Аутоиммунные полигландулярные нарушения при миотонической дистрофии

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Миотоническая дистрофия (МД) является наиболее частым заболеванием мышц у взрослых. МД – наследственное заболевание с аутосомно-доминантным типом наследования, практически 100% пенетрантностью и выраженным клиническим полиморфизмом. Механизм развития заболевания заключается в том, что мутантный ген *DMPK* (протеинкиназы миотонической дистрофии) нарушает нормальный метаболизм РНК, что приводит к дефекту созревания и трансляции мРНК. Нарушение в гене *DMPK* затрагивает не только поперечнополосатую мускулатуру, но и гладкие миоциты и кардиомиоциты. Основным клиническим симптомом, отличающим МД от других, является спонтанная или провоцируемая неспособность расслаблять мышцы (феномен миотонии). К эндокринным нарушениям, возникающим при МД 1-го типа (МД1) с более высокой частотой, чем в среднем в популяции, относят гипергонадотропный гипогонадизм, нарушение толерантности к глюкозе с гиперинсулинизмом, а также инсулинорезистентность. Функция щитовидной железы может оставаться нормальной, хотя описано много случаев аутоиммунного тиреоидита с исходом в гипотиреоз, а также болезни Грейвса. Приводится описание пациента, страдающего МД1 с рядом эндокринных расстройств, таких как: гипергонадотропный гипогонадизм, аутоиммунное поражение щитовидной железы, гиперинсулинизм, а также нарушение фосфорно-кальциевого обмена. Важными особенностями является отсутствие каких-либо значимых жалоб со стороны мышечной системы при наличии характерного для этого заболевания повышения уровня креатинфосфокиназы (КФК), а также временна́я динамика тиреоидного статуса и характера аутоиммунного поражения щитовидной железы.

Ключевые слова: миотоническая дистрофия, гипогонадизм, болезнь Грейвса, гипотиреоз, тиреоидит, полигландулярная недостаточность, клинический случай.

Autoimmune polyglandular disorders in myotonic dystrophy

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Myotonic dystrophy (MD) is the most common muscle disorder in adults. MD is a hereditary disease with an autosomal dominant mode of inheritance, almost 100% penetrance and pronounced clinical polymorphism. The mechanism for the development of the disease is that a mutation of the DMPK (dystrophia myotonica protein kinase) gene disrupts the normal metabolism of RNA, which leads to a defect in the maturation and translation of mRNA. The disorder in the DMPK gene affects not only striated musculature, but also smooth myocytes and cardiomyocytes. The main clinical symptom that distinguishes MD from others is a spontaneous or provoked inability to relax muscles (myotonia phenomenon). Endocrine disorders arising from type 1 MD (MD1) with a higher than average frequency in the population include hypergonadotropic hypogonadism, impaired glucose tolerance with hyperinsulinism, and insulin resistance. Thyroid function may remain normal, although many cases of autoimmune thyroiditis resulting in hypothyroidism, as well as Graves' disease, have been described. A description is given of a patient suffering from MD1 with a number of endocrine disorders, including hypergonadotropic hypogonadism, autoimmune thyroid disease, hyperinsulinism, and also impaired calcium-phosphorus metabolism. Important features are the absence of any significant complaints from the muscular system in the presence of an increase in creatine phosphokinase (CPK), which is characteristic of this disease, as well as the temporal dynamics of thyroid status and the nature of the autoimmune thyroid disease.

Keywords: myotonic dystrophy, hypogonadism, Graves' disease, hypothyroidism, thyroiditis, autoimmune polyendocrinopathy, case report.

Background

Myotonic dystrophy (MD) is the most common muscle disease in adults. MD is a hereditary disease with an autosomal dominant mode of inheritance, almost 100% penetrance and pronounced clinical polymorphism. This condition is reported to affect one in 8,000 individuals annually [1]. Typical clinical symptoms include myotonia, distal muscle weakness, cataracts, cognitive impairment, fatigue, hair loss and various endocrine disorders. However, the main clinical symptom that distinguishes MD disease from other muscle pathologies is a spontaneous or provoked inability to relax the muscles (i.e. a myotonia phenomenon) [2]. Myotonia is manifested by the inability to open the hand or the weakness of the proximal muscles that presents as having difficulty performing physical activities, such as standing up from a chair, getting onto public transport or combing one's hair. Progressive muscle atrophy is most pronounced in the temporal, masticatory, sternocleidomastoid, quadriceps, peroneal, anterior tibial and small muscles of the upper limbs.

