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Research Article

NEONATAL DIABETES MELLITUS AND POLYCYSTIC OVARIES IN A CHILD WITH SEVERE INSULIN RESISTANCE CAUSED BY A VARIANT IN THE *INSR* GENE. DESCRIPTION OF THE CLINICAL CASE

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Rare severe insulin resistance syndromes such as Donohue syndrome, Rabson–Mendenhall syndrome, and type A insulin resistance are caused by mutations in the insulin receptor (INSR) gene. Donohue and Rabson–Mendenhall syndromes are caused by biallelic mutations in the α- and / or β-subunits of INSR, are characterized by a severe course with severe clinical symptoms and an unfavorable prognosis. The difficulty of managing and treating these patients is associated with a low incidence, lack of practice in managing such patients, as well as a lack of experience in surgical interventions in these patients.

All insulin resistance syndromes are characterized by a significant increase in the level of insulin in the blood plasma in the absence of obesity, progressive diabetes mellitus and an excess of androgens. Polycystic ovary syndrome or stromal hyperthecosis develops in adult patients with syndromic forms of insulin resistance.

We present a rare clinical case of a complicated course of Donohue syndrome, diagnosed in a 2-month-old patient. A feature of this clinical case was the giant growing multifollicular ovaries, which became an absolute indication for organ resection surgery.

The experience of treatment and observation of this patient reflects the importance of early verification of the diagnosis, timely appointment of adequate therapy, allows you to objectively assess the effectiveness of the treatment, helps in choosing medical tactics and predicting the course and outcome of the disease.

Keywords: insulin resistance; Donohue syndrome; Rabson–Mendenhall syndrome; insulin resistance type A; INSR gene mutation; ovarian hyperthecosis; multifollicular ovaries; hyperglycemia; neonatal diabetes mellitus.

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Научная статья

НЕОНАТАЛЬНЫЙ САХАРНЫЙ ДИАБЕТ И ПОЛИКИСТОЗ ЯИЧНИКОВ У РЕБЕНКА С ТЯЖЕЛОЙ ИНСУЛИНОРЕЗИСТЕНТНОСТЬЮ, ОБУСЛОВЛЕННОЙ ВАРИАНТОМ В ГЕНЕ *INSR*. ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

© Д.О. Иванов, А.Н. Тайц, Л.В. Дитковская, Н.Н. Матвеева, О.Л. Красногорская, А.В. Поздняков, И.В. Мызникова, А.А. Малышева, С.В. Кузьминых, А.Д. Орлова, А.А. Веретенникова

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В основе редких тяжелых синдромов резистентности к инсулину, таких как синдромы Донахью, Рабсона – Менденхолла и инсулинорезистентность типа А, лежат мутации в гене рецептора инсулина (INSR). Синдромы Донахью и Рабсона – Менденхолла обусловлены биаллельными мутациями в α- и/или β-субъединицах INSR, характеризуются тяжелым течением с выраженной клинической симптоматикой и неблагоприятным прогнозом. Для всех синдромов резистентности к инсулину свойственно значительное повышение уровня инсулина в плазме крови при отсутствии ожирения, прогрессирующего сахарного диабета и избытка андрогенов. Синдром поликистозных яичников и/или стромальный гипертекоз развивается у взрослых пациенток с синдромальными формами инсулинорезистентности. Трудность наблюдения и лечения таких пациентов связана с низкой частотой встречаемости, а потому и с отсутствием практики консервативной терапии и с малым опытом оперативных вмешательств.

Мы представляем редкий клинический случай осложненного течения синдрома Донахью, диагностированный у 2-месячной пациентки. Особенностью данного клинического случая были гигантские растущие мультифолликулярные яичники, ставшие абсолютным показанием для удаления пораженного органа.

Опыт лечения и наблюдения данной пациентки отражает важность ранней верификации диагноза, своевременного назначения адекватной терапии, позволяет объективно оценить эффективность проводимого лечения, помогает в выборе врачебной тактики и прогнозировании течения и исхода заболевания.

