CYSTIC FIBROSIS RELATED DIABETES: CLINICAL CASES IN TERMS OF PRINCIPLES OF PEDIATRIC PALLIATIVE CARE

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Summary.

Cystic fibrosis related diabetes (CFRD)- is the most common comorbidity in people with cystic fibrosis , occurring in 20% of adolescents and 40–50% of adults**.** According to the Guidetothe Development of Children's Palliative Care Services life-limiting conditions may be delineated at four broad groups. Cystic fibrosis is a problem from group 2 - conditions where there may be long periods of intensive treatment aimed at prolonging life and allowing participation in normal childhood activities, but premature death is still possible.

Basic aspects of CFRD were discussed, such as cause of the disease, genetic defects, differential diagnosis and principles of treatment. Two clinical cases of pediatric CFRD patients resented to highlight problems of management in terms of potential palliative care.

According to our observations, patients with the CFRD, unfortunately, are perceived as patients with cystic fibrosis with no clear attention to diabetes. Both of them were presented with pure diabetes control due to unclear understanding

CFRD with concomitant diet incompliance, irregular records, missed insulin injections, exercising limitations.

We concluded that CFRD patients must be assessed by members of multidisciplinary team at CF centers, working by the principle of palliative care. There is necessary since the moment of CF diagnosing to involve endocrinologist and dietician due to of endocrine problems. Psychologist, social worker and well-trained educators are necessary to increase awareness of the CF comorbidities problem.

Key words: Cysticfibrosis, cysticfibrosis related diabetes, pediatric palliative care, multidisciplinary team

Анотація.

Цукровий діабет асоційований з муковісцидозом - найбільш поширене ускладнення у осіб, що страждають на муковісцидоз, яке реєструється у 20% підлітків та 40-50 % дорослих. Відповідно до рекомендацій з надання паліативної допомоги дітям, умови для обмеження життя можуть бути визначені у чотирьох широких групах. Муковісцидоз є проблемою, що відноситься до другої групи - стани, при яких передчасна смерть неминуча, але тривале інтенсивне лікування може збільшити тривалість життя дитини і дозволить зберегти якість і фізичну активність.

В статті обговорено основні поняття про цукровий діабет асоційований з муковісцидозом, такі як причини захворювання, генетичні дефекти, диференційний діагноз та принципи лікування. Два клінічних випадки педіатричних пацієнтів розглянуто з метою вивчення проблем лікування з точки зору потенційної паліативної допомоги.

Згідно з нашими спостереженнями, пацієнти з цукровим діабетом асоційованим з муковісцидозом, сприймаються як пацієнти з муковісцидозом без чіткої уваги до діабету. Обидва пацієнти не мали адекватного

глікемічного контролю із-за нечіткості розуміння проблеми, що призводило до недотримання дієти, нерегулярності записів у щоденниках самоконтролю, пропущені ін'єкцій інсуліну.

Ми прийшли до висновку, що пацієнти з цукровим діабетом асоційованим з муковісцидозом мають спостерігатися членами міждисциплінарної команди в спеціалізованих центрах, що функціонують за принципом паліативної допомоги. Починаючи з моменту діагностики муковісцидозу до таких команд необхідно залучати ендокринолога та дієтолога із-за високого ризику ендокринних розладів. Психолог, соціальний працівник та добре навчені педагоги необхідні для підвищення обізнаності про проблему та супутні захворювання.

Ключові слова: муковісцидоз, цукровим діабетом асоційований з муковісцидозом, дитяча паліативна допомога, міждисциплінарна команда

Анотация.

Сахарный диабет, ассоциированный с муковисцидозом - наиболее распространенное осложнение у лиц, страдающих муковисцидозом, которое регистрируется у 20 % подростков и 40-50 % взрослых. В соответствии с рекомендациями по оказанию паллиативной помощи детям, условия для ограничения жизни могут быть определены в четырех широких группах. Муковисцидоз является проблемой, которая относится ко второй группе - состояния, при которых преждевременная смерть неизбежна, но длительное интенсивное лечение может увеличить продолжительность жизни ребенка и позволит сохранить качество и физическую активность.