Two types of this disease exist. MD type 1 (MD1) was first described by Steinert more than 100 years ago. The development of MD1 was triggered by the accumulation of trinucleotide CTG repeats. Normally, the number

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(CTG)n does not exceed 50. With MD1, however, the number of repeats of the mutant allele at locus 19q13.3 can reach 4,000. The main mechanism here is that the mutant DMPK gene (MD protein kinase) disrupts normal RNA metabolism, which leads to the impaired regulation of alternative compounds, messenger RNA (mRNA) translation and mRNA maturation [3]. With an increase in the number of repetitions, an early onset of the disease and highly pronounced clinical manifestations are noted. In addition, the phenomenon of 'genetic anticipation' is typical for this disease, which involves the fact that, in patients with long CTG repeats and, accordingly, considerably severe clinical manifestations, spontaneous shortening (CTG)n in gametogenesis occurs, which leads to mild clinical manifestations. In mild forms of the disease, on the contrary, there is great (CTG)n stability and, as a result, an increase in repetitions in gametogenesis.

Hypergonadotropic hypogonadism, impaired glucose tolerance with hyperinsulinism and insulin resistance are endocrine disorders that occur in conjunction with MD1 with a higher frequency than average. MD is often accompanied by phosphorus and calcium metabolic disorders; however, hyperparathyroidism develops rarely. Thyroid function in individuals with MD1 may be normal, but there are also a sufficient number of reported cases of autoimmune thyroiditis with the outcomes of hypothyroidism and Graves' disease [4].

MD type 2 (MD2) is a mild form of MD. The disease is caused by an increase in the number of CCTG repeats (approximately 5,000) as a result of a defect in the ZNF9 gene located at the 3q21 locus. MD2 is characterised by a small clinical organ polymorphism and a rare occurrence of endocrine lesions.

In the forthcoming clinical case, a patient suffering from MD1 presented with hypergonadotropic hypogonadism, an autoimmune thyroid lesion, hyperinsulinism and also a calcium–phosphorus metabolic disorder within the context of this disease. To our knowledge, the literature has not previously described a case of autoimmune thyroid lesion within the framework of MD1 proceeding first as autoimmune thyroiditis with an outcome in hypothyroidism, followed by the development of Graves' disease.

Case description

A 40-year-old male patient first visited the National Medical Endocrinology Research Center for infertility as diagnosed in the Department of Assisted Reproductive Technologies in 2012.

At the time of the first visit, the patient's follicle-stimulating hormone (FSH) level was determined to be 6.51 (1.6–9.7) U/L, the luteinising hormone (LH) level was 2.63 U/L (2.5–11.0), the testosterone level was 2.08 nmol/L (11–35.5) and hypogonadism was detected. Spermogram analysis was performed, and oligoasthenoteratozoospermia was diagnosed. In 2015, during a follow-up examination, an increase in the level of blood gonadotropins [LH: 12.59 (1.14–8.75) mIU/mL; FSH: 32.47 (0.95–11.95) mIU/mL] was noted and a gain of 0.4 ng/mL (0.1–0.2) in the progesterone level was recorded. At the same time, an increase in the insulin level to 20.6 (5–10) μIU/ml was revealed. In February 2016, as seen during a follow-up examination, the increased FSH and LH values persisted, and the level of testosterone was 33.1 (11–35) nmol/L. A normal prolactin level of 298.7 (60–510) mU/L was recorded.

At that time, an increase in the TSH level to 5.79 (0.4–4.0) mIU/L was noteworthy, and the level of free T4 was within the normal range and amounted to 14.5 (9–20) pmol/L. An increased level of antibodies to thyroid peroxidase was also noted (>1,000). These observations suggested the patient's condition to be subclinical primary hypothyroidism; thus, therapy with low-dose levothyroxine sodium (50 μg/day) was initiated. In 2014, the TSH level was recorded as 4.73 mIU/L; hence, the dose of levothyroxine sodium was gradually increased to 88 μg/day. In February 2016, according to the results of a dynamic examination, the TSH level was 0 mIU/L. At this point, thyrotoxicosis was diagnosed, and the levothyroxine sodium was stopped.