Ключевые слова: инсулинорезистентность; синдром Донахью; синдром Рабсона – Менденхолла; инсулинорезистентность типа А; мутации в гене *INSR*; гипертекоз яичников; мультифолликулярные яичники гипергликемия; неонатальный сахарный диабет.

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Rare severe insulin resistance syndromes, such as the Donohue syndrome and Rabson–Mendenhall syndrome, and type A insulin resistance are induced by mutations in the insulin receptor (*INSR*) gene. Donohue and Rabson–Mendenhall syndromes are caused by biallelic mutations in the *INSR* α- and/or β-subunits and are characterized by a severe course, pronounced clinical symptoms, and poor prognosis [1, 2, 4, 6, 15]. Most patients die during the first years of life from recurrent infections alongside severe progressive hypotrophy or hypertrophic cardiomyopathy [6, 7, 13]. Type A insulin resistance, the mildest form with an adolescent onset and a favorable prognosis, is usually associated with heterozygous mutations in the β-subunit of the insulin receptor [1, 4, 15].

The main clinical and laboratory signs of all insulin resistance syndromes include *acanthosis nigricans*, a significant increase in plasma insulin levels in the absence of obesity, progressive diabetes mellitus, and androgen excess. The probability of diabetes onset and its severity depend directly on the degree of insulin resistance [3, 5, 6, 13]. Thus, in the case of Donohue syndrome, neonatal diabetes mellitus generally develops, whereas in patients with type A insulin resistance, diabetes or impaired glucose tolerance is considered one of the latest manifestations and can be well compensated with biguanides (metformin) [10]. Polycystic ovary syndrome and/or stromal hyperthecosis in patients with syndromic forms of insulin resistance rarely occur at an early age. Only isolated clinical cases have been described [6, 9, 12, 13]. Insulin stimulates the hormonal activity of ovarian granulosa and theca cells, which increases the synthesis of sex steroids. The influence of insulin on ovarian steroidogenesis and growth of granulosa cells is realized through insulin receptors and is mediated by the receptors of insulin-like growth factor 1 (IGF-1). Insulin increases the activity of 17α-hydroxylase and 17α-lyase, key enzymes of androgen biosynthesis in the ovaries, and the level of free testosterone by reducing the synthesis of globulin-binding sex steroids [11, 14–16]. In addition, with hyperinsulinemia, steroidogenesis is activated following an increase in the number of luteinizing hormone receptors in the granulosa. With increased production of androgens, folliculogenesis is disrupted, which results in the formation of multiple small follicles and stromal hyperplasia. The growth effects of insulin on the ovaries are manifested in the stimulation of interstitial cells, thereby increasing their volume [14–16].

The difficulty of treating newborns with syndromic forms of insulin resistance is due to the severity of the disease course, low incidence, and consequently the lack of experience in working with such patients. In this regard, early diagnostics and timely initiation of pathogenetic therapy are extremely important.

To date, the most effective treatment method is the use of recombinant IGF-1 preparations in combination with biguanides [11, 13]. In addition to pathogenetic therapy aimed at reducing insulin resistance, adequate nutritional support and symptomatic therapy are also performed.

CLINICAL CASE

The female patient was born at term on November 14, 2020, with low birth weight and growth retardation (weight, 1760 g [–3.57 SDS); body height, 45 cm [–1.93 SDS]). Delivery was performed by cesarean section because of worsening intrauterine fetal hypoxia. The Apgar score was 8/8 points.

The anamnesis revealed that it was the second pregnancy (the first child is healthy), associated with chronic placental insufficiency. At weeks 16–17, the mother contracted COVID-19. Ultrasonography revealed pronounced fetal growth retardation at weeks 38–39 (fetal weight, 1948 ± 243 g). The marriage was closely related, without a negative family history of diabetes mellitus.

