RESPIRATORY FAILURE AS THE INITIAL CLINICAL MANIFESTATION OF MYASTHENIA GRAVIS IN THE INTENSIVE CARE UNIT: A CASE REPORT

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Abstract

Introduction: Myasthenia gravis is an autoimmune disorder affecting the neuromuscular junction. Regarding pathophysiology, autoantibodies target postsynaptic muscle membrane antigens, causing endplate depletion leading to muscle weakness. The clinical spectrum varies from a purely ocular form to severe general weakness affecting limb, bulbar and respiratory muscles. Myasthenic crisis, a medical emergency resulting from involvement of respiratory muscles, may manifest as the initial clinical presentation of myasthenia gravis.

Case report: Herein, we report a case of a 23-year-old male, who presented to the Emergency Department of the University Hospital of Larissa after a car accident. The patient had mild lung injury, without any neurological symptomatology. During hospitalization the patient manifested acute respiratory failure with hypercapnia leading to cardiac arrest, requiring cardiopulmonary resuscitation. The patient was intubated and admitted to the Intensive Care Unit. Despite clinical and laboratory improvement, patient had elevated carbon dioxide levels, disallowing his weaning from ventilation and oxygen supply. Patient's history revealed episodes of blepharoptosis and muscle fatiguability in the form of difficulty performing physical tasks, while neurological examination showed bulbar symptoms, facial, neck and upper extremities muscle weakness, unraveling a potential Myasthenia Gravis phenotype. Serum immunology study disclosed positive antibodies against muscle specific kinase. The patient was treated with intravenous immunoglobulin (IVIg) and then plasma exchange sessions, leading to clinical improvement.

Conclusion: Myasthenia Gravis should be suspected in case of respiratory failure and inability to wean off mechanical ventilation, especially in young adults. When treating a respiratory failure due to a potential myasthenic crisis, plasma exchange or IVIg should be carefully evaluated as an aggressive and rapid treatment option with good prognosis.

Keywords: Myasthenia Gravis, Myasthenic crisis, plasmapheresis, IVIg, intensive care unit;

ΑΝΑΠΝΕΥΣΤΙΚΗ ΑΝΕΠΑΡΚΕΙΑ ΩΣ ΠΡΩΤΗ ΕΚΔΗΛΩΣΗ ΜΥΑΣΘΕΝΕΙΑΣ GRAVIS ΣΤΗ ΜΟΝΑΔΑ ΕΝΤΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ: ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ

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Νευρολογική Κλινική, Πανεπιστημιακό Νοσοκομείο Λάρισας, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας, Λάρισα, Ελλάδα

Περίληψη

Εισαγωγή: Η μυασθένεια Gravis αποτελεί μια χρόνια αυτοάνοση διαταραχή που επηρεάζει τη νευρομυϊκή σύναψη. Παθοφυσιολογικά, αυτοαντισώματα στοχεύουν αντιγόνα της μετασυναπτικής μυικής μεμβράνης, οδηγώντας σε βλάβη της τελικής κινητικής πλάκας και μυική αδυναμία. Το κλινικό φάσμα των συμπτωμάτων κυμαίνεται από μια μεμονωμένη προσβολή των οφθαλμικών μυών έως σοβαρή γενικευμένη μυϊκή αδυναμία που επηρεάζει τους μύες των άκρων, τους προμηκικούς και αναπνευστικούς μύες. Η μυασθενική κρίση, μια επείγουσα ιατρική κατάσταση στην οποία προσβάλλονται οι αναπνευστικοί μύες, μπορεί να αποτελέσει

