Published in final edited form as:

Muscle Nerve. 2010 March ; 41(3): 416–419. doi:10.1002/mus.21528.

Coexistent Autoimmune Autonomic Ganglionopathy and Myasthenia Gravis Associated with Non-Small Cell Lung Cancer

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Abstract

We report a case of a 55 year old man with non-small cell lung cancer who underwent radiation, chemotherapy with carboplatin and paclitaxel, and left upper lobe removal two years prior to evaluation. He was referred for disabling orthostatic hypotension (113/69 supine, 66/47 mmHg standing after 10 minutes without a compensatory heart rate increase (57 to 59 bpm), fatigue, and constipation with episodes of ileus. Clinical examination showed mild ptosis bilaterally, fatiguable neck flexor weakness and hip flexor weakness. Blood pressure response to Valsalva maneuver was abnormal with absence of phase 4 overshoot and a Valsalva heart rate ratio of 1.04. The plasma norepinephrine level was low (79 pg/ml supine to 330 pg/ml standing). Single fiber EMG of the right extensor digitorum communis revealed normal mean MCD (jitter) but several pairs exceeded a jitter of 100 μ s. Antibodies against muscle acetylcholine receptor [(AChR) 0.66 nmol/L, normal <0.02] and ganglionic AChR (0.34 nmol/L, normal <0.02) were present. Treatment with plasma exchange normalized responses to standing posture (105/68 supine to 118/82 mmHg standing, 66 to 79 bpm), to Valsalva (normal blood pressure overshoot, HR ratio 1.47), norepinephrine (194 pg/ml supine, 763 standing), and jitter measurements. We conclude that autoimmune autonomic ganglionopathy and myasthenia gravis can coexist and suggest that the latter should be excluded in patients with autoimmune autonomic ganglionopathy who complain of fatigue that is improved with non-supine rest.

Keywords

autoimmune autonomic ganglionopathy; myasthenia gravis; paraneoplastic syndrome

Introduction

Acetylcholine receptors (AChR) are major antigenic targets in two disorders, myasthenia gravis (MG) and autoimmune autonomic ganglionopathy (AAG). Neuronal and ganglionic AChR antibodies were described in 1998, but they were not thought to have cross reactivity with muscle AChRs¹. Patients with MG typically do not have symptoms of autonomic dysfunction, in contrast to Lambert-Eaton myasthenic syndrome (LEMS), which is mediated by antibodies to P/Q voltage gated calcium channels and has prominent symptoms of parasympathetic dysfunction

Neuronal AChR antibodies are found in a subset of patients with autonomic failure¹. These patients often have substantial GI symptoms of severe constipation, ileus, diarrhea, and gastroparesis in addition to orthostatic hypotension, fatigue, inability to sweat, bladder atonia, and impotence². Post-ganglionic innervation is intact, as demonstrated by positron emission tomographic scanning with 6-[¹⁸F]fluorodopamine-derived radioactivity³. Patients may have dramatic improvement in symptoms after plasma exchange but typically require additional immunomodulatory therapy^{4,5}.

We report a case which is different from previous cases of coexistent MG and AAG with thymoma in that the patient had a prior diagnosis of non-small cell lung cancer. In addition, the case highlights many features of AAG including significant gastrointestinal symptoms and dramatic improvement following plasma exchange.

Case Report

We report a 55 year old man who was previously in good health until two years prior to evaluation, when he was diagnosed with non-small cell lung cancer. He underwent radiation, chemotherapy with carboplatin and paclitaxel, and left upper lobectomy. Eight months later he had ligation of the thoracic duct and pleurodesis for multiple recurrent pleural effusions. He then developed orthostatic hypotension causing syncopal episodes, and severe ileus causing bowel obstruction and megacolon. He denied diplopia, but he had dysphagia.