From birth, the child's condition was of moderate severity. A disproportionate physique was prominent, including relative macrocephaly, limb shortening, pronounced thinning of the subcutaneous fat, muscle hypotrophy, *acanthosis nigricans*, hypertrichosis, developmental anomalies of the facial skull (i.e., a high forehead, large protruding eyes, wide nasal dorsum, wide nostrils, and gum hyperplasia ["elfin face"]), thelarche, macrogenitalism, hypertrophied clitoris, umbilical hernia without signs of strangulation, rectal prolapse, and reduced spontaneous motor activity (Fig. 1). The child had no respiratory or hemodynamic disorders. Breast milk was given in the delivery room, and she received supplementary feeding with formula. From the first days of life, low weight gain was noted despite sufficient enteral nutrition.

On day 7 of life, an ultrasound examination of the abdominal cavity and small pelvis revealed signs of "old" thrombosis of the interlobular veins without damage to the main renal and inferior vena cava, atypical division of the portal vein trunk into branches, and enlarged multifollicular ovaries.

From week 3 of life, the patient's condition sharply deteriorated due to a fever of up to 39°C,

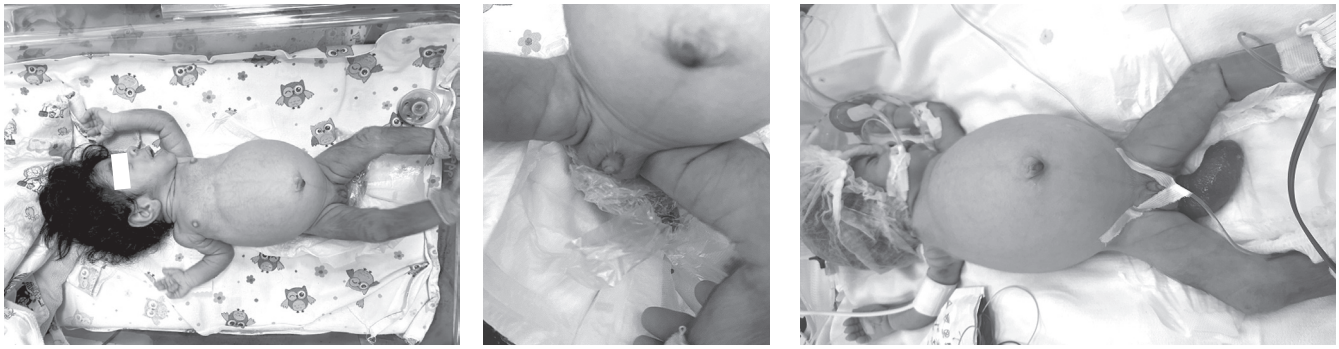


Fig. 1. The appearance of a patient with Donohue syndrome
Рис. 1. Внешний вид пациента с синдромом Донахью

tachycardia, tachypnea, moderate abdominal distension, and acholic stools. The patient stayed in the intensive care unit. Clinical blood tests revealed a decrease in hemoglobin level to 110 g/L, leukocytosis to 23.6–34.2 thousand, and change in the leukogram because of an increase in the stab neutrophil count. The biochemical blood test revealed hypoproteinemia up to 40.0 (Normal range [N] 44–76) g/L; hyperenzymemia with alanine aminotransferase of 60.0 (N 0–40) U/L and aspartate aminotransferase of 62.0 (N 0–40) U/L, gamma-glutamyl transferase of 387.0 (N 9–36) U/L; hyperbilirubinemia with a total bilirubin of 63.5 (N 3.4–20.5) mmol/L and direct bilirubin of 45.4 (N 0.0–8.6) mmol/L. Urinalysis showed marked proteinuria up to 8.8 g/L, erythrocyturia of 10,501.0 cells/μL, leukocyturia of 358.0 cells/μL, and persistent oxaluria.

