CASE STUDY

COMPLEX ORPHAN PATHOLOGY: COMORBIDITY OF MUCOVISCIDOSIS AND CONGENITAL DYSFUNCTION OF ADRENAL GLANDS CORTEX (REFERENCES REVIEW AND OWN RESEARCH)

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ABSTRACT

The aim: The clinical case was studied: comorbidity of mucoviscidosis and congenital dysfunction of adrenal glands cortex.

Materials and methods: The clinical case of combined orphan pathology – cystic fibrosis and congenital dysfunction of adrenal glands cortex (adrenogenital syndrome) has been described.

Clinical case: A 2-month child has been diagnosed with mucoviscidosis, of a mixed form, which was genetically confirmed. The proband and the father were found to be heterozygotes for the F508del mutation of the CFTR gene (the father suffers from mucoviscidosis). Congenital dysfunction of the adrenal glands, a viral form, was diagnosed when he was three years old. The child is currently receiving: Creon 100 000 units per day with eating, Colomycin 1 vial per day, Pulmozyme 2.5 mg/2.5 ml daily in the morning for inhalations, Ursofalk 600 mg every day constantly, Hydrocortisone 50 mg/day.

Conclusions: This clinical case can be attributed to rare, as most such pathological conditions are usually diagnosed in maternity homes along with the prescription of appropriate therapy. This is an example of late diagnosis of the viral form of congenital adrenal dysfunction against the background of cystic fibrosis, indicating the need for earlier detection and timely introduction of substitution therapy to improve favourable prognosis for a disease.

KEY WORDS: Mucoviscidosis, congenital dysfunction of the adrenal glands, orphan diseases

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INTRODUCTION

The problem of rare diseases in Ukraine is becoming more and more relevant, but practitioners are little aware of these conditions [16]. In Ukraine, neonatal screening for cystic fibrosis and adrenogenital syndrome was conducted in 2013-2014. In 2015, screening was temporarily stopped due to a lack of funding; since the fall of 2018 it has been restored.

Orphan diseases are rare diseases that lead to shortening of life expectancy of a person or to their disability. There are about 7000 orphan diseases in the world, including well-known pathologies, various syndromes and anomalies [14]. Orphan diseases occur at a frequency of 1 case per 2,000 people (according to the European Committee of Experts on Rare Diseases, EUROCERD), are life threatening or cause progressive disease development [6].

In the United States, the act of rare diseases defines orphan diseases as "diseases or conditions that occur in less than 200,000 people in the United States", or in about one person per 1500 people [6, 15].

In Japan, rare diseases are defined as conditions that occur in less than 50,000 patients, or about 1 in 2500 people, in Ukraine the prevalence of orphan diseases is 1 per 2000 people [16, 19].

In the medical sources, similar definitions have been admitted with a prevalence rate from 1 per 1000 to 1 per 200,000 [21].

According to world statistics, 50% of patients with orphan diseases are children, 10% of which attain the age of five years, 12% – of fifteen years [10, 18]. About 50% of orphan diseases lead to disability, one in five diseased suffers from pain, and one in three cannot lead an independent lifestyle [18]. Rare diseases have a severe chronic and progressive course.

The comorbidity of several rare diseases in one patient is a casuist and quite complicated phenomenon both from the point of view of timely diagnosis of all diseases, and the choice of priority treatment approaches that take into account the specificity of concomitant pathology. The presence and detection of two or more unrelated mutations in one child occurs rarely. This is due to the fact that the accumulation of genetic "errors" in the fetus leads to

a significant risk of spontaneous miscarriage, and a child born with a combined genetic pathology may not survive until the verification of all diagnoses due to the severity of the condition and the complexity of molecular-genetic diagnostics of certain syndromes [9].

