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A clinical case of hypothalamic syndrome combined with Klinefelter syndromeKys Maryna¹, Halushko Yuri-Daniel¹, Yerokhovych Viktoriia²¹Student, Bogomolets National Medical University, Kyiv, Ukraine.²Endocrinology department, National Medical University, Kyiv, Ukraine.**Adress for correspondence:**

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Abstract: *the article describes a clinical case of a hypothalamic syndrome associated with a congenital disease - Klinefelter syndrome in a 21-year-old patient. Dysmetabolic complications were studied against the background of endocrine and genetic pathologies. Klinefelter syndrome was diagnosed in the patient at the age of 10, mosaic variant of karyotype 47XXY/46XY was detected. Against the background of a rare genetic pathology, signs of a hypothalamic puberty syndrome began to appear at the age of 15: acne, pink stretch marks on the lateral areas of the abdomen and breasts, gynecomastia, and excess weight. General clinical laboratory studies, carbohydrate metabolism indicators, sexual and thyroid hormones did not differ from reference values. The cortisol level in the blood was 23.4 mcg/dL, slightly exceeding the upper limit of the reference values (4.30-22.4 mcg/dL), indicating a state of mild hypercorticism. Manifestations of dysmetabolic cardiomyopathy were noted in the cardiovascular system, complicated by stable stage II arterial hypertension. The peculiarity of the clinical case is the combination of endocrine pathology with genetic pathology, which determines the specific appearance of the patient, and the presence of dysmetabolic complications without disturbances of carbohydrate metabolism in stage III obesity. The acceleration of puberty, which often occurs with the hypothalamic syndrome, did not occur due to the concomitant hypoandrogenic effect of Klinefelter syndrome. In the presence of hypothalamic syndrome in the patient, the late development of secondary sexual characteristics was noted, which is more characteristic of Klinefelter syndrome, but normal mental activity was preserved, which is rarely observed with the mosaic form of this genetic pathology. Another clinical feature is the absence of typical manifestations of hypogonadism in the post-pubertal period, which is confirmed by a normal level of male and female sex hormones in the blood, which is atypical. Due to the peculiarity of this clinical case, the patient's fertility can be preserved. In addition to the existing dysmetabolic complications in the patient and metabolic syndrome, there is a high risk of developing type 2 diabetes, atherosclerosis, osteoporosis, and breast cancer; because Klinefelter syndrome and hypothalamic syndrome complicate each other. Therefore, it is important to study the issue of the combination of these two pathologies, possible consequences, and ways to overcome them to improve the patient's clinical prognosis and quality of life.*

Keywords: [Diabetes Mellitus](#), [Genetic Syndrome](#), [Gynecomastia](#), [Metabolic Syndrome](#), [Obesity](#).

Introduction

The combination of the hypothalamic syndrome (HS) with Klinefelter syndrome (KS) is a rare variant, with a complicated clinical picture. KS is a genetic disorder characterized by the presence of an extra X chromosome in the male karyotype and is the most common cause of primary hypogonadism with a prevalence of approximately 1-2.5 per 1000 men (Matsumoto and Anawalt, 2020). HS ranks third among all endocrine disorders, with only diabetes and thyroid gland pathology surpassing it (Sorokman et al., 2019). The neuroendocrine form of hypothalamic syndrome is a symptom complex that arises from hypothalamic damage and is one of the most common metabolic and endocrine disorders among adolescents, with a prevalence of 45.5 per 100,000 individuals (Wen et al., 2021). For both syndromes (KS, HS), there is a certain periodicity of the appearance of clinical signs, which applies to the pubertal and post-pubertal periods, respectively. In the pubertal period, KS is characterized by hypogonadism, while in adulthood, there is hypergonadotropism with varying degrees of androgen deficiency due to the lack of feedback inhibition from the gonads to the intact pituitary and excessive production of luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (Sorokman et al., 2019).

Aim

The purpose of this clinical case report is to analyze the metabolic manifestations of the hypothalamic syndrome in association with Klinefelter syndrome. It is important to investigate the mutual complication of clinical symptoms in the patient, analyze the possible consequences of metabolic manifestations, and explore ways to overcome them. The patient's reproductive function should also be taken into consideration.