The patient received infusions, antibiotic therapy (cefaperazone and vancomycin), and total parenteral nutrition. Further examination revealed persistent hyperglycemia up to 30 mmol/L; according to the acid–base state, signs of metabolic acidosis were observed. Hyperglycemia was accompanied by glycosuria (urinary glucose up to 2000 mg/dL) and ketonuria. The child was diagnosed with neonatal diabetes mellitus. According to vital indications, intravenous administration of common insulin at a rate of 0.05–0.2 units/(kg · h) was started, depending on blood glucose values.

Before the insulin therapy was initiated, the levels of insulin and C-peptide were prohibitively high (insulin > 302.0 μIU/mL [N 2.0–25.0]; C-peptide > 16.0 ng/ml [0.5–3.2]). During daily monitoring of blood glucose levels against the insulin therapy, significant variability of glycemia during the day from 1.7 mmol/L to 22.0 mmol/L was recorded, and hypoglycemia occurred repeatedly before feeding. Enteral nutrition was restored with an adapted formula product given fractionally through a tube; however, weight gain was poor. Insulin was gradually decreased, episodes of hypoglycemia became more frequent, and the drug was discontinued. Subsequently, to correct carbohydrate metabolism disorders and increase the sensitivity of peripheral receptors to insulin, biguanide therapy (metformin) at a dose of 70 mg/(kg · day), in four doses, *per os*, was prescribed, which achieved target glycemia levels without significant decrease in insulin and C-peptide levels. In addition, a significant increase in the abdomen volume, constant reducible prolapse of the rectal mucosa, hairiness of the pubic region and armpits, and enlargement of the clitoris were noted. In addition, the patient was diagnosed with congenital heart disease, namely, stenosis of the pulmonary artery valve.

Considering the pronounced signs of hyperandrogenism, karyotyping (46XX karyotype, normal female) and an extended hormonal study revealed 17-hydroxyprogesterone, 1.90 (N 0.1–3.1) ng/mL; luteinizing hormone, 1.11 (N 0.02–8.0) mIU/L; follicle-stimulating hormone, 0.5 (N 0.7–6.7) mIU/L; prolactin, 9.3 (N 2.0–20.0) ng/mL; IGF-1, 395.2 (N 44–206) ng/mL; estradiol, 115.3 pg/mL; testosterone, 0.92 (N 0.03–0.17) nmol/L; and androstenedione, 23.4 (N 0.3–5.0) nmol/L.

On ultrasound examination at the age of 2 months, visualization was complicated. The volume of the abdominal cavity was nearly filled with a heterogeneous volumetric formation represented by multiple cystic structures with hyperechoic septa up to 3 cm^3 in volume.

Multislice spiral computed tomography revealed a large cystic multi-chamber lesion originating from the pelvic organs, with clear smooth edges, partitions in the structure (85 × 105 × 90 mm), enlarged kidneys, and rectal prolapse.

Repeated examinations revealed an enlargement of the ovaries. In the pelvic area, with propagation into the abdominal cavity, large cystic formations were located adjacent to each other. The largest one

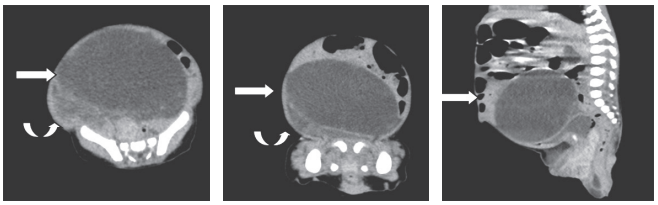
measured 94 × 56 × 65 mm (straight arrow), with a uniform density of 10–15 HU and a thin capsule. On the right, a lesion measured 42 × 15 × 25 mm (curved arrow) with a uniform density of 10–15 HU and a thin capsule. After intravenous administration of a contrast agent, a more distinct visualization of the cyst capsule was obtained (Fig. 2).

