DOI: 10.20514/2226-6704-2020-10-4-314-321

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The Case of Acute Steroid-Induced Myopathy in the Patient with Autoimmune Thrombocytopenia

Abstract

The article concerns one of the common adverse effects during treatment — steroid myopathy. The information about pathogenic specifics of myopathy development in administration of glucocorticoids, the most typical clinical manifestations are described, and results diagnostic methods with estimation of a role of enzyme level evaluation, electromyography, ultrasound study of the muscle tissue, computer and magnetic resonance tomography. There is description of muscle weakness development in 49-year old woman who has been receiving methylprednisolone 88 mg/day due to revealed thrombocytopenia. One week after the treatment was started the patient experienced onset and progression of muscle weakness limiting her motion and self-maintenance. After performing of investigation including electromyography steroid genesis of myopathy was suggested. The patient's condition began to improve after discontinuation of glucocorticoids and administration of calcium supplements, vitamin D, and anabolics, and the patient was discharged.

Key words: *thrombocytopenia, methylprednisolone, glucocorticoids, adverse effects, steroid myopathy, treatment*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 12.05.2020

Accepted for publication on 21.06.2020

For citation: Vatutin N.T., Ignatenko G.A., Taradin G.G. et al. The Case of Acute Steroid-Induced Myopathy in the Patient with Autoimmune Thrombocytopenia. The Russian Archives of Internal Medicine. 2020; 10(4): 314-321. DOI: 10.20514/2226-6704-2020-10-4-314-321

ALT — alanine aminotransferase, AST — aspartate aminotransferase, BP — blood pressure, CCR — cell-color ratio, CPK — creatine phosphokinase, CRP — C-reactive protein, dsDNA — double-stranded DNA, ENMG — electroneuromyography, ESR — erythrocyte sedimentation rate, GCs — glucocorticoids, LC3-I — protein I light chain 3, MP — methylprednisolone, MRC — Medical Research Council Weakness Scale, MRI — magnetic resonance imaging, mRNA — matrix ribonucleic acid, MU — motor unit, PMU — potential of motor units, UPS — ubiquitin-proteasome system

Introduction

Harvey Williams Cushing was the first to describe glucocorticoid-induced myopathy in 1932 as one of the manifestations of Cushing's syndrome [1]. It is a quite common adverse effect of glucocorticoids (GCs) in Cushing's syndrome: its incidence varies from 42% to 83% of cases [2]. Although long-term

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use of any GC can cause myopathy, it is most often caused by fluorinated GCs, such as dexamethasone, triamcinolone and betamethasone [3]. There are also reports on steroid-induced myopathy when using non-fluorinated GCs (prednisolone, methylprednisolone (MP), hydrocortisone) [4]. Myopathy in Cushing's syndrome significantly affects proximal parts of lower limbs; its treatment can take from several months to several years. It should be noted that myopathy is somewhat more common in ectopic than in adrenal Cushing's syndrome, and is significantly more prevalent in men than in women [2].

Pathogenesis

An excessive amount of GCs affects the structure and function of skeletal muscles in different ways. GCs cause atrophy of type II muscle fibers through both anti-anabolic and catabolic effects [5]. Firstly, steroids inhibit the transportation of amino acids into muscle cells [6], thus limiting intracellular protein synthesis [3]. Secondly, GCs block the stimulating effect of insulin, insulin-like growth factor I and amino acids (in particular, leucine) on the phosphorylation of eIF4E-binding protein 1 and ribosomal protein S6 kinase 1, two factors that play a key role in the anabolic mechanism by controlling the initiation of translation of matrix ribonucleic acid (mRNA) [7].

