Evidence of Spontaneous Activity in Two Cases of Severe Myasthenia Gravis

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Abstract
Electromyography is an important element of clinical diagnostics and often helps physicians to find the appropriate diagnosis between different neuromuscular disorders. By having a closer look on electromyографical findings in myasthenia gravis, myopathic changes predominantly occur in proximal muscles next to a pathological decrement, which can underscore the diagnosis of this neuromuscular disorder. In polymyositis, next to myogenic changes more often signs of spontaneous activity like fibrillations and complex repetitive discharges are found as signs of muscle inflammation.

Here, we present two cases of myasthenia gravis, which had with classical electrophysiological features of myasthenia gravis, but also showed pathological spontaneous activity in the electromyographical investigation next to muscle pain, which complicated the differential diagnosis to diseases like polymyositis.

Keywords: Spontaneous activity; Myasthenia gravis; Polymyositis; Concurrence

Introduction
Myasthenia gravis (MG) is a disease with a prevalence of 20/100000 patients. It is caused by autoantibodies against postsynaptic acetylcholine receptors (AChR) or against muscle specific receptor tyrosine kinase (MuSK). The typical clinical manifestation can be divided into five grades (I-V; Myastenia Gravis Foundation of America (MGFA) classification) [1]. MGFA class I includes only ocular onset; class II includes mild generalised onset; class III includes moderate generalised onset; class IV includes severe generalised fatigue; class V patients need mechanical ventilation. For class II-IV a further classification in subclass 'a' indicates prevalent limb muscle involvement, while subclass 'b' includes patients with predominant bulbar muscle involvement.

Polymyositis (PM) is a more rare (incidence of 5-10/100000 patients per year) systemic auto-inflammatory disease of skeletal muscles with perivascular lymphocyte infiltration of cytotoxic CD8⁺ lymphocytes with MHC I positive fibres. In the pathophysiological cascade, cytotoxic T-cell-lymphocytes invade and destroy muscle cells. The resulting necrosis is caused by perforin granula, which is secreted by T-cells, in association with interferone gamma, interleukine-1 and TNF [2], the resulting clinical manifestation is symmetric proximal pure motor paresis often with myalgic pain and arthralgia. Concomitant malignant diseases are found in some cases [3]. In etiological classification systems, this disease belongs to the category of collagenoses.

Although the clinical profile and pathogenesis of MG and PM are quite different, they both share typical features of autoimmune diseases, e.g., the presence of autoantibodies, the fluctuating course of the disease, the association with other autoimmune disorders, and the effectiveness of immunosuppressive therapy. Moreover, PM is, though less frequently, accompanied by elevated AChR-antibodies [4]. However, myasthenic symptoms in patients with PM are a rare phenomenon [5-9].

Here, we report two cases of patients with MG, who had electromyographical and clinical features of PM.

Patient #1
A 58-year old woman was admitted to our hospital as an inpatient with a sore throat, dryness of the mouth, and dyspnoea and a progradient weakness of her muscles. Neurological examination revealed dysarthria, dysphagia and paresis of limb-girdle muscles and muscle pain of the proximal limbs. Deep tendon reflexes were regularly evoked. AChR-antibody levels were significantly increased (110 nmol/l). MuSK-antibody levels (5.46 nmol/l) and creatine kinase levels were normal (Table 1). Electrocardiography, cerebral magnetic resonance imaging and testing on human immunodeficiency remained inconspicuous. In the electrophysiological examination repetitive stimulation revealed a significant decrement of 35% (reference <10%; Figure 1). Additionally, pathological spontaneous activity and a myogenic pattern on electromyography were observed in several muscles (Table 2), which supported the diagnosis of a concomitant polymyositis. Unfortunately, a muscle biopsy of the left quadriceps muscle was performed after initiation of corticosteroid treatment as an outpatient. Histopathological examination revealed partly atrophic and atrophic angulated muscle fibers as well as nuclei clumps consistent with a neurogenic muscular atrophy. There was a predominant but not selective atrophy of type-II-muscle fibers. Immunohistochemistry did not show endomysial inflammatory infiltrates or expression of MHC class I-antigen on muscle fibers. No congophilic amyloid was found (Figure 2). The findings were compatible with, however, not typical for MG. Thus the diagnosis of PM, suggested by electromyographical results, could not be confirmed in muscle biopsy. Moreover, the