В статье обсуждены основные понятия о сахарном диабете ассоциированного с муковисцидозом, такие как причины заболевания, генетические дефекты, дифференциальный диагноз и принципы лечения. Два клинических случая педиатрических пациентов рассмотрено с целью изучения проблем лечения с точки зрения потенциальной паллиативной помощи.

Согласно нашим наблюдениям, пациенты с сахарным диабетом ассоциированным с муковисцидозом, воспринимаются как пациенты с муковисцидозом без четкой внимания к диабету. Оба пациента не имели адекватного гликемического контроля из-за нечеткости понимания проблемы, что приводило к не соблюдению диеты, не регулярности записей в дневниках самоконтроля, пропущенных инъекций инсулина.

Мы пришли к выводу, что пациенты с сахарным диабетом ассоциированным с муковисцидозом должны наблюдаться членами междисциплинарной команды в специализированных центрах, которые функционируют по принципу паллиативной помощи. Начиная с момента диагностики муковисцидоза к таким командам необходимо привлекать эндокринолога и диетолога из-за высокого риска эндокринных расстройств. Психолог,

социальный работник и хорошо обученные педагоги необходимы для повышения осведомленности о проблеме и сопутствующих заболеваниях.

Ключевые слова: муковисцидоз, сахарный диабет ассоциированный с муковисцидозом, детская паллиативная помощь, междисциплинарная команда

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (WHO, 1998) [1].

Palliative care for children and young adults, defined as the "active, total care" of a young person's body, mind, spirit, and family, from life-limiting diagnosis until death, is an internationally recognized priority [2].

There is a limited access to the pediatric palliative care in low- and middle-income countries [3]. It's clear as the growing demand for palliative care, coupled with financial constraints, demands a sustainable public health approach. That's why WHO emphasis that palliative care is a component of integrated treatment throughout the life course and demand a hierarchical approach to structure of relevant healthcare service with multidisciplinary management [4]. In this way, the first book in pediatric palliative care for doctors and other trainees published in Ukraine looks as a serious progress in the field [5].

Life-limiting conditions may be delineated at four broad groups [6]:

- Group 1. Life-threatening conditions for which curative treatment may be feasible but can fail. Palliative care may be necessary during periods of prognostic uncertainty and when treatment fails. Children in long-term remission or following successful curative treatment are not included. Examples include cancer, irreversible organ failure of heart, liver, or kidney.
- Group 2. Conditions where there may be long periods of intensive treatment aimed at prolonging life and allowing participation in normal childhood activities, but premature death is still possible. Examples include cystic fibrosis and muscular dystrophy.
- Group 3. Progressive conditions without curative treatment options, for which treatment is exclusively palliative and commonly may extend over many years. Examples include Batten's disease and the mucopolysaccharidoses.

- Group 4. Conditions with severe neurological disability, which may cause weakness and susceptibility to health complications, and may deteriorate unpredictably, but are not usually considered progressive. Examples include severe multiple disabilities such as those that can follow brain or spinal cord injuries (including some children with severe cerebral palsy)

Cystic Fibrosis (CF) ICD-10: E84.0, E84.1, E84.8, E84.9; ORPHA: 586; OMIM: 219700 - is the most common genetic disorder among Caucasian children. The incidence varies between populations: the condition is considerably less common in Asian and African populations than in the white populations of Europe and North America, with variation within each country. The exact prevalence in Europe is unknown, but estimates range between 1/8,000 and 1/10,000 individuals.

CF is characterized by alterations in the CFTR protein, which plays a role in the regulation of transmembrane hydro electrolytic flux. Alterations in the protein lead to changes in the characteristics of exocrine excretions. An absence of functional CFTR in the epithelial cell membrane leads to the production of sweat with a high salt content (associated with a risk of hyponatremic dehydration) and mucus secretions with an abnormal viscosity (leading to stasis, obstruction and bronchial infection). Cystic fibrosis is a monogenic autosomal recessive disease caused by mutations in the CFTR gene (chromosome 7). More than 1250 mutations have been reported. Nearly 70% of all cases are caused by the delta F508 allele, with 30 other mutations accounting for a further 20% of cases. There is no clear correlation between genotype and phenotype. In addition to the allelic heterogeneity and the occurrence of multiple mutations in the same gene, a wide range of other factors may influence the phenotype, including the environment and disease modifying genes [7].