Given that the patient had multiple microanomalies of development, pronounced signs of facial dysmorphism, neonatal diabetes mellitus associated with extremely high levels of insulin and C-peptide, absence of subcutaneous adipose tissue, progressive hypotrophy, clinical and laboratory signs of hyperandrogenism, *acanthosis nigricans*, and multifollicular ovaries, the Donohue syndrome was suspected (leprechaunism). To clarify the diagnosis, a blood sample was sent for molecular genetic testing at the National Research Center for Endocrinology of the Russian Ministry of Health (Moscow). A molecular genetic study (sequencing of the panel "Diabetes mellitus – hyperinsulinism") revealed type A insulin resistance (PMID:11260230; OMIM 610549), a previously described pathogenic variant of the nucleotide sequence in the exon 3 of *INSR* c.G839A: p.c280y, (HGMD: CH010893) in the homozygous state, confirming a syndromic form of insulin resistance (Donohue syndrome) in the child.

In connection with the progressive deterioration of the condition caused by metabolic disorders associated with neonatal diabetes mellitus, the development of intra-abdominal tension syndrome due to a critical enlargement of the ovaries, pain syndrome, and poor food intake, a case conference was held, followed by a collegial decision to continue drug therapy with biguanides, considering the prescription of recombinant IGF-1 and palliative surgery to reduce the volume of the ovaries.

Under aseptic conditions with endotracheal anesthesia, supraumbilical minilaparotomy was performed, with ovarian cyst puncture on the right and resection of both ovaries (Fig. 3). Laparoscopic hernioplasty and umbilical hernia repair were also performed.

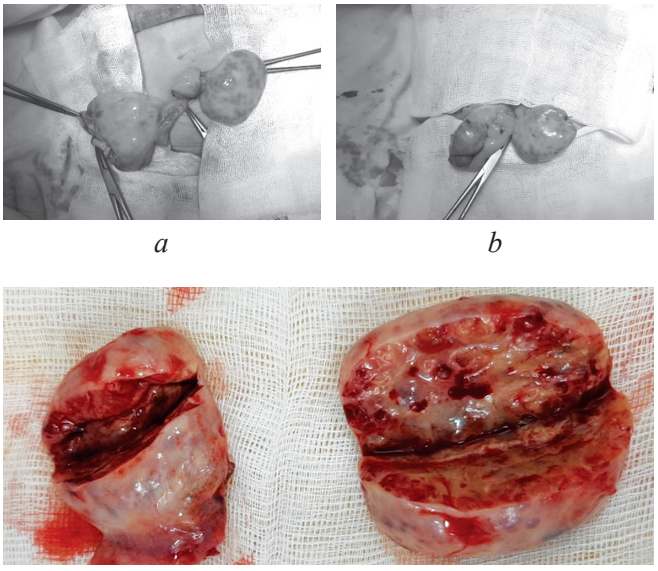
The ovaries measured 4.4 × 3.5 × 2.5 cm on the right and 5.2 × 4.5 × 1.5 cm on the left. On the incision in both ovaries, multiple cysts, with a maximum size of 0.5 × 0.4 cm, were revealed. The histological examination determined multiple follicular cysts lined with multi-row follicular epithelium with pronounced cell proliferation, dystrophic changes, and luteinization phenomena. A wide layer of large theca cells was adjacent to the follicular cysts. The identified morphological changes corresponded to secondary hyperthecosis (Fig. 4).



a *b* *c*

Fig. 2. CT reconstructions: *a* — axial, *b* — coronal, *c* — sagittal projections. Arrows indicate cystic formations

Рис. 2. Результаты мультислайсной спиральной компьютерной томографии. Реконструкции в проекциях: *a* — аксиальной, *b* — коронарной, *c* — сагиттальной. Стрелками обозначены кистозные образования



a *b* *c*

Fig. 3. Surgical treatment: *a*, *b* — resection of the right ovary; *c* — macropreparation, resected ovaries

Рис. 3. Хирургическое лечение: *a*, *b* — резекция правого яичника; *c* — макропрепарат, резецированные яичники

During therapy and surgery, the desired result was not achieved. The postoperative ultrasound examination of the pelvic organs revealed rapidly enlarging cystic ovaries (Table) and kidneys, and rectal prolapse was noted over time. The abdominal circumference reached 40 cm, with persisting intra-abdominal tension syndrome.

