Cystic fibrosis-related diabetes in adolescents

Relația dintre fibroza chistică și diabet la adolescenți

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Abstract

Cystic fibrosis-related diabetes is the most common comorbidity of cystic fibrosis patients. It may occur at any age, even in infancy, but the prevalence increases as patients get older. We present a case of a female patient (15 years old) and a male patient (17 years old) hospitalized at the Cystic Fibrosis Center. The patients had lung symptoms as chronic daily cough with mucopurulent, yellow dark viscous sputum in large quantity, intensefied in the morning, with recurrent streaks of blood, dyspnea during moderate physical effort and permanent wheezing. The main complaints were polyuria, polydipsia and after the laboratory tests were performed, they were diagnosed with cystic fibrosis-related diabetes. Cystic fibrosis-related diabetes can be frequently overlooked in clinical practice due to cystic fibrosis symptoms.

Keywords: ***cystic fibrosis, cystic fibrosis-related diabetes, cystic fibrosis comorbidities***

Rezumat

Diabetul zaharat asociat fibrozei chistice este cea mai frecventă comorbiditate la pacienții cu fibroză chistică și poate apărea la orice vârstă, inclusiv în copilărie, dar prevalența crește odată cu înaintarea în vârstă. Prezentăm cazul unei paciente de sex feminin (15 ani) și cazul unui pacient de sex masculin (17 ani) internați în Centrul de fibroză chistică. Pacienții aveau simptome pulmonare precum tuse cronică zilnică cu spută vâscoasă mucopurulentă în cantitate mare, de culoare galben-închisă, mai intens dimineața, cu striuri de sânge recurente, dispnee în timpul efortului fizic moderat și respirație șuierătoare permanentă. Acuzele principale erau poliurie, polidipsie și, după efectuarea testelor de laborator, au fost diagnosticați cu diabet zaharat asociat fibrozei chistice. Diabetul zaharat asociat fibrozei chistice poate fi frecvent omis în practica clinică, din cauza simptomelor fibrozei chistice.

Cuvinte-cheie: ***fibroză chistică, diabet zaharat asociat fibrozei chistice, comorbiditățile fibrozei chistice***

Introduction

Cystic fibrosis (CF) is one of the most common life-threatening autosomal recessive diseases in developed countries. The incidence of CF varies greatly in different geographical regions and in Europe is accounted for 1 in 2000-3000 newborns. About one in 25 people in Europe is a carrier[(1,2)] .

Nowadays, the implementation of new programs which help to diagnose patients in early infancy period and complex treatment regimen for patients with CF lead to the increase in median life expectancy beyond 37 years for females and 40 years for males in some countries[(3)] . Currently, unfavorable prognosis of the disease, with death, not necessarily characterizes the early childhood. Now, for these patients there are better perspectives and a better quality of life.

A significant increase in the structure of adult CF patients emphasizes the importance of late complications of the affected systems: cardio-respiratory failure, cystic fibrosis-associated liver disease, cystic fibrosis-related diabetes (CFRD) and others[(4)].

Case report

We present two cases: a 15-year-old female patient and a 17-year-old male patient with CF. The diagnosis of CF was confirmed by positive sweat test (Macroduct USA), the identification of CFTR mutation (F508del/F508del), and small amounts of elastase in stool. The patients received specialized medical care provided in the CF Center from Pediatric Pulmonology Department of Mother and Child Institute, with systemic examination of disease evolution and adaptation of treatment.

At the time of admission, the patients presented lung symptoms such as chronic daily cough with mucopurulent, yellow dark viscous sputum in large quantity, intensely in the morning, periodically with streaks of blood, dyspnea during moderate physical effort and permanent wheezing. The patients' nutritional status was supported by administering pancreatic enzymes as a replacement therapy. The patients complained about frequent urination (polyuria) and thirst (polydipsia), which are two classic symptoms of diabetes. These symptoms are caused by high blood sugar levels (hyperglycemia). However, people with CF often may drink more (and thus may have frequent urination) because of the dry mouth and viscous sputum. Other symptoms included fatigue and weight loss without trying or having a hard time gaining weight, and an unexplainable loss of lung function. The patients were hospitalized because of the frequent exacerbations of the pulmonary disease.

Physical examination reveals mesomorph body type, nutritional status according to the normal values of the age, deformation of the chest and marked Hippocratic digits (clubbing). During chest percussion there was a dull sound situated bilateral subscapular. On auscultation: bilateral heavy breathing, crackles of different caliber over the entire pulmonary area on the background of attenuated breathing sound.