Certain CFTR genotypes that cause complete lack of protein function, such as delF508 (also referred to as F508del, p.Phe508del, or c.1521_1523delCTT), carry a much higher risk of pancreatic problems than do genotypes that partially spare protein function [8, 9].

Cystic fibrosis related diabetes (CFRD) - is the most common comorbidity in people with cystic fibrosis (CF), occurring in ~20% of adolescents and 40–50% of adults [10].

The primary cause is a relative insulin deficiency related to destruction of pancreatic islets. Insulin resistance also may play a role, especially in association with acute exacerbations or chronic progression of pulmonary disease [11].

Defective CFTR function reduces the volume of pancreatic secretions, predisposing to plugging of small ducts, and increases acidity, promoting premature activation of digestive enzymes [12].

Abnormal glucose tolerance is notably prevalent among young children with cystic fibrosis. Children with cystic fibrosis lack the normal increase in insulin secretion that occurs in early childhood despite increased glucose. Thus, glycemic abnormalities begin very early in cystic fibrosis, possibly because of insufficient insulin secretion. [13].

Cystic fibrosis-related diabetes is a distinct form of diabetes mellitus that is an important complication of cystic fibrosis. It is different from either type 1 or type 2 diabetes mellitus, but shares features of both [14].

There are common features between CFRD and both type 1 and type 2 diabetes (table 1).

Table 1.

Differential diagnosis of CFRD [15].

Characteristics	Type 1 Diabetes	Type 2 diabetes	CFRD
Age of onset	Young	Predominantly in adults	Young
Onset	Acute	Gradual	Gradual
Islet antibodies	Present	Absent	Usually absent
Genetics	Multiple susceptibility alleles including HLA class II	Polygenic association with more than 20 gene variants	Most common in patients with homozygous Phe508del mutation of CFTR. Possible association with TNF, HSP60 and chaplain 10.
Insulin secretion	Eventually absent	Diminished	Gradual deterioration
Insulin sensitivity	Variably decreased	Severely diminished	Diminished (severely during acute exacerbations)
Propensity to ketoacidosis	No	Yes	No

Since the cause of diabetes associated with CF is insulinopenia due to damage to the pancreatic tissue, the main method of treatment is replacement insulin therapy. The long-term use of beta-cell-stimulating drugs is still limited. Patients with CFRD are susceptible to early onset of chronic complications of diabetes, and therefore require appropriate regular follow-up [16]. On the other hand, better glycemic control is associated with better respiratory function and less common infections [17].

On the one hand, CFRD is a violation of carbohydrate metabolism, which requires compliance with diet, exercise and insulin replacement therapy. Dietary recommendations for CFRD include individualized based reginens [18]. On the

other hand, CFRD is one of the symptoms of cystic fibrosis with a high risk of premature death due to the rapid progression of pulmonary dysfunction, which requires intensive long-term therapy. Thus, Patients need to comply with the diet, constant respiratory therapy and insulin injections.

Obviously, children with CFRD and their families need permanent social and psychological support. It's a reason for the creation of volunteer, parental and patients' organizations. Recent studies show that palliative care and intensive care do not exclude each other in CF patients.

We analyzed the medical records of two pediatric patientswith CFRD to highlight problems of management in terms of potential palliative care.

Clinical case # 1

The girl V., at the age of 3 weeks was diagnosed an acute pneumonia followed by several exacerbations for next months. After the examination, at the age of 8 months she was diagnosed with cystic fibrosis, pulmonary-intestinal form, severe course (genotype delF508).

The exacerbations occurred once a month, except for the summer months. At the age of 9 years, the child developed polydipsia, polyphagia, polyuria and CFRD was diagnosed. Basis-bolus regiment of Insulin treatment (Novo Rapid and Levemir) used to compensate hyperglycemia with an average dosage 1.07 U/kg/24h. Diabetes control was not satisfactory.