αρχικό σύμπτωμα της μυασθένειας Gravis.
Περιγραφή περιστατικού: Το περιστατικό που περιγράφεται αφορά άνδρα ηλικίας 23 ετών, που παρουσιάστηκε στο νοσοκομείο μετά από τροχαίο ατύχημα. Ο ασθενής εμφάνισε σημεία ήπιας θλάσης πνευμονικού παρεγχύματος, χωρίς νευρολογική σημειολογία. Κατά τη διάρκεια της νοσηλείας του ο ασθενής παρουσίασε αναπνευστική ανεπάρκεια με υπερκαπνία που οδήγησε σε καρδιοαναπνευστική ανακοπή, όπου και απαιτήθηκε καρδιοαναπνευστική αναζωογόνηση. Ο ασθενής διασωληνώθηκε και εισήχθη στην Μονάδα Εντατικής Θεραπείας. Παρά την κλινική και εργαστηριακή βελτίωση, τα αυξημένα επίπεδα CO2 του ασθενούς εμπόδισαν τον απογαλακτισμό του από τον επεμβατικό αερισμό και την παροχή οξυγόνου. Το ιστορικό του ασθενούς αποκάλυψε επεισόδια βλεφαρόπτωσης και κοπωσιμότητα των μυών με τη μορφή δυσχέρειας στην επιτέλεση καθημερινών δραστηριοτήτων, ενώ η νευρολογική εξέταση ανέδειξε προμηκικά συμπτώματα, μυϊκή αδυναμία προσωπικών μυών , μυών του αυχένα και των άνω άκρων, αποκαλύπτοντας έναν πιθανό φαινότυπο Myasthenia Gravis. Από τον εργαστηριακό έλεγχο ανιχνεύθηκαν αντισώματα κατά της ειδικής μυικής κινάσης. Ο ασθενής έλαβε θεραπεία με ενδοφλέβια γ-σφαιρίνη και έπειτα συνεδρίες πλασμαφαίρεσης , οδηγώντας σε κλινική βελτίωση.
Συμπέρασμα: Το περιστατικό αυτό αναδύει την αναπνευστική ανεπάρκεια και την αδυναμία απογαλακτισμού από το μηχανικό αερισμό, ειδικά σε νεαρούς ενήλικες, ως μια αρχική εκδήλωση της Μυασθένειας Gravis, ειδικά της υποομάδας με αντισώματα έναντι της μυικής ειδικής κινάσης. Κατά τη θεραπεία αναπνευστικής ανεπάρκειας πιθανόν στα πλαίσια μυασθενικής κρίσης, η χορήγηση ενδοφλέβιας γ-σφαιρίνης ή η πλασμαφαίρεση θα πρέπει να αξιολογείται προσεκτικά ως μια επιθετική και ταχεία θεραπευτική επιλογή με καλή πρόγνωση.

Λέξεις ευρετηρίου: Μυασθένεια Gravis; μυασθενική κρίση; πλασμαφαίρεση; μονάδα εντατικής θεραπείας;

Introduction

Myasthenia gravis (MG) is the most common disorder impacting the neuromuscular junction (NMJ) of the skeletal muscles. The cardinal symptoms of MG are muscle weakness and fatigue, predominantly impacting face, neck, eyes, lower and upper limbs muscles [1]. Autoantibodies attack against specific postsynaptic membrane proteins, resulting to electrical impulse transmission reduction across the NMJ, which subsequently generates MG clinical phenomenology [2]. Nicotinic acetylcholine receptors (n-AChRs), muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), are the main NMJ-related proteins involved as autoantibodies targets in the realm of MG. Myasthenic crisis is a life-threatening and potentially fatal MG exacerbation, characterized by weakness worsening, necessitating intubation or noninvasive ventilation [3]. Although respiratory muscle involvement resulting to respiratory failure, signs of bulbar muscle weakness frequently coexist or may even be the main clinical symptoms in myasthenic crisis course [4]. Here we report a case of respiratory failure due to MuSK-MG, newly diagnosed in intensive care unit, as a result of patient's hypercapnia and inability to wean off ventilation. Written informed consent for the publication of the case report was given by the patient. Detailed information is available on reasonable request from the corresponding author.

