Autoimmune polyglandular syndrome 1st like bible sisters

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Abstract: The article gives information about autoimmune polyglandular syndrome 1st like bible sisters.

Keywords: autoimmune hypoparathyroidism, hypothyroidism, alopecia, oophoritis, hypocortisolism, hypogonadism

Introduction. In the practice of an endocrinologist, hereditary syndromes caused by gene mutations are a rare pathology. The occurrence of these diseases is almost independent of the environment; they can occur at any age, although 98% of this pathology manifests itself before the end of puberty. Heredity and variability together ensured the preservation of life on Earth. Hereditary diseases are part of the hereditary variability that has accumulated during evolution. The problem of diagnostics and mechanisms of development of autoimmune polyglandular syndromes remains relevant in scientific terms and in the direct work of an endocrinologist. Hereditary diseases are often characterized by pleiotropy, interest in the process of many organs and tissues, both endocrine and non-endocrine. In patients with APGS-1, the manifestation of this pathology is manifested by damage to 2 or more peripheral glands, which leads to their failure. APGS-1 is a disease with an autosomal recessive mode of inheritance, caused by a mutation in the only autoimmunity-regulating gene AIRE-1, located on chromosome 21q22.3. It is characterized by a triad of syndromes: mucocutaneous candidiasis, hypoparathyroidism, primary chronic adrenal insufficiency (CAI), but sometimes primary hypothyroidism, primary hypogonadism, oophoritis, and alopecia occur [1; 2]. The AIRE gene encodes the AIRE protein, which is an autoimmune regulator that forms a mechanism for eliminating immune cells that affect the body's own structures. Mutations in this gene cause the development of autoimmune polyendocrine syndrome type 1 - APECED syndrome (Autoimmune polyendocrinopathy-candidiasisectodermal dystrophy /dysplasia), the main manifestations of which include hypoparathyroidism, candidal lesions of the skin and mucous membranes, primary hypocortisolism. If the AIRE protein is defective,

autoreactive cells can leave the thymus and, circulating in the body, cause autoimmune inflammation [3].

The purpose of our workis a clinical and laboratory assessment of the course of autoimmune polyglandular syndrome type 1 (APPS-1) in 2 siblings. Observation #1. Patient L., 23 years old, was examined in the endocrinology department of Samarkand. The patient complained of severe weakness, headache, dizziness, decreased vision, and stool instability. Patient L. has suffered from candidiasis of the mucous membranes since birth, and at the age of 1 year she suffered from candidal-staphylococcal pneumonia, pleurisy, pneumothorax and candidal sepsis. Since the age of 5, he has been experiencing convulsions, often with “grand seizures,” so epilepsy was diagnosed and anticonvulsant therapy was prescribed. The family was examined in Tashkent, where the genetic nature of the disease was established. The carrier of pathological autososome chromosome 21 is the father. At the age of 10 and 12 years, she underwent cataract surgery in the right and left eyes, respectively. From the age of 15, I began to notice weight loss, persistent hypotension, “black tan” skin, frequent vomiting and diarrhea. At the age of 16, she was first hospitalized in the endocrinology department with a clinical diagnosis of adrenal (Addisonian) crisis, which had a severe course and was resistant to therapy with glucocorticoids and mineralocorticoids. On admission, body weight 65 cm, height 160 cm. The skin is smoky-gray with slight hyperpigmentation in areas of friction, hyperkeratoses, and elbows. The nail plates are dull, yellowish, and brittle. Nutrition reduced. Breathing is vesicular, no wheezing. The boundaries of the heart are within normal limits. Heart sounds are muffled and rhythmic. Heart rate-84 per minute. Blood pressure - 105/70 mm Hg. The tongue is dry, coated at the root with a white coating. The abdomen is soft, moderately painful along the large intestine, rumbling upon palpation. Liver +1.5 cm, painless. Stool with tendency to constipation. SSPO is negative. There are no dysuric disorders. The thyroid gland is not enlarged. Chvostek's syndrome is weakly positive, Trousseau's syndrome is negative. Female-type hair growth, sparse on the pubis and axillary areas. No meningeal symptoms or focal neurological symptoms were identified. Blood calcium 2.03 mmol/l (with a norm of 2.2 - 2.75), in urine: calcium - 20.5 mmol/day (with a norm of 0.25 - 4.99), phosphorus - 46 mmol/day (at a norm of 19.37 - 31.29). Blood test for cortisol - 423 nmol/l (230 - 750). When examining stool for dysbacteriosis, enteropathogenic Escherichia and a large number of conditionally pathogenic flora were sown. Urine culture for microflora revealed: Enterobacter aerogenes in titer 30, streptococcus letis 50, candida albicans 30, ECG shows diffuse changes in the myocardium. Sinus rhythm, 78v/1 min. Ultrasound examination revealed diffuse changes in the kidneys, possibly a developmental anomaly. The adrenal glands are not changed. The ophthalmologist describes pseudophakia on both sides, on the fundus without pathology. An attempt