Mucoviscidosis, as well as adrenogenital syndrome, belong to orphan diseases [13]. Cystic fibrosis is the most common lethal hereditary disease in the world among the white race population. The incidence worldwide varies from 1 per 377 live births in some parts of the United Kingdom to 1 per 90,000 live births in Asia [1, 3]. There are no accurate data on the prevalence of cystic fibrosis in Ukraine. Women with mucoviscidosis, compared to men, are more likely to suffer from pulmonary form, and are of younger age at the time of death. The average age of patients with cystic fibrosis varies in different countries of the world – the highest rate is observed in the USA – 41.1 years. In general, the average life expectancy constitutes 36.9 years. This rate is only 16 years in Ukraine. This is due to untimely diagnostics and imperfection of the screening system. The development of the newest treatment methods in the last decade has made it possible to significantly improve the prognosis for life in these patients [4, 11].

Taking into account the carrier frequency, birth rate and average life expectancy of patients with cystic fibrosis in Ukraine (12-15 years), their number should be from 1700 to 4000. However, according to the Ministry of Health of Ukraine, there are 670 children-patients with cystic fibrosis registered. Insufficient detection of mucoviscidosis is explained by low awareness of doctors of the clinical manifestations of the disease. In Ukraine, cystic fibrosis diagnostics is clinical at the first stage, and genetic – at the second one. Therefore, only when the doctor has suspected this pathology, the diagnosis could be further confirmed or refuted, by means of laboratory methods of examination and molecular-genetic analysis [2, 12].

Mucoviscidosis is the most common hereditary disease with autosomal recessive type of inheritance, universal multi-system exocrinopathy. The main manifestations of cystic fibrosis are the following: chronic obstructive process in the respiratory tract, which is accompanied by a recurrent bacterial infection; disturbances of the digestive system with exocrine pancreatic insufficiency; increase in the electrolyte content in the sweat fluid; obstructive azoospermia in men, caused by the congenital bilateral agenesis of the seminal ducts.

The reason for the characteristic pathological changes is the presence of mutations in both alleles of the gene, which is localized on the long arm of the chromosome 7 (7q31). This gene has 27 exons and controls the synthesis of cystic fibrosis transmembrane conductance regulator of protein (CFTR), which acts as a chloride channel on the apical surface of the epithelial cells and is regulated by cyclic adenosine monophosphate. Currently about 2000 mutations and more than 200 polymorphisms of the CFTR gene, whose frequency varies widely in different ethnic groups, is described. DelF508, del121kb, 1_138t8,3944c1e1Tc, dell507, 1677delTA, 2143delT, 2184teA, 394delTT mutations are diagnostically significant for patients with mucoviscidosis. Such mutations as F508del (52%), CFTRdel2,3 (21kb) (6.3%), N1303K (2.4%), 2184insA (1.8%), 2143delT (2%), W1282X (2.7%) most commonly occur in other countries, for instance, in Russia [22].

The type of mutation affects the nature and severity of the course of the disease to some extent, but it is impossible to predict the peculiarities of the pathology in a particular patient based on the genotype of the CFTR. The presence of mutations in the CFTR gene can be detected at any stage of development (preconception, prenatal, neonatal, postnatal), which will confirm the diagnosis of cystic fibrosis.

The average life expectancy of patients with mucoviscidosis in developed countries from 1969 to 2009 increased from 14 to 38-40 years.

The estimates of the average life expectancy of patients with cystic fibrosis in the UK, which is over 50 years in those born after 2000 [7], look quite realistic.

Congenital adrenal cortex dysfunction (CACD) is a group of autosomal recessive diseases characterized by a defect in one of the enzymes or transport proteins involved in the synthesis of cortisol in the cortical substance of the adrenal glands. Currently, there are 7 forms of CACD described: lipoid hyperplasia of the adrenal cortex (StAR-protein deficiency); 20,22-desmolase deficiency; 17α-hydroxylase/17,20-lyase deficiency; 3β-hydroxysteroid dehydrogenase deficiency; 21-hydroxylase deficiency; 11β-hydroxylase deficiency; oxidoreductase deficiency.

The most common form of CACD, occurring in more than 90% of cases, results from the deficiency of the 21-hydroxylase enzyme [5, 8, 20]. In its turn, CACD is divided into non-classic and classic (virile and salt-losing) forms due to the 21-hydroxylase deficiency. The prevalence of classic forms of 21-hydroxylase deficiency constitutes from 1:10000 to 1:20000 newborns in the world [20], from 1:280 (Alaska) to 1 37 220 (Switzerland) according to neonatal screening data [17].