At the age 15 y.o. against the background of diabetes, number of CF exacerbations increased up to 8-10 times per year. Inflammatory process was more protracted with no response at massive antibacterial and enzymatic therapy. There was accelerated lung function deterioration - FEV1 decreased from 51 % to 30 % on spirometry [19], which is prognostically unfavorable for CF patients according to the literature as FEV1is a well-established predictor of survival in CF [20, 21].

Her physical development was disharmonious: weight - 38 kg., height - 146 cm (-2.3 SD), BMI - 17.82 kg/m^2 (15 percentile). Puberty – Tanner stage 1. Thus,

girl presented with the short stature, underweight and delayed puberty. Fluctuations in blood glucose from 3.0 mmol/l to 20.0 mmol/l, HbA1 level - 8.6 %.

Clinical case # 2

The boy A was diagnosed with CF at the age 4 years. At the age 14 y.o. he was hospitalized to the ICU due to vomiting, thirst and polyuria, where CFRD was established when hyperglycemia with random blood glucose 17.9 mmol/l revealed.

After 6-month CFRD was diagnosed, he admitted clinic due to pneumonia with atelectasis. Portal hepatic fibrosis revealed as well. Diabetes control was not satisfactory due to problems with self-control. There were difficulties with diet and diary records. Fluctuations in blood glucose from 4.1 mmol/l to 21.1 mmol/l, HbA1 level - 8.9 %. Basis-bolus regiment of Insulin treatment (Actrapid and Protaphane) used to compensate hyperglycemia with an average dosage 0.92 U /kg/24h.

At the moment of admission his physical development was disharmonious: weight – 32.5 kg., height - 151 cm (-2.5 SD), BMI - 14.25 kg/m^2 (< 5 percentile). Puberty – Tanner stage 1. Asthenic body composition and clubbing fingers attracted attention during inspection (fig.1, 2).

