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CASE BASED REVIEW

Adalimumab-induced myasthenia gravis: case-based review

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Abstract

Myasthenia gravis (MG) is an autoimmune disease characterised by the presence of acetylcholine receptor antibodies and by blocking the transmission of the signal in the neuromuscular junction causing muscle weakness. It can be associated with several autoimmune diseases and certain drugs, between them Etanercept an anti-tumour necrosis factor (TNF) agent. A 42-year-old woman with rheumatoid arthritis (RA) refractory to methotrexate, was treated with adalimumab (ADA), a human monoclonal antibody against the TNF, in a dosage scheme of 40 mg every 14 days subcutaneously. The patient responded well to ADA therapy with sustained remission for 18 months when she developed blurred vision and eyelid ptosis of the left eye. The diagnosis of ocular MG was made. ADA has been discontinued and she started a treatment with pyridostigmine showing an excellent response and complete remission within a 2-month period. This is the first report making an association of ADA and ocular MG. Thus, rheumatologists dealing with patients treated with TNF inhibitors should be aware of the possible development of neurological adverse events, among them MG.

Keywords Myasthenia gravis · Anti-TNFα · Etanercept · Adalimumab · Neuromuscular junction · Muscle weakness

Introduction

Nowadays, the biological (b) disease-modifying anti-rheumatic drugs (DMARDs), especially those targeting TNF (tumor necrosis factor) α have revolutionized the treatment of inflammatory arthritides (IA) including rheumatoid arthritis (RA). On the other hand, TNFα is also a component of the immune system, which is involved in a variety of physiological immune responses [1]. Therefore, by blocking TNFα, many adverse events may occur, such as viral or bacterial infections, opportunistic infections and autoimmune phenomena [2]. Many autoimmune diseases and phenomena have been reported ranging from the isolated presence of an autoantibody to full-blown autoimmune diseases, organ specific or even systemic diseases.

Myasthenia gravis (MG) is an autoimmune disease characterised by the presence of antibodies against nicotinic acetylcholine receptors (AchRs), which block the transmission of nerve-to-muscle signals (neuromuscular junction). As a result, muscle weakness occurs. It affects individuals between 30 and 45 years and especially women. As a clinical entity, it can occur alone or in association with thymic hyperplasia, thymoma, several autoimmune diseases such as systemic lupus erythematosus (SLE), RA, Sjogren's syndrome (SS) and others [3, 4]. It has also been associated with the intake of many drugs (antibiotics, antihypertensive, antiarrhythmics etc.) [5, 6]. TNF inhibitors are used in the last two decades to treat patients with IA, including RA, inflammatory bowel disease, psoriasis and uveitis [7]. There are some reports which suggest an association of Etanercept (ETN), an IgG Fc fusion protein with MG [8].

In the present report, we describe a female RA patient treated with Adalimumab (ADA), a human monoclonal antibody against TNF, who developed MG and we review the

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relevant literature [9]. A written informed consent has been obtained and signed by the patient.

Case presentation

A 42-year-old woman with RA treated with methotrexate (MTX) 20 mg/week and ADA presented to us with blurred vision and eyelid ptosis after watching TV for many hours in the Christmas day. The diagnosis of RA has been made 2 years earlier on the basis of a 7-week duration symmetrical polyarthritis affecting the wrists, the metacarpophalangeal and proximal interphalangeal joints. Laboratory evaluation revealed positive IgM rheumatoid factor (IgMRF) in a titer of 1/320 (latex test), high erythrocyte sedimentation rate (ESR) 72 mm/h and high c-reactive protein (CRP) 18 mg/dl (normal values < 6) [10]. The anticitrullinated protein antibodies (ACPA) and antinuclear antibodies were negative. The rest of the laboratory tests were within normal limits. Past medical and family history were unremarkable. She was an ex-smoker.

She was treated with MTX 15 mg/week plus folic acid supplementation and prednisone 10 mg/day. Two months later, she had some clinical and laboratory improvement. The dose of prednisone was tapered and MTX was increased to 20 mg/week. However, after 6 months of treatment no significant improvement has been noted and after the appropriate screening, ADA has been added in a dose of 40 mg every 14 days subcutaneously. Two months later, she had a significant clinical response with normalization of the ESR and CRP values. She was in clinical remission for about 18 months when she presented to us with the eye problem. Clinical examination showed no frank arthritis. Muscle evaluation revealed weakness and fatigability of the external ocular muscles of the left eye followed by eyelid ptosis. Eye examination revealed no abnormalities. Muscle evaluation in other regions of the body was negative for weakness. Routine laboratory tests showed no abnormalities, while the immunological tests revealed positive ANAs at a titer of 1/320 with a fine speckled pattern. The extractable nuclear antigens (ENAs), anti-double-stranded DNA (dsDNA) as well as AchR antibodies were negative. Further evaluation with magnetic resonance imaging (MRI) of the brain and computed tomography (CT) scan of the chest showed no abnormalities. Single fiber electromyography (SFEMG) was normal. After that, neostigmine was given intramuscularly at a dosage of 0.5 mg. After 30 min, a significant improvement of the eyelid ptosis and diplopia was noted, lasting for 10 min (Fig. 1). At that point, the diagnosis of ocular MG was made. ADA has been discontinued and she was treated with pyridostigmine, an acetylcholinesterase inhibitor [11]. After 2 months, a complete resolution has been noted and pyridostigmine was gradually tapered and stopped.

