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Neuromuscular Disorders 29 (2019) 771–775

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Case report

A novel case of inclusion body myositis and myasthenia gravis

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Received 13 June 2019; received in revised form 30 August 2019; accepted 3 September 2019

Abstract

The co-existence of myasthenia gravis and other inflammatory myopathies has been reported in the literature before, but no clinical cases involving inclusion body myositis have been reported. We report a case of a 67-year-old patient who presented with dysphagia, exhibiting the typical electrophysiological features of postsynaptic neuromuscular junction defect with positive muscle acetylcholine receptor antibodies, consistent with the diagnosis of myasthenia gravis. Nevertheless, response to acetylcholinesterase inhibitors and immunomodulatory treatment was unexpectedly poor. As the disease progressed, the patient developed asymmetric muscle weakness, initially affecting mainly the quadriceps and the finger flexors. Muscle MRI imaging supported the presence of an inflammatory myopathy and muscle biopsy confirmed the diagnosis of inclusion body myositis. Thus, our patient represents the first reported overlap case of myasthenia gravis and inclusion body myositis.
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Keywords: Inclusion body myositis; Myasthenia gravis; Autoimmune disease; Inflammatory myopathy.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies targeting the neuromuscular junction, which in most cases are directed towards the skeletal muscle acetylcholine receptor (AChR) [1]. The pathophysiology of MG is accepted to be immune mediated [2]. Sporadic inclusion body myositis (IBM) is considered the most common inflammatory myopathy in patients over 50 years old, but its pathophysiology remains to this day an enigma: It is still unclear whether it is a primary degenerative disease with secondary dysimmune reaction or vice versa [3].

The two diseases do not seem to share any common pathophysiological ground and the coexistence of both diseases in a single patient has not been reported in the literature to our knowledge. In the current case study, we report of a patient who presented with isolated dysphagia and exhibited the typical laboratory and electrophysiological findings of myasthenia gravis. However, the lack of satisfactory response to immunomodulatory treatment and the development of clinical features incompatible with myasthenia prompted us to seek for an alternative diagnosis.

2. Case report

A 67-year-old patient presented in our outpatient clinic with a 4-month history of progressive dysphagia without significant fatigability or symptom variability. The patient had already undergone a gastroscopy which revealed a superficial gastritis and duodenitis. An ENT evaluation revealed no significant pathology. Barium swallow examination was negative for gastroesophageal reflux.

The patient's history was insignificant apart from a left brachial plexopathy 26 years previously with no residual symptoms and an appendectomy in childhood. He was not on any medication. The family history was negative for neuromuscular disorders.

Clinical examination revealed no skeletal muscle weakness. Apart from the reported mild to moderate dysphagia there were no dysarthria, muscle wasting or fasciculations and no sensory deficit.

Routine blood tests were unremarkable apart from a moderate CPK elevation with 520 U/L (normal range 26–171 U/L), mild AST elevation with 41 U/L (normal

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https://doi.org/10.1016/j.nmd.2019.09.004
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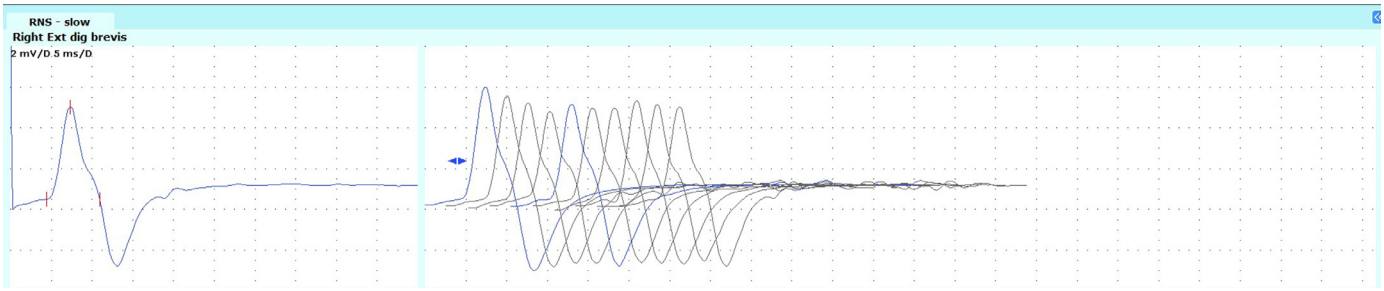

Fig. 1. Decrement of 15.6% between the first and fifth compound muscle action potential in the immediate post-activation 3 Hz-repetitive stimulation performed after 60 s maximum voluntary contraction at the right extensor digitorum brevis.

range 3–38 U/L) and mild LDH elevation with 567 U/L (208–480 U/L). Autoantibody panel failed to reveal any significant autoantibody titre. Serological markers for hepatitis B, C, Syphilis and HIV were negative. Thyroid hormones, PSA, Vitamin B12, Vitamin D and folic acid levels were within normal range. Protein electrophoresis was normal. Anti-AchR antibody in serum was with 0.9 nM (normal range < 0.6 nM) borderline positive. Anti-MuSK, anti-VGCC and anti-LRP4 antibodies were negative.