Clinical case description

A 21-year-old patient was admitted to the endocrinology department of the hospital for a routine annual check-up and complaints of excessive sweating, excessive weight, periodic increases in blood pressure up to 160/100 mmHg, and cramps in the calf muscles, changes in mood, general weakness, and headaches during the examination. A rapid increase in body weight was observed since the age of 9. A year later, he was referred to an endocrinologist for examination. The

doctor recommended a karyotype investigation, and as a result, a mosaic variant of Klinefelter syndrome was detected using cytogenetic testing. During puberty, a concomitant diagnosis of the hypothalamic syndrome was made based on the patient's clinical presentation during routine examinations. At the time of the examination, the patient had a body weight of 140 kg, a height of 185 cm, and a BMI of 40.9 kg/m², which corresponds to grade III obesity. Blood pressure was 145/90 mmHg, and heart rate was 72 bpm. The skin was pale, with acne, and pink stretch marks in the lateral abdomen and breast areas. And there was android type fat distribution. True bilateral gynecomastia and thickened mammary glands were present. Male pattern hair growth started late, at the age of 19. According to cytogenetic testing, there was a mosaic variant of Klinefelter syndrome (47XXY/46XY karyotype). General clinical laboratory studies, carbohydrate metabolism indicators, and sex and thyroid hormones were in the normal range. The cortisol level in the blood was 23.4 mcg/dL, slightly exceeding the upper limit of the reference range (4.30-22.4 mcg/dL), indicating a state of mild hypercortisolism. According to instrumental studies, there were ultrasound signs of diffuse goiter, echocardiographic signs of fibrosis of the posterior leaflet of the mitral valve, and there were also electrocardiographic signs of vagotonia. Based on the patient's history, clinical presentation, laboratory and instrumental investigations, the diagnosis has been established as Klinefelter syndrome (47XXY/46XY mosaic variant). Hypothalamic syndrome with the neuro-endocrine-metabolic form. Bilateral true gynecomastia. Grade III obesity. Dysmetabolic cardiomyopathy, stage 2, grade 2 hypertension, heart failure Stage A. Diffuse non-toxic goiter. Euthyroidism. Dysmetabolic encephalopathy of grade I with cerebro-asthenic syndrome. The patient has undergone correction therapy for dysmetabolic manifestations with aminoacid arginine, anticholinesterase, cytoprotective and membrane-stabilizing drugs. The patient has also received anticonvulsant and antihypertensive treatment and correction of magnesium and vitamin D deficiencies at therapeutic dosages. The patient received recommendations for following

a low-carbohydrate diet, engaging in optimal active physical activities with controlled cardio exercise, and annual monitoring of hormonal indicators of sexual function and thyroid, pituitary hormones. The patient was provided with recommendations for regular visits to the family doctor and endocrinologist, and consultation with an andrologist when planning to conceive a child. The combination of Klinefelter syndrome with the hypothalamic syndrome is a mutually aggravating factor because they increase the likelihood of dysmetabolic complications such as insulin resistance, type II diabetes, and osteoporosis. It is also necessary to consider the presence of initial stages of dysmetabolic complications, which, without proper control, can lead to the progression of these pathologies. It is important to monitor free and total testosterone, FSH, LH, and Inhibin B levels in the future for timely diagnosis and treatment of sexual dysfunction. It is also important to examine semen analysis parameters to determine fertility and fecundity prognosis. It is known that with an increase in the number of X chromosomes, a number of genes are expressed in the germ cells of the testes, which can affect meiotic division and play a role in the etiology of infertility in men with Klinefelter syndrome. This is confirmed by an increase in the expression of the specific protein TEX11 (a protein of germ cells of the ovary, encoded by genes of the X chromosome), which is most clearly observed in spermatogonia and early spermatocytes and manifests itself by inhibiting cell proliferation in seminiferous tubules (Sorokman et al., 2019). In the patient, erectile function and normal development of the sexual glands and organs are preserved, and the genetic ability of spermatozoa to fertilize an egg cell may be present or absent.

Results

The patient was discharged with an improved condition, and he has been informed about recommendations for lifestyle modifications, preventive measures, and annual screenings.

Discussion

The peculiarity of this clinical case is the combination of hypothalamic syndrome with the mosaic variant of Klinefelter syndrome. The issue of screening and early diagnosis of prediabetes, diabetes, and other endocrine pathologies in