to get pregnant at age 20 ended in spontaneous abortion. Final diagnosis. Autoimmune polyglandular endocrine syndrome type 1 (chronic adrenal insufficiency, congenital primary hypoparathyroidism, primary hypothyroidism, congenital immunodeficiency, generalized mucocutaneous candidiasis, hypogonadism). Currently, the patient's condition is stable and she is being treated with replacement therapy, which includes: prednisolone 15 mg/day, cortinef 200 mg/day, L-thyroxine 100 mg/day, calcium supplements (usually calcium-D3 Nycomed), antifungal drugs (Diflucan), eubioics (lacto- and bifidobacterin, bactisubtils). Observation No. 2 Patient S., 18 years old, the sister of patient L., was treated in the endocrinology department. She takes prednisolone 5 mg, cortinef 1 tablet, L-thyroxine-100 25 mg per day, calcium supplements. There were no complaints upon admission. Objectively: The condition is satisfactory. Consciousness is clear, position is active. Contact. The skin is pale, there are pockets in the corners of the mouth. Deformation of nails in/extremities. Reduced nutrition. Weight 40 kg, height 158 cm. CVS: The heart area is not changed. The limits of relative cardiac dullness are within normal limits. Blood pressure 110/70 mm Hg. Pulse 72 beats/min. Heart sounds are clear and rhythmic.DS: Breathing through the nose is free. BH 18/min. Breathing over the lungs is vesicular, there are no wheezes. Gastrointestinal tract: The tongue is moist, covered with a white coating. The abdomen is soft, b/w. Liver along the edge of the costal arch. The chair is without any features. Urination is free, up to 8 times/day. Diuresis is sufficient. There is no swelling. ES: nutrition reduced. Female pattern hair growth. Appearance corresponds to passport age. The thyroid gland is palpated in the form of a small cord, its lobules are not differentiated. Chvostek's sign and Trousseau's sign are negative. She is 11 weeks pregnant. She categorically refused to interrupt it, despite repeated conversations about a hereditary predisposition to this disease and the possibility of this pathology manifesting itself in a child. General blood and urine analysis - without pathology. Hormones: cortisol 339.7 nmol/l (150-660), TSH 0.1 (0.1-4.0) Biochemical blood test. Glucose - 5.7 mmol/l (3.3-6.1), total protein 68 g/l, creatinine 81.9 μmol/l (46-106), bilirubin 16.9 mmol/l, ALT-14, 7 units (0-32), phosphorus - 1.5 mmol/l (0.87-1.20), calcium 2.2 mmol/l (2.02-2.60). ECG from 22.05 Sinus rhythm 74 per minute. Shortened PQ interval (CLC syndrome). Possible early repolarization syndrome. Right atrial R wave. Final clinical diagnosis: Autoimmune polyendocrine. Chronic adrenal insufficiency. Hypoparathyroidism. Candidiasis. Pregnancy 11 weeks. Treatment: prednisolone 5 mg 1 tablet in the morning, cortinef 1 tablet in the morning, L-thyroxine-100 25 mg in the morning, calcium chloride solution 10% 45 ml x 3 times a day. The mother of both patients is healthy, in her first marriage she has 2 healthy ones children (boy and girl), hereditary diseases, or predispositions to them (survey,anamnesis data) we did not identify. The girls' father was raised in an