MRI of the brain and cervical spine failed to reveal any relevant pathology. CT scan of the thorax was negative for thymoma. Nerve conduction studies (NCS) were unremarkable. Electromyography (EMG) revealed widespread mild chronic denervation with no signs of active denervation or fasciculations. Single fiber electromyography in the right orbicularis oculi displayed significant jitter with mean MCD 31 μs and MSD 29 μs as well as blocking in 9/20 potentials. 3 Hz-repetitive stimulation at rest was normal at the right abductor digiti minimi, right trapezius and right extensor digitorum brevis. However, immediate post-activation 3 Hz-repetitive stimulation (RNS) performed after 60 s maximum voluntary contraction at the right extensor digitorum brevis revealed a decrement of 15.6% between the first and fifth compound muscle action potential, a finding suggestive of a post-synaptic neuromuscular junction defect (Fig. 1). Nevertheless, the atypical electrophysiological decrement with the subsequent MAP increase after the initial drop, along with the lack of reproducibility of the abnormal RNS findings in another muscle or frequency, may reflect a technical error rather a true abnormality.

Based on the positive anti-AchR antibodies and electrophysiological findings, especially the significantly abnormal single-fiber EMG, the diagnosis of myasthenia gravis was made and Pyridostigmine 180 mg/day was initiated. The patient however did not improve and Prednisone 10 mg every other day was added. Again, the dysphagia remained unchanged and the patient, four months after the initial presentation, started having difficulty climbing stairs. Prednisone was increased to 30 mg every other day and the patient was admitted for a course of intravenous immunoglobulin (IVIG) at a dose of 2 g/kg of body weight. Pyridostigmine was in the meantime discontinued due to palpitations and lack of effect.

The dysphagia improved moderately after the IVIG administration but there was further deterioration of his lower limbs weakness, with the quadriceps muscle being most affected. Clinical examination 6 months after the initial presentation revealed mild muscle weakness (MRC 4/5) on the right biceps, brachioradialis, triceps and both quadriceps (MRC 4-/5). Due to possible steroid induced myopathy prednisone was reduced to 10 mg every other day.

Again, no improvement was seen and the patient was readmitted for another course of IVIG. However his motor deficits did not respond at all to IVIG and only a mild improvement of the dysphagia was noted again. The muscle weakness in the lower extremities, particularly the quadriceps, continued to deteriorate despite another course – the third in total - of IVIG ten months after initial presentation.

A repeat EMG and NCS once more failed to reveal signs suggestive of myopathy or neuropathy. Most muscles exhibited chronic denervation with some exhibiting spontaneous activity, which was attributed to radiculopathies. MRI of the lumbar spine failed to reveal any significant pathology.

Approximately one year after initial presentation the patient complained of fine motor movement dysfunction with his hands. On examination there was finger flexion weakness bilaterally present. Meanwhile the patient developed muscle wasting, most prominent on the left quadriceps and in the tibialis anterior muscles (Fig. 2). CPK was increased to 1812 U/L. Genetic testing for X-linked spinal and bulbar muscular atrophy was negative. Anti-AchR antibodies were retested in another laboratory and came back 139 × $10^{*}-10$ mol strongly positive (normal values 0–5 × $10^{*}-10$ mol).

Although the patient initially exhibited symptoms and diagnostic tests suggestive for myasthenia gravis, it was clear that a concurrent disorder involving the muscles had to be present.