In addition to endocrine disorders, the indolent weakness of the proximal muscles of the lower extremities was noted. A similar condition was also observed in the patient's grandmother, who showed difficulty when getting up or entering public transport. A genetic study was not conducted. However, neither the mother nor the grandmother of the patient had endocrine disorders.

Given the family history of muscle weakness and the presence of concomitant endocrine pathology, a genetic study was conducted in 2011, which confirmed MD1 (a mutation in the DMPK gene was detected). Subsequently, this disease was genetically confirmed in the patient's mother who had clinical manifestations in the form of muscle weakness.

Since 1997, urolithiasis with multiple microliths in both kidneys has been noteworthy as a concomitant condition. According to the laboratory studies, the patient periodically had an increase in his level of total blood calcium and daily calcium excretion in the urine at a normal parathyroid hormone level. **Table 1** thoroughly presents the laboratory indicators.

A repeat visit to the Federal National Medical Endocrinology Research Center was made in July 2016 due to the complaints of episodes of palpitations and tremor of the upper extremities. These complaints were noted to have been ongoing for several months by that point in time.

During hospitalisation, a high titre of antibodies to TSH receptors was detected (29.2 U/L), suggesting manifested thyrotoxicosis, as the TSH level was 0 mIU/L, free T4 level was 30.8 pmol/L and free T3 level was 16.8 pmol/L. The high titre of thyroperoxidase antibodies remained. The high levels of FSH (50 U/L) and LH (33.8 U/L) were noted.

Основные лабораторные показатели пациента *Т.* в динамике

Parameters	2012	2014	2015	02.2016	07.2016	08.2016
TSH, mIU/L	5,79	4,73	–	0	0	29,7
Free T3, pmol/L	–	–	–	–	16,8	1,9
Free T4, pmol/L	14,5	–	–	–	30,8	5,8
Thyroperoxidase antibodies, U/L	–	–	>1000	–	>1000	–
TSH receptor antibodies, U/L	–	–	–	–	29,2	40
FSH, U/L	6,5	–	32,5	31,5	50,0	–
LH, U/L	2,6	–	12,6	11,7	33,8	–
Testosteron total, nmol/L	2,08	–	-	33,1	52,5	–
Insulin, μE/ml	–	-	30,6	–	–	–
Creatine phosphokinase, U/L	–	-	–	93,0	84,0	675,0
Creatine phosphokinase MB, U/L	–	-	–	–	16,8	22,0
Parathyroid hormone, pg/ml	–	39,3	–	32,7	21,0	-
Ca total, mmol/L	–	2,61	2,76	2,49	2,57	2,49
Ca^{2+}, mmol/L	–	1,18	–	1,19	1,22	1,19
P, mmol/L	–	–	–	1,69	0,92	–

The level of total testosterone during injection therapy with human chorionic gonadotropin within the preparation for IVF was 52.5 nmol/L. Moreover, the creatine phosphokinase levels were normal. The high levels of blood phosphorus (0.92 mmol/L) were noted, along with the normal levels of ionised calcium.

According to the ultrasound of the thyroid gland, the total volume was 27.7 mL, the echostructure was hypoechoic, there was a diffuse increase in blood flow as noted by CDI, and enlarged lymph nodes without suspicious signs were observed. Thus, the patient the manifestation of diffuse toxic goitre was diagnosed, and tyrosol therapy at a dose of 30 mg/day was started. Further, due to the presence of tachycardia, bisoprolol therapy was also initiated. According to the results of the ophthalmologist consultation, no endocrine ophthalmopathy was detected. Taking into account all of the data obtained, radioactive iodine therapy was proposed as a method for the radical treatment of Graves' disease.

Two weeks after discharge from the hospital, during the follow-up examination, a positive effect of thurostatics in the form of a decrease in the levels of free T3 and T4 was noted (see **Table 1**). An increased level of total creatinphosphokinase (675 U/L) was detected at a normal level of the MB fraction (22 U/L). Subsequently, the diffuse toxic goitre was treated with radioactive iodine to achieve hypothyroidism.

