CLINICAL OBSERVATION OF SEVERE ITSENKO-CUSHING DISEASE

Scientific adviser: **Daminov A.T**
Assistant of the Department of Endocrinology,
Samarkand State Medical University

[1] **Norkulov Alijon**
[2] **Turamudov Rahim**
[3] **Zayniddinova Dinora**
Students of the Samarkand state Medical University

Annotation. *Itsenko-Cushing disease is a serious disease of the neuroendocrine system caused by excessive release of adrenocorticotropic hormone by a pituitary tumor. The incidence of this disease is 39.1 cases per 1 million population, and the incidence is from 1.2 to 2.4 cases per 1 million. Typical symptoms include rapid weight gain combined with muscle weakness, hypertension, diabetes mellitus and osteoporosis . The main diagnostic method is MRI of the brain after laboratory confirmation of hypercortisolemia, and the main treatment method is transnasaladenomectomy, which allows achieving remission in 65–90% of cases. This article describes a clinical observation of severe Itsenko-Cushing disease, which remained undiagnosed for a long time. The stages of the diagnostic search, the difficulties of differential diagnosis and the results of dynamic observation, including selective blood sampling from the inferior petrosal sinuses are considered. A multidisciplinary approach and teamwork make it possible to ensure timely diagnosis, prevent the development of complications of Itsenko-Cushing disease, and improve the patient's prognosis and quality of life.*

Keywords:*Itsenko-Cushing's disease, clinical observation, hypercorticism, hypercortisolemia, ACTH, somatostatin receptor scintigraphy, transsphenoidaladenomectomy.*

Introduction. Itsenko-Cushing's disease is a severe neuroendocrine disease caused by chronic overproduction of adrenocorticotropic hormone (ACHT) by a pituitary tumor. The incidence of this disease is 39.1 cases per 1 million population, and the incidence is from 1.2 to 2.4 cases per 1 million. Typical symptoms of Itsenko-Cushing disease include rapid weight gain combined with muscle weakness, arterial hypertension (hypertension), diabetes mellitus (DM) and osteoporosis. The most common signs of hypercortisolism are obesity and hypertension (occurring in 86 and 68% of patients, respectively). Successful treatment of hypercortisolemia leads to a

reversal of symptoms, but does not completely eliminate the signs of Cushing's syndrome [1, 2]. Bone mineral density and cognitive dysfunction improve after successful surgical treatment, but do not normalize in all patients [3]. We present a clinical observation of a severe course of Itsenko-Cushing's disease, which remained undiagnosed for a long time, which led to multiple manifestations of hypercortisolemia.

Clinical observation. Patient K., 44 years old, consulted an endocrinologist at the Russian Scientific and Practical Center for Emergency Medicine on an outpatient basis for correction of oral glucose-lowering therapy. History of the disease. He considers himself sick since 2018, when he began to notice an increase in blood pressure to 220/120 mmHg. Art., but did not consult a doctor, did not take regular antihypertensive treatment. In August 2020, he was urgently hospitalized at the Regional Hospital of Samarkand in the neurological department for the treatment of patients with acute cerebrovascular accident with a diagnosis of cerebrovascular disease. Intracerebral hemorrhage in the vertebrobasilar region. Chronic cerebral ischemia stage II. Atherosclerosis of the brachiocephalic arteries. For surgical treatment he was transferred to the neurosurgical department of the Regional Clinical Hospital. On August 6, 2020, he underwent emergency surgery under endotracheal anesthesia, resection trepanation of the posterior cranial fossa on the right was performed, and a cerebellar hematoma was removed.In 2021, he noted an increase in body weight of about 10 kg over 2 months. Since January 2022, I noticed changes in appearance (moon-shaped face, increased abdominal volume, weight loss in the limbs, the appearance of purple stretch marks on the abdomen, dry skin). In April 2021, diabetes was detected and hypoglycemic therapy was prescribed - metformin, extended-release tablets, 750 mg orally in the evening.Due to the fact that the patient noted a decrease in height by 8 cm throughout his life, an MRI of the lumbosacral spine was performed on 02/04/2022. An MR picture of a compression fracture of the L2 vertebra and the consequences of a compression fracture of the bodies of the L1 and L5 vertebrae are described; static disorders, degenerative changes in the lumbosacral spine, L4-L5 disc herniation, L3-L4 disc protrusion. Spondyloarthrosis.In May 2022, a mass in the right lung was detected. Consulted at the Samarkand branch of the Oncology Center, a fragment of the bronchial mucosa was taken for cytology. According to the results of a cytological study: bronchial epithelial cells against a background of mucus. On May 30, 2022, a PET CT scan was performed - no reliable data were obtained on the presence of an active neoplastic process at the time of the study. Severe hepatosteatosis. No data on oncopathology of the OGK were identified. In June 2022, after dental intervention for acute pulpitis, he began to notice swelling and pain in the right cheek, and was hospitalized in the department of maxillofacial surgery (MFS) with a diagnosis