The patient was referred to the Vanderbilt Autonomic Dysfunction Center for further evaluation and treatment. Clinical examination on admission revealed mild ptosis bilaterally, fatigable neck flexor weakness and mild hip flexor weakness. Pupillary response to light was normal, although formal testing not performed. Deep tendon reflexes were normal. The rest of the examination was normal. He had significant orthostatic hypotension, with a drop in systolic blood pressure of 44 mm Hg upon standing (from 129/75 mm Hg supine to 97/62 standing) without a compensatory heart rate increase (from 60 bpm supine to 58 standing). The patient had an abnormal blood pressure response to Valsalva maneuver with absent phase II recovery and phase IV overshoot (Figure 1a). Changes in heart rate were also blunted (Valsalva ratio, 1.04; normal greater than 1.4). Sinus arrhythmia was impaired (E:I or expiration: inspiration ratio 1.03, Figure 2a; normal value greater than 1.2). There was minimal increase in blood pressure after hand grip and cold pressor tests. Plasma norepinephrine levels were decreased, although in the normal range [norepinephrine 79 pg/ml supine, 330 pg/ml standing (normal supine 75–501 pg/ml, standing 92–1304 pg/ml); epinephrine supine 5.3 pg/ml, standing 12.5 pg/ml (normal epinephrine supine 0–87 pg/ml, standing 0–315 pg/ml)]. Repetitive stimulation of the ulnar nerve and spinal accessory nerves produced no amplitude decrement or facilitation. Single fiber EMG, recording from the extensor digitorum communis, revealed increased jitter (several pairs with jitter greater than 100 us) in the extensor digitorum communis. A paraneoplastic antibody panel revealed elevated levels of both muscle AChR binding antibody (0.66 nmol/L) and ganglionic AChR antibody (0.34 nmol/L) (Normal levels <0.02 nmol/L). Calcium channel antibodies were not present.

The patient was treated with plasma exchange (one exchange daily for five days). After treatment systolic blood pressure increased by 8 mm Hg after standing (from 109/66 mm Hg supine to 118/82 standing for 10 minutes) (Figure 3). Sinus arrhythmia E:I ratio improved to 1.19, Valsalva ratio to 1.47 (figure 2a and 2b). Blood pressure increased in response to hand grip and cold pressor testing from 8 mm Hg before PE to 13, and from 8 mm Hg to 18, respectively.; Plasma norepinephrine and epinephrine levels increased after plasma exchange (norepinephrine 194 pg/ml supine and 763 pg/ml standing; epinephrine 14.1 pg/ml

supine and 21.8 pg/ml standing). The patient was discharged on prednisone and pyridostigmine.

Abnormalities in single fiber EMG improved after one plasma exchange. Clinically the patient had increased strength after five exchanges were performed. Levels drawn after five exchanges showed a decrease in the muscle AChR binding Ab level from 0.66 to 0.23 nmol/L and in the ganglionic AChR Ab level from 0.34 to 0.05 nmol/L.

At his follow up admission three months after the initial plasma exchange, the patient had declined clinically, both in autonomic and myasthenic symptoms. Repeat autonomic testing revealed similar abnormalities as his initial evaluation. In addition, he had increased dyspnea, and was unable to generate 40 mm respiratory pressure during the Valsalva maneuver. He subsequently improved after repeat plasma exchange in both myasthenic and autonomic symptoms.

Discussion

This case highlights the potential for clinical improvement in AAG and dramatic normalization of autonomic function test results after treatment. To date, there have been seven patients reported with antibody documented AAG and MG. Those cases manifesting as a paraneoplastic syndrome were associated with thymoma^{6,7}. There have also been two cases of coexistent MG and autonomic failure. Several cases of MG and pseudo-obstruction were reported before and after ganglionic antibody assays were available so the antibody status of some cases is unknown⁸⁻¹¹. Our patient had a non-small cell lung cancer as the primary tumor and no evidence for thymoma. We are not aware of previous cases of AAG and MG associated with lung cancer.

The ganglionic and muscle AChR are thought to be immunologically distinct due to the different subunits found in the two receptors, although 3% of patients with MG may have coexistent antibodies (18).. In myasthenia gravis, antibodies are directed against the $\alpha 1$ subunits of nicotinic muscle AChRs. Antibodies directed against neuronal AChRs present in sympathetic and parasympathetic autonomic nerves are directed toward the $\alpha 3$ subunit, which is similar in homology to the muscle $\alpha 1$ subunit¹². Muscle and neuronal AChRs are found in human thymic tissue which is thought to play a role in autoimmunity in myasthenia gravis.¹³⁻¹⁵. Therefore, the presence of thymoma in previously described patients with coexistent MG and AAG is not surprising given that thymic tissue displays multiple acetylcholine receptor subunits¹⁶. Nicotinic acetylcholine receptors (nAChR) are also present in bronchial epithelium, alveolar epithelial cells, pulmonary neuroendocrine cells, and human small cell lung cancer cell lines which could explain the association with non-small cell lung cancer^{15, 17, 18}.