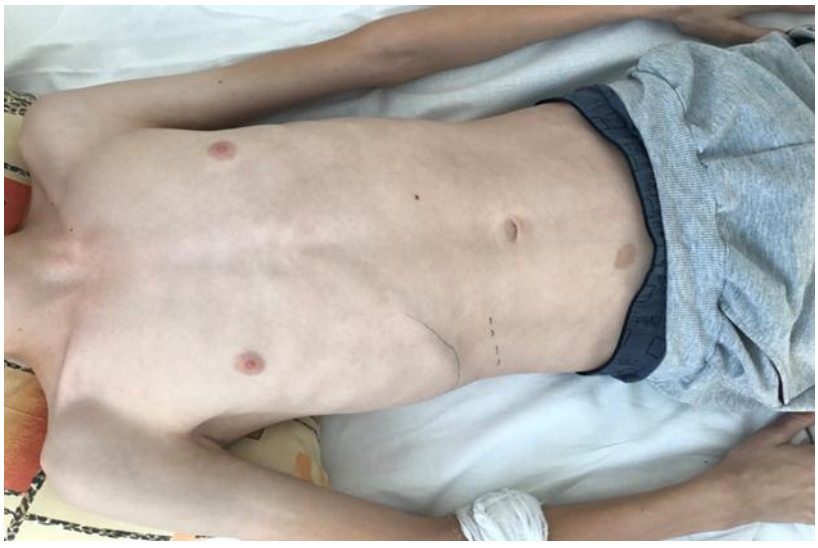

Figure 1. General appearance of 14 y.o. male patient with CFRD

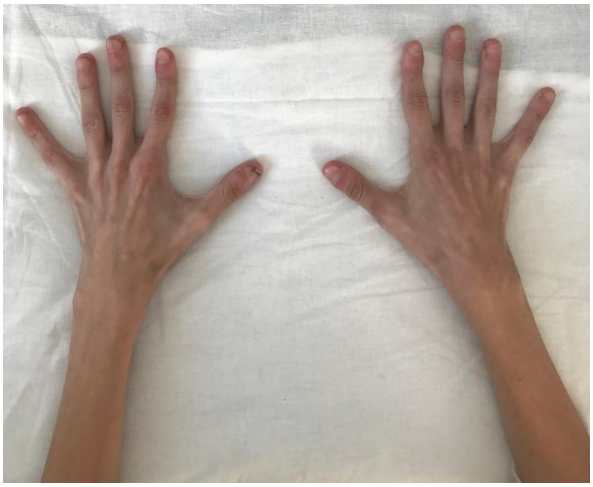

Figure 2. Clubbing of fingers of 14 y.o. male patient with CFRD

Patients had different course of CF and CFRD - patient #2 had later onset of CF and CFRD as well. In both cases, patients had delayed physical development (both short stature and underweight) and puberty. Both of them were presented with pure diabetes control due to common problems listed below:

- diet incompliance (wrong or absent calculation of bread units for carbs intake control; irregular records)
- insulin injections (which were missed time to time)
- exercising limitations due to impaired respiratory function
- unclear understanding that DM is a serious complication of CF, which is an independently potentially life-threatening problem.

Specific approach to management is recommended for CF and DM separately. So combination of respiratory therapy, insulin and diet are indicated for the patient with CFRD.Regardless of DM type, it is prognostically unfavorable for the

complications. Thus, in patients with CFRD acute diabetic complications are associated with bad glucagon response to hypoglycemia [22]. They also have a brisk catecholamine response and normal hypoglycemia awareness. Meanwhile, severe hypoglycemia is less common in CF than in Type 1 diabetes [23]. Diabetic microvascular complications occur in CFRD, although the prevalence of retinopathy and nephropathy appears to be less than that found in other forms of diabetes [24].

According to our observations, patients with the CFRD, unfortunately, are perceived as patients with cystic fibrosis. There is a lack of a unified system of care for such children, which leads to difficulties in attracting the patient's family to work in the school of diabetes. As a consequence, these children do not adhere to the recommended diet, glycemic control, which affects the level of glycemic control and is especially aggravated by such factors as the restriction of physical activity.

Our data matches results of other researchers, who emphases on problems with patient and parent perceptions of the diagnosis and management of CFRD. Accessibility of the health care team is imperative for most patients. Patients valued that their health care team not only recognized how important it was for the CFRD regimen to fit into their lives, but also helped them come up with strategies to integrate it. It is important to find physicians who were knowledgeable about both CF and diabetes. According to the data, improvement in lung function associated with better diabetes control was motivating for patients [25].

There is no specific correction of nutritional status, growth and puberty for the CFRD. Meanwhile, endocrinologist and dietician are necessary members of multidisciplinary team as might early manage the named problems. Dietitians/nutritionists of the CF center are responsible for the recommendations and education of patients and their caregivers on the basic principles of diet in CF and CFRD. Some of them are: determining nutritional requirements and meeting these requirements at different stages of the disease, pancreatic enzyme

replacement therapy, vitamin and mineral supplementation etc. Age-specific recommendations, plans for nutritional intervention and nutritional care, appropriate to the nutritional and clinical status, should be developed. Process of patients' education is a continuous and evolving process [26].

The same nutritionist should provide patient counseling both at the inpatient and outpatient stages of treatment to ensure continuity of care [27].

Conclusions.

Complex of endocrine disorders aggravates the patient's quality of life, worsens the prognosis of the disease, leads to disability and is the basis for an additional increase in the number and duration of hospitalization.So endocrinologist, dietician must be a full members of CF management team since the moment of CF diagnosing. It is necessary because of risk of delaying physical development and puberty, as well as due to potential CRFD onset.

On the other hand, there are lot of psychological problems and social issues related to CFRD such as pure problem awareness of patients parents and, unfortunately, healthcare specialists. There is necessary to involve psychologist, social worker and well-trained educators into the team.

Thus, CFRD patients must be assessed by members of multidisciplinary team at CF centers, working by the principle of palliative care. Besides CFRD patients requires additional attention in the structure of palliative care of subjects with chronic diseases. Algorithm of specific multidisciplinary surveillance is a promising area of palliative service development in low- and middle income countries.

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