Discussion

This clinical case represents a clear example of endocrine lesions developing in the presence of MD1.

Endocrine disorders that occur in conjunction with MD1 with a higher frequency than the average include hypergonadotropic hypogonadism, impaired glucose tolerance with hyperinsulinism and insulin resistance. With MD1, a calcium–phosphorus metabolic disorder is seen although its nature is not completely understood, while hyperparathyroidism develops rarely. A decrease in basic metabolism with normal thyroid function is also typically observed. Among the affected patients, thyroid function is usually described as normal, but several cases of hyper- and hypothyroidism have been reported [5].

Endocrine dysfunction and muscle disorders in MD1 are assumed to be progressive in nature. In MD1, the incidence of hyperparathyroidism is raised by 78% and that of type 2 diabetes mellitus is raised by 300%, the prevalence of TSH deviation from normal values is increased by 133%, and androgen deficiency is increased by 85%. An increase in hormonal dysfunction does not correspond to the disease severity as there is no association between hormonal dysfunction progression and the loss of muscle strength or the number of repetitions (CTG)n. In addition, the prevalence of hormonal dysfunction does not depend upon the age at disease onset [6].

One study that examined endocrine dysfunction over time in the MD1 patients revealed that, initially, 30 of 68 patients had at least one kind of hormonal dysfunction. After eight years, upon re-evaluation, 57 of the 68 patients presented with at least one endocrinopathy. Diabetes mellitus was diagnosed in one patient (at the beginning of the observation period) and later in four patients. Hyperparathyroidism was registered in 25% of cases, and nonreference TSH values were seen after eight years in 21% of cases as compared with in 14% and 9% of cases at the beginning of the study. Further, 16 of 33 males in the study had increased the LH levels at eight years when compared with only seven males at the beginning of the study. These results demonstrate that endocrine abnormalities among the MD1 patients increase over time [7].

In men, a high incidence of testicular atrophy with the development of hypergonadotropic hypogonadism can be observed. Various phenomena associated with this disease have been described and include, among others, carbohydrate intolerance with an increase in blood plasma insulin levels, a change in calcium–phosphorus metabolism (al-

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though its nature is not completely understood), and a decrease in basal metabolism in normal thyroid function [8].

Ken et al. described the case of MD1 with a rare combination of multiple endocrinopathies, namely, diabetes mellitus, a combined form of hypogonadism and the dysfunction of the hypothalamic–pituitary–adrenal system. Diabetes mellitus was accompanied by severe insulin resistance and hyperinsulinemia. Hypogonadism replacement therapy with testosterone was conducted. It is noteworthy that the analysis of the component composition of the body revealed an increase in the muscle component of the body weight and a decrease in the adipose component of the body weight in this patient during treatment. Thus, the manifestations of hypogonadism may be the larvate symptoms of MD. The symptoms of adrenal insufficiency were not detected; therefore, adrenal dysfunction detected in the laboratory was carefully monitored without replacement therapy. A published study report emphasises the need to evaluate and treat multiple endocrinopathies in the MD1 patients. It is known that approximately 10% of the MD1 patients suffer from diabetes mellitus characterised by severe insulin resistance. The lesions of the hypothalamic–pituitary–adrenal system in the MD1 patients are characterised by the abnormal daily rhythms of the secretion of adrenocorticotropic hormone (ACTH) and cortisol, a pronounced reactive increase in blood ACTH after stimulation with corticotropin-releasing hormone and a low response to the adrenal cortex of ACTH.

Hockings et al. suggested the existence of a disorder of the dihydropyridine-sensitive Ca^{2+} transfer in corticotrophs in the MD1 patients after using nifedipine and naloxone. These researchers also theorised the validity of a relationship between the protein kinase of muscular dystrophy and Ca^{2+} channel regulation.

