-induced myopathy is among one of their established adverse effects. Clinical spectrum of statin-induced myopathy includes myalgia, myositis, rhabdomyolysis, and asymptomatic raised creatine kinase[1]. However, statin-associated myasthenic weakness is uncommonly recognized. Since 2002, there have been 14 cases of statin-associated myasthenic weakness described in literatures[2-7], but its underlying mechanism is still unclear.

Case Report

A 50-year-old woman developed generalized, limb predominated, MG in 1990. She was managed with cholinesterase inhibitor and corticosteroid. Later, corticosteroid was switched to cyclophosphamide. Thymectomy was done 1 year after the onset. The pathology revealed thymic hyperplasia. Her symptoms had gradually improved to the point that her MG status was "minimal manifestation" (MM-2)[8] for seven years until 2003 when her symptoms were spontaneously exacerbated. She was then started on azathioprine with a good response, making her MG status be a minimal manifestation (MM-3)[8] since 2004. In 2007, she received 20 mg/day of simvastatin for hyper-cholesterolemia. A few weeks later, she reported dysphagia and nasal speech. These symptoms noticeably improved with temporarily increased dose of cholinesterase inhibitor and discontinuation of simvastatin. The dosage of azathioprine was increased. She was then back to her previous state in one month. In 2008, 10 mg/day of simvastatin was re-administered. Two weeks later, she again developed bulbar weakness for which she stopped statin. Examination revealed fatigability of bulbar muscle without weakness of the limb or neck muscles. Antibody to acetylcholine receptors (AChR-Ab) was measured 4.25 nmole/L. (normal < 0.45 nmole/L). Serum creatine phosphokinase

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was normal. Electrophysiologic study showed evidences of postsynaptic neuromuscular junction disorder without myopathy. Cholinesterase inhibitor was temporarily increased without any changes in previous immunomodulatory therapy. She was back to her previous status in two months. Hypercholesterolemia was then controlled with ezetimibe without any worsening in MG status.

Discussion

Statin-associated myasthenic weakness is uncommonly recognized. Among 15 cases (including the present case), seven cases had no preceding MG[2-7], while an other eight cases were previously diagnosed MG in various statuses[4,5]. However, in the group with apparent new onset of disease, it is still unclear whether these patients represent statin-induced MG or aggravation of sub-clinical disease (unmasked MG).

Overall, the timing interval of myasthenic weakness and initiation of statin treatment ranges from less than one week to three months. Predominantly oculobulbar weaknesses were the most common presentation, found in all except one, experiencing neck-limb weakness. Association between statin and myasthenic weakness has been reported in all brands of statin. In addition, worsening of myasthenic weakness was observed in seven cases, being re-challenged with either the other brands or the same brand of statin. Statin was discontinued in all cases. Three cases with mild symptoms required no other treatment, two cases received only cholinesterase inhibitor and one case continued on the same previous treatment. Another nine cases also required addition or changes of immunomodulatory therapies. The myasthenic symptoms were resolved or back to previous state in one week to 22 months. However, one case receiving several kinds of immunomodulatory treatments, remained diplopia[6].

Three possible mechanisms have been debated[3-5]. These are 1) Statin-unmasked or statin-aggravated autoimmune MG, 2) Statin-induced de novo autoimmune MG and 3) Statin-induced myotoxicity, exacerbating MG. Oh et al favored an effect of statins in alterations of antibody production, giving the evidences that statins are known to induce other autoimmune diseases[4] and the changes of AChR-Ab levels, correlated with exacerbation and resolution of symptoms[5]. In addition, Elsais et al recently reported a case of statin-associated myasthenic weakness, whose AChR-Ab level remained elevated during a 3-year observation, after statin had been stopped[6]. The long-termed elevation of AChR-Ab in their case also suggests that the patient had "unmasked MG". Purvin et al proposed a statin-induced de novo induction of autoantibodies, citing d-penicillamine-induced seropositive myasthenia gravis[4]. However, due to the lack of long-term (years) follow-up, showing complete clinical and immunological resolution, this mechanism has not been clearly supported. Statin-induced myopathy is a well-established entity. However, the pattern of bulbar and asymmetrical ocular weakness is against the myopathic process, since statin-induced myopathy generally affects proximal muscles of the limbs, symmetrically. In addition, there has been no electrophysiologic or laboratory findings supporting this mechanism. Thus, it is the most unlikely mechanism.