The reason for the development of any form of CACD is the mutation of the genes responsible for the synthesis of enzymes or transport proteins involved in the biosynthesis of cortisol. CACD, resulted from the deficiency of 21-hydroxylase, is caused by the mutation in the *CYP21 (CYP21A2, CYP21B)* gene, located in the HLA-complex on the short arm of the chromosome 6 (6p21.3). Most of mutations (75-80%) account for point microconversions between the *CYP21* gene and homologous to it *CYP21P (CYP21A1P, CYP21A)* pseudogene, and only 20-25% account for significant mutations – deletions and conversions, leading to more severe forms of CACD. In addition, there exist rarer sporadic mutations. In most cases, the deficiency of 21-hydroxylase is characterized by the presence of phenotype-genotype correlation. Thus, mutations that are accompanied by the preservation of more than 5% of the enzyme activity, lead to a non-classic form of the disease; large deletions and splicing mutations, in which the activity of the enzyme is reduced to 0-2%, lead to the classic forms [5].

Genetic disorders in transport proteins result in the decreased production of cortisol and aldosterone in the

adrenal cortical substance, which leads to adrenal insufficiency, that, in its turn, causes an increase in the production of pituitary adrenocorticotropic hormone, which regulates the adrenal glands functioning.

The hypersecretion of adrenocorticotropic hormone contributes to the development of adrenal hyperplasia and the increase in the production of male sex hormones – androgens. An increase in the concentration of androgens leads to hyperandrogenism, which is clinically manifested by premature sexual development in boys.

CLINICAL CASE

Boy M., 2008 year of birth, from the second full-term pregnancy, which was passing against the background of the miscarriage threat. The child was born during the 40th week, weighing 3900 g, with the height 53 cm. Discharged on the 5th day in a satisfactory condition. He was breastfed. At the age of two months, the boy was admitted to the department of pathology of newborns with severe dystrophy (a mass deficit equalled to 1,400 g (26%)) and retardation of psychomotor development.

The laboratory and instrumental studies revealed the following: coprogram results (March 31, 2008): 2-3 leukocytes in the field of view, neutral fat covers the entire field of view, the flora is normal.

Biochemical blood test (March 31, 2008): potassium – 4.0 mmol/l, sodium – 136 mmol/l, total protein – 58.4 g/l.

Sweat fluid test dated March 29, 2008: sweat chloride – 17 mmol/l, (April 04, 2008) – 60.0 mmol/l in 100 ml.

Rate of alpha amylase (diastase) in urine (April 08, 2008) – 3.2 mg (norm – 3.3-8.9 mg).

The Shwachman test dated 10.04.2008 is positive (enzymes are present) in the father, and negative (no enzymes) in the child.

Ultrasound examination of the internal organs and the heart dated 08.04.2008 did not detect any pathology.

Chest X-ray results (April 7, 2008): pulmonary infiltrations on both sides, more pronounced in the left lung; signs of inflammation, violation of bronchial patency. The waist of the heart is closed, sinuses of the pleura and diaphragm are not changed.

Cystic fibrosis of an atypical form, a hypotrophic variant, has been diagnosed for the first time. Moderate, protein-energy insufficiency has been detected.

The child has been referred to the Institute of Hereditary Pathology (City of Lviv) for further molecular genetic study. The DNA extraction and the CFTR gene study have been carried out to detect the presence of specific mutations by means of PCR method and subsequent heteroduplex analysis or RFLP (restriction fragment length polymorphism) technique. The proband and the father were found to be heterozygotes by the F508del mutation of the CFTR gene (the father suffers from cystic fibrosis, pulmonary form). The mother has no mutations.

The consultation was conducted in 2010, in the Institute of Pediatrics, Obstetrics and Gynecology, city of Kyiv. Cystic fibrosis, of mixed form, with severe pancreatic insufficiency was diagnosed. Intestinal dysbiosis of the III stage. Type II rickets of pathologic course, period of reconvalescence.