The stimulating effect of GCs on muscle proteolysis is due to the activation of major proteolytic systems in cells [8]: ubiquitin-proteasome system (UPS), lysosomal system (autophagy), and calcium-dependent system of proteinases (calpains). The increased excretion of 3-methylhistidine and extracellular matrix proteins of muscle tissue indicates that protein destruction caused by GCs primarily affects its myofibrillar types [9]. GCs trigger this mechanism by stimulating the secretion of several UPS components that have an impact on the attachment of ubiquitin to target protein [10] or are directly responsible for the degradation of proteasome protein [11]. This activation of gene transcription is associated with the increased frequency of protein ubiquitination and increased proteolytic activity of the proteasome itself [12]. The blocking of different proteolytic pathways demonstrated that GCs stimulate not only UPS-dependent proteolysis but also calcium-dependent and lysosomal proteolysis [8]. The role of the lysosomal system, also called autophagy, in the atrophic effect of GCs is confirmed by the increased expression of cathepsin L [13] and enhanced transformation of microtubule-associated protein I light chain 3 (LC3-I) into LC3-II, which is the indicator of autophagy [14] in the muscles of animals treated with GCs. Since proteasomes do not destroy intact myofibrils, it is assumed that actin and myosin should separate from myofibrils prior to their possible destruction by UPS. Thus, the activation of caspase-3 is required for the transformation of actomyosin and protein myofibrils into substrates destroyed by UPS [15].

Another adverse effect of GCs is hypokalemia, which develops as a result of potassium excretion by kidneys; it can contribute to the development of muscle weakness, and, when used for a long time, to skeletal muscle atrophy [16].

Skeletal muscle atrophy is characterized by a decrease in the size of muscle fibers. It was found that GCs cause atrophy of fast-twitch type II muscle fibers (in particular, IIx and IIb) with less or minor effect on type I fibers [17]. Consequently, glycolytic muscles (e.g. anterior tibial muscle) are more sensitive to GCs than oxidative muscles (e.g. soleus muscle). In mixed-type muscles, type II muscle fibers become atrophied to a greater extent. The mechanism of such muscle specificity can be realized through a higher expression of GC receptors in the anterior tibial muscle than in the soleus muscle [18].

Clinical Picture

GC-induced myopathy can occur in acute or chronic form. In chronic myopathy, muscle weakness develops gradually and usually without pain [19, 20]. Weakness develops mainly in proximal parts of limbs; muscles of lower limbs are affected more than these of upper limbs; muscles of the pelvic girdle are affected much more often than these of the thoracic girdle; muscles innervated by cranial nerves and sphincters are usually not involved [19]. Respiratory muscles can be involved in pathological process. Chronic myopathy can lead to muscle atrophy, which slowly develops for up to several weeks and even months after the withdrawal of GCs [4]. Patients taking steroids for less than four weeks rarely suffer from said complication, since its development usually correlates with

the dose and duration of treatment with GCs. Prednisolone or an equivalent drug at a dose of less than 10 mg/day rarely leads to steroid myopathy. Higher doses of GCs induce rapidly developing clinical signs of muscle weakness, which can be observed within two weeks after the beginning of treatment [21]. Clinical management of such patients is complicated by the fact that there are almost no methods for accurate determination of the onset of the myopathy before its clinical presentation [22, 23].

Diagnosis

Direct quantitative measurement of isometric muscle strength can be an alternative approach to the semi-quantitative assessment of muscle strength [24]. This measurement is a simple, accurate, and reliable method that has a strong predictive relationship with the functional capabilities of the muscular system. When measuring isometric strength, the values obtained are assessed in comparison with normal values for a certain gender, age and physical activity [25]. It should be noted that the widely used hand dynamometers enable to assess the muscle strength of hands and arms, which may not be informative in primary myopathy when proximal muscle groups are primarily affected. Despite that not only muscle but also neural mechanisms may cause muscle weakness in patients with steroid myopathy [26], it is thought that the regular use of state-of-the-art dynamometers in routine examinations of patients can be of practical value for the diagnosis and monitoring of myopathy [23].

Needle biopsy most often reveals atrophy of type II muscle fibers and the apparent absence of signs of necrosis and regeneration [23]. Atrophy of oxidative (type I) muscle fibers can also be present, but to a lesser extent. Aggravation or correction of excessive GCs accordingly change biopsy results: actually, in severe steroid myopathy, there is a decrease in the size and content of lipid droplets in type I muscle fibers, while after the correction of hormonal disorders or withdrawal of GCs, muscle fibers are restored. However, it should be noted that said changes can also be found in other conditions characterized by predominant atrophy of type II muscle fibers, such as senile involution of muscle tissue, neuropathy, muscle atrophy in chronic diseases. Therefore, this method has very high sensitivity but low specificity.

