Exacerbation of myasthenia gravis after amoxicillin therapy: a case series

Veria Vacchiano1 · Piergiorgio Solli2 · Ilaria Bartolomei3 · Giulia Lai4 · Rocco Liguori1,5 · Fabrizio Salvi3

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Abstract

Introduction Myasthenia gravis (MG) can be aggravated by several classes of drugs, including antibiotics. Penicillins are considered safe drugs for the management of infectious disease in patients with MG. However, a few cases of MG exacerbations after penicillin treatment have been reported in literature.

Case reports We report six patients with MG developing acute worsening of symptoms after amoxicillin or amoxicillin/clavulanate treatment. In most of the cases, symptoms started in a few days after antibiotic administration. In all cases, we observed a worsening of the Myasthenia Gravis Foundation of America (MGFA) clinical classification. Most patients required a therapeutic intervention with dosage increase of the previous therapy or the introduction of new drugs for MG. All patients had a full recovery to baseline neurological conditions within 1–2 months.

Conclusions We concluded that patients receiving amoxicillin should be closely monitored for possible acute relapse.

Keywords Myasthenia gravis · Drugs · Penicillin · Amoxicillin

Introduction

Myasthenia gravis (MG) is an autoimmune disease resulting from antibodies binding to nicotinic acetylcholine receptors or to other related molecules in the postsynaptic membrane at the neuromuscular junction [1]. The disorder is characterized by fluctuating weakness that can involve ocular, bulbar, limb, and respiratory muscles.

Many factors can exacerbate myasthenia symptoms, including pregnancy, infections, systemic illness, and several classes of drugs, such as antibiotics, neuromuscular blocking agents, cardiovascular drugs (beta blocker, procainamide), and others [2].

Among antibiotics, fluoroquinolones, aminoglycosides, ketolides, and macrolides have been associated with unmasking or exacerbation of MG [2–5]. In particular, fluoroquinolones and macrolides have the most evidence to support avoiding their use in patients with MG [3, 4].

Penicillins are considered safe drugs for the management of infectious disease in patients with MG. However, the overall literature is limited, and a few cases of acute and transient clinical worsening after penicillin administration in MG patients [6, 7] have been reported.

We report six patients with MG presenting with exacerbation of symptoms after amoxicillin or amoxicillin/clavulanate therapy.

Case reports

Six patients (four males, two females, age ranging from 52 to 84 years) developed clinical worsening after amoxicillin or amoxicillin/clavulanate therapy (Table 1). Three patients had only mild ocular symptoms (MGFA I), clinically controlled with pyridostigmine. The other three patients had generalized myasthenia (MGFA IIA), on treatment with pyridostigmine...
and low-dose steroids. Therapeutic indications for antibiotic therapy were mild or moderate infections (three afebrile), and in one case (case 6) surgical prophylaxis for thymectomy. In most patients, neurological worsening developed in a few days after antibiotic administration.

In all cases, we observed a worsening of the MGFA. Patients with MGFA I developed generalized weakness and/or respiratory symptoms (two cases classified as MGFA II and one case as MGFA V). Patients with MGFA II A developed bulbar and/or respiratory symptoms (MGFA II B).

Five patients required dosage increase of the previous therapy (steroid or pyridostigmine) or the introduction of new therapies for MG (plasma exchange, steroid therapy, and rituximab), due to the persistence of symptoms. All patients had a full recovery to baseline neurological conditions within 1–2 months.

In one patient (case 6), amoxicillin/clavulanate was used as antibiotic prophylaxis before video-assisted thoracoscopic thymectomy. The patient was previously in a stable phase of disease, showing only fluctuating ocular symptoms. Anticholinesterase drug therapy was discontinued the evening before surgery. Anesthesia was performed using propofol and fentanyl, considered safe in MG as short-acting drugs [8]. Amoxicillin/Clavulanate (2 g) was administered before anesthetics and repeated after 3 h. At the end of the surgery, during the weaning from anesthetics, the patient developed respiratory failure, needing tracheostomy with mechanical ventilation. The myasthenic crisis was managed by three weekly plasma exchanges. In the following weeks, the patient progressively improved, recovering in about 2 months.

### Discussion and conclusions

In this report, we describe six MG patients which presented with a clinical worsening possibly related to amoxicillin or amoxicillin/clavulanate therapy. Another case of MG relapse after amoxicillin treatment has already been reported in literature [6]. The patient developed nasal speech, diplopia, weakness, and dyspnea after 3 days of amoxicillin 250 mg orally 3 times daily. He gradually improved within a month after a large dose of pyridostigmine and a cycle of intravenous immunoglobulin.

Two other cases have been previously reported in relation to ampicillin [7], which is different from amoxicillin only by a hydroxyl group on the benzene ring.

These two patients developed transient ptosis and general weakness after ampicillin administration, with improvement in a few days after its discontinuation. In one of these patients, a clinical challenge with ampicillin 1500 mg intravenously followed by 500 mg orally caused the clinical deterioration after 12 h, proving the sensitivity to ampicillin. The authors also showed that the administration 500 mg/kg of ampicillin
in three rabbits with experimental autoimmune myasthenia increased the pre-existing electrical decrement, while the drug had no the same effects in normal animals [7].

Clavulanate is a beta-lactamase inhibitor used in association with amoxicillin to prevent beta-lactam antibiotics hydrolysis. We did not find any other report in literature about a possible effect on neuromuscular junction. Due to its use only in combination with amoxicillin and due to the cases of MG worsening after amoxicillin (without clavulanate), we can reasonably conclude that the neurological deterioration is related to amoxicillin administration.

In most of our cases, a possible alternative cause for MG exacerbations could be the intercurrent infection, which is a common cause of MG relapse [9]. However, we consider the infections less likely related to the clinical worsening, due to the presence of mild and afebrile disorders and a local dental inflammatory process. Moreover, our patients denied significant exacerbations during other previous episodes of infectious diseases, not treated with penicillins. Nevertheless, other unknown predisposing factors could influence this peculiar response to the amoxicillin administration, including the age factor, being our patients aged between 52 and 84 years.

Interestingly, we can identify a close temporal relation between the antibiotic administration and the onset of symptoms in all patients, consistently with previous cases described [6, 7].

Regarding the last patient (case 6), we could not exclude a role of anesthetics and surgical treatment. However, the advent of mini-invasive surgery and the widespread use of short-acting anesthetic drugs have substantially changed the postoperative course of myasthenic patients who underwent thoracoscopic thymectomy. In a recent study [8] on a population of 110 patients who underwent video-assisted thoracoscopic extended thymectomy, the authors showed that only 1.8% patients developed myasthenic crisis, probably due to the optimization of the preoperative evaluation and preparation of the patients, to the anesthesia with short-acting drugs and with minimal use of muscle relaxants. In our case, the same standardized protocol has been used. Therefore, we can reasonably ascribe the neurological deterioration to the antibiotic administration.

Although the mechanism of action of amoxicillin on the neuromuscular junction is still unknown, we observed that amoxicillin could be rarely harmful in treating MG patients, probably in associations with other unclear predisposing factors. In conclusion, we underline that MG patients must be treated with the most effective anti-infectious treatment, but they should be closely monitored after receiving amoxicillin, due to possible rare acute exacerbations.

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**Compliance with ethical standards**

**Conflict of interest** V. Vacchiano, P. Solli, I. Bartolomei, G. Lai, and F. Salvi report no disclosures.

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**Informed consent** Informed consent was obtained from all individual participants included in the study.

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