Premature sexual development was diagnosed for the first time in 2011 (3 years) in Chernivtsi Regional Children's Clinical Hospital (RCCH) №2. Condition at admission to the RCCH №2 was of moderate severity due to dyspeptic and intoxication syndromes. Asthenic physical constitution, reduced nutrition. Pale skin, digital and nail clubbing. Pilosis, enlargement of the penis and hyperpigmentation of the scrotum are noted on the pubis. Cardiovascular system has no peculiarities. Harsh breathing and occasional disseminated dry rales are auscultated over the lungs when breathing in and out. The abdomen is moderately enlarged, symmetrical, bloated, painless at palpation. The liver and spleen are not enlarged. Evacuations occur 2-3 times a day, the stool is mushy or formed.

Data of the laboratory and instrumental research methods: coprogram results (04 September 2011): the stool is formed, soft textured, of usual color and odor, digested muscle fibers +, vegetable fiber cells +, starch +, soap +, 2-4 epithelial cells in the field of view, 2-4 white blood cells in the field of view, helminth eggs are not found.

Blood sugar (04.09.2011): 4.3 mmol/l. Blood calcium (04.09.2011): 2.02 mmol/l.

Pancreatic elastase in feces (04.09.2011): 16.1 mg/g (norm – more than 200).

X-ray of hands (04.09.2011): bone age – 9 years (passport age – 3 years). Growth areas are preserved.

Blood test for hormones (04.09.2011): prolactin – 27 ng/ml, FSH – 3.7 mIU/ml, testosterone – 2.3 ng/ml, LH – 4.2 mIU/ml, thyrotropin – 1.4 mmol/ml.

Ultrasound examination of testicles (04.09.2011): right – 1.72x0.70x1.05 cm, left – 2.17x0.90x1.07 cm. Both testicles are echogenic and structurally unchanged.

Ultrasound examination of the abdominal cavity organs (04.09.2011): liver: vertical dimension of the right lobe is 114 mm, of the left one – 58 mm, usual location, liver contours are unchanged, edge is rounded, echogenicity is slightly increased, uniform, diffuse, echostructure is homogeneous, parenchyma is fine-grained, moderate perivascular infiltration, diffuse, vasculature is unchanged, transverse fissure of the liver is slightly infiltrated, blood vessels of the hepatic fissure are unchanged. The diameter of the hepatic portal vein is 8 mm, the diameter of the inferior hollow vein is 15 mm.

The gall bladder is visualized, the dimensions are enlarged 71x25 mm, the form is oval, the walls are slightly uniformly infiltrated, the content is unechogenic. The pancreas is not visualized. Adrenal glands: right – 9x6 mm, left – 9x8 mm, echogenic and structurally unchanged.

From 02.11 till 04.11.2011 the patient stayed in the National Children's Specialized Hospital "OHMATDET" in the department of endocrinology. Diagnosis made: congenital hyperplasia of the adrenal cortex, classical, viral form. False premature sexual development. Endocrine gigantism.

At admission: height – 118 cm (+4 sigmas), weight – 22 kg. BMI – 15.8. The body area is 0.85 m^2. Physical development + 4 sigmas.

Passport age is 3 years and 9 months. Bone age is 12.5-13.0 years.

Blood test for hormones: free T_4 – 1.08 (norm 0.8-2.0); TSH – 3.64 (norm 0.7-5.97), FSH – 0.332 IU/l (0.25-1.92), LH – 0.101 IU/l (norm 0.032-1.03), free testosterone – 340 ng/dl (norm up to 12), bound testosterone – 15.2 pg/ml (norm up to 0.6), 17-hydroxyprogesterone – 491 ng/ml (norm 0.07-1.7), dihydroepiandrosterone – 3.47 umol/l (norm 0.01-0.53).

Sampling with testosterone and diphereline was conducted in hospital settings.

Dexamethasone two-day test (positive):

Before the test: testosterone – 240 ng/dl (norm up to 12), bound testosterone – 15.2 pg/ml (norm up to 0.6), dihydroepiandrosterone – 3.47 umol/l (norm 0.01-0.53). After the test: testosterone – 39.4 ng/dl (norm up to 12), bound testosterone – 0.1 pg/ml (norm up to 0.6), dihydroepiandrosterone – 0.66 umol/l (norm 0.01-0.53).

