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## Case report

# Association of myasthenia gravis and Behçet's disease: A case report



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## ABSTRACT

Myasthenia gravis is a disease of neuromuscular junction due to auto-immune destruction of the acetylcholine receptors. Behçet's disease, on the other hand, is a multisystemic vascular-inflammatory disease. Both conditions are not common in the general population although their association has not been reported in the literature. We wanted to present our patient who developed clinical course of myasthenia gravis following discontinuation of medications due to complications of corticosteroid for Behçet's disease. It was observed that clinical findings of myasthenia gravis recovered following restarting steroid treatment and he did not experience attacks of both conditions. Although Myasthenia gravis and Behçet's disease are distinct entities clinically as well as in terms of pathogenesis, they share common physiopathological features and their treatment is based on their common features.

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## 1. Introduction

Myasthenia gravis (MG) is a disease of muscles developing as a consequence of autoimmune destruction of nicotinic acetylcholine receptors [1]. It is characterized by muscle weakness manifesting with ophthalmoplegia, ptosis, and repetitive movements [2]. It is usually associated with other autoimmune conditions such as rheumatoid arthritis, hyperthyroidism, and

hypothyroidism [2]. In treatment, anti-choline esterase agents are often used and corticosteroids, plasmapheresis, and immune suppressive agents, and thymectomy in severe cases [3].

Behçet's disease (BD) is a chronic vascular-inflammatory disease of unknown pathogenesis presenting with mucocutaneous lesions, attacks of uveitis that may lead to blindness, involvement that may be fatal of many organs and systems including nervous, vascular, musculo-skeletal, and gastrointestinal systems. According to the new criteria the ocular

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lesions, genital and oral aphthous lesions, skin lesions, neurological findings, vascular findings, and the pathergy test are evaluated. The skin lesions and neurological and vascular findings are each given one point while others are given 2 points. The pathergy test is optional and given one point. Total score is estimated from the points given to each criterion and 4 or higher scores are considered as Behçet's disease [4].

A strong association has been found between positivity of HLA-B51 and prevalence of the disease [5,6]. BD is referred as Neurobehçet Disease (NBD) if it is associated with involvement of the CNS [7].

The subject presented here had clinical course of MG occurring after discontinuing the medication due to complications of the corticosteroids in a male patient who had been using prednisolone for 17 years without interruption due to diagnosis of BD. We did not find any data in the literature on association of both conditions.

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## 2. Case report

A 42 years old man presented to outpatient clinic of Neurology Department of Medical Faculty of University with speech disorder, dysphagia, and nasal regurgitation of food.

In March of 2014, the patient had been scheduled to have operation in orthopedics clinic in a state hospital for rupture of tendon of Achilles and his treatment with prednisolone and azathioprine had been discontinued. Findings of myasthenia gravis with bulbar involvement were observed 5 days after the medication had been discontinued. Thus, the patient was admitted to our clinic. The patient developed speech disorder, dysphagia, and ptosis. The otolaryngologist whom the patient had visited for complaint of dysphagia started antibiotic treatment with Ampicillin but complaints of the patient increased despite antibiotic treatment. The subject was admitted to our clinic with presumed diagnosis of Behçet's disease – Neuromuscular disease.

History of the patient revealed that the patient was diagnosed as having BD in an outer center that he presented with oral and genital aphtas and 2 attacks of uveitis in 1998 and then he was started treatment with colchicine. The patient reported that he did not experience attacks of oral or genital aphtas and uveitis 15 years after treatment with prednisolone at dose of 8 mg/day and azathiopyrine 150 mg/day. Pathergy test was positive.

On physical examination, the patient had no skin lesion, arterial pulsations were palpable on both lower and upper limbs, and there were no signs of venous insufficiency. On auscultation, cardiac sounds were rhythmic and pulmonary sounds were normal. No organomegaly was found on abdominal examination.

On the neurological examination; minimal restriction in bilateral conjugated and upward gaze (ranging between 15 and 30 degrees). There was ptosis on the left lid. Ptosis worsened and gaze restriction increased with fatigue test. Ptosis markedly improved with ice test. Eye closing was bilaterally weak, muscle strength of the neck flexors was 4/5, speech was moderately nasal in character, and gag reflex was bilaterally absent. There was no another significant finding on neurological examination.

Routine biochemical investigations (fasting blood glucose, hepatic function tests, renal function tests, muscle enzymes, and electrolytes), hemogram, complete urine analysis, vitamin B12, folic acid, thyroid function tests, and sedimentation rate were all within normal limits.

Thoracic CT and whole-abdominal CT performed for detecting malignancy were normal. Cranial MRI, MR-angiography and MR-venography were all within normal limits. No pathological finding was found in consultation with otorhinolaryngology department conducted for dysphagia. Nasopharyngeal MRI was considered as normal performed to exclude malignancy in the nasopharynx due to involvement of the cranial nerve VI. No lesion was found to explain restricted gaze in orbital MRI investigation.

In the serum, antibody to acetylcholine was positive. Incremental response (20%) was found on EMG investigation of the subject.

Pridostigmine was started and its dose was gradually increased to 120 mg/day three times daily. Intravenous immune globulin was given for 5 days at dose of 0.4 mg/day. IVIG treatment was started third day after the admission. His complaints reduced four days later. Remarkable improvement occurred at the end of day 7. On the neurological exam on the 7th post-IVIG treatment day it was observed that ptosis recovered, gaze restriction regressed, gag reflex was positive, swallowing improved, and speech of nasal character regressed. Prednisolone at dose of 4 mg/day was added to his treatment. The patient whose symptoms regressed and bulbar signs disappeared is currently being followed in neuromuscular out-patient clinic. Currently, the patient is on treatment with 35 mg/day of corticosteroid and azathiopyrine and has no symptoms of MG or BD.