this patient remains relevant. The elevation of circulating insulin levels and the development of insulin resistance with the hypothalamic syndrome is possible in the future. If we consider the pathomechanism of metabolic disorders in HS, it is necessary to note an increase in the level of leptin, which resembles leptin resistance. Leptin levels, combined with dysfunction of the autonomic nervous system and insulin resistance, lead to metabolic disorders and metabolic syndrome in the future (Müller et al., 2022). In addition to obesity, the hypothalamic syndrome also includes arterial hypertension, and these two conditions are risk factors for atherosclerosis (Ziegler et al., 2019). With Klinefelter syndrome, there is also an increased risk of developing type 2 diabetes and metabolic syndrome. So, according to recent research, individuals with KS have elevated levels of irisin (a protein produced in response to physical activity) which leads to an increased risk of visceral obesity and insulin resistance regardless of testosterone levels (Radellini et al., 2022). Irisin is a myokine that participates in the thermogenesis of adipose tissue and acts as an insulin-sensitizing hormone. It is believed that irisin improves glucose and lipid metabolism in the liver, promotes the functioning of β -cells in the pancreas, and helps reduce insulin resistance and the risk of type 2 diabetes (Waseem et al., 2022). However, data on the correlation between the level of irisin and metabolic complications are controversial. Some studies have shown a direct correlation, while others have shown an inverse relationship between the level of irisin and visceral obesity, insulin resistance, and type 2 diabetes (Radellini et al., 2022). Thus, it can be assumed that with prolonged elevation of irisin levels, resistance to irisin may develop, although this issue requires further investigation.

In the case of hypothalamic syndrome, the secretion of leptin by adipose tissue increases, leading to leptin resistance, disruption of the mechanism of energy saturation, and progression to obesity. A high level of leptin increases the risk of developing breast cancer, and the likelihood of this disease is also increased in patients with Klinefelter syndrome. Visceral obesity leads to insulin resistance and, as a result, metabolic

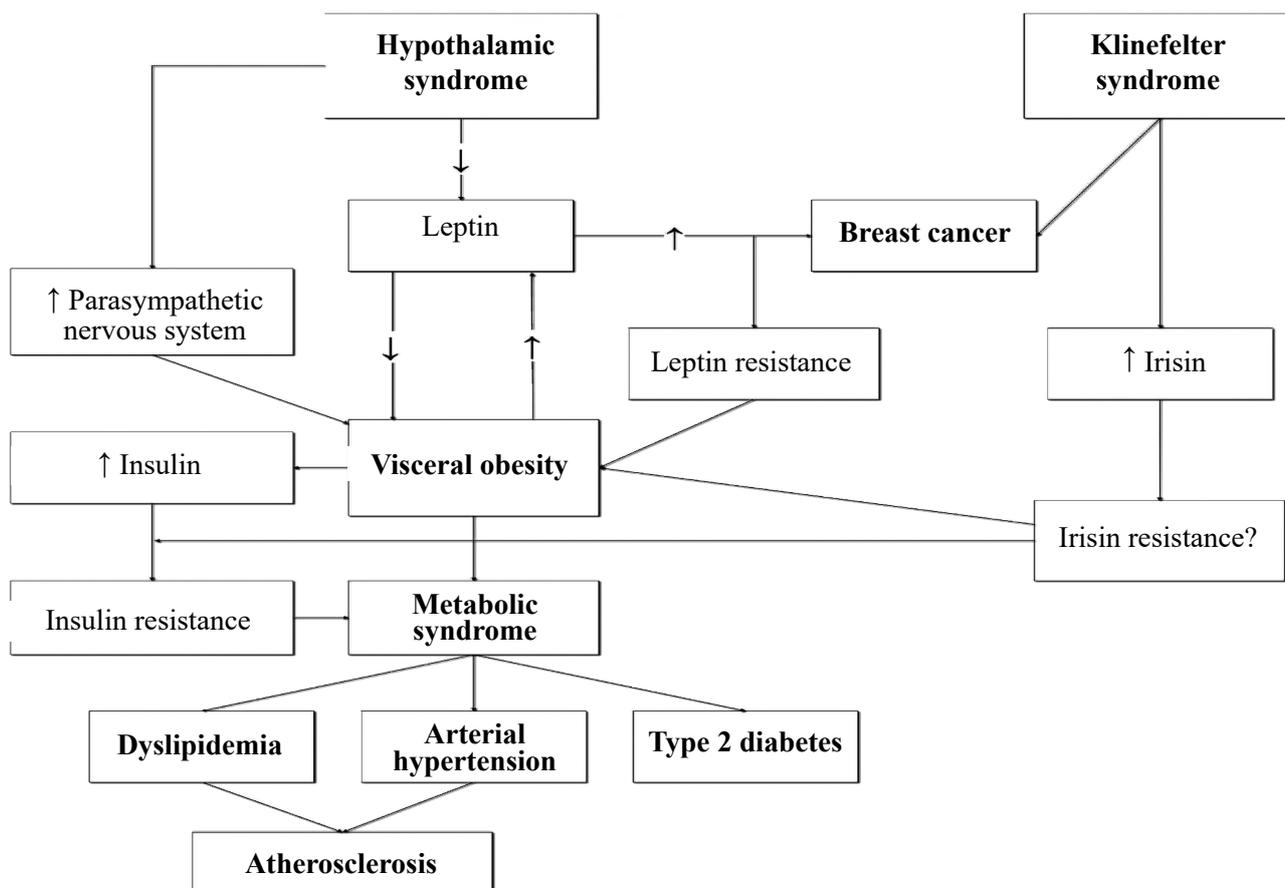


Fig. 1. Pathogenesis of the interconnection between HS and KS.