Case report

A 23 years old male adult, without any notable medical or family history presented to the hospital after a car accident. Patient's vital signs were stable, the level of consciousness was excellent (Glascow Coma Scale (GCS)=15/15), while laboratory findings revealed a low elevation of carbon dioxide levels (pCO_2=47 mmHg and pH=7.34). A full body computer tomography (CT) was performed revealing a mild lung injury. Consequently, the patient was admitted to cardiothoracic unit. After a couple of hours, the patient was unconsciousness (GCS=7) and manifested cardiac arrest, necessitating cardiopulmonary resuscitation and intensive care unit (ICU) admission for further evaluation and monitoring. Her vital signs revealed hypoxia (pO_2=55 mmHg and SpO_2=82%) and high levels of Carbon dioxide (pCO_2=78 mmHg). As such, mechanical ventilation was applied. A second urgent full body CT was conducted without revealing any further radiological deterioration and after 3 days the patient was awake, but oxygen supply and noninvasive ventilation were still required because of hypercapnia episodes. A neurological examination revealed diminished gag reflex, mild bilateral facial muscle weakness, drop head and proximal muscular weakness in upper extremities, with preserved tendon reflexes and without pyramidal signs, spasticity, and sensory impairment. A brain MRI was performed with unremarkable findings (figure 1). Serum antibodies against AChR, LRP4, Titin and P/Q VGCC were negative, while serum immunology analysis showing positive IgG antibodies against MusSK. The patient was initially treated with intravenous immunoglobulin (2g/kg) and then due to minor clinical improvement, 7 plasma exchange

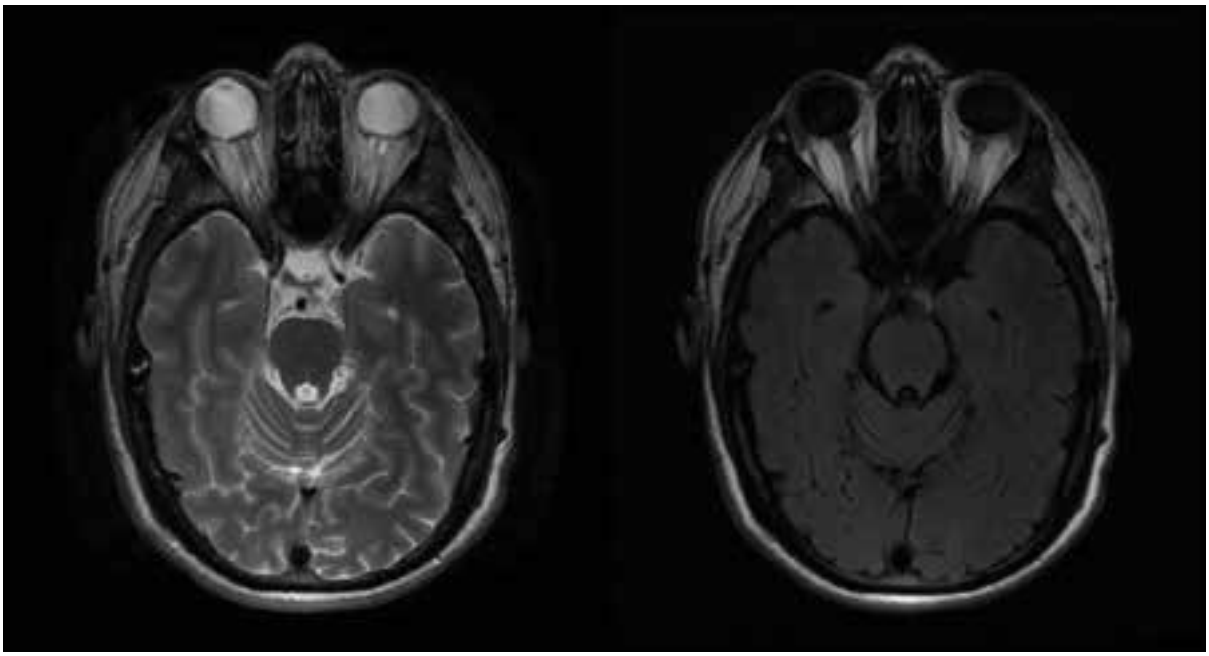

Figure 1: Brain MRI with unremarkable findings in T2 (left) and FLAIR T2 (right) sequences.

sessions were performed. Gradually the patient's muscle strength was increased, and he was able to wean off noninvasive mechanical ventilation and oxygen supply. Prednisolone (50mg) was added in treatment in order to maintain the clinical outcome and the patient discharged at home after 30 days of hospitalization with minimal neurological deficit (mild facial muscle weakness). During the 2-month follow-up the neurological examination was unremarkable without clinical signs indicative MG.

