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Case Report

Clinical Case of Autonomic Dysfunction in a Young Patient with Exogenous Constitutional Obesity

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Abstract

The article describes a clinical case of progressive obesity with early development of complications and cardiometabolic risk in a 19-year-old patient with an analysis of the course features and identification of the most likely factors that cause these features. Particular attention was paid to the analysis of heart rate variability indicators in relation to the age and phenotype of the patient. Authors accessed prognostic significance of these indicators in a personalized approach to the patient. Both metabolic and regulatory disorders were diagnosed in the patient, which indicate the tension of regulatory mechanisms, which in the near future may lead to maladjustment of the body, an increase in the risk of developing other concomitant diseases and, first of all, an increase in the risk of early development of cardiovascular diseases.

Keywords: Exogenous-Constitutional Obesity; Heart Rate Variability; Arterial Hypertension; Cardiometabolic Risk

Obesity is a recognized growing public health problem. The number of overweight and obese people has doubled in the last 40 years. As a result, approximately one third of the world's population is considered medically overweight or obese [1]. In 2000, the World Health Organization (WHO) defined obesity as "a chronic disease resulting from complex interactions between genetic predisposition, lifestyle and environmental influences" [2]. In 2016, more than 1.9 billion adults worldwide were overweight and 650 million were obese, far more than the number of normal weight people [3].

Obesity has an adverse effect on the body as a whole, activating the processes of systemic vascular inflammation, oxidative stress, leads to the development of insulin resistance, increased blood pressure, dyslipidemia and endothelial dysfunction, and, accordingly, an increased risk of developing cardiovascular diseases [4].

Recently, we have seen a great interest of the medical community in this problem. Clinical recommendations are being developed and refined, and new concepts are being introduced into practice - metabolically healthy and metabolically unhealthy obesity phenotype (MHOP and MUOP) [5]. MUOP has clear clinical signs: an increase in waist circumference, a high percentage of visceral fat, early development of metabolic disorders such as carbohydrate intolerance, dyslipidemia, hyperuricemia, etc.

Obesity does not only reduce the quality of life, but also shorten its duration [6]. A large waist circumference in a patient, even within the normal weight range in general, is associated with cardiometabolic abnormalities and outweighs cardiovascular risk and the risk of premature death. Every 10 cm increase in waist circumference increases the risk of mortality by 8% and 12% in men and women respectively [4]. Also, according to the results of a pooled analysis of 11 prospective cohort studies in Western

countries, calculations showed that a further increase in waist circumference for every 5 cm in men and women increases the risk of death by 7% and 9%, respectively [7]. It has been established that obesity is a risk factor for a number of cardiovascular diseases, such as arterial hypertension, dyslipidemia, and acute myocardial infarction [8].

However, the cardiovascular risk in these patients is associated not only with dysmetabolic disorders, but with a violation of the processes of neuroendocrine regulation at the system level. It has been proven that the physiological variability in the time interval between heartbeats, the so-called heart rate variability (HRV), is pathologically reduced in individuals with cardiovascular diseases [9,10].

A meta-analysis conducted in 2017 found that behavioral, environmental, occupational and metabolic risks led to 34 million cardiovascular deaths [11]. In this context, the ranking of risk factors resulted in the following: high systolic blood pressure, smoking, high fasting plasma glucose, and high body mass index (BMI) accounted for 4.7 million deaths and 148 million patient disability. BMI was also among the risks that increased the most in the last decade. An increase in metabolic risk can also lead to an increase in mortality from cardiovascular diseases, which requires the development of more successful strategies to reduce this risk [12]. Autonomic dysfunction associated with obesity [13] can also have varying degrees of cardiac autonomic neuropathy [14] and is a potentially serious, partially reversible complication of metabolic conditions, which increases the risk of death to 3.6 in cases of diabetes mellitus [15]. For patients with cardiovascular diseases on the background of obesity, the assessment of HRV parameters is also of great interest [16].