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A 74-year-old man was referred to our hospital with slowly progressive weakness of the masseter muscles, dysphagia, and weakness of limb-girdle muscles. His past medical history included arterial hypertension, diabetes mellitus type 2, prostate hyperplasia, and Helicobacter pylori-positive chronic gastritis. The neurological examination revealed dysarthria, dysphagia, and paresis of limb-girdle muscles. The deep tendon reflexes were normal. Laboratory investigations showed increased creatine kinase levels (286 U/l) and significantly increased AChR-antibody levels (23 nmol/l). MuSK-antibody levels, however, were normal (<0.5 nmol/l; Table 1). Anti-Jo-1 antibodies were also negative. Electromyographical examination showed a decrement of 20%, indicating a myasthenic reaction (reference <10%). Pathological spontaneous activity, a myogenic pattern and a muscle edema in the MRI of the left shoulder were indicative of PM (Table 2). In contrast, a muscle biopsy of the left deltoid revealed signs of chronic neurogenic atrophy and myopathic features. Selective type-II muscle atrophy was found, however, no signs of inflammation typical for myositis were detected. Further examinations (doppler- and duplex sonography, electroencephalography, and electrocardiography) did not show any pathological findings. Total-body (18F) fluorodeoxyglucose positron-emission-tomography was performed. No signs of malignant disease, especially a thymoma, were found. Treatment with azathioprine (100 mg/d), pyridostigmine (240 mg/d), and methylprednisolone (60 mg/d) and immune suppression with prednisolone and azathioprine were initiated which controlled the symptoms. Unfortunately, the patient developed a severe infection of the sternum postoperatively and several complications during immunosuppression, including widespread spondylodiscitis of the thoracic spine, which necessitated operative treatment and long-term mechanical ventilation for several weeks. The patient improved slowly over the course of several months and was ambulatory at one year with a significant improvement of clinical and neurophysiological findings (Figure 3). The diagnosis of myasthenia gravis was confirmed by combination of myasthenic symptoms, improvement under medication and diagnostic findings (as illustrated above). Because of the muscle pain of the proximal limbs and the pathological spontaneous activity in the electromyographical the possibility of a concomitant myositis such as PM has to be discussed.

**Patient #2**

An 18-year-old woman was referred to our hospital with slowly progressive weakness of the proximal leg and arm. She was ambulatory at one year with a significant improvement of clinical and neurophysiological findings (Figure 3). The diagnosis of myasthenia gravis was confirmed by combination of myasthenic symptoms, improvement under medication and diagnostic findings (as illustrated above). Because of the muscle pain of the proximal limbs and the pathological spontaneous activity in the electromyographical the possibility of a concomitant myositis such as PM has to be discussed.
had no lasting effect. The course of the disease worsened with progressive dysarthria and dysphagia, walking became impossible. After five immunoadsorption sessions, symptoms improved for several months. In summary pathological spontaneous activity, the myogenic pattern and the muscle edema in the magnetic resonance imaging (MRI) perturbed the classical diagnosis of MG.

Discussion

These two cases show difficulties in determining the exact differential diagnosis between myasthenia gravis and polymyositis because of the simultaneous appearance of myasthenic and myopathic symptoms in clinical and diagnostic results. In summary, it appears possible that there is a concomitant clinical manifestation of MG and myositis (see introduction).

However, there is still no clear knowledge concerning the pathophysiological cascade and the overlap of these two diseases. By having a closer look PM and MG can both be induced by autoimmune mechanisms. Autoantibodies against human tissue may play a pathophysiological cascade and the overlap of these two diseases. By having a closer look PM and MG can both be induced by autoimmune mechanisms. Autoantibodies against human tissue may play a certain role in the development of the disease. Perhaps even overlaps between PM and MG exist, but further diagnostic and therapeutic strategies may be demanded.

With these two cases, we want to make clinicians be attentive to have a closer look on electromyographical changes in patients with severe MG. In the presence of AChR antibodies there should be no doubt of the diagnosis of MG. As the presented cases show, pathological EMG patterns do not exclude the diagnosis of MG. Therefore further studies on the correlation of myogenic changes, the AChR titer and the extent of decrement in the repetitive stimulation have to be performed.

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