Sampling with diphereline:

Before the test: FSH – 0.322 IU/l (0.25-1.92), LH – 0.101 IU/l (0.032-1.03). After the test: FSH – 1.83 IU/l (0.25-1.92), LH – 1.3 IU/l (0.032-1.03). This result indicates gonadotropin-independent premature sexual development.

Ultrasound examination of the adrenal glands: right – 33x22 mm, left – 34x15 mm, the tissue is diffusely heterogeneous due to multiple hypoechogenic inclusions, more pronounced on the left side.

Chronic endobronchitis complicated the clinical picture in 2012. Colonization of bronchi by S. aureus.

Consultation of the children's endocrinologist on 29 May, 2012: free testosterone is 11.4 pmol/l (norm 0.3-11.1), DHEAS - 180.55 мg/dl (<44), 17-oxyprogesterone – 309.8 ng/ml (0.07-1.7).

On 30.10.2012 he was admitted to the gastroenterological department with suspected acute appendicitis, which was not confirmed. Diagnosed: cystic fibrosis, mixed form. Chronic pancreatitis, exacerbation period, chronic cholecystocholangitis, period of exacerbation. Acetonemic syndrome. Helminthic invasion (enterobiasis). Cerebral asthenia syndrome. Congenital hyperplasia of the adrenal glands, classical form, virile. False precocious puberty. Endocrine gigantism.

Height – 120 cm (more than 95 percentiles), weight – 28 kg (more than 95 percentiles). BMI – 19.4 (more than 95 percentiles).

Examination: acetone in the urine ++++, in the coprogram – neutral fat ++, 3-4 pinworms in the field of view.

Alpha amylase in blood – 48 IU/l.

Analysis for hormones dated 17.01.2013: 17-oxyprogesterone – 420 ng/ml (norm 0.07-1.7), total testosterone – 5.67 nmol/l (less than 0.35).

In May 2013, he had a left-sided pneumonia (inflammation of the upper lobe of the left lung). Bilateral sinusitis.

Consultation of children's endocrinologist (19.06.2013): passport age – 5 years, CACD. Simple virile form. Height – 137.2 cm (+5.38), weight – 31.3 kg (+3.35 sigma), BMI – 16.03 (79 percentiles). Tanner's scale of sexual development – stage III.

Ultrasonography of the abdominal cavity organs: gallbladder – the walls are not thickened, calcification is present up to 6 mm in size.

The patient underwent bilateral polypoid ethmoidectomy and adenotomy on 08.07.2014.

On 24.02.2016 (8 years 1 month): height – 155 cm (+7.73), weight – 41 kg (+6.39), was admitted to the clinic with complaints of severe pain in the epigastric and right iliac regions, vomiting with the admixture of bile.

Intestinal invagination was detected during the examination. Manual intestinal colo-caeco-iliac disvagination, appendicectomy were performed.

04.11.2016 (8 years 9 months): height – 159 cm, weight – 47 kg. Right-sided scoliosis of the lumbar region of the skeleton was revealed.

Chronic polypoid polysinusitis was diagnosed on 02.05.2018. The surgery "polypotomy" was carried out.

The child is currently receiving: Creon 100 000 IU per day with eating, Colomycin 1 vial per day, Pulmozyme 2.5 mg/2.5 ml daily in the morning for inhalations, Ursofalk 600 mg every day constantly, Hydrocortisone 20-20-10 mg/day (body area 1.4 m^2).

DISCUSSION

The screening system of pregnant women and newborns has greatly facilitated the diagnosis of hereditary diseases, but untimely diagnostics leads to errors. This clinical case demonstrated late diagnosis of both cystic fibrosis (aged 2 months) and congenital adrenal cortex dysfunction (at the age of three years) due to the lack of screening of newborns for these diseases at the time of birth of the given child [18].

Mucoviscidosis, as a genetically determined disease, is characterized by a wide variability of clinical manifestations depending on the nature of mutations in the gene. Mutations that lead to severe forms of cystic fibrosis, as well as mutations, leading to a milder course of the disease, have been detected. Often there are patients with the same mutations, but with different course of the disease [7].