DISCUSSION

Muscle specific kinase is a membrane protein, which orchestrates AChR clustering in NMJ. Specifically, Agrin-LRP4 unit triggers MuSK phosphorylation and in turn a downstream signaling pathway is activated, resulting to the clustering of AChR and signal transduction in muscle endplate level. MuSK-MG accounts for about 5-8% of all MG cases, while antibodies against MuSK presented to approximately 40% of patients with generalized MG who are seronegative for AChR antibodies (Abs) [5]. Compared to AChR-positive MG, MuSK-MG has a different clinical, serological, and therapeutical pattern. Immunologically, MuSK Abs are not potent activators of complement and cell-mediated cytotoxicity, primarily belonging to IgG4 subclass, explaining the long-lasting efficacy of B-cell depletion treatment [6]. Moreover, MuSK Abs titers have been associated with disease severity and less favorable outcome in myasthenic crisis [4]. AChR and MuSK antibodies seropositivity has seldom been observed, reinforcing that these MG-subtypes considered to be distinct entities [2,7].

Regarding of clinical status, MuSK-MG predominantly affects young adults and craniobulbar muscular weakness appears to be more prominent neurological sequelae than AChR- MG. Moreover, acute onset and aggressive disease progression , an increased tendency for myasthenic crisis development, the rare participation of thymus gland with either thymoma or hyperplasia, limited response to cholinesterase inhibitors and worse long-term outcome are all strong indicators of MuSK-MG [5,8,9]. More than 40% of patients experienced bulbar weakness, typically combined with neck and respiratory muscles dysfunction [10]. In MuSK-MG cases drop head due to neck extensor weakness constitutes a crucial neurological symptom, whereas AChR-MG individuals exhibit neck flexor involvement. Compared to AChR-MG, limb weakness is typically milder and less common [11]. Furthermore, despite high doses of immunosuppression, MuSK-MG associated spontaneous exacerbations and myasthenic crises are common [12]. Approximately 10–15% of MuSK- MG patients have a refractory disease or experience disease relapses when their immunosuppressive treatment being tapered, highlighting the importance of aggressive treatment.

Myasthenic crisis constitutes a detrimental condition affecting 15% to 20% of MG patients at least once in their lives. The median period from clinical MG onset to the first myasthenic crisis appearance varies between 8 to 12 months, and myasthenic crisis may be the initial manifestation of MG in 20% of patients [13]. Patients requiring endotracheal in-

tubation during myasthenic crises, hospitalized for an average of 17 days, with 18% necessitating rehabilitation center. The most common trigger factors of a myasthenic crisis are mainly infections and subsequently exposure to temperature extremes, trauma, several medications, surgeries, sleep deprivation, biological stress and roughly one-third to one-half of MG cases have no clear precipitating factor suspected to myasthenic crisis [14]. The goal standard treatment of myasthenic crisis is to secure the airway, quickly initiation of rapid immunomodulatory and immunosuppressive therapy, and to treat as soon as possible identified trigger factors [14,15]. Management of myasthenic crisis includes acute causal treatment by immunoadsorption/plasmapheresis or alternatively with intravenous immunoglobulins. Although both treatment options seem to have equal impact on myasthenic crisis management, progression and long-term effect, a recent systematic review and meta-analysis demonstrated, statistically not significant, that plasmapheresis may have a faster beneficial effect on myasthenia crisis prevention, when compared to IVIG therapy [16].

Conclusion

This case-report proposes respiratory failure as a primary manifestation of MuSK-MG in a young male adult. The involvement of respiratory muscles may combine with cranial and bulbar muscle weakness. In conclusion, given the great heterogeneity of clinical manifestations of MuSK-MG, this case highlights the need for MuSK-Abs testing in patients with unexplained hypercapnia or respiratory failure, especially in cases without an underlying pulmonary disease.

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