In another study, 25 MD1 patients (13 men and 12 women) were analysed. The levels of basal cortisol and ACTH were studied, and a stimulation test with 250 μg of ACTH and a test with corticoliberin were conducted. Five healthy people comparable in terms of age and gender were studied as a control group. Consequently, primary adrenal insufficiency in the absence of antibodies to 21-hydroxylase was diagnosed in one MD1 patient. In the remaining cases, there was no difference between the basal levels of ACTH in the patients and the control group, and the response of cortisol to ACTH was normal. The patients showed a lower basal cortisol level ($p<0.01$). In addition, after the corticotropin-releasing hormone stimulation, there was a lower cortisol response ($p<0.05$) with high mean ACTH values observed. As a result of the study, the conclusion was made to diagnose adrenal hypofunction due to the lack of ACTH efficacy at its receptor or postreceptor levels in the MD1 patients [9].

The MD1 patients are predisposed to hypogonadism, and approximately 80% have testicular atrophy. According to laboratory studies, there is an increased level of basal gonadotropins, an excessive response of gonadotropins after stimulation with gonadotropin-releasing hormone (GRH) and symptoms consistent with primary hypogonadism. According to the results of a morphological study, testicular lesions in various departments were noted, including predominant tubular lesions over interstitial tissues. The high levels of FSH and LH were noted, as was an insufficient reaction to an increase in testosterone in response to the administration of human chorionic gonadotropin (hCG). However, hypogonadotropic hypogonadism was also noted in the MD1 patients, confirmed by a low response of gonadotropin to the stimulation of GRH.

In the presence of a secondary or mixed form of hypogonadism, the choice of therapy between hCG and testosterone is generally determined by the patients' desire to restore fertility [10].

Despite the fact that erectile dysfunction is often found in MD1 patients, the study of this function in patients with this pathology has almost never been conducted. Along with this, hypogonadism, which is reported to be one of the causes of erectile dysfunction in the general population, is often found in the MD1 patients. It was revealed that, in the MD1 patients, the average levels of gonadotropins (FSH and LH) were statistically significantly increased ($p = 0.0001$) and that the average levels of testosterone ($p = 0.0001$) were statistically significantly decreased in comparison with the control group. In one study, 12 patients were characterised by the normal values of LH, testosterone and FSH, while 18 patients had the hormonal signs of hypogonadism and tubular insufficiency (i.e. elevated values of FSH). Additionally, interstitial insufficiency was observed in 14 patients, including seven with primary hypogonadism (increase in LH and decrease in testosterone values) and seven with compensated hypogonadism (increased LH and normal testosterone values). Patients with the hormonal confirmation of interstitial insufficiency had a long duration of the disease ($p = 0.013$), a high rate of disease development ($p = 0.004$) and a low rate of erectile function ($p = 0.02$). Erectile dysfunction was diagnosed in 13 patients with hypogonadism with interstitial insufficiency [11].

According to the literature, in which testicular arthrophy is reported to be the most characteristic feature in approximately 80% of the MD1 patients, scientists observed testicular hypotrophy and oligospermia among the MD1 patients. Histological studies have confirmed that the testes of the MD1 patients are characterised by an increase in the number and size of Leydig cells and tubular atrophy, hyalinisation, fibrosis of the seminiferous tubules and reduced spermatogenesis [12].

In another study, the lesions of the nervous system in patients with this disease were examined. The results of this study revealed that, in the MD1 patients, several cognitive functions were affected, including amnesia involving visual–spatial disorders. The assessment showed that a high percentage (51.6%) of the MD1 patients did not know about the existence of the disease in them, which led to a deterioration in their quality of life associated with the nervous system and muscle injuries [13, 14].

In the literature, the case of a 46-year-old female with a family history of MD1 was described. She was diagnosed with cardiac arrhythmia and required pacemaker implantation. It was noted that she also had bilateral cataract. She complained of muscle weakness, diffuse myalgia and palpitations. Laboratory studies indicated high levels of serum calcium (2.83 mmol/L), phosphorus (1.2 mmol/L), parathyroid hormone (362.5 pg/ml), thyroid-stimulating hormone (0.02 mIU/L) and negative antibodies against thyroperoxidase [15].

In another clinical case, a 53-year-old male with MD1 presented with hyperthyroidism and Addison's disease. The presence of antibodies to the thyroid and adrenal glands indicated that two endocrine disorders can be autoimmune in nature. This case study noted a decrease in myotonic symptoms during therapy for autoimmune endocrinopathies [16].