of exacerbation of odontogenic chronic osteomyelitis of the lower jaw on the right. Subperiosteal abscess of the lower jaw on the right. During hospitalization, surgical intervention was performed to the extent of opening and draining the abscess. According to DEXA data from 06/08/2022, the mineral density of bone tissue in the left hip is -1.0 SD (according to the Z-criterion) in the lumbar spine 0.5 SD (according to the Z-criterion). Deoxypyridinoline/creatinine ratio in urine as of June 10, 2022: 6.6 nmol/mmol (2.3–5.4 nmol/mmol). On August 16, 2022, he consulted an endocrinologist at the Russian Scientific and Practical Center for Emergency Medicine on an outpatient basis for correction of glucose-lowering therapy. Gozogliptin 30 mg in the morning, metformin extended-release tablets 1000 mg in the evening were recommended. During an objective examination, attention was drawn to a change in appearance according to the Cushingoid type: a moon-shaped face of a purple color, fat deposition mainly on the abdomen in combination with muscle atrophy, burgundy striae. The patient notes these changes in appearance for two years. A laboratory and instrumental examination was prescribed and carried out. On August 29, 2022, a CT scan of the adrenal glands was performed (without contrast), the results of the study revealed diffuse enlargement of the adrenal glands on both sides, with the presence of a space-occupying formation on the left with smooth, clear contours measuring 1.6×1.0 cm, with a density of up to 2.5 units. N. According to MRI of the brain dated September 17, 2022, no evidence was obtained for the presence of a pituitary adenoma. According to laboratory tests, the level of cortisol in saliva as of September 19, 2022 is 34.6 nmol/l (<7.56 nmol/l), the level of cortisol in the blood in the morning is 1067 nmol/l (101.2–535.7 nmol/l) (determination of free cortisol in urine, overnight suppression test was not performed), ACTH level 9.19 pg/ml (7.2–63.3 pg/ml); potassium and sodium levels were 3.51 mmol/L (3.5–5.1 mmol/L) and 145 mmol/L (136–145 mmol/L), respectively (reference values in parentheses).Hospitalized and examined at the Russian Scientific and Practical Center for Esthetic Physics from 09/30/2022 to 10/06/2022. Due to increasing swelling of the lower jaw on the right, he was consulted by an oral and maxillofacial surgeon, then transferred to the maxillofacial surgery department for opening and drainage of the abscess. In November 2022, he was hospitalized in the regional hospital in Samarkand. According to the results of laboratory tests, endogenous ACTH-dependent hypercortisolism was confirmed: the level of cortisol in the blood in the evening was 1219 nmol/l (79.0–477.8 nmol/l), in the saliva in the evening - 100.3 nmol/l (<7.56 nmol /l), daily cortisol excretion - 1505.6 nmol/day (<485.6), the ACTH rhythm is disturbed: the ACTH level in the morning was 33.22 pg/ml (7.2–63.3 pg/ml), in the evening - 35.89 pg/ml (7.2–63.3 pg/ml). Moderate hypokalemia of 2.57 mmol/L (3.5–5.1 mmol/L) was also detected. In order to correct hypokalemia, infusion therapy with a 4% solution of potassium chloride was carried

