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Case Report

MYASTHENIC CRISIS AS A SIDE EFFECT OF METHIMAZOLE THERAPY: CASE REPORT

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SUMMARY – Myasthenia gravis and Graves' disease are two autoimmune diseases with a similar mechanism, both having circulating organ autoantibodies and cell specific autoantibodies. It is not unusual for these diseases to occur together. There is a large body of data proving that antithyroid drugs such as methimazole and propylthiouracil have an immunomodulatory effect in addition to their thyrosuppressant action. This case report describes a 34-year-old woman hospitalized for just diagnosed myasthenic crisis (Osserman IV). She had a prior history of hyperthyroidism and treatment with methimazole was initiated. However, improvement in thyroid disease led to the burst of myasthenia. The phenomenon described as worsening of one disease while improving the other, the so-called 'see-saw' relationship, occurred in this case. The question is whether antithyroid drugs improve hyperthyroidism while unveiling or worsening myasthenia. Is the 'see-saw' relationship actually a therapeutic side effect of antithyroid drug? The proposed mechanism of methimazole action is intracellular: it lowers the level of proliferating cell nuclear antigen (PCNA). PCNA promotes selective apoptosis in some T lymphocyte clones. In this way, $CD4^+CD25^+$ regulatory T cells might 'skip' immune self-tolerance and autoantibodies against acetylcholine receptor may occur. Do antithyroid drugs actually create an immune 'thymic surrounding'?

Key words: *Hiperhyroidism – complications; Hiperhyroidism – drug therapy; Myasthenia gravis – complications; Myasthenia gravis – drug therapy; Methimazole – adverse effects*

Introduction

Thyroid gland is the organ with perhaps most common autoimmune pathology. Having one autoimmune disease in the body increases the chance of developing another one[1] . There also are syndromes that include more autoimmune features connecting thyroid gland and myasthenia gravis, e.g., polyglandular syndrome type II (Schmidt's syndrome)[2]. Schmidt's syndrome is characterized by the presence of two or more autoimmune diseases, usually affecting thyroid gland, adrenal glands and endocrine pancreas. It is not unusual that other diseases like myasthenia, hypogonadism, pernicious anemia, Parkinson's disease and celiac disease occur. Polyglandular syndrome type II is linked with HLA DR3 and HLA DR4 locus, inherited in the autosomal dominant mode with variable expressivity[3]. There are a number of reports describing the same incidence of myasthenia gravis and thyroid disease, with or without polyglandular syndrome, so that statistically as many as 5%-10% of patients suffering from myasthenia have some kind of thyroid autoimmunity[4,5]. The prevalence of myasthenia gravis in Graves' disease is 0.14%[6] . Although there are known HLA typing points to the possible HLA DQ3 association in patients with myasthenia and hyperthyroidism, the exact relationship between these two diseases

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remains unknown[7] . The mechanism of both diseases is autoimmune, with circulating organ autoantibodies and cell specific autoantibodies (anti-acetylcholine receptor antibody in myasthenia and anti-thyrotropin receptor antibody in Graves' disease). Both diseases produce neuromuscular symptoms that sometimes resemble each other (weakness and fatigue). Both diseases are more common in females and in younger patients[8]. A 'see-saw' relationship between Graves' disease and myasthenia gravis has already been documented, describing worsening of one disease while improving the other[9,10]. It is well known that thyrostatic drugs have both thyrosuppressant action and an additional immunomodulatory effect. While treating hyperthyroidism, microsomal antibodies and thyrotropin receptor antibodies decrease independently of the thyroid hormone level[11,12]. Other autoimmune events have also been reported while treating patients with antithyroid drugs. In some patients, development of the insulin autoimmune syndrome was observed[13]. Even agranulocytosis, a well known side effect of thyrostatic drugs, is by some authors explained by immunoreactivity[14]. Antineutrophil cytoplasmic antibody (ANCA)-mediated vasculitis is also associated with this therapy[15]. Finally, psoriasis, a skin disease mediated by activated T cells, seems to improve during treatment with thyrostatic drugs[16]. Considering all information mentioned above, it should not be taken for surprise that some other autoimmune diseases occur during thyrostatic treatment for Graves' disease. We suggest that the 'see-saw' relationship observed in myasthenia and Graves' disease is actually a side effect of thyrostatic therapy. This drug therapy improves hyperthyroidism while unveiling or worsening the already existing myasthenia gravis.