A MRI of the proximal muscles of the upper and lower extremities was performed, which showed diffuse oedema, compatible with inflammation, more prominent in vastus lateralis, intermedius and vastus longus (Fig. 3). CT-Thorax and CT-abdomen failed to reveal any evidence for malignancy. A muscle biopsy was performed with findings consistent with inclusion body myositis (Fig. 4), and the final diagnosis of

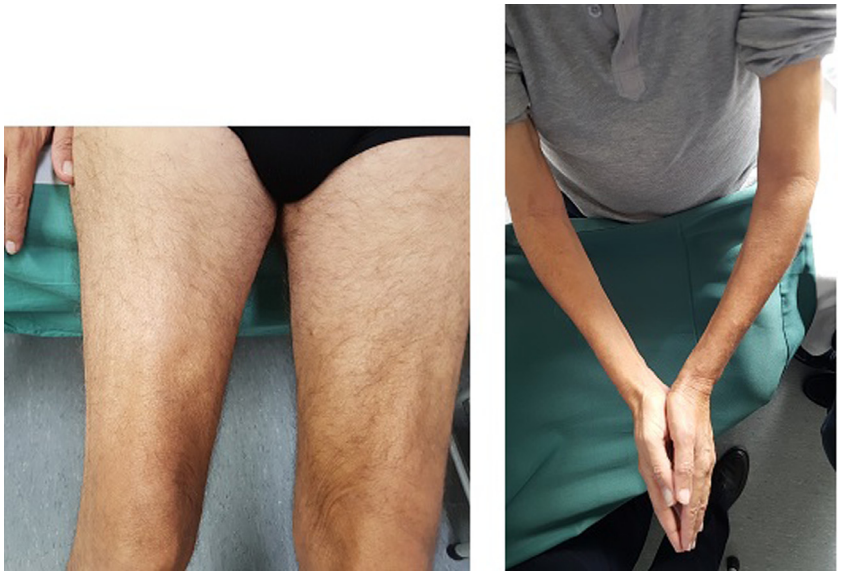

Fig. 2. Significant wasting of the quadriceps muscle bilaterally (left) and of the forearm flexors bilaterally (right).

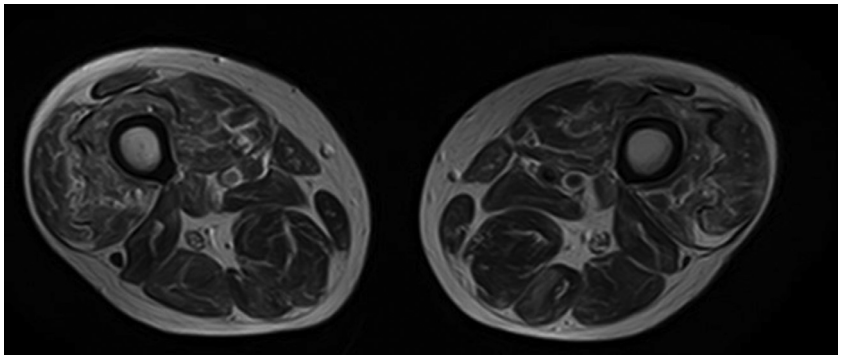

Fig. 3. Axial T2 MRI showing diffuse signal inhomogeneity in the proximal lower limb muscles, more prominent in the quadriceps bilaterally.

myasthenia gravis and inclusion body myositis was made. Anti-cN1A was negative.

3. Discussion

The co-existence of myasthenia gravis and other inflammatory myopathies has been reported before [4–6]. However this is, to our knowledge, the first case of a patient presenting clinically with sporadic inclusion body myositis with concurrent neurophysiological and immunological evidence of myasthenia gravis.

While anti-AChR antibodies are relative specific for myasthenia gravis, they can be found in other (mostly autoimmune and less commonly neurodegenerative) diseases [7,8]. Nevertheless the combination of high titre AChR antibodies, abnormal single fiber EMG in the orbicularis oculi muscle and the electrophysiological evidence for post-synaptic neuromuscular junction defect on the repetitive nerve stimulation was highly suggestive of myasthenia gravis. The clue against this being symptomatic myasthenia was perhaps the lack of clinically apparent fatigability of dysphagia. It is worth mentioning that most of the patients with coexisting inflammatory myopathies and myasthenia gravis described in the literature in contrast to our case did exhibit some or all of the classic symptoms of myasthenia, namely fatigability, diplopia, ptosis and opthalmoparesis [4–6].