out with positive dynamics (according to the results of control tests, the potassium level was 3.11 nmol/l (3.5–5.1 mmol/l)). For the purpose of topical localization of the formation, MSCT of the thoracic and abdominal cavities with contrast enhancement was performed; According to the results of the study, nodular adrenal hyperplasia and segmental hyperplasia of the left adrenal gland were registered; no data were obtained for the presence of space-occupying formations. According to the MRI results, there is no evidence for the presence of a pituitary adenoma.Taking into account the lack of clear evidence for the presence of a pituitary adenoma, the severity of hypercortisolism, and severe hypokalemia, for the purpose of differential diagnosis of ACTH-dependent hypercortisolism, it was decided to conduct selective blood sampling from the lower petrosal sinuses, followed by somatostatin receptor scintigraphy. According to the results of simultaneous bilateral selective blood sampling from the inferior petrosal sinuses, the maximum ACTH gradient between the center and periphery was 6.682; ACTH/prolactin-normalized ratio was 1.672, which indicated a central genesis of the disease. The results of the study are presented in the table. According to somatostatin receptor scintigraphy in the “whole body” mode, no scintigraphic signs of hormonally active formations with overexpression of somatostatin receptors were detected. The patient was consulted by a neurosurgeon: planned surgical intervention was recommended.On November 28, 2022, the patient underwent endoscopic endonasaltranssphenoidal removal of an endosellar pituitary adenoma. A morphological study of postoperative material from the pituitary gland confirmed a pituitary adenoma. In the postoperative period, the patient showed an improvement in general condition. Changes in the patient’s appearance during follow-up after adenomectomy are presented. According to a hormonal study of blood serum on the 3rd day after surgery: ACTH in the morning - 1 pg/ml (7.2-63.3), cortisol in the morning - 150.3 nmol/l (171-536). The data obtained indicate the development of secondary adrenal insufficiency and the effectiveness of surgical treatment. Hormone replacement therapy with hydrocortisone at a dose of 30 mg/day was initiated. There were no objective data for electrolyte disturbances. However, according to laboratory tests, an increase in sodium levels was detected to a maximum of 148 mmol/l, with normalization on the 8th day. During the entire period of hospitalization, no episodes of polyuria/polydipsia were observed. The levels of thyroid-stimulating hormone and free thyroxine are within the laboratory reference values, which indicates the absence of the development of secondary hypothyroidism.

Discussion. Itsenko-Cushing disease is a serious neuroendocrine disease caused by a hypothalamic-pituitary disorder and characterized by an increase in the production of adrenal hormones, which leads to clinical manifestations of hypercortisolism. One of the main signs is the uneven distribution of subcutaneous fat, leading to an increase

in body weight, especially in the shoulder girdle, supraclavicular spaces and abdomen, with preservation of thin limbs. The skin becomes thin, dry, purple-cyanotic in color, and red-violet stretch marks may appear on it. Itsenko-Cushing disease can also lead to serious disorders of the cardiovascular system, such as hypertension and chronic circulatory failure. Other manifestations include myopathy, muscle atrophy, and carbohydrate metabolism disorders, which can lead to type 2 diabetes. Cognitive impairment may also be characteristic of this disease. There are several degrees of severity of Itsenko-Cushing disease, depending on the severity of hypercortisolism and the formation of clinical symptoms. The mild form is characterized by moderate severity of symptoms of the disease, the moderate form is characterized by the severity of all symptoms without complications, the severe form is characterized by the severity of symptoms and the presence of complications. At the first stage of diagnosis, increased production of cortisol is detected in patients. In order to identify hypercortisolism, the daily rhythm of cortisol secretion in the blood in the morning and evening is determined. In Itsenko-Cushing's disease, the level of cortisol in the morning is increased, and the secretion rhythm is disturbed. Determination of daily excretion of free cortisol in urine is also a necessary laboratory diagnostic method to confirm hypercortisolism. A small test with dexamethasone is performed in doubtful cases for differential diagnosis between pathological endogenous and functional hypercortisolism. If cortisol secretion does not decrease by 50% or more from the initial level, this indicates the presence of hypercortisolism. Itsenko-Cushing's disease is characterized by normal or increased morning ACTH levels and the absence of its decrease at night. In ACTH-ectopic syndrome, ACTH secretion is increased and can range from 100 to 200 pg/ml and higher, while there is also no rhythm of its secretion.