Of interest, in the presented patient, there was a very close temporal association between the initiation of simvastatin treatment and exacerbation of MG in the two occasions. This shows a strong association between statin treatment and myasthenic weakness. In addition, statin-associated myasthenic weakness reoccurred though this patient received a minimal dose of statin. MG has bimodal age of onset, young and elderly. Elderly patients have a higher chance of having hypercholesterolemia. Therefore, physicians treating MG patients should be aware of this potential adverse effect of statins.

Conclusion

According to the possible underlying mechanisms, the authors favor the immunological mechanism of statin, unmasking MG (in those with new onset of disease) and aggravating MG (in those with preexisting illness). Because of the wide use of statins in clinical practice, physicians should be aware of this potential adverse effect. Furthermore, patients should also be informed of the potential adverse effect. The incidence of statin-associated myasthenic weakness should be clearly investigated. Challenge with other brands of statin or with reduced dosage is not beneficial. Non-pharmacological treatment and non-statin medications should be considered in these patients.

Potential conflicts of interest

None.

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อาการอ่อนแรงไมแอสทีเนียที่สัมพันธ์กับยาสเตติน

ณัฐ พสุธารชาติ, กัมมันต์ พันธุมจินดา

ภูมิหลัง: *อาการอ่อนแรงไมแอสทีเนียที่สัมพันธ์กับยาสเตตินพบได้ไม่บ่อยนัก ตั้งแต่ปี พ.ศ. 2545 มีรายงานผู้ป่วยในวารสารการแพทย์แล้วจำนวน 14 ราย อย่างไรก็ตามกลไกการเกิดโรคนี้ยังไม่ทราบ*

รายงานผู้ป่วย: *ในปี พ.ศ. 2550 ผู้ป่วยหญิงอายุ 50 ปี รายหนึ่งซึ่งป่วยเป็นโรคกล้ามเนื้ออ่อนแรงไมแอสทีเนีย ซึ่งมีอาการแสดงของโรคเพียงเล็กน้อย และมีอาการอ่อนแรงของกล้ามเนื้อแขนขาเป็นอาการเด่น เกิดอาการอ่อนแรงปานกลางของกล้ามเนื้อการพูดและการกลืนแบบเป็น ๆ หาย ๆ หลังได้รับยาซิมวาสเตติน ขนาด 20 มิลลิกรัม ต่อวัน มานานสองถึงสามสัปดาห์ อาการอ่อนแรงดังกล่าวหายไป และผู้ป่วยมีอาการกลับไปในสภาวะเดิมในเวลา 1 เดือน หลังหยุดยาซิมวาสเตตินและเพิ่มขนาดของยายับยั้งโคลีนเอสเทอเรสชั่วคราว ในปี พ.ศ. 2551 อาการอ่อนแรงของกล้ามเนื้อการพูดและการกลืนเกิดขึ้นอีกครั้งหลังได้รับยาซิมวาสเตตินในขนาด 10 มิลลิกรัม ต่อวัน เป็นเวลาสองสัปดาห์ ระดับแอนติบอดีต่อตัวรับอเซทิวโคลีนวัดได้ 4.25 นาโนโมลต่อลิตร ระดับครีเอทีนฟอสโฟไคเนสเป็นปรกติ การตรวจไฟฟ้าวินิจฉัย พบหลักฐานของรอยโรคหลังรอยต่อประสาทและกล้ามเนื้อ โดยไม่พบหลักฐานของความผิดปรกติที่กล้ามเนื้อ อาการอ่อนแรงดังกล่าวหายไปเช่นเคยหลังหยุดยาซิมวาสเตติน และเพิ่มขนาดของยายับยั้งโคลีนเอสเทอเรสชั่วคราว ผู้ป่วยกลับไปอยู่ในสภาวะเดิมใน 2 เดือนต่อมา ภาวะโคเลสเตอรอลสูงถูกควบคุมด้วยอิเซทิไมโดยไม่ทำให้อาการอ่อนแรงไมแอสทีเนียเลวลงอีก*

สรุป: *เนื่องจากมีการใช้ยาสเตตินกันอย่างมากในทางคลินิก แพทย์จึงควรระมัดระวังถึงอาการข้างเคียงดังกล่าวนี้ ควรมีการศึกษาอุบัติการณ์ของอาการอ่อนแรงไมแอสทีเนียที่สัมพันธ์กับยาสเตติน การเปลี่ยนชนิดของยาสเตตินหรือการลดขนาดยาไม่เกิดประโยชน์ในผู้ป่วยกลุ่มนี้ ควรพิจารณาเลือกการรักษาโคเลสเตอรอลสูงด้วยวิธีที่ไม่ใช้ยาหรือ ใช้ยาที่ไม่ใช่สเตตินแทน*