Most patients with steroid myopathy can demonstrate no changes during needle electroneuromyography (ENMG); some patients may show only a slight decrease in amplitude of the potential of motor units (PMU) [3, 23].

The first motor unit (MU) that takes part in voluntary contraction consists of type I muscle fibers (slow MUs). Since these muscle fibers are not affected as much as type II fibers, slight electrophysiological dysfunction is observed. If the patient is asked to increase muscle contraction in order to engage MUs consisting of type II fibers (fast MUs), some abnormalities occur, although they may not be noticed. When fast MUs are engaged, too many slow MUs are activated at the same time, creating an overlap of PMU, thereby causing loss of information. However, when the disease becomes more pronounced and type I muscle fibers are affected, disorders appear that can be observed even with low contraction force [23]. It should be noted that such electrophysiological disorders can also be found in patients with some other physiological (long-term immobilization) or pathological conditions (aging, neuromuscular disorders, drug-induced myopathy), which are accompanied by a decrease in the volume of muscle fibers. That is why this study has high sensitivity but low specificity.

Khaleeli A. A. et al. (1983) revealed a high ratio of 3-methylhistidine to creatinine in urine and decreased activity of creatine phosphokinase (CPK) in plasma of patients with Cushing's syndrome [27]. A possible explanation for these phenomena may be increased muscle protein breakdown (high ratio of 3-methylhistidine to creatinine) and decreased muscle protein synthesis (low levels of CPK and myoglobin in blood serum). However, at present, there is no reliable biomarker (blood or urine) for the verification of steroid myopathy in clinical practice, as well as for monitoring changes and response to therapeutic measures [23].

Magnetic Resonance Imaging (MRI) is a relatively new and informative method for the diagnosis of inflammatory myopathies and monitoring changes in their course [19, 28]. For example, MRI can be used for diagnosing the severity of sarcopenia, since not only muscle size is estimated, but also infiltration of the muscle with fat [29, 30]. Unfortunately, no studies have been conducted to determine the effectiveness of MRI in the diagnosis and

monitoring of steroid myopathy [23]. Ultrasound is an alternative method for measuring muscle size. Despite its simplicity, accuracy, reliability [31, 32] and the fact that this method was previously used for the quantitative assessment of changes in muscle size in different physiological and pathological conditions [33, 34], there are only a few studies of GCs-induced muscle tissue disorders performed with the help of ultrasound [35].

The diagnosis of steroid myopathy is a challenging task. The onset of muscle weakness while taking GCs is the main reason to exclude this complication of steroid therapy in patients who have no history of neurological or neuromuscular diseases, even if this weakness appears very early (during the first 1–2 weeks, or even days of treatment). Medical history, results of laboratory tests and instrumental examinations are of importance in the diagnosis of steroid myopathy, although the role of latter more auxiliary than diagnostic. We present our clinical observation as a demonstration of some features of the diagnosis of steroid-induced myopathy.

Case Report

In October 2018, a patient, 49 years old, suffered an uncomplicated hypertensive crisis after emotional stress, with blood pressure (BP) 165/95 mm Hg, headache, tinnitus, palpitations and nosebleed. She had never experienced an increase in BP in the past. When managing the hypertensive crisis in the Therapeutic Department at her place of residence, the patient underwent general examination; CBC results revealed thrombocytopenia (55×10^9/L). After the crisis management, she was referred to the Department of Hematology for further examination and treatment. At the time of transfer to the Department of Hematology (October 22, 2018), platelet count was 46 x 10^9/L. The diagnosis was the following: Principal — «Primary immune thrombocytopenia, newly diagnosed»; secondary — «Hypertensive disease, grade 2, stage II, moderate risk (according to the Russian Hypertension Classification)». The treatment included hemostatic drugs (dicinone, ascorbic acid); then therapy with GCs was started (MP at a dose of 1 mg/kg/day, i.e. 88 mg/day). Daily dose was divided as follows: 32 mg in the morning, 32 mg in the afternoon and 24 mg in the evening.