Fig. 1 Neostigmine test is a pharmacological test demonstrating the clinical improvement of patients with myasthenia gravis. **a** Shows a patient with myasthenia gravis with eyelid ptosis of the left eye. **b** Demonstrates the clinical improvement with eyelid elevation after neostigmine test

Search strategy

We searched Medline and Scopus, for English-language sources using the following keywords: Myasthenia gravis, Etanercept, Golimumab, Adalimumab, Infliximab, Certolizumab, biological disease-modifying anti-rheumatic drugs, anti-tumour necrosis factor, including also their abbreviations. We did not put time limitations regarding the publication dates. The results showed one case of ETN as the cause of myasthenia gravis-related adverse event, but no other TNF inhibitors have been implicated so far. In contrary, animal studies have implicated TNFα in the pathogenesis of MG and trials using TNFα blockers have shown a clinical improvement in these patients.

Discussion

MG is caused by an antibody-mediated autoimmune response to muscle AchRs which results in impairment of neuromuscular transmission leading to muscular weakness. The weakness increases with sustained exertion during the course of the day and improves by rest. It is worsened in high temperatures and it often improves by the cold. Infections, emotional stress and menses can worsen

the MG symptoms. Exposure to bright light may increase the ocular symptoms. External ocular muscles are affected in about 90% of the cases during the disease course and the symptoms respond to anticholinesterase drugs. It is associated with many autoimmune diseases [3–6] and drugs such as d-penicillamine, procainamide, ion channel blockers and others [3–6, 11].

Because TNF blockers are large protein molecules, they can become immunogenic and may expect to cause autoimmune adverse events. However, the immune deviation phenomenon of TNF inhibitors is more target-related than agent-related. For example, infections are the prototypical manifestations of immunodeficiency, while the presence of autoantibodies is most typical of autoimmunity. A mechanistic classification of adverse events related to the use of bDMARDs include [2]: (1) cytokine release syndrome or cytokine storm, (2) hypersensitivity (acute infusion reaction, injection site reactions, the presence of antidrug antibodies), (3) immunodeficiency and immunosuppression and, d. autoimmunity.

In the last two decades, TNF blocking agents have revolutionised the treatment of IA, including RA [7]. However, blocking TNF has been resulted in adverse events. TNF agents induce autoimmune phaenomena ranging from an isolated presence of autoantibodies, especially ANAs or ds-DNA, to full-blown autoimmune diseases such as SLE, vasculitis, demyelinating disorders, optic neuritis, peripheral neuropathies and others [12, 13]. Searching the PubMed and Scopus, MG induced by TNF inhibitors has been reported in only one case in an RA patient treated with ETN, an IgG fusion protein [8]. However, no other TNF blockers have been associated with this disorder so far. The authors, describe a case of a 66-year-old patient with RA and other concomitant diseases (diabetes mellitus, coronary artery disease with bypass grafting), who developed myasthenia gravis whilst on treatment with ETN. More specifically, the patient developed dysphagia with no involvement of the ocular muscles. From the work-up, the patient had positive AchR antibodies and the nerve conduction studies with SFEMG were consistent with a defect of neuromuscular transmission and axonal polyneuropathy. The symptomatology improved after withdrawal of ETN with no additional treatment.

In the present study, our patient with RA treated with ADA, developed ocular MG after long-exposure to the bright light of the TV screen. All the above are contributing factors for MG development. Indeed, ADA-induced positive ANAs, and ocular manifestations of MG. On the other hand, we have excluded other possibilities of MG such as thymoma, brain tumour, and drug intake. Regarding MTX, which is an immunosuppressant drug, it has been used for many decades for the treatment of RA and other IA. All these years no such side effects have been reported. Indeed, our patient was receiving MTX for 2 years and no adverse events have been manifested. The possible association of RA and MG is also weak, since our patient had no such clinical symptoms on disease onset and she had also negative ANAs, which became positive after exposure to ADA. The absence of AchR antibodies can be explained because in isolated MG, like in our patient, positive AchR antibodies are found in about 50% of the cases [3–6, 11]. SFEMG is considered the most sensitive test for MG and detects impaired nerve-to-muscle transmission. However, in ocular MG or isolated MG this test is less sensitive [3–6, 11].

This is the first report of ADA association and ocular MG. This phaenomenon is very intriguing because TNF inhibitors have been proposed for the treatment of MG. Indeed, animal studies have implicated TNFα in the pathogenesis of MG and trials using TNFα blockers have shown a clinical improvement in these patients [14–17]. However, other studies investigating serum TNFα levels in patients with MG, found that TNFα levels varied greatly among MG patients [18]. Our patient responded very well to the treatment with pyridostigmine, after ADA withdrawal, without any additional treatment. This could be explained because our patient had isolated MG restricted to ocular muscles and was seronegative. Studies have shown that these patients respond very well to pyridostigmine and show high remission rates [19, 20].

In conclusion, rheumatologists dealing with patients treated with TNFα inhibitors should be aware that several neurological side effects may emerge and MG is one of them.

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Compliance with Ethical Standards

Conflict of interest The authors (Pelechas, Memi, Markatseli, Voulgari, Drosos) have no conflict of interest.

Ethics approval This case is complying with the ethical standards of the University Hospital of Ioannina as it has been obtained an informed consent from the presented patient (informed consent has been uploaded as a different file—supplementary material).

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