Paraneoplastic disorders affecting the neuromuscular junction:

Myastenia gravis associated with paraneoplastic syndrome

- case report -

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Абстракт

Паранеопластичните невролошки пореметувања можат да го зафатат било кој дел од невролошкиот систем. Ретко кога моторниот неврон или моторните аксони можат да бидат афектирани кај пациенти со канцер,но сепак доколку се зафатат води до појава на клинички знаци и симптоми кои наликуваат на Амиотрофична латерална склероза. Друго заболување кое е прототип за автоимуно заболување на нервниот систем е Myasthenia gravis. Во повеќето случаеви етиологијата е идиопатска и начините за продукција на автоантителата за ацетилхолинските рецептори сеуште не се познати. Сепак 15% од пациентите имаат паранеопластична форма на Myasthenia gravis асоцирана со тимом. Пациентите обично имаат генетализирана форма со доцен почеток и истите бараат долгогодишен третман со имуносупресија. Друга форма на нарушување на невромускулната синапса е Sy. Lambert – Eaton, што често е придружен со ситноклеточниот карцином на белите дробови.

Клучни зборови:

Паранеопластичните невролошки пореметувања,Миастенија гравис,тимом , долгогодишен третман со имуносупресија.

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Abstract

Paraneoplastic neurologic disorders can affect any part of the nervous system. Rarely, the motor neuron or motor axons may be affected in patients with cancer , leading to clinical signs and symptoms that resemble ALS. Myasthenia gravis (MG) is the prototypic autoimmune disorder of the nervous system. In most cases ,MG is an idiopathic disorder, and the events leading to the production of acetylcholine receptor autoantibodies are not known. About 15% of the patients have a paraneoplastic form of MG associated with a thymic neoplasm (thymoma).Patients with paraneplastic MG typically have late-onset generalized MG and require long –term immunosuppression. Another form of neuromuscular junction disorder , the Lambert- Eaton myasthenic syndrome, often occurs a as a paraneoplastic manifestation of small cell lung cancer. Together, MG and Lambert-Eaton syndrome are the most common paraneoplastic neurologic disorders.

Key words :

Paraneoplastic neurologic disorders. Myasthenia gravis, thymoma ,long term immunosuppression.

Introduction:

Paraneoplastic neurologic disorders are diseases of nervous system that occur in association with cancer but are not due to direct effects of the tumor or its metastases. These disorders are causes by remote effects of malignancy believed to be mediated by immune system. The mechanism likely involves the expression of antigens by the tumor that stimulates an immune response involving T cells , antibodies, or both, that is directed against not only tumor cells but also neutral or nerve/muscle cells.

An association of MG with thymic tumor first was reported in 1903 (Laquer,1903)(1). As many as 40% to 50% of patients with thymoma have MG, and approximately 15% of patients with MG have thymoma (Thomas CR,1999)(2). MG is caused by autoantibodies

against postsynaptic nicotinic acetylcholine receptors (AChRs) at neuromuscular junction (Willcox,1993)(3). The resulting deficit in neuromuscular transmission results in the characteristic symptoms of weakness and fatique of bulbar and proximal muscles.

Paraneoplastic MG is clinically identical to MG without thymoma with few exceptions. The majority of patients with thymoma are older than 50 years, with a mean age of 55. However, thymoma may be found in myasthenic patients as young as 20 years and rarely in childhood MG.

The female predominance seen in younger patients with MG is not evident in paraneoplastic or thymomatous MG. The symptoms of myasthenia are typically generalized, may have a more rapid onset, and may be difficult to control until the thymoma is removed. After appropriate thymoma treatment , contemporary studies indicate that the prognosis of paraneoplastic MG is similar to other cases of late-onset similar to other cases of late-onset, nontymomatous MG (Bril et al,1998,de Perrot et al ,2002)(4) .

Thymoma is a relatively rare neoplasm of thymic epithelial cells, which is unique because of its frequent association with autoimmunity , probably due to dysregulation of lymphocyte selection (Morgenthaler et al, 1993)(5). Thymoma-related autoimmunity also may be caused by presentation of self -antigens expressed by the neoplastic cell. Autoractive T lymphocytes may proliferate , leave the tumor, and stimulate B cells for antibody production. Unlike the case for tymic hyperplasia, no significant autoantibody production occurs within the tymus itself. Other tumors that originate in the anterior mediastinum (lymphoma, carcinoid) do not demonstrate the same association with autoimmunity.

Antibody profiles in Paraneoplastic Myasthenia Gravis

Autoantibodies specific for skeletal muscle AChR, striated muscle antigens as well as neuronal antigens , are common in patients with thymoma and may be found even in absence of clinical evidence of MG (Vernino and Lennon, 2004)(6). Muscle AChR antibodies are the most commonly detected antibodies with thymoma. In most studies , all patients with thymoma and MG have muscle AChR binding antibodies (Lindstrom et al,1998)(7). In other words, thymoma is associated with neither seronegative MG nor musclr- specific receptor tyrosine kinase (MuSK) antibodies (Leite et al, 2005)(8). AChr modulating antibodies cause a reduction in surface AChr, and blocking antibodies are those those that interfere with the acetylcholine) AChR modulating antibody levels are generally high in patients with thymoma.

Striational antibodies were the first autoantibodies recognized with thymoma and MG. These antibodies recognize muscle cytoplasmic proteins, including titin, myosin, actin alpha-actinin. Striational antibodies are detected in a majority of patients - 85% with thymomatous MG and also in a minority of thymoma patients without MG (Somnier and Engel,2002)(9). Other antibodies that can be found are against glutamic acid decarboxylase (GAD65),collapsing-response mediator protein (CRMP5),voltage-gated potassium channels (VGKCs),antinuclear antibodies ,antimitochondrial antibodies and others.