syndrome, which includes arterial hypertension, type 2 diabetes, and dyslipidemia. Patients with KS have an increased level of irisin, and there is an increased risk of developing obesity and insulin resistance regardless of hypogonadism. The described mechanism of pathophysiological changes in the body determines a high risk of developing diabetes in the presence of hypothalamic syndrome associated with Klinefelter syndrome.

Conclusions

Therefore, the combination of hypothalamic syndrome with Klinefelter syndrome is a rare, complicated clinical variant of the condition that can lead to dysmetabolic complications and an increased risk of developing related pathologies. Therefore, a detailed study of the mechanisms of the interconnection of these pathologies is necessary, which will allow the development of new treatment methods, prevent complications, and conduct screening for type 2 diabetes and breast cancer. It is necessary to determine the prognosis

for fertility, control, and compensation of possible reproductive dysfunctions to ensure the patient's high quality of life and socialization.

Financing

This study did not receive any external funding.

Conflict of interest

There is no conflict of interest that could compromise the impartiality of the research.

Consent to publication

Written informed consent was obtained from the patient for the use of research data and publication of this work, in accordance with the guidelines of the scientific publication ethics committee.

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A – Work concept and design, B – Data collection and analysis, D – Writing the article, E – Critical review, F – Final approval of the article.

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Клінічний випадок гіпоталамічного синдрому, асоційований з синдромом Клайнфельтера

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Анотація: у статті описано клінічний випадок гіпоталамічного синдрому, асоційованого з вродженим захворюванням - синдромом Клайнфельтера в 21-річного пацієнта. Вивчалися дисметаболичні ускладнення на фоні ендокринної та генетичної патологій. Синдром Клайнфельтера було діагностовано в пацієнта у 10-ти річному віці, виявлено каріотип 47XXY/46XY, мозаїчний варіант. На фоні наявності рідкісної генетичної патології в 15 років почали наростати прояви гіпоталамічного синдрому пубертатного періоду: акне, стрії рожевого кольору на латеральних ділянках живота та молочних залозах, гінекомастія, надлишкова вага. Загально-клінічні лабораторні дослідження, показники вуглеводного обміну, статеві й тиреоїдні гормони не відрізнялися від референтних значень. Рівень кортизолу в крові 23,4 мкг/дл, децю перевищував верхню межу референтних значень (4,30-22,4 мкг/дл), що вказує на стан помірного гіперкортицизму. З боку серцево-судинної системи відмічалися прояви дисметаболичної кардіоміопатії, яка ускладнювалася стійкою артеріальною гіпертензією II ступеня. Особливістю клінічного випадку є поєднання ендокринної патології з генетичною, що обумовлює специфічний зовнішній вигляд пацієнта, наявність дисметаболичних ускладнень без порушень вуглеводного обміну при ожирінні III ступеню. Прискорення темпів пубертату, яке часто відбувається при гіпоталамічному синдромі, не відбувалося через супутній гіпоандрогенний вплив супутнього синдрому Клайнфельтера (СК). За умови наявності гіпоталамічного синдрому

в пацієнта відмічався пізній розвиток вторинних статевих ознак, що більш характерно для СК, при цьому збережена нормальна розумова активність, що при мозаїчній формі даної генетичної патології спостерігається рідко. Також клінічною особливістю є відсутність типових проявів гіпогонадізму в постпубертатному періоді, що підтверджується нормальним рівнем чоловічих та жіночих статевих гормонів у крові, що не характерно зазвичай для синдрому Клайнфельтера. Враховуючи особливість даного клінічного випадку, може бути збережена фертильність пацієнта. Окрім наявних дисметаболічних ускладнень у хворого та метаболічного синдрому, відмічається високий ризик розвитку цукрового діабету 2 типу, атеросклерозу, остеопорозу, раку молочних залоз - через взаємне обтяження двох синдромів. Саме тому важливим є вивчення питання щодо поєднання цих двох патологій, можливих наслідків та шляхів їх подолання, щоб покращити клінічні прогнози та якість життя пацієнта.

Ключові слова: Генетичний синдром, гінекомастія, метаболічний синдром, ожиріння, цукровий діабет.



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