The progressive muscle weakness with complete lack of response to acetylcholinesterase inhibitors along with the partial and temporary response to the immunomodulatory therapies prompted us to search for alternative diagnoses. The MRI of the proximal muscles showing diffuse muscle oedema more prominent in the quadriceps muscles confirmed the suspicion that we were not only dealing with myasthenia gravis, but with an inflammatory myopathy as well, highlighting the usefulness of imaging in the diagnosis of neuromuscular diseases with atypical presentations. The presence of rimmed vacuoles in muscle fibers in the biopsy the criteria for the diagnosis of clinically defined sporadic inclusion body myositis were fulfilled [9]. While not so frequent, IBM can present with isolated dysphagia [10–12] and responds partially to IVIG [13]. In retrospect

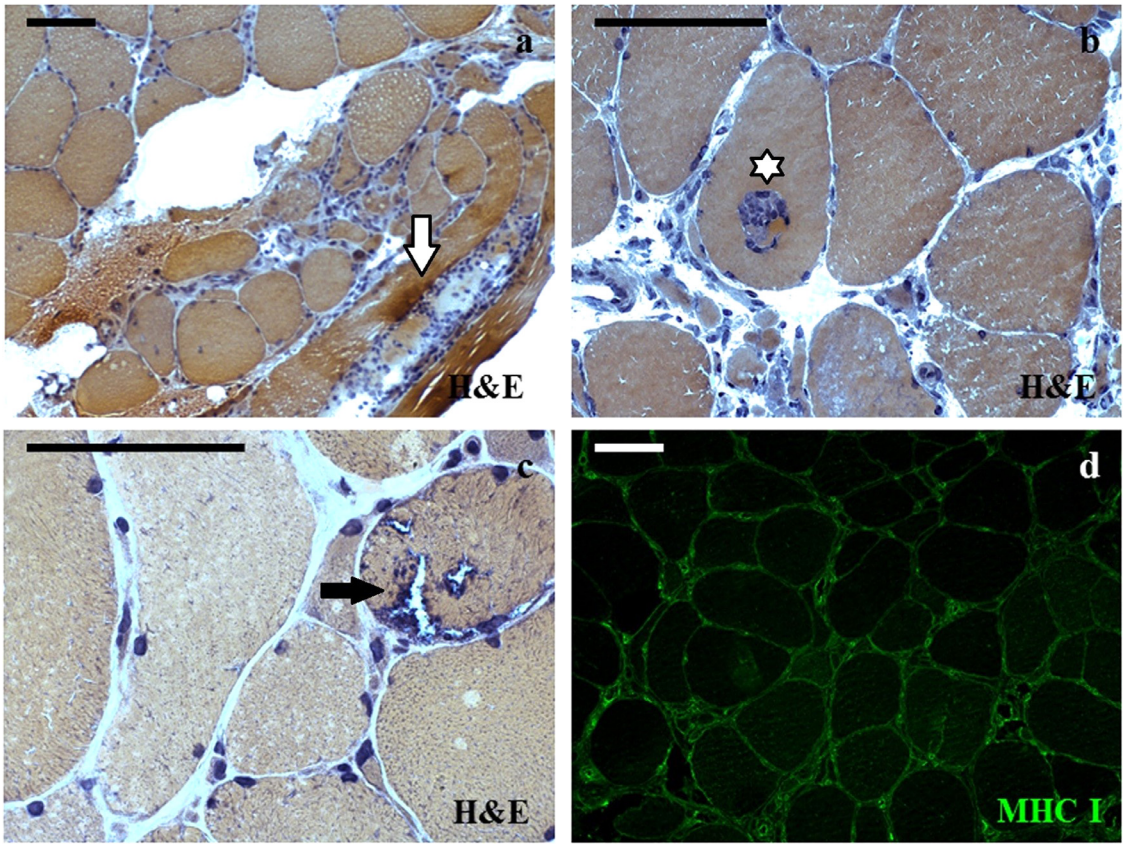

Fig. 4. (a) A muscle fiber undergoing phagocytosis (white arrow) and endomyseal mononuclear infiltrate (CD3 T-cell positive –not shown), (b) mononuclear cells infiltrating healthy myofiber (asterisk) (c) myofibre containing rimmed vacuoles (black arrow) (d) MHC type I upregulation. (bar equal 50 μm).

our patient belonged to the latter group, he presented with clinically with a rare presentation of IBM. He did not at any time have undue fatigability out of proportion to his weakness.

There is one report in the literature of a patient with Parkinson's disease presenting with symptoms of myasthenia gravis who was seropositive and had IBM changes on biopsy of the paraspinal muscle but did not exhibit the hallmark symptoms of IBM such as weakness of the quadriceps and the finger flexors [14].

It is unclear whether in our case we are dealing with overlapping autoimmune diseases. What this case however highlights is extending the spectrum of inflammatory myopathies which can co-exist with myasthenia gravis which should now include sIBM. Moreover, the presence of both inflammatory myopathies and immune-mediated neuromuscular junction diseases may not be as rare as previously thought and should be incorporated in the differential diagnosis in cases with atypical presentations or drug resistant Myasthenia Gravis.

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