It should also be noted that shortly before hospitalization at the Hematology Department, according to the patient, her body weight decreased sharply, by about 10 kg, for no obvious reason. After a week of treatment with MP, the patient started feeling muscle weakness. According to CBC results, platelet count reached normal values (205×10^9/L). The MP dose was reduced according as follows: by 8 mg once every 5 days, although this caused a decrease in platelet count ($<100 \times 10^9$/L); then the initial dose (88 mg/day) was used again for two months. Muscle weakness increased; hand tremor appeared, and memory and attention worsened.

On December 18, 2018, after two months of taking GC at a dose of 88 mg/day, the patient was hospitalized at the V. K. Gusak Institute of Emergency and Reconstructive Surgery with complaints of the inability to perform self-care activities due to severe muscle weakness. She also noted a significant decrease in the volume of legs and frequent constipations. Objective examination revealed hyperemia of the face and collar zone. There were no signs of hemorrhagic syndrome or lymphadenopathy. No cardiovascular or respiratory abnormalities were found. Electrocardiogram and echocardiography findings were within normal. BP was 154/96 mm Hg on both arms. Neurological status (December 21, 2018): the patient is awake, fully oriented. No oculomotor disorders found. Function of bulbar and expression muscles is not impaired. No weakness of neck or axial muscles. No respiratory muscle function disorders. Muscle strength in hands — 5 of 5 points (MRC — Medical Research Council Weakness Scale), in the proximal parts of lower limbs — 2 of 5 points, in the distal part of lower limbs --3 of 5 points. Hypotrophy in thigh muscles. Muscle tone is decreased. Deep reflexes are decreased. No myalgic syndrome. Bowel and bladder functions within normal.

Given the scarce information about the patient's condition before admission to the hospital, several theories about the causes of thrombocytopenia, increasing weakness and decreased muscle strength were proposed. As a result, the patient underwent tests aimed at excluding diseases of the hematopoietic system (repeatedly — CBC, myelogram), autoimmune diseases (systemic lupus erythematosus, systemic scleroderma, dermatomyositis/ polymyositis, antiphospholipid syndrome), and infectious

diseases, including viral infections. A systemic autoimmune disease was the most probable variant at the beginning of observation, taking into account thrombocytopenia and weakness that developed shortly after detection of decreased platelet count. Newly diagnosed immune thrombocytopenia remained the working diagnosis based on repeated CBC results with decreased platelet count less than 100 x 10^9/L and the absence of other obvious initiating and/ or underlying causes of thrombocytopenia [36].

Complete blood count on December 19, 2018: Hb — 160 g/L, RBC — 4.4 × 10^{12}/L cell-color ratio (CCR) — 1.0, WBC — 8.4 g/L, erythrocyte sedimentation rate (ESR) — 3 mm/h, myelocytes — 2%, stab neutrophils — 1%, segmented neutrophils — 84%, monocytes — 2%, lymphocytes — 11%, hematocrit — 43%, platelets — 136 g/L, reticulocytes — 0.9%. Blood biochemistry on December 19, 2018: total bilirubin — 15.47 mol/L (direct — 3.86, indirect — 11.61 mol/L), aspartate aminotransferase (AST) — 21 U/L, alanine aminotransferase (ALT) — 34 U/L, total protein — 75.0 g/L, urea — 8.32 mmol/L, creatinine — 89.64 mmol/L, rheumatoid factor — 9.49 U/ml, C-reactive protein (CRP) — 1.3 mg, K^+ — 4.3 mmol/L, Na^+ — 138 mmol/L, Cl^- — 97 mmol/L, Ca^{2+} — 1.23 mmol/L. Urinalysis on December 19, 2018: reaction — acid, no protein, no glucose, RBC — 1 in preparation, WBC — 2–4 per field of vision, squamous epithelium — small amount, transitional epithelium — 0–3 per field of vision. In addition, glycemic profile test revealed hyperglycemia (January 10, 2019: fasting blood glucose 08:00 a.m. — 5.9 mmol/L, 12:00 p.m. — 9.3 mmol/L, 04:00 p.m. — 14.08 mmol/L; January 15, 2019: fasting blood glucose — 6.2 mmol/L; January 18, 2019 — 6.45 mmol/L; January 23, 2019 — 6.3 mmol/L). Glycated hemoglobin (HbA1c) — 6.6%. Lactate dehydrogenase — 696 U/L (reference values 135–214 U/L), CPK — 5.5 U/L (<167 U/L).