On the last neurological exam, it was observed that eye closing was moderately weak and neurological exam was normal in all other aspects, and that the patient had no oral and genital ulcers and attacks of uveitis.

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## 3. Discussion

Myasthenia gravis (MG) is an autoimmune neuromuscular disease due to defect in neurotransmission developing through formation of auto-antibodies to acetylcholine receptors, and rarely to the post-synaptic molecule, i.e., muscle specific kinase (MUSK). Eyelids and ocular muscles are usually first involved. As the condition advances, weakness spreads gradually from the cranial to the extremity and axial muscles [8].

In regard to pathophysiology of MG, pathogenesis appears to be due to B cells but in fact there is autoimmune response depending on both T and B cells. T-cell dependent immunological attack occurs due to damage to the post-synaptic membranes on the neuromuscular junction [9]. At the neuromuscular junction, antibodies to acetylcholine (ACh) receptor and complement components accumulate [9,10]. Receptor blockage, complement-mediated post-synaptic damage, antibody-dependent receptor destruction, and receptor internalization occur. Ultimately, number of the receptors decrease and neuromuscular transmission weakens. T cells involved in this process activate B cells and the pathogenesis is primarily dependent on the B cells. T cell receptors, CD4, B7,

and CD28 play important role in interaction between the T and B cells. Furthermore, B cells produce pro-inflammatory cytokines for proliferation such as IL-6 and IFN- $\alpha$  [11-14].

Diagnosis of MG made based on the clinical findings fluctuating in day with oculobulbar manifestations dominating and response to the anti-cholinesterase agents. Presence of anti-AChR or anti-MUSK antibodies, sequential nerve stimulations and one-fiber electromyography are adjuvant diagnostic investigations [15,16].

Behçet's disease (BD) has recently been recognized that the condition is a multisystemic chronic inflammatory disease presenting with remission and exacerbations associated with some dermatological, vascular, neurological, locomotor, intestinal, urogenital, and cardiopulmonary symptoms in addition its classical triad [5,17]. Although recent studies have suggested that the disease is an auto-inflammatory disease, recent studies have demonstrated that BD is a pattern between non-specific inflammation and auto-immune disorder [18].

Behçet's disease (BD) is a systemic vasculitis with unknown etiology and pathogenesis. Only HLA-B51 is known to be directly involved in its pathogenesis. Particularly, hypersensitivity of T cells to many antigens is critical in the pathogenesis. The cytokines and chemokines released from the APC and T cells lead to hyperactivation of the neutrophils. Activated neutrophils prime themselves as well as stimulate Th1 cells through the cytokines they release. Interaction between APC, Th1 lymphocytes and neutrophils is the basis of immune response in BD [19]. The fact that cell-mediated cytotoxicity demonstrated against oral mucosal antigens especially during exacerbations of BD and immune complexes in the circulation support the presence of immune reaction of both Th1 and Th2 types [17]. Activated monocytes in BH produce some pro-inflammatory cytokines such as IL-1, IL-6, IL-8, TNF- $\alpha$ , and granulocyte-macrophage colony stimulating factor (GM-CSF) and these cytokines leading to tissue damage probably via neutrophils contribute to leukocyte activation by interacting with the endothelial cells. These pro-inflammatory cytokines may activate non-pathogenic T- and B-cell responses. Particularly IL-8, known as major chemokine to attract and activate leukocytes, is considered to play major role in pathogenesis of the disease, and increased serum level of IL-8 has been demonstrated in the patients with BD [17,18,20,21].

Both MG and BD may be associated with other autoimmune diseases. Association of MG with thyrotoxicosis, mixed connective tissue disease, anti-cardiolipin antibodies, polymyositis has been demonstrated with a frequency beyond being co-incidence [22,23]. Association of MG has been reported with such autoimmune diseases as neuromyelitisoptica, Morvan's syndrome, paraneoplastic syndromes [24], primary progressive multiple sclerosis [25], Gullian-Barré syndrome [26], multiple sclerosis [27], Addison's disease [28], myasthenic syndrome [29], anti-phospholipid antibody syndrome [30], myositis [31], myotonic dystrophy [32], and Isaac's disease [33]. The disease frequently accompanying Behçet's disease include ankylosing spondylitis [34], IgA nephropathy [35], anti-phospholipid antibody syndrome [36], Vogli-Kayanagi-Harada syndrome [37], Sjögren's syndrome [38], Takayasu disease [39], rheumatoid arthritis, systemic lupus erythematosus [40].

T helper cells (TH), immunoglobulin-synthesizing B-cells, and TNF- $\alpha$  which is one of the pro-inflammatory cytokines,

and IL-6 are involved in common pathophysiology of both diseases.

Association of MG and BD is very rare with no case has been found in the literature except for one letter in 2004 [41].

Both BD and MG has been associated with autoimmune and other diseases characterized by inflammation. Our case had presented clinical course of MG starting after discontinuation of his medications in another center for complications of prednisolone and azathioprine that the patient had used for 17 years without interruption. It was observed that symptoms of both MG and BD disappeared after starting corticosteroids. Improvement in clinical findings of both diseases suggested us a common pathophysiology.

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### Conflict of interest

None declared.

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AK, USS: preparation of the case and discussion; RB: the follow up of the case's clinic; MB, HY, and DS: interpretation of the discussion.

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### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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