REFERENCES:

1. Отамуродов УГ угли, Абдужамбилов АН угли, Сабирова ДШ. Гипертиреоз. *ScienceandEducation*. 2023;4(5):134-139.
2. Шухратовна СД, Рустамовна РГ, Нодир Р. Изменения уровня хг в системе мать-плацента-плод прирезус несовместимой беременности. *Достижения науки и образования*. 2020;(10 (64)):91-93.
3. Хамраев Х, Содиков С, Хамраева Д, Собирова Д. Клинико-функциональное состояние печени у больных с сахарным диабетом. *ЖПБМ*. 2018;(1 (99)):189-191.
4. Shukhratovna SD, Suratovich OF. МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ КОРЫ НАДПОЧЕЧНИКОВ ПОТОМСТВА КРЫС В ОНТОГЕНЕЗЕ В УСЛОВИЯХ ВНУТРИУТРОБНОГО ВОЗДЕЙСТВИЯ ПЕСТИЦИДОВ ЧЕРЕЗ ОРГАНИЗМ МАТЕРИ (ОБЗОРНАЯ СТАТЬЯ). *JOURNAL OF*

BIOMEDICINE AND PRACTICE. 2023;8(4). Accessed January 12, 2024. https://tadqiqot.uz/index.php/biomedicine/article/view/8217
5. Мизамова МАК, Эшпулатова ГНК, Эшмуродова ЗНК, Салимова ДЭ. Осложнения акромегалии, связанные со здоровьем, текущие и перспективные варианты лечения. *ScienceandEducation*. 2023;4(4):187-195.
6. Нарбаев А, Джураева З, Курбонова Н, Кувондиков Г, Давранова А, Содиков С. Особенности изучения многофакторного управления сахарным диабетом 2 типа. *Журнал проблемы биологии и медицины*. 2017;(4 (97)):78-79.
7. Ибрагимов УС, Туракулов ЖТУ, Гуломов ШНУ, Салимова ДЭ. Просвещение пациентов: Гипогликемия (низкий уровень глюкозы в крови) у людей с диабетом. *ScienceandEducation*. 2023;4(4):226-233.
8. Содиков С, Каримова Н, Каримова З. Реабилитация больных пожилого возраста сахарным диабетом 2-типа. *ЖПБМ*. 2017;(4 (97)):105-106.
9. Хамидова МН, Исматова ИФ, Бердиеров ЖШ, Негматова ГШ, Даминов АТ. САХАРНЫЙДИАБЕТИ COVID-19. *Eurasian Journal of Medical and Natural Sciences*.2022;2(13):190-204.
10. Шухратовна СД, Кахрамонович ЮУ, Махмудович КТ. Структурные изменения сосудисто-стромального комплекса щитовидной железы при эутиреоидной и токсических формах зоба. *Научный журнал*. 2019;(10 (44)):67-69.
11. Собиржоновна КН, Саллохидинович СС, Акбаровна ОМ. Эпидемиологический Статус И Факторы Риска Сахарного Диабета На Сегодняшний День. *MiastoPrzyszłości*. 2023;32:212-219.
12. Salimova DE, Daminnov AT. A CLINICAL CASE BASED ON THE EXPERIENCE OF TREATING HYPERTENSION IN A PATIENT WITH TYPE 2 DIABETES MELLITUS, OBESITY AND VITAMIN D DEFICIENCY. *Educational Research in Universal Sciences*. 2023;2(12):150-154.
13. Takhirovich DA. ASSESSMENT OF HEARING FUNCTION IN INDIVIDUALS WITH TYPE 2 DIABETES. *American Journal of Pediatric Medicine and Health Sciences (2993-2149)*. 2023;1(9):124-126.
14. Qahramonov FA, Amirov BY, Tursunboyeva LI, Daminov AT. Autoimmuntireoiditbilankasallanganbemorlardagifunksionalbuzilishlarningdifferensionaldiagnostikasidaqalqonsimonbezzichliginianiqlash.*Science and Education*. 2023;4(3):82-86.
15. Nazira K, Siddikovna TG, Davranovna DA, Takhirovich DA, Tulkinovich OS. Cardiovascular complications in patients who have had covid on the background of diabetes mellitus 2.*1*. 2021;2(3):37-41.
16. Choriyev S, Gadoeva Z, Mardonova F, Jurakulov F, Hafizov S, Daminov AT. Changes in the thyroid gland in the long period after a new coronavirus infection.*Science and Education*. 2023;4(12):102-106.
17. Kamalov T, Bahriev N, Yuldashev U, Sabirova D. CLINICAL AND HORMONAL CHARACTERISTICS OF PRIMARY HYPOGONADISM IN PRESCHOOL BOYS. *MedFarm*. 2019;10(9). doi:10.32743/2658-