Given the progressive enlargement of the ovaries, worsening intra-abdominal tension, and deterioration of the general condition, surgical interventions were repeated, including bilateral laparoscopic adnexectomy and elimination of the rectal prolapse (Delorme surgery). The postoperative course was uneventful. The girl was discharged with adequate weight gain and controlled glycemia.

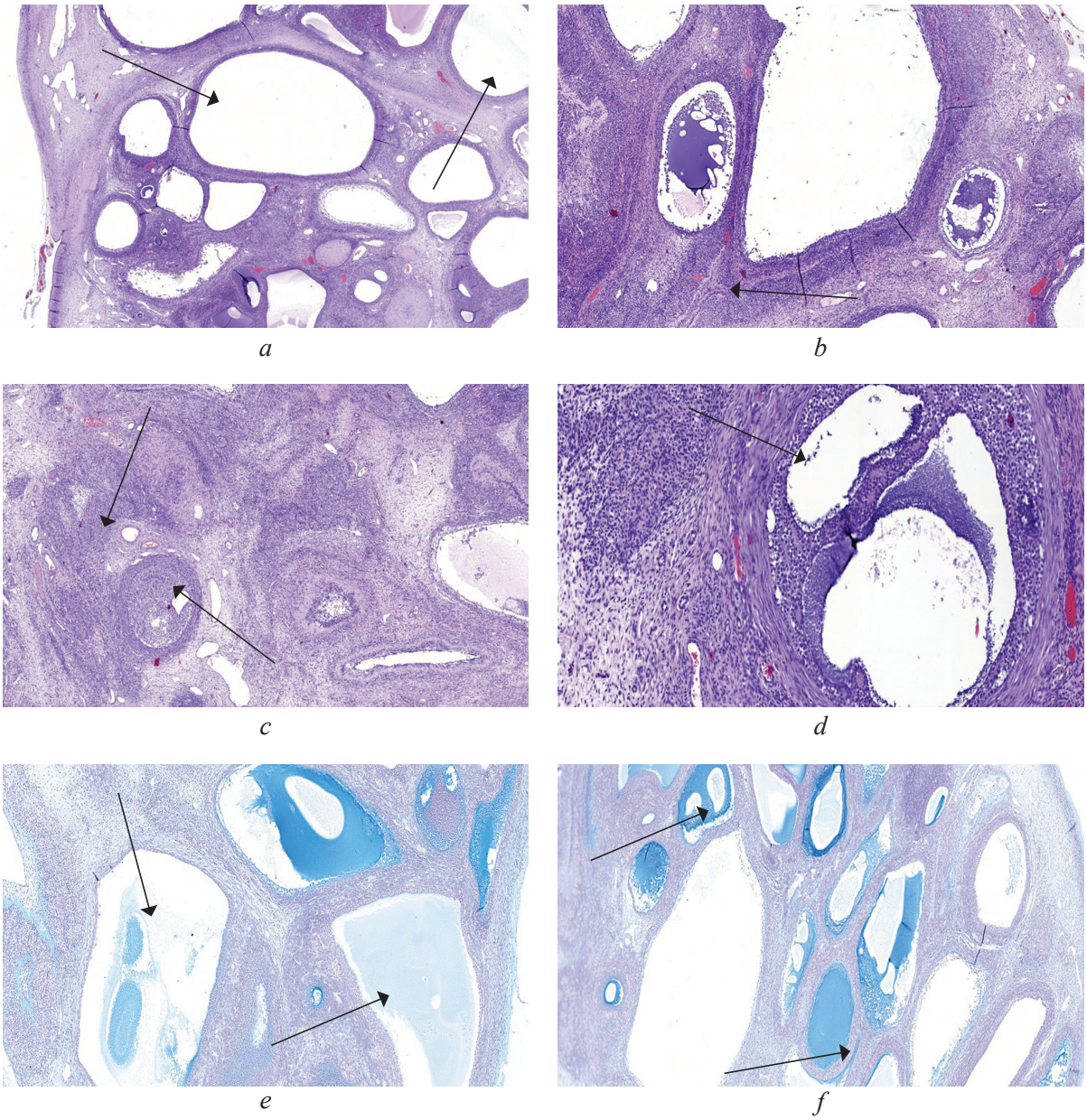


Fig. 4. Micropreparation. Ovarian tissue: *a* — staining hematoxylin-eosin. Magnification ×25. Big and small follicular cysts (arrows), the wall is formed by fibrous connective tissue; *b* — staining hematoxylin-eosin. Magnification ×40. Big and small follicular cysts (arrow), the wall is formed by fibrous connective tissue; *c* — staining hematoxylin-eosin. Magnification ×20. Cysts with luteinization, theca cells (arrows); *d* — staining hematoxylin-eosin. Magnification ×40. Cysts with luteinization, theca cells (arrow); *e* — staining: alcyan blue. Magnification ×40. Big and small follicular cysts (arrows), the wall is formed by fibrous connective tissue; the lining of cysts is formed by multinuclear follicular epithelium; *f* — staining alcyan blue. Magnification ×40. Big and small follicular cysts (arrows), the wall is formed by fibrous connective tissue; the cyst lumen has basophilic alcyan-positive content

Рис. 4. Микропрепарат. Ткань яичника: *a* — окраска гематоксилином и эозином. Ув. ×25. Крупные и мелкие фолликулярные кисты (стрелки), стенка представлена волокнистой соединительной тканью; *b* — окраска гематоксилином и эозином. Ув. ×40. Крупные и мелкие фолликулярные кисты (стрелка), стенка представлена волокнистой соединительной тканью; *c* — окраска гематоксилином и