The clinical course of this patient is typical for patients with AAG, as he had a severe ileus that led to hospitalization^{2,4}. He experienced a dramatic response to plasma exchange which was supported by objective improvement in his autonomic function test results and catecholamine levels. This was accompanied by a significant reduction in his muscle AChR and ganglionic AChR levels. This patient had relatively low levels of antibody compared to other reported cases, but he still improved after treatment. His levels are consistent in with presentation, given that he had less severe orthostatic hypotension and no pupillary abnormalities compared to other patients previously reported¹⁹. The reversibility of his test results supports the diagnosis of AAG, despite his previous exposure to chemotherapeutic agents which can also cause autonomic neuropathy. The failure of prednisone alone to maintain his improvement is also similar to other cases reported⁵.

Our patient had normal repetitive stimulation and required single fiber EMG evaluation to corroborate the diagnosis. However, it is important to continue to screen patients using repetitive stimulation to differentiate coexistent MG and AAG with Lambert-Eaton myasthenic syndrome. LEMS is a disorder which affects presynaptic neuromuscular junction transmission and is associated with autonomic symptoms, weakness, and antibodies to the P/Q type calcium channel.

Clinically, patients with myasthenia and autonomic failure both complain of fatigue. This is worsened by prolonged activity in myasthenia and prolonged upright posture in autonomic failure. The history of dysphagia and diplopia would not have been expected in AAG alone. Because the immunomodulatory treatment for both AAG and MG is similar, patients may experience improvement in both disorders, making it harder to identify coexistent MG and AAG. Specific electrodiagnostic testing including single fiber EMG, autonomic function test and careful clinical examination should be performed on patients with AAG or MG to rule out the other disorder. Appropriate evaluation to rule out an underlying malignancy should also be performed at time of diagnosis.

Acknowledgments

This study was funded by the National Institutes of Health 1K23 NS056009-01A1; P01 HL056693, R01 HL071784 and by Vanderbilt CTSA grant 1 UL1 RR024975.

Abbreviations

AChR	acetylcholine receptor
MG	myasthenia gravis
AAG	autoimmune autonomic ganglionopathy
NSLC	non-small cell lung cancer
AFT	autonomic function test
MCD	mean consecutive difference (jitter)
BPM	beats per minute
LEMS	Lambert Eaton myasthenic syndrome
Pg/ml	pictogram/milliliter
E:I ratio	expiration to inspiration ratio
EMG	electromyography

Reference List

1. Vernino S, Adamski J, Kryzer TJ, Fealey RD, Lennon VA. Neuronal nicotinic ACh receptor antibody in subacute autonomic neuropathy and cancer-related syndromes. *Neurology*. 1998; 50:1806–1813. [PubMed: 9633732]
2. Sandroni P, Vernino S, Klein CM, Lennon VA, Rud-Larson L, Sletten D, Low PA. Idiopathic autonomic neuropathy: comparison of cases seropositive and seronegative for ganglionic acetylcholine receptor antibody. *Arch Neurol*. 2004; 61:44–48. [PubMed: 14732619]
3. Goldstein DS, Holmes C, Dendi R, Li ST, Brentzel S, Vernino S. Pandy's autonomic neuropathy associated with impaired ganglionic neurotransmission and circulating antibody to the neuronal nicotinic receptor. *Clin Auton Res*. 2002; 12:281–285. [PubMed: 12357282]