4093.2019.9.10.188
18. Daminov A, Khaydarov O, Hasanova M, Abdukakhorova R. COMPLICATIONS OF GLUCOCORTICOID THERAPY IN PATIENTS DIABETES SURVIVED COVID-19. *Евразийскийжурналмедицинскихиестественныхнаук*. 2023;3(4):197-200.
19. Takhirovich DA, Corners SJA, Shukhratovna NG, Shukhratovna SG, Zaynuddinovna MG. COURSE OF COVID-19 IN PATIENTS WITH DIABETES MELLITUS. *Web of Scientist: International Scientific Research Journal*. 2022;3(02):73-76. doi:10.17605/OSF.IO/B6FU2
20. Shukhratovna NG, Erkinovna SD, Suxrobovna XM, Ikromovna AZ. DIABETES MELLITUS, ISCHEMIC HEART DISEASE AND ARTERIAL HYPERTENSION. *PEDAGOG*. 2022;5(5):381-386.
21. O‘g‘li SOS, O‘g‘li RSO, Taxirovich DA. DIFFUZTOKSIKBUQOQ. *Лучшиеинтеллектуальныеисследования*. 2023;4(1):131-133.
22. G.Sh N, D.e S, Oybekovma XS, Qamariddinovna XA, O‘g‘li BJA. ENDOCRINE GLANDS, STRUCTURE, AGE FEATURES, FUNCTIONS. *PEDAGOG*. 2022;5(5):341-345.
23. Sobirjonovna KN. FACTORS DETERMINING THE CLINICAL SIGNIFICANCE OF DEPIPTIDYL PEPTIDASE 4 INHIBITORS IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS. *World Bulletin of Public Health*. 2022;8:67-72.
24. Daminov AT, Djabbarova D, Abduvohidova N, Furkatova D, Farxodova S, Ibragimova P. Features of bone tissue remodeling in patients with type 2 diabetes mellitus. *Science and Education*. 2023;4(11).
25. DaminovAbdurasulTakhirovich RSU. FEATURES OF THE CLINIC, REHABILITATION, TREATMENT OF AUTOIMMUNE THYROIDITIS IN THE CONDITIONS OF THE IODINE-DEFICIENCY REGION.Published online April 12, 2023. doi:10.5281/ZENODO.7820412
26. Shuhratovna NG, Shukhratovna SD. Features of the course of autoimmune hepatitis in children as a variant of autoimmune polyglandular syndrome. *Asia Journ of MultidimensiResear (AJMR)*. 2020;9(7):89. doi:10.5958/2278-4853.2020.00228.1
27. Erkinovna SD. Features of the Course of Diabetes Mellitus Type 2 with Arterial Hypertension. *JournalNX*.Published online 2020:460-461.
28. Takhirovich DA, Zafarovna KM, Isroilovna IS. FEATURES OF TYPE 1 DIABETES IN CHILDREN WHO HAVE COVID-19.*American Journal of Pediatric Medicine and Health Sciences (2993-2149)*. 2023;1(9):121-123.
29. Xudoyorov S, Mirkomilova M, Burxonov U, Sayfieva G, Sheralieva N, Daminov AT. Fourniers gangrene in modern conditions. *Science and Education*. 2023;4(12):107-117.
30. Alimovna KN, Sobirjanovna KN, Abdurasul D, Tulkinovich OS. GROWTH HORMONE FOR THE TREATMENT OF HEREDITARY DISEASES IN CHILDREN. 10.