эозином. Ув. ×20. Кисты с явлениями лютеинизации, тека-клетки (стрелки); *d* — окраска гематоксилином и эозином. Ув. ×40. Кисты с явлениями лютеинизации, тека-клетки (стрелка); *e* — окраска альциановым синим. Ув. ×40. Крупные и мелкие фолликулярные кисты (стрелки), стенка представлена волокнистой соединительной тканью; выстилка кист представлена многорядным фолликулярным эпителием; *f* — окраска альциановым синим. Ув. ×40. Крупные и мелкие фолликулярные кисты (стрелки), стенка представлена волокнистой соединительной тканью; в просветах кист базофильное альциан-позитивное содержимое

Table / Таблица

Ovarian size growth during the observation period
Объем яичников после двусторонней резекции яичников по данным ультразвукового исследования

Indicator / Показатель	Observation period, days / Период наблюдения, сут				
	45	51	67	79	100
The right ovary, cm^3 / Правый яичник, $см^3$	9.14	14.54	17.39	19.41	22.90
The left ovary, cm^3 / Левый яичник, $см^3$	—	12.85	13.61	19.47	42.36

DISCUSSION

This study presents a clinical case of insulin resistance syndrome in a child with neonatal diabetes mellitus and polycystic (hyperthecosis) ovaries.

The causes of insulin resistance in newborns and young children are hereditary diseases associated with variants in *INSR*, such as Donohue and Rabson–Mendenhall syndromes. Mutations in the *INSR* α-subunit are more common in patients with Donohue syndrome, whereas mutations in the β-subunit are more common in patients with Rabson–Mendenhall syndrome. Insulin resistance type A is generally associated with heterozygous mutations in the β-subunit of the insulin receptor, with adolescent onset, less pronounced clinical manifestations, and a favorable prognosis for life [1, 4, 6, 15].