Motive and Purpose:

Timely treatment of patients with Myasthenia gravis which is associated with thymoma improves the quality of life, reduce complications , reduces morbidity on the one hand and prolongs survival time of the other.

The purpose of the cases is to see the connection of Myasthenia gravis with thymoma as often paraneoplastic neurological disease.

Material and Methods: The study is a review of two cases (case report):

First case:

- Patient 32 years old, female, unemployed.
- The disease began in June 2009 with progressive bilateral symmetrical ptosis, diplopia in horizontal view left and right, dysarthria and proximal muscle weakness of all limbs, mostly in upper limbs. At the same time, the patient complained of dyspnea with lower limb swelling.
- Because of the above symptoms the patient is hospitalized et neurological unit
- During hospitalization are made several examinations: laboratory with normal findings. The creatine kinase level was elevated. Prostigmine test was positive after 15 minutes with improvement the ptosis, diplopia and muscle weakness. Echocardiogram revealed mild dilated cardiomyopathy with reduced ejection fraction. Chest CT showed a well-encapsulated anterior mediastinal mass. Conciliar thoracic surgeon: set indication for surgery
- Before the operation the patient was treated with corticosteroids, with inhibitors of acetylcholine esterase and plasma exchange on three occasions.
- Performances improvement of clinical picture with the withdrawal of neurological symptoms.
- Complete thymectomy is made and after the operation the patient is set on corticosteroid and immunosuppressive therapy (azathioprine) and pyridostigmine with recommended regular audits by the neurologist and surgeon.
- Ambulatory before surgery was advised to make test serum present antibodies to acetylcholine receptors. Serum tests were positive for AChR-binding (12.0 nmol/l) and AChR – modulating (96% loss of AChR) antibodies.

Results: the patient is with stable clinical picture of the disease and set regular therapy for Myasthenia gravis

Comments and discussion: even though this patient is young, the subacute onset of severe generalized form of Myasthenia gravis as well as the presence of serum antibodies raises the suspicion of paraneoplastic Myasthenia gravis related to thymoma. The coexistence of myocarditis has increased the likelihood of the presence of thymoma.

Second case:

- Patient 76 year old, man
- The first symptoms of disease have occurred in October 2011 with an intense dry cough
- Because of the above symptoms the patient is hospitalized et internal unit.
- During hospitalization are made several examinations: laboratory with normal findings, but the sedimentation was elevated. X ray chest showed expansion of anterior mediastinum and advised to make chest CT. Chest CT showed large anterior mediastinal mass with indistinct margins encasing the great vessels as well as pleural metastases. Conciliar thoracic surgeon: set indication for surgery

- He underwent subtotal resection of en invasive thymoma followed by radiation therapy.

- Before surgery and 6 months later the patient had no neurological symptoms of Myasthenia gravis

- Six months later, he came to neurologist with progressive dysphagia, dyspnea and proximal muscle weakness. Neurological examination demonstrated moderate weakness of m .orbicularis oculi, neck flexors and proximal limb muscles after performing tests of neuromuscular fatiguing.

- Ambulatory before surgery was advised to make test serum present antibodies to acetylcholine receptors. Serum tests were positive for AChR-binding (4 nmmol/l) AChR – modulating (100% loss of AChR) and striational antibodies.

- Repeat chest CT showed residual thymoma in anterior mediastinum encasing the great vessels as well as pleural metastases. Prostigmine test was positive after 15 minutes with improvement in limb and neck strength, but swallowing and respiratory symptoms persisted.

- The patient is set on corticosteroids, immunosuppressive therapy and physiostigmine with regular controls et neurologist and surgeon.

Results: the patient is with stable clinical picture of the disease and set regular therapy for Myasthenia gravis. In the same time he is monitored by the surgeon and internist because of symptoms from local tumor invasiveness.

Comments and discussion: However, in about 2% of cases, the first Myasthenia gravis symptoms develop after the initial treatment of thymoma. One – third of thymoma cases are diagnose during evaluation of chest symptoms such as cough or dyspnea.

All autoantibodies can be present in patients with thymoma who have no signs or symptoms of Myasthenia gravis, and they do not necessarily indicate that Myasthenia gravis will develop later. In cases of malignant thymoma that fail initial therapy, however, the prognosis is guarded because of local complication of invasive tumor

Chemotherapy has been shown to improve survival in metastatic thymoma. With invasive thymoma, symptoms of dysphagia and dyspnea may be attributed to damage to the phrenic or recurrent laryngeal nerves from tumor invasion, radiation or surgery rather than Myasthenia gravis. Because of that those symptoms may not respond to Myasthenia gravis therapies.

The relapse rate for encapsulated tumors is less than 5% but the relapse rate is much higher for invasive or more malignant tumors. Thymoma recurrence can be heralded by worsening of myasthenia or the appearance of other paraneoplastic phenomena.

Postoperative radiotherapy is used for invasive malignant thymoma or other incomplete resection. Radiotherapy alone in unresectable, widely invasive disease can produce local disease control with a 5 year survival rate of 45% to 50%.

Conclusion: Thymomatous MG was considered to be more severe and refractory to treatment than MG without thymoma. This observation probably reflected the older age in these patients, or coincidence of other autoimmune conditions.

Recent case series show no significant difference in long – term MG prognosis related to the presence of thymoma. Likely factors leading to this improvement in outcome are advances in diagnostic imaging that allow earlier detection of thymoma , improvements in thymectomy techniques , and better perioperative myasthenia management.

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