Based on the recent symptoms suggestive for diabetes (polydipsia, polyuria, weight loss) and frequent exacerbations, a more detailed examination was performed.

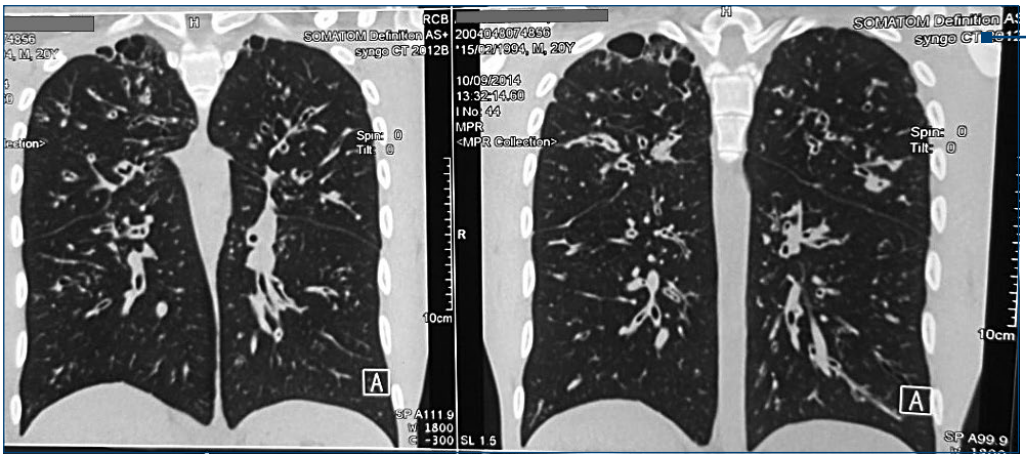

Figure 1. Patients CT scan (male, 17 years old)

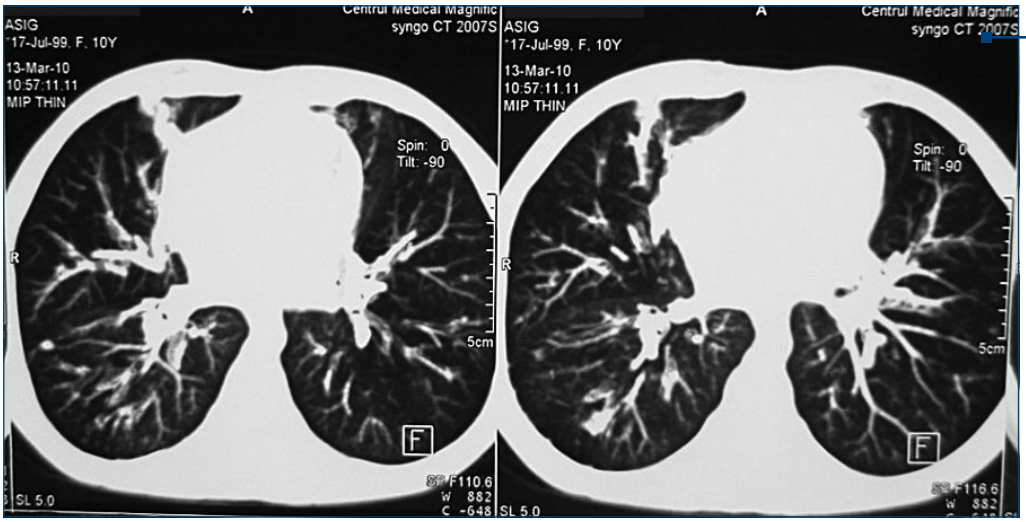

***Figure 2.** Patients CT scan (female, 15 years old)*

On the background of pulmonary exacerbation, both patients had fasting hyperglycemia (9.8 mmol/l - the male patient; 14.1 mmol/l - the female patient). Subsequently, it triggered clinical symptoms.

There were significant variations of serum glucose during the day: 7.8-15.8 mmol/l (the male patient) and 10.4-21 mmol/l (the female patient). The glycated hemoglobin (HbA1c) values were increased (7.3% - the male patient; 14.1% - the female patient).

C-peptide values were low (0.624 ng/ml - the male patient; 0.513 ng/ml - the female patient). The glucose concentration in urine was 7.3 g/l (the male patient), respectively 37.1 g/l (the female patient), and in both cases ketones were not detected. Thus, the confirmation of diabetes was achieved by several tests: blood glucose test, blood glucose profile, HbA1c, C peptide, and the presence of glucose in the urine.