Early screening for autonomic dysfunction can be clinically promising and can be performed using a variety of techniques, ranging from moderately invasive electroneurographic recordings of sympathetic activity of the body [17] to non-invasive analysis of heart rate variability (HRV) and cardiac baroreflex [9]. This method can also be used to assess the reversibility of autonomic disorders with weight loss [13] or physical activity [18].

However, in the above studies, as a rule, we are talking about middle-aged and elderly patients. What is the importance of the preservation of autonomic balance and the development of autonomic dysfunction in the pathogenesis of obesity is a poorly understood question.

In this regard, the clinical observation of a young patient, whom we examined with the inclusion of methods for assessing heart rate variability and blood pressure, is of interest.

Patient V., 19 years old. On an outpatient visit, he complained of an increase in blood pressure up to 150/90 mm Hg, uncontrolled weight gain (6 kg in the last 6 months), shortness of breath with little physical exertion, daytime sleepiness, and decreased ability to work. The patient from the 1st pregnancy, the period of pregnancy and childbirth proceeded without complications. Natural breastfeeding up to six months. Living conditions in childhood were satisfactory. He studied well, did not lag behind his peers in physical and mental development. From the age of 6, he was observed by a pediatric endocrinologist for overweight, impaired glucose tolerance (according to the patient). Progressive weight gain coincided with the onset of puberty. At the age of 14, an oral glucose tolerance test (OGTT) was performed: glycemia 4.4-7.8-6.3 mmol/l. From the same time, he notes a periodic increase in blood pressure up to 150-160/90 mm Hg. He did not receive regular therapy, with an increase in blood pressure he took 1 tablet of captopril with a good therapeutic effect. He was repeatedly examined for the "hypothalamic syndrome of puberty", independently tried to reduce weight by restricting food, and while following a low-calorie diet, he managed to reduce body weight, but the effect was short-lived - when returning to a normal diet, the weight was restored. Over the past three years, the patient has been registered with a cardiologist, receives antihypertensive therapy, regularly takes perindopril 10 mg + amlodipine 5 mg, after treatment BP holds at 130/70 mm Hg. Currently, the patient is studying at the University, attending full-time classes.

Upon admission, the condition is satisfactory, the position is active, consciousness is clear. Height - 178 cm, weight - 136 kg, BMI 43 kg/m^2. The skin is of physiological color, moderately moist, warm to the touch. On the skin of the inner surface of the shoulders, the lateral parts of the abdomen, pale pink striae 4-5 mm wide are noted. There is no edema. Waist circumference 136 cm, hip circumference 143 cm (F/R - 0.95). Respiratory rate - 22 per minute, vesicular breathing, carried out in all parts of the lungs, no wheezing. Heart sounds are muffled, rhythmic, there are no noises,

blood pressure is 140/85 mm Hg, heart rate - 90 beats per minute. Pulsation of peripheral arteries: preserved in full on a. dorsalis pedis, on the rest it is not determined due to the large thickness of the subcutaneous fat. The condition of the veins without features. Tongue moist, pink, not coated. The abdomen is enlarged due to fatty tissue, soft, painless. The liver is 0.5 cm below the edge of the costal arch. The symptom of effleurage is negative on the right and left. The thyroid gland is not enlarged (grade 0, WHO, 2001), dense elastic consistency, mobile, nodules are not detected.

In the blood test: hemoglobin -15.6 g/dl, hematocrit - 45.8%, erythrocytes - 5.53 million/μl, MCV (mean volume of erythrocytes) - 82.8 fl, RDW (erythrocyte distribution width) - 12.4%, MCH (mean hemoglobin content in an erythrocyte) - 28.2 pg, MCHC (mean erythrocyte hemoglobin concentration) - 34.1 g/dl, platelets 267 thousand/μl, leukocytes 6.88 thousand/μl.