All mutations in the *CFTR* gene are divided into five classes depending on the primary defect.

- class 1: mutations, blocking the CFTR protein synthesis process – nonsense mutations (G542X, W1282X, R553X, 2143delT, 1677delTA);
- class 2: mutations that cause blocking of CFTR maturation – missense mutation (del F508, del I 507, N1303 K, S541 I, S549 R);
- class 3: mutations that cause impairments in the regulation of functions of the CFTR, that reaches the apical membrane but cannot be activated – missense mutations (G551 D, G1224 E, S1255 P);
- class 4: mutations that lead to a decrease in the conductivity of the Cl- ions (R117 H, R334 W, R347 P);
- class 5: decrease in synthesis of CFTR, but it functions normally (A455 E, 3849 + 10kbC-T, IVS8 (5T0).

1-3 mutation classes are referred to the so-called "severe", which determine the pronounced clinical picture of the disease, and the mutations of 4-5 classes are usually "mild",

in which the clinical picture of cystic fibrosis is not distinct, with minimal pancreatic dysfunction. A mutation of class 2 (del F508) [2] has been detected in our patient.

CFTR gene mutations can be combined into four groups according to the predictable clinical manifestations:
1) lead to the development of cystic fibrosis;
2) lead to the development of CFTR-related disorders;
3) without established clinical manifestations;
4) have unproven or uncertain clinical significance.
Therefore, mutational analysis can be used to establish a diagnosis of cystic fibrosis in patients with relevant clinical manifestations.

There are mutations in which the function of the pancreas in patients with cystic fibrosis remains sufficient (R117H, 849 + 10kbC> T, A455E, G178R, R352Q, R117C, 3272-26A> G, 711 + 3A> G, D110H, D565G, G576A, D1152H, L206W, V232D, D1270N) or preserved (R347P, R334W). These mutations never occur in patients with meconium ileus in anamnesis. Such patients usually have normal physical development in the first years of the disease manifestation. Their body weight remains within the age norm until severe lung deficiency or acute pancreatitis develops.

Most mutations lead to pancreatic insufficiency (F508del, G542X, G551D, N1303K, W1282X, R553X, 394delTT, and many others).

Geographic distribution of mutations is diverse. The most common mutations in the *CFTR* gene are the following: delF508, G542X, N1303K, G551D, W1282X. Their frequency is, on average, 66.8%; 2.6%; 1.6%; 1.5% and 1.0% respectively. "Deletion delF508" mutation has the highest relative frequency in Germany (87.2%) and it is the lowest in Algeria (26.3%). As already mentioned, it is no accident, that this mutation is widespread in Europe and follows a certain gradient: from north to south and from west to east. The frequency of delF508 mutation in the European part of Russia is, on average, about 50% [2].

Therefore, mutational analysis can be used to establish a diagnosis of mucoviscidosis in patients with relevant clinical manifestations.

DelF508 mutation in the *CFTR* gene has been detected in the described patient; it belongs to "severe" mutations with a classical clinical picture of the disease and pronounced insufficiency of the exocrine pancreatic function, was detected. The severity of the patient's condition is also stipulated by the presence of congenital dysfunction of the adrenal glands (virile form), requiring constant administration of hydrocortisone.

CONCLUSIONS

Orphan (rare) diseases are a multidisciplinary problem due to the presence of a hereditary factor, involvement of multiple bodily systems and a high prevalence in general.

High mortality and severe disabling course of orphan diseases necessitate the development of a national strategy for their diagnosis and treatment.

This clinical case can be referred to rare, as most such pathological conditions are diagnosed in maternity institutions with the prescription of necessary therapy. Subsequently, these patients are on a dispensary record for life, which allows timely evaluation of the basic parameters of vital activity.

Consequently, this clinical case is an example of a late diagnosis of the viral form of congenital adrenal dysfunction against the background of cystic fibrosis and is indicative of the need for early diagnosis and timely administration of substitution therapy to improve the prognosis of the disease.

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