Our patient had a pathogenic homozygous variant of *INSR* c.G839A: p.c280y (HGMD: CH010893), previously described for type A insulin resistance, localized in exon 3 in the β-subunit of the insulin receptor. Probably, it was the biallelic nature of the mutation that determined the early onset and severity of the disease, which are characteristic of Donohue syndrome.

Severe insulin resistance that develops in Donohue syndrome leads to a significant increase in blood levels of insulin, impairment of intracellular glucose uptake, depletion of insulin-dependent adipose and muscle tissues, and atrophy. In addition, changes in INSR were assumed to result in impaired IGF-1 and somatotrophic hormone functions in some tissues and may cause growth retardation in patients with Donohue syndrome [8, 14].

Our patient had pronounced thinning of the subcutaneous fat, muscle hypotrophy, and growth retardation. She also had other phenotypic signs of the syndrome, such as *acanthosis nigricans*, hypertrichosis, developmental anomalies of the facial skull (high forehead, large protruding eyes, wide nasal dorsum, wide nostrils, gum hyperplasia, large mouth, and pseudoacromegaly [“elfin face”]), thelarche, macrogenitalism, hypertrophied clitoris, umbilical hernia without signs of strangulation, rectal prolapse, distended abdomen, liver enlargement, and ovarian cystic changes.

Along with the phenotypic aspects, the child had metabolic and hormonal disorders, including neonatal diabetes mellitus associated with hyperinsulinemia and hyperandrogenism. The course of diabetes mellitus was extremely labile. Carbohydrate metabolism disorders were manifested by an increase in both basal and postprandial blood glucose levels. Hypoglycemia, described in other patients with Donohue syndrome, occurred in intervals between feedings. At the initial stage of the correction of metabolic changes, insulin therapy was prescribed; however, after laboratory confirmation of the insulin resistance syndrome, the patient was successfully switched to biguanide therapy (metformin).

This clinical case is characterized by the development of polycystosis (hyperthecosis) of the ovaries in a newborn child. The severity of the condition was due to the development of intra-abdominal tension syndrome caused by rapid growth. The huge ovaries filled the entire abdominal cavity and squeezed the internal organs, which led to respiratory failure, dysphagia, and prolapse of the rectal mucosa. The literature describes the mechanisms of action of insulin, which increases the synthesis of androgen. Insulin has a direct effect on ovarian theca cells, similar to the effect of luteinizing hormone, being an independent mitogen of granulosa cells in the absence of gonadotropin-dependent ovarian function. With increased production of androgens, folliculogenesis is disrupted, which induces the formation of multiple follicles and stromal hyperplasia. In women with polycystic ovary syndrome associated with hyperinsulinemia, ovarian enlargement may have a similar

pathogenesis. In addition, insulin increases the levels of free testosterone by reducing the synthesis of globulin-binding total steroids.

A similar case of giant ovarian cysts associated with severe insulin resistance in a girl with Donohue syndrome was previously described [10]. The patient's condition was stable and did not require surgery. Against high doses of insulin in combination with biguanides, significant regression in ovarian size was achieved by the age of 15 months. In our case, surgery was performed according to vital indications.

CONCLUSION

This clinical case demonstrates the effect of hyperinsulinemia on androgen-dependent ovarian tissue in patients with insulin resistance syndrome. This is an important confirmation of the independent effect of insulin on the ovarian stroma as one of the key links in the pathogenesis of the formation of multifollicular ovaries. The difficulty of monitoring and treating these patients is attributed to the low prevalence, lack of practice of conservative therapy, and little experience with surgical interventions in such patients. Timely genetic verification is needed to determine the optimal, personalized approach to patient management and provide timely medical genetic counseling.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

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