Case Report

A 34-year-old woman was admitted to the hospital for extreme muscular weakness and cyanosis. Blood gas analysis suggested hypoventilation syndrome (saturation 55%) that required immediate intubation and mechanical ventilation. Her medical history included left optical nerve excision long time before, with consequential ptosis of the left superior palpebra. She was treated four years for hyperthyroidism due to diffuse antibody negative goiter. Thyroid gland ultrasonography showed diffusely inhomogeneous tissue measuring 8.3x2.8x3.6 cm in the left lobe and 8.8x2.9x2.7 cm in the right lobe. Ophthalmologic examination revealed thyrotoxic orbitopathy and ptosis of the left palpebra. The patient had several relapses due to non-compliance with her thyrostatic drug; she was reluctant to other types of therapy, not visiting endocrinologist regularly. The last relapse occurred two months before admission, predominantly manifesting with cardiologic symptoms, paroxysm and atrial flutter. Her laboratory findings at the time of relapse were as follows: TSH 0.1; T3 7.6 nmol/L; and T4 400 nmol/L (normal ranges: TSH 0.4-4.2 mIU/L; T3 1.3-2.5 nmol/L; and T4 70-165 nmol/L); free T3 3.6-7.8 pmol/L; and free T4 8-23 pmol/L; so methimazole was administered. Atrial flutter was converted to sinus rhythm. Two months later, thyroid function improved and so did laboratory findings (T3 2.1 nmol/L and T4 80 nmol/L). During this period, she experienced muscle weakness, fatigability of upper and lower extremities, dysphonia, dysphasia, and progressive breathlessness. Her symptoms improved at rest and deteriorated upon muscular work, during conversation in particular. Since neuromuscular disease was suspected, a neurologist was consulted and Prostigmine test was performed. A positive result confirmed myasthenic crisis (grade Osserman IV or American Myasthenia Gravis Foundation grade V)[17], although prior ptosis of the left superior palpebra made the diagnosis somewhat difficult. Computer tomography (CT) scan showed no thymus, but anti-AChR antibodies were positive. Therapeutic regimen included three plasmapheresis procedures, glucocorticoid (methylprednisolone) and acetyl cholinesterase inhibitor (pyridostigmine). Following plasmapheresis, her clinical status rapidly improved. The patient was improving quickly and was extubated on day 6. Thyroid hormone levels dropped (T3 0.6 nmol/L and T4 19 nmol/L). At that time, methimazole was discontinued. She was discharged from the hospital with oral corticoid and pyridostigmine. Further endocrinologist evaluation showed no other elements of polyglandular syndrome, but levothyroxine substitution was introduced due to the low thyroid hormone levels. Then, laboratory findings showed T3 1.3 nmol/L; free T3 4.7 pmol/L; T4 78 nmol/L; free T4 9.4 pmol/L; and levothyroxine dosage was corrected. Her muscular

strength improved even more. Two months later, total thyroidectomy was performed while being euthyroid (histopathology: Basedow's goiter), with no difficulties in anesthetic procedure. Her postoperative recovery was unremarkable, and she was discharged on postoperative day 6. Following surgery, myasthenia persisted with gradual improvement and she was able to perform almost all daily activities. Several months after the surgery, she had no muscular symptoms; the corticoid and pyridostigmine dosage was tapered and eventually discontinued. At the last follow up, her neuromuscular status was normal. The only medication she took was 100 mg of levothyroxine.

Antithyroid Drugs and Occurrence of Myasthenia

Antithyroid drugs were discovered by accident about 60 years ago. Hypothyroidism was found as a side effect during the treatment of heart disease with thiocyanate. Thyrostatic drugs, thionamides, contain a sulphhydryl group with thiourea part placed in the heterocyclic structure. Propylthiouracil (6-propyl-2 -thiouracil) and methimazole (1-methyl-2-mercaptoimidazole) are frequently used, while carbimazole, a methimazole analogue, is used occasionally. Thionamides inhibit thyroid peroxidase, an enzyme that enables iodination of tyrosine residues in thyroglobulin. Propylthiouracil inhibits conversion of thyroxin to triiodothyronine both in the gland and peripherally[18].

A number of autoimmune events mentioned above are the consequences of immunomodulatory action of thyrostatic drugs. *In vitro*, they might interfere with mitogenic activation of lymphocytes. They suppress the activation of lymphocytes stimulated by phytohemagglutinin and concanavalin A, and enhance the activation of lymphocytes stimulated by pokeweed mitogen (PWM)[19,20]. Thyrostatic drugs increase the ratio of T suppressor/cytotoxic cells to T helper cells, and increase total number of T-cells in peripheral blood[21]. Antithyroid drugs decrease the IgM and IgG production from lymphocytes in peripheral blood, stimulated by PWM[19]. Methimazole has been shown to enhance the natural killer cell activity[20].