Sternal puncture was performed. Bone marrow cell differential count: bone marrow is cellular, there are single mitotic figures, and focal hematopoiesis in erythroid lineage was registered, megakaryocytic lineage remained unchanged. Profile of antinuclear antibodies on December 20, 2018: no antinuclear antibodies found. No antibodies against double-stranded DNA (dsDNA), antinuclear antibodies (anti-Sm, Scl-70, Jo-1, PCNA, against nucleosomes, histones, ribosomal proteins) found. Antibodies against cardiolipin IgG — 3.2 U/ml, IgM — 1.6 U/ml, lupus anticoagulants (screening) — negative (SD = 0.98). No antibodies against HIV, viral hepatitis, herpes simplex virus type I and II (IgM) and cytomegalovirus (IgM) found.

The patient was examined by an endocrinologist and diagnosed with steroid-induced diabetes mellitus. According to the patient, the glycemia level at the prehospital stage was within the normal range, although there were no data confirming euglycemia. During ENMG, there were no signs of lesions of the neural or synaptic level (parameters of M-response and sensory potential of peripheral nerves in lower limbs were within normal; there was no decrement/ increment of M-response). Results of needle ENMG suggested a myogenic lesion: spontaneous activity in the form of fibrillation potentials (+++) was registered in the muscles of the peroneal group; in minimal contraction state, PMU duration decreased by 36.6%, with a 52% pathological decrease in PMU amplitude. Fibrillation (spontaneous) potentials (+++) were registered in the muscles of the medial thigh group; during dosed muscle contraction, PMU duration decreased by 47.9%, with a 56.1% abnormal decrease in PMU amplitude (Fig. 1).

Constipation and painful bowel movements during further examination (examination by a surgeon, fibrocolonoscopy) were attributed to coprostasis associated with long-term uncontrolled use of steroids that resulted in paresis of intestinal muscles. Intestinal motility improved in the course of symptomatic therapy (diet, micro-enema).

The patient was diagnosed with «Newly diagnosed primary immune thrombocytopenia; complications: steroid myopathy, steroid-induced diabetes mellitus, intestinal hypotension with coprostasis; secondary: hypertensive disease stage II, AH grade 2, risk 2 (according to the Russian Hypertension Classification)».

Gradual tapering of the MP dose was conducted (4 mg/day for 3 days) with platelet control simultaneously with the examination. Also, potassium ororate, calcium and vitamin D, an anabolic drug (nandrolone decanoate, injections), antihypertensive treatment (ramipril, bisoprolol), and a proton pump inhibitor (omeprazole) were prescribed. The patient went through movement therapy and physiotherapy.

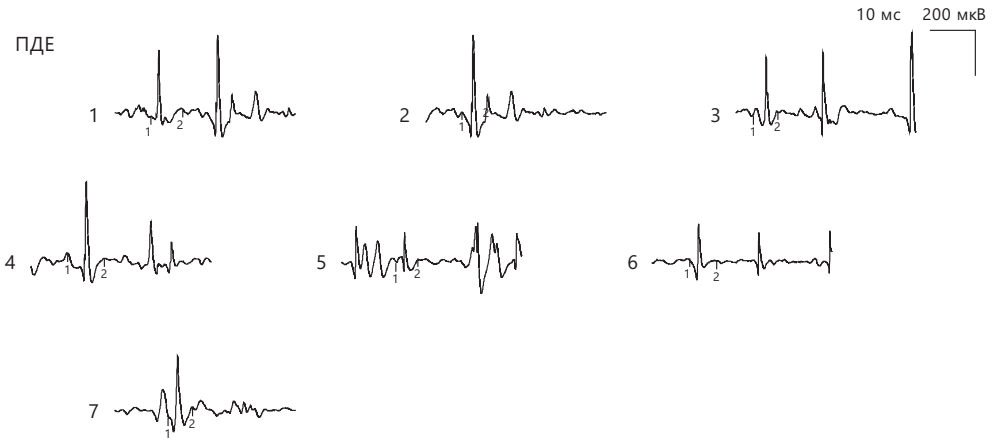

Figure 1. *Quantitative electroneuromyography*

left, Tibialis anterior, Peroneus, L4 L5 s1
Note: MUP — motor unit action potential.
Description. The illustration of myogenic restructuring of motor unit potentials (MUP) according to data of needle electroneuromyography indicating decrease in duration and amplitude of potentials in the observed patient