In a biochemical blood test: ALT activity - 40 U/l, AST - 22 U/l, total bilirubin - 7.7 μmol/l, glucose - 5.6 mmol/l, creatinine - 70 μmol/l, urea - 4, 6 mmol/l, uric acid - 419 μmol/l, total protein - 71 g/l, triglycerides - 1.11 mmol/l, cholesterol - 4.86 mmol/l, HDL - 0.78 mmol/l, LDL (according to Friedwald) - 3.58 mmol/l, atherogenic coefficient - 5.3%.

Blood test for hormones: insulin - 22.3 mcU/ml, TSH (thyroid-stimulating hormone) - 0.770 mU/l, testosterone - 14.25 nmol/l, cortisol - 177 nmol/l, prolactin -133 (73-407) mU/l, vitamin 25(OH)D - 13 ng/ml, ACTH (adrenocorticotropic hormone) <5.00 pg/ml, cortisol < 27.6 nmol/l (norm in the morning 102 - 535, in the evening after 17:00 79-477), HOMA-IR index - 5.5 (norm < 2.7), APTT - 34.9 sec.

According to the ECG: sinus tachycardia - up to 110 bpm. Horizontal EOS. Myocardial changes in the posterior, lateral wall, apex of the left ventricle.

Ultrasound of the abdominal cavity: the liver is enlarged (left lobe 63 mm, right lobe 158 mm), contours are even, parenchyma with signs of fatty infiltration. Portal vein 9.7 mm. Gallbladder 79x42 mm, with a kink in the neck; the walls are unevenly compacted, 4.4 mm thick. Bile is heterogeneous. Pancreas (26-13-22 mm), wavy contours, hyperechoic parenchyma, heterogeneous. Spleen 87x45 mm. Kidneys of normal size, parenchyma 18 mm. Calyces up to 11 mm in size are visible.

24-hour Holter ECG monitoring: sinus rhythm was registered during the day. The average heart rate is 72 beats/min. The minimum heart rate is 42 beats/min. The maximum heart rate is 165 beats/min; supraventricular ectopic activity was recorded, 326 beats.

Particular attention was paid to the analysis of heart rate variability in the frequency spectrum. The frequency ranges were represented by the following wave spectrum: 0.004-0.08 Hz (very low frequencies - VLF) - reflects the functional state of suprasegmental structures; 0.09-0.16 Hz (low frequencies - LF) - reflects the activity of the sympathetic system; 0.17-0.5 Hz (high frequencies - HF) - activity of the parasympathetic nervous system at the segmental level. ULF - the power of ultra-low frequency waves reflects the activity of higher heart rate control centers.

Two coefficients were also determined - LF/HF (vagosympathetic balance coefficient) - this is the ratio of the power of low frequency waves (LF) to the power of high frequency waves (HF) (average absolute value in healthy people: 0.7-1.5). And the index of centralization - IC - shows the ratio of the activity of the central circuit of regulation to the autonomous one. Calculated by dividing the sum of the low frequency wave powers (LF and VLF) by the high frequency wave power (HF). The maximum value in healthy people during rest: 3.

The data obtained made it possible to assess not only the predominance of sympathetic or parasympathetic activity, but also the degree of tension in the regulatory systems.

Figure 1: Daily monitoring of heart rate variability in patient B.

According to the results of the daily ECG, the predominance of parasympathetic activity in the wave frequency spectrum was revealed not only at night (expected phenomenon) - HF - 25.8% (against LF - 14.9%), but also in the daytime - HF - 22.0% (against LF - 6.4%), and during the day - HF - 20.5% (against LF - 7.2%) (Figure 1). It was confirmed by low values of the coefficient of vagosympathetic balance. Although it is generally accepted that hypersympathicotonia predominates in overweight patients. High values were revealed in the structure of the spectrum of high (VLF) and ultra-high (ULF) frequencies - the total daily indicators are more than 70% (Figure 1).

The patient was diagnosed with Exogenously constitutional obesity, III degree, metabolically unhealthy phenotype. Complications: Dyslipidemia. Arterial hypertension stage I, I degree, MCC risk 2. Impaired glucose tolerance (prediabetes).