Another clue could be the 'nuclear level of action'. Propylthiouracil and methimazole lead to a decrease in the level of proliferating cell nuclear antigen (PCNA)[22]. PCNA is a protein molecule that regulates cell apoptosis. The PCNA gene is induced by p53, a tumor-suppressor gene. If there is no PCNA, or if its level is low, or if PCNA is non-functional, cell apoptosis occurs[23]. According to this concept, non-activated lymphocytes have low to none PCNA level, whereas stimulated lymphocytes have high PCNA[22]. Anti-PCNAs are also found in some patients suffering from systemic lupus erythematosus[24].

The question is whether such changes could provoke an autoimmune event, e.g., myasthenia gravis. The possible hint could be in one of the most common causes of myasthenia, the thymus. All kinds of thymic abnormalities are found in nearly 75% of patients with myasthenia, so thymus is a good model for investigation of immune changes in these patients[17]. Myasthenia gravis is principally caused by anti-acetylcholine receptor antibodies produced by B-cells, although it seems that T-suppressor cell is the major regulator of autoimmune response. T suppressor cell, as its name says, suppresses immune response of other cells. There are specific so-called regulatory T cells (Treg) that are derived from thymus, are denoted as CD4+CD25+ and are basic for the balance of immune self tolerance. Studies with molecular mimicry between microbial and self-antigen have proposed that $CD4^+CD25^+$ regulatory T cells are able to provoke autoimmunity, e.g., to raise the threshold of auto-reactive T cell response triggering[25].

Myasthenia gravis is a CD4+ T cell-dependent autoimmune disease with thymus as the site of origin[26]. In the initial course of myasthenia, thymus is hyperplasic with auto-reactive activated CD4+CD25+ T cells[27]. It was shown that thymectomy decreased CD4 or CD8 T cell concentrations whenever thymopoiesis was active before thymectomy[28]. The question is whether antithyroid drugs could induce some intracellular changes while influencing PCNA, which could lead to selective apoptosis in some clones of T lymphocytes. In this way, $CD4^+CD25^+$ regulatory T cells could be able to create a 'skip' in the immune self tolerance, thus leading to autoantibodies against acetylcholine receptor. Are antithyroid drugs actually making an immune 'thymic surrounding'?

There is another similar report suggesting that worsening of myasthenia gravis might be induced by methimazole[29]. In 1991, Kuroda *et al.* described a 19-year-old patient with ocular type of myasthenia gravis associated with autoimmune hyperthyroidism and

thymic hyperplasia. Myasthenia worsened abruptly upon initiation of methimazole administration. Laboratory findings showed an increase in serum levels of antibodies to thyroid microsome and TSHR and in the proliferative response of peripheral blood lymphocytes to phytohemagglutinin[29].

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Sažetak

MIASTENIČNA KRIZA KAO NUSPOJAVA LIJEČENJA METIMAZOLOM: PRIKAZ SLUČAJA

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Miastenija gravis i Gravesova bolest su dvije autoimune bolestI sa sličnim mehanizmom nastanka, u objema se nalaze cirkulirajuća antitijela te stanično specifična autoantitijela. Pojava navedenih bolesti zajedno nije neuobičajena. Postoji mnogo podataka koji pokazuju da antitireoidni lijekovi kao što su metimazol i propiltiouracil uz tireosupresivno djelovanje imaju i imunomodulacijski učinak. Opisuje se slučaj 34-godišnje bolesnice koja je hospitalizirana zbog prvi puta dijagnosticirane miastenije sa slikom miastenične krize (Osserman IV.). U njenoj ranijoj povijesti bolesti navodila se hipertireoza, zbog čega je započeto liječenje metimazolom. Međutim, uz poboljšanje bolesti štitnjače došlo je do pojave miastenije. Fenomen "klackalice", tj. *see-saw relationship*, je pojava opisana kao poboljšanje jedne bolesti za vrijeme pogoršanja druge. Pitanje je poboljšavaju li antitireoidni lijekovi hipertireozu, u isto vrijeme razotkrivajući ili pogoršavajući miasteniju?. Je li fenomen "klackalice" zapravo nuspojava tireostatika? Pretpostavljeni učinak metimazola je unutarstanični: on snižava razinu nuklearnog antigena stanične proliferacije (PCNA). PCNA potiče selektivnu apoptozu u nekim klonovima T limfocita. Na taj bi način CD4+CD25+ regulatorni T limfociti mogli 'zaobići' imunu toleranciju prema vlastitom tkivu te dovesti do pojave autoantitijela protiv acetilkolinskog receptora. Stvaraju li zapravo doista antitireoidni lijekovi okruženje slično onome u timusu?

Ključne riječi: *Hipertireoza – komplikacije; Hipertireoza – terapija lijekovima; Miastenija gravis – komplikacije; Miastenija gravis – terapija lijekovima; Metimazol – štetni učinci*