The patient's condition gradually improved, and after bowel function recovery and diet stabilization, the patient recovered quickly. At a daily MP dose of 8 mg, there was a sharp decrease in platelet count (to 39 × 10^9/L) without signs of hemorrhagic syndrome. It was decided to further reduce the GC dose with daily monitoring of complete blood count. However, platelet count later started increasing gradually: February 4, 2019 — 85 × 10^9/L, February 6, 2019 — 97 × 10^9/L, and February 7, 2019 — 155 × 10^9/L. Fasting blood glucose — 5.6 mmol/L, BP — 138/90 mm Hg on both arms. The patient was discharged from the hospital in satisfactory condition with the following recommendations: platelet control; with decreased platelet count less than 30–50 × 10^9/L without hemorrhagic syndrome — vessel-strengthening therapy; with decreased platelet count less than 30–50 × 10^9/L and hemorrhagic syndrome — immunoglobulin i.v. (first-line therapy); second line therapy — splenectomy; Romiplostim, Eltrombopag; third-line therapy — Rituximab, immunosuppressive drugs [37].

Discussion and Conclusion

The case described above is interesting in several aspects. Despite that the MP prescribed for thrombocytopenia is not a fluorinated GC, its administration at a dose of 88 mg/day or less (with dose tapering) led to clinically significant steroid myopathy. In literature, there are descriptions of GC-induced myopathy as a complication of treatment with MP [16]. A case of acute myopathy after two-day oral administration of MP was described: 24 mg on the first day of treatment, and 20 mg on the second day. Treatment was discontinued due to myalgia and severe drowsiness [38]. There is even a case of steroid myopathy after a single dose of prednisolone (40 mg) prescribed for exacerbation of chronic obstructive pulmonary disease [39]. In our case, the patient noticed the first signs of myopathy (muscle weakness) after a week of treatment with MP. Based on the analysis of the obtained data and early signs of steroid myopathy cited in literature (less than 14 days) [40], we can conclude that treatment with GCs of any duration, including single doses per day and possibly even several hours, can result in acute GC-induced myopathy.

In regard to the verification of the diagnosis, we think that muscle symptoms were associated with the prescribed GC. Although during hospitalization of the patient, versions of secondary immune thrombocytopenia were discussed as a syndrome in connective tissue systemic disease [41], the absence of any additional signs, along with negative results of immunological tests, cast doubts over the secondary nature of thrombocytopenia. Most important of all, the onset of myopathy coincided with the start of GC therapy, and complaints of muscular symptoms completely disappeared at the time of GC withdrawal and subsequent treatment. When discussing the cause of muscle symptoms, taking

into account long-term treatment with MP, we also considered hypokalemia as a common complication of treatment with GCs [42]. However, the normal potassium level in the period of maximum severe muscle weakness excluded hypokalemia from the reasons discussed.

Thus, this case once again demonstrates steroid myopathy as a typical complication of treatment with GCs. In such cases, accurate diagnosis requires the close attention of the general practitioner, therapist, hematologist and rheumatologist. The following is required: thorough analysis of medical history and examination, which enables the objective assessment of the functional state of the muscular system for justified and timely adjustment of management tactics. The first step here will be the withdrawal of GCs and, if necessary, a switch to another immunosuppressive treatment.

Contribution of Authors:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Vatutin N.T. (ORCID ID: https://orcid.org/0000-0003-4307-1522): generation of the idea and general manuscript presentation, case management, the final approval of the manuscript

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Kanisheva I.V.: collection and an analysis of clinical and laboratory data, writing of the review, clinical data and results of investigations

Shajmurzin M.R. (ORCID ID: https://orcid.org/0000-0003-3770-6851): performing and data design of electromyographic investigation, participation in the manuscript writing

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