4. Schroeder C, Vernino S, Birkenfeld AL, Tank J, Heusser K, Lipp A, Benter T, Lindschau C, Kettritz R, Luft FC, Jordan J. Plasma exchange for primary autoimmune autonomic failure. *N Engl J Med*. 2005; 353:1585–1590. [PubMed: 16221781]
5. Gibbons CH, Vernino SA, Freeman R. Combined immunomodulatory therapy in autoimmune autonomic ganglionopathy. *Arch Neurol*. 2008; 65:213–217. [PubMed: 18268189]
6. Vernino S, Cheshire WP, Lennon VA. Myasthenia gravis with autoimmune autonomic neuropathy. *Auton Neurosci*. 2001; 88:187–192. [PubMed: 11474561]
7. Rakocevic G, Barohn R, McVey AL, Damjanov I, Morte PD, Vernino S, Lennon V. Myasthenia Gravis, Thymoma, and Intestinal Pseudo-Obstruction: A Case Report and Review. *J Clin Neuromuscul Dis*. 2003; 5:93–95. [PubMed: 19078726]
8. Senda Y, Sugimura K, Koike Y, Matsuoka Y, Takahashi A. [Concurrence of acute autonomic and sensory neuropathy and myasthenia gravis--a case report and pathogenetic considerations]. *Rinsho Shinkeigaku*. 1989; 29:332–335. [PubMed: 2665997]
9. Tabbaa MA, Leshner RT, Campbell WW. Malignant thymoma with dysautonomia and disordered neuromuscular transmission. *Arch Neurol*. 1986; 43:955–957. [PubMed: 3741215]
10. Tan CK, Ng HS, Ho JS, Theobald DM, Lim YC. Acute intestinal pseudo-obstruction due to malignant thymoma. *Singapore Med J*. 1993; 34:175–178. [PubMed: 8266165]
11. Anderson NE, Hutchinson DO, Nicholson GJ, Aitcheson F, Nixon JM. Intestinal pseudo-obstruction, myasthenia gravis, and thymoma. *Neurology*. 1996; 47:985–987. [PubMed: 8857731]
12. Vernino S, Lindstrom J, Hopkins S, Wang Z, Low PA. Characterization of ganglionic acetylcholine receptor autoantibodies. *J Neuroimmunol*. 2008; 197:63–69. [PubMed: 18485491]
13. Engel EK, Trotter JL, McFarlin DE, McIntosh CL. Thymic epithelial cell contains acetylcholine receptor. *Lancet*. 1977; 1:1310–1311. [PubMed: 68406]
14. Kirchner T, Tzartos S, Hoppe F, Schalke B, Wekerle H, Muller-Hermelink HK. Pathogenesis of myasthenia gravis. Acetylcholine receptor-related antigenic determinants in tumor-free thymuses and thymic epithelial tumors. *Am J Pathol*. 1988; 130:268–280. [PubMed: 2449082]
15. Mihovilovic M, Hulette C, Mittelstaedt J, Austin C, Roses AD. Nicotinic neuronal acetylcholine receptor alpha-3 subunit transcription in normal and myasthenic thymus. *Ann N Y Acad Sci*. 1993; 681:83–96. [PubMed: 8357212]
16. Mihovilovic M, Butterworth-Robinette J. Thymic epithelial cell line expresses transcripts encoding alpha-3, alpha-5 and beta-4 subunits of acetylcholine receptors, responds to cholinergic agents and expresses choline acetyl transferase. An in vitro system to investigate thymic cholinergic mechanisms. *J Neuroimmunol*. 2001; 117:58–67. [PubMed: 11431005]
17. Maus AD, Pereira EF, Karachunski PI, Horton RM, Navaneetham D, Macklin K, Cortes WS, Albuquerque EX, Conti-Fine BM. Human and rodent bronchial epithelial cells express functional nicotinic acetylcholine receptors. *Mol Pharmacol*. 1998; 54:779–788. [PubMed: 9804613]
18. Zia S, Ndoye A, Nguyen VT, Grando SA. Nicotine enhances expression of the alpha 3, alpha 4, alpha 5, and alpha 7 nicotinic receptors modulating calcium metabolism and regulating adhesion and motility of respiratory epithelial cells. *Res Commun Mol Pathol Pharmacol*. 1997; 97:243–262. [PubMed: 9387186]
19. Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. *Auton Neurosci*. 2009; 146:8–12. [PubMed: 19144572]

Figure 1.

Heart rate response to deep breathing before (a) and after plasma exchange (b). There is restoration of the normal difference in R-R interval during expiration and inspiration after plasma exchange. There was a mild improvement in respiratory effort, which may partially explain the improvement in heart rate response.

Figure 2. Heart rate and beat-to-beat blood pressure response to Valsalva maneuver before exchange (a) is improved after plasma exchange (b). Note the patient generated a similar Valsalva positive pressure (40 mm Hg) during the baseline as well as post-exchange, demonstrating that respiratory effort did not account for the improvement in blood pressure response.

Orthostatic Mean Arterial Blood Pressure

Figure 3.

Mean arterial pressure (MAP) is significantly reduced upon standing at baseline compared to lying MAP. It normalized after day one of plasma exchange and continues to be normal.