The clinic provided individual training for the patient and his parents on the rules of rational nutrition; an individual diet was compiled with a daily calorie content of 1700 kcal. To expand the amount of physical activity, swimming was recommended. Given the patient's morbid obesity, surgical treatment was considered; however, due to the patient's categorical refusal, Orlistat therapy was prescribed 120 mg x 3/day. Considering hyperinsulinemia and insulin resistance, metformin 1500 mg/day was also initiated. It is recommended to continue taking antihypertensive drugs.

Discussion and Conclusion

The presented clinical case is of particular interest due to several aspects. The first being a differential diagnosis between primary and secondary forms of obesity. The exclusion of the secondary form is associated with the early onset of the disease - the patient was overweight from an early age and was observed by a pediatric endocrinologist due to obesity. At the same time, the TSH (thyroid-stimulating hormone) test performed at that time did not reveal any abnormalities of carbohydrate metabolism. In adolescence, the patient was observed with hypothalamic syndrome of puberty, which explains the presence of pink striae on the inner surface of the shoulder and abdominal skin, but since the patient is already classified as a young (adult) age (according to WHO classification from 2021), these manifestations require the exclusion of hypercortisolism as a cause of secondary obesity. Cortisol levels were within normal limits, as were thyroid-stimulating hormone and testosterone levels. However, the patient showed a multiple excess of insulin levels and a high index of insulin resistance - HOMA-IR 5.5 (norm - no more than 2.7). The data obtained, as well as the lack of anamnestic data on the presence of injuries or chronic diseases, allowed us to focus on the diagnosis - primary exogenous constitutional obesity. The degree of obesity, in accordance with the WHO classification (1997), III stage.

Particular attention was paid to prognosis and the optimal treatment tactics. From these positions we evaluated the results of the study of heart rate variability. Evaluation of variability makes it possible to obtain not only the data on the state of the cardiovascular system, but also to analyze the state of the body's functional reserves and its rehabilitation capabilities. Physiological functioning includes three supersystems of regulation - neurovegetative, endocrine-metabolic and immune. Any exogenous or endogenous effect on the body first includes autonomous regulatory mechanisms, and, if they are insufficient, central regulatory mechanisms. The unity of the regulatory system is always preserved, and the mobilization of energy and metabolic resources is activated through nervous and humoral mechanisms.

In young patients without obesity, parasympathicotonia predominates in the tone of the autonomic nervous system, however, in patients with metabolic syndrome, including arterial hypertension, hypersympathicotonia is the leading factor in increasing blood pressure, so the data obtained in our patient did not meet expectations. The data obtained with an estimate of the power of the spectrum according to the frequency characteristics of HRV, showing a steady decline in the level of activity of regulatory systems, as well as a decline in the activity indices of the parasympathetic link of autonomic regulation, but with the predominance of parasympathetic activity, turned out to be consistent with the patient's age. However, since we evaluated the relative performance, it was noted that a significant part of the spectrum was occupied by the VLF and ULF waves, totaling more than 70%. This indicates the tension of regulatory mechanisms and the transition of regulation to a higher and more energy-intensive level of management - the level of centralization and the expected failure of adaptation in the near future. And, although the diagnosis based on the assessment of anthropometric and metabolic parameters indicates cardiometabolic risk I, further progression of the disease can be expected.

Possibly, the low efficiency of therapy is also associated with this circumstance, since the disease was steadily progressing throughout the entire period. And the patient at his age already needs a constant intake of ACE inhibitors and calcium channel blockers of the II generation. But at the same time, systolic blood pressure exceeds 130 mm Hg.

Thus, the patient has not only metabolic, but also regulatory disorders, which indicate the tension of regulatory mechanisms, which may in the near future lead to maladaptation of the body, increase the risk of associated diseases and conditions, first of all, an increase in the risk of early development of cardiovascular disease, vascular pathology.

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