Thyroid function is most often described as normal in affected individuals although, generally, low thyroid hormone levels are detected [17].

The relationship between MD1 and the 'reduced' thyrotropin (TSH) response to the intravenous administration of thyroliberin at normal nonstimulated TSH levels and a decrease in the thyroid uptake of radioactive iodine have also been discussed. The pathological response of thyroid-stimulating receptors to thyroliberin activation may explain the deterioration of the TSH response in these patients. Such disorders of TSH receptors may explain the high incidence of goitre [3]

With hypothyroidism, a special form of muscle damage called pseudomyotonic hypothyroid myopathy can develop, which cannot be considered true myotonia, as contraction and relaxation are impaired in this pathology, which clinically distinguishes it from true myotonia. However, it can be difficult to differentiate this condition clinically from true myotonia in the absence of electromyography data.

A decrease in the basal metabolic rate is often described in MD1, which is probably associated with a decrease in the total muscle mass, even with the presence of normal thyroid function.

Finally, the nature of the development of autoimmune damage to the thyroid gland within MD1 is unclear. However, Berthold reported that the autopsy of patients with MD revealed cell infiltration in the thyroid gland had occurred in 37% of cases [18].

Some studies have highlighted the negative effect of hyperthyroidism on MD, and its early diagnosis is extremely important to ensure a favourable course of the disease.

Given that a disorder in the DMPK gene affects not only striated muscles but also smooth myocytes and cardiomyocytes [19], the main cause of the onset of infertility in this context is considered to be damage to peritubular myocytes, leading to the atrophy of the spermaducts, as well as lesions on Leydig cells as a cause of hypogonadism [20]. The absence of hypogonadism in MD women can be explained by the absence of myoid cells in the ovary. Myoid cells play a role in the paracrine control of tubular function [21].

There are studies that have analysed the development of diabetes mellitus in MD1. In one such investigation, during the course of an oral glucose tolerance test, an excess and delayed increase in insulin levels in MD patients was noted although the glucose values were normal in most patients. In the presented clinical case, according to laboratory studies, the patient's blood glucose values were within normal limits, while the level of glycated haemoglobin was not determined, and an oral glucose tolerance test was not performed. The body mass index was normal (20.7 kg/m^2). The correlation between body weight and peak insulin values was statistically significant in 23 patients, excluding two patients who had diabetes mellitus according to the oral glucose tolerance test, while the body mass index was inversely proportional to muscle strength. These findings may indicate that hyperinsulinemia in the case of MD is closely correlated with muscle atrophy and excess adipose tissue [22].

Changes in calcium–phosphorus metabolism have been described. The most significant of these is an increase in calcium absorption in the intestine, which is associated with an increased level of 1,25-dihydroxyvitamin D, and that, in turn, is a consequence of the initial increase in thyroid function. Affected patients develop hypophosphataemia, an increase in the plasma levels of 1,25-dihydroxyvitamin D and the increased nephrogenic excretion of cyclic adenosine monophosphate, while basal calcium and fasting urinary calcium excretion are normal. The cause of hyperparathyroidism is unclear; one possible explanation may be an insufficient sensitivity to the negative control of parathyroid hormone secretion by serum calcium. In other words, in some cases, MD involves the development of PTH renal receptor dysfunction. Some articles present data on membrane-impaired calcium transport in MD patients [23].

Conclusion

The described clinical case presents the majority of concomitant MD1 endocrine disorders. Significant aspects include the absence of any complaints about the muscular system in the presence of a documented increase in the level of CPK characteristic of the disease **(Table 1)** and a change in thyroid status and the nature of the autoimmune thyroid lesion over time. Infertility was the first complaint that prompted the patient to visit the endocrinologist. Hyperinsulinemia and disorder of the calcium–phosphorus metabolism in the form of a transient increase in the levels of total calcium and phosphorus in blood were not clinically significant at this stage.

The data obtained show the need not only for routine screening for the above disorders during the formal diagnosis of MD1 but also for regular lifelong follow-up of these patients by the endocrinologist.

Additional information

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