The computer tomography investigation of the lungs showed bronchial wall thickening and distortion with the presence of multiple dilations of the bronchi (cylindrical and cystic types), signs of bronchiolitis (Y-type and "tree in bud" structures in the cortical layers) – Figure 1 and Figure 2.

The patients received treatment with insulin, as it is recommended in the international guidelines. Glargine (Lantus®), which is a basal insulin, gives in one dose a constant amount of insulin for about 24 hours with no peak. Basal insulin is not strong enough to give the extra insulin needed to cover meals. Patients still need to cover meals with rapid-acting insulin as Aspart (NovoRapid®). The insulin must be administered 5 to 15 minutes before the meal. The treatment resulted in clinical benefits by achieving glycemic and clinical syndromes control. Glycated hemoglobin (HbA1c) values were decreased three months after the initiation of the treatment (6.8% - the male patient; 9.1% - the female patient). The variation of serum glucose during the day three months after the diagnosis was 5.8-8.9 mmol/l (the male patient), respectively 6.3-11.3 mmol/l (the female patient). There were no clinical symptoms (polydipsia, polyuria, weight loss) and the number of exacerbations decreased.

Discussions

CFRD can occur at any age, including infancy, but the prevalence increases as patients get older[5]. The incidence and prevalence of diabetes in patients with CF is higher than in any other age-matched groups. The prevalence for type 1 diabetes mellitus is 0.2%, for type 2 diabetes mellitus is 11% and for CFRD is 35%[6]. In the

Republic of Moldova, from 66 registered patients with CF, only two (3.03%) were diagnosed with CFRD. These results differ from other reports which demonstrate that CFRD is a frequently encountered comorbidity among CF patients.

In the Republic of Moldova, CF is suspected based on symptoms and then confirmed by sweat test and genetic testing. Neonatal screening has not been implemented yet, and the average age of diagnosis is 2.3-2.9 years. Genetic testing was performed in 61 patients. The results demonstrated that 36.67% were homozygous F508del mutations, 40% were heterozygous F508del and 23.33% were non-F508del genotype.

CFRD is a combination between reduced insulin secretion and peripheral insulin resistance, which is specific for CF**.** CFRD is associated with a decline in lung function, poor nutritional status and high mortality rate, specifically in females, although more recent studies demonstrate that this gap is no longer visible, probably due to treatment[5,7,8] .

A position statement of the American Diabetes Association (ADA) and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society, underline several criteria for diagnosing CFRD in case of an acute illness. The diagnosis of CFRD can be made in CF patients with acute illness (intravenous antibiotics in the hospital or at home, systemic steroid therapy) when fasting plasma glucose (FPG) levels ≥126 mg/dl (7 mmol/l) or 2-hour postprandial plasma glucose levels ≥200 mg/dl (11.1 mmol/l) persist for more than 48 hours[9] .

During a period of stable health, the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. Three criteria should be present: 2-hour oral glucose tolerance test plasma glucose ≥200 mg/dl (11.1 mmol/l), FPG ≥126 mg/dl (7 mmol/l), HbA1c ≥6.5%[9] .

Glycated hemoglobin (HbA1c) is another test that is used to diagnose diabetes, but it is not recommended for patients with CF. Elevated HbA1c is an evidence of hyperglycemia, but a normal value does not exclude it.

The measurement of the C-peptide can help determine how much of his own natural insulin a person can produce as C-peptide is secreted in equimolar amounts as insulin. C-peptide levels are measured instead of insulin levels because C-peptide can assess the person's own insulin secretion even if they receive insulin injections. It may also help differentiate CFRD with type I diabetes mellitus since CF patients can also have this condition[10] .

The management of CFRD patients should be performed in a reference center by a multidisciplinary team. The additional diagnosis of CFRD does not affect CF diet since they have special nutrition requirements, which are well established and are based on the fact that CF patients need a high-calorie diet that is usually 120-150% of the daily recommended intake for age. Thus the goal is to achieve and maintain good nutritional status and normalize blood glucose levels[9].

Conclusion

A high index of suspicion of CFRD should be present as patients grow older. Current paper is documenting the first described two CFRD cases in the Moldavian population, representing 3.03% of total CF patients from our registry (the reported two cases). ■

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