31. Negmatova .G.Sh, D.e S, Qizi MZO, Mannobovich MS, Orifjonovich MM. HERPETIC MENINGITIS. *PEDAGOG*. 2022;5(5):346-348.
32. Ahrorbek N, Myungjae L, Jungjae L, et al. Hormonal Regulation. *Texa Jour of Mutl Stud*. 2023;25:39-43.
33. Ismoilova SI. Impact of vitamin D deficiency on the risk of developing type 1 diabetes.*Science and Education*. 2023;4(3).
34. T DA, Umidbekovna UM, Muhitdinovna KN. Methodology of Using Modern Graphics Programs in Teaching Engineering Graphics. *1*. Published online December 8, 2023:158-162.
35. Sabirjanovna KN, Takhirovich DA, Jahongir D, Najmiddin X, Samandar G, Mehrangiz X. Negative Impact of Covid-19 on the Endocrine System. *American Journal of Pediatric Medicine and Health Sciences (2993-2149)*. 2023;1(8):148-153.
36. Takhirovich DA, Zafarovna KM, Isroilovna IS. NEVROLOGIYADA ENDOKRIN O‘ZGARISHLAR.*SO‘NGI ILMIY TADQIQOTLAR NAZARIYASI*. 2023;6(12):417-422.
37. Negmatova GS, Salimova DE. Qandlidiabet 2-tipning arterial gipertenziyabilanbirgalikdakechishxususiyatlarivaularnidavolashusullari. *Science and Education*. 2023;4(2):516-519.
38. Taxirovich DA, J T, O E, I A. QANDLI DIABET-2 TIPI BOR BEMORLARDA COVID-19 KASALLIGINI GLUKOKORTIKOIDLAR BILAN DAVOLASH DINAMIKASINI BAHOLASH. *Gospodarka i Innowacje*. 2023;34:78-81.
39. G.Sh N, D.e S, Alisherovich BA, Erkin R is the son of S, Bektash U is the son of S. RELATIONSHIP BETWEEN DIABETIC NEPHROPATHY AND CARDIAC DISORDERS IN PATIENTS WITH TYPE 2 DIABETES. *PEDAGOG*. 2022;5(5):337-340.
40. Shukhratovna NG, Erkinovna SD, O‘g‘li IBI, Qizi ADD. THE ROLE OF GASTROINTESTINAL HORMONES IN THE PATHOLOGY OF THE DIGESTIVE SYSTEM.*PEDAGOG*. 2022;5(6):408-412.
41. Ulugbekovna NP, Bakhtiyorovna RI, Almosovich RA, Takhirovich DA. Thyroid Diseases during Pregnancy and their Impact on Maternal and Fetal Outcomes.*American Journal of Pediatric Medicine and Health Sciences (2993-2149)*. 2023;1(8):188-190.