orphanage, he has no information about his parents, and was not previously married. An examination by a geneticist in St. Petersburg revealed the presence of the AIRE gene. When interviewing the patients' mothers, it was revealed that the girls' father suffers from broncho-obstructive disease (smoker) and has had subtotal baldness since the age of 20. He was not examined for the presence of fungal pathology. It can be assumed that the father has a mild or latent form of APGS-1. Considering that the mother is healthy and has two healthy children in her first marriage, the disease is autosomal dominant; the pathological, mutant gene has a high penetrance. The clinically more pronounced course of a hereditary disease in daughters compared to the father is called anticipation in genetics. The boundaries of APGS-1 syndrome have not yet been determined, despite the discovery of the genetic basis of the disease. Many authors include non-endocrine manifestations in this disease: autoimmune hepatitis and gastritis, pernicious anemia, juvenile cataracts, malabsorption phenomena. Apparently, this clinical condition will not soon acquire a clear form as a nosological unit [2]. We draw our attention to the fact that the sisters we describe have common parents, living conditions, and nutritional habits, but the severity of clinical symptoms and laboratory data differs. The genotype is transformed into a phenotype under the influence of various modifying factors. The epigenetic factor plays an important role. The epigenetic background underlies the developing organism. Epigenetics evaluates changes in the expression of certain DNA. Genomic imprinting performs an important function during the development of an organism and depends on parental genes. Both the first and second pregnancies with a fetus with high penetrance of the pathological gene of the AIRE protein contributed to the birth of children with hereditary pathology. But during the second pregnancy, the mother’s healthy body, already familiar with a similar pathology in the first case, the second time, perhaps with the help of epigenetic mechanisms, had a positive corrective effect on the fetus [4; 5]. Patient 1 had a more severe course of the disease, decreased immunity, had candidal sepsis, convulsive syndrome, regarded as a manifestation of hypoparathyroidism, neurologists do not exclude the presence of epileptic seizures, with low sensitivity to antiepileptic drugs. One of the severe manifestations of the pathology is severe adrenal insufficiency with episodes of adrenal crises. An episode of non-developing pregnancy, ending with spontaneous miscarriage in the early stages, are likely signs of hypogonadism. Modern views of obstetricians and gynecologists suggest that this pathology may be based on the non-viability of the fetus, pathological inertia of the endometrium, and disturbances in the hemostatic system [4; 5]. Genetic factorsdetermining this process may be a violation of the process of implantation of a fertilized egg due to a defect in the formation of a complete vascular system of the chorion and placenta. The factor necessary for placentation and trophoblast fixation is the vascular endothelial growth factor -

angiogenesis factor - VEGF-A [5; 6]. Reduced folate levels in combination with hyperhomocysteinemia may be the cause of non-developing pregnancy. The presence of the VDR gene, located on the long arm of chromosome 12, contributes to recurrent miscarriage. In the situation we are discussing, we find it difficult to name a specific reason; it could be the non-viability of the fetus; the role of vitamin D3 is actively discussed [6; 7]. Patient 2 also had chronic adrenal insufficiency, hypoparathyroidism, and mild candidiasis. There are no signs of hypogonadism; the pregnancy, according to follow-up data, ended successfully with the birth of a boy without signs of APGS-1 at the present time. Laboratory and genetic examination of the child has not yet been carried out. Both of our patients suffered from increased muscle and nervous excitability to varying degrees. However, attacks of tetany, manifested by convulsive contractions of skeletal and smooth muscles, are often caused by a decrease in the concentration of total and ionized calcium in the blood serum, only in patient 1. Tetany is a condition that develops as a result of insufficient secretion of parathyroid hormone, a decrease in the reabsorption of calcium in the kidney tubules and a decrease in its absorption in the intestine . Neurological symptoms caused by magnesium deficiency, especially tetany, correlate with the development of hypocalcemia and hypokalemia. Some consulting neurologists regarded the seizures as equivalent to an epileptic seizure in patient #1. However, it was not possible to achieve positive dynamics of convulsive syndrome when using antiepileptic drugs. We have recorded a unique syndrome of tonic convulsions, which rarely ends with a clonic convulsive component [8; 9]. The endocrine and immune systems have a close relationship; the resulting gene mutation can give clinically pleiotropic, systemic manifestations, which depends on the penetrance of the gene. The immune component in APGS-1 reduces the activity of the adrenal glands, thyroid and parathyroid glands, and provokes the development of candidiasis. To understand the mechanisms of development of this disease, the theory of fetal microchimerism is proposed [12].Patient 2 also had chronic adrenal insufficiency, hypoparathyroidism, and mild candidiasis. There are no signs of hypogonadism; the pregnancy, according to follow-up data, ended successfully with the birth of a boy without signs of APGS-1 at the present time. Laboratory and genetic examination of the child has not yet been carried out. Both of our patients suffered from increased muscle and nervous excitability to varying degrees. However, attacks of tetany, manifested by convulsive contractions of skeletal and smooth muscles, are often caused by a decrease in the concentration of total and ionized calcium in the blood serum, only in patient 1. Tetany is a condition that develops as a result of insufficient secretion of parathyroid hormone, a decrease in the reabsorption of calcium in the kidney tubules and a decrease in its absorption in the intestine . Neurological symptoms caused by magnesium deficiency, especially tetany, correlate with the

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CONCLUSIONS

1. Both patients suffered from APGS-1 of varying severity.

2. The cause of the disease was their father, who had a mutant AIRE protein gene with high penetrance.3. It can be assumed that the milder course of APGS-1 in patient 2 is due to epigenetic factors of the patient's healthy mother, acquired during the 1st pregnancy by patient 1.4. Convulsive conditions with APGS-1 have the peculiarity of manifesting not only tonic, but sometimes clonic convulsions.

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