

The Heart and Cystic Fibrosis-It Is Not Only Cor Pulmonale

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Abstract

The heart in cystic fibrosis (CF) could be affected as a cor pulmonale, as a primary myocardial damage with necrosis or as in associated heart conditions. We present four cases of CF patients with heart involvement.

Aim: To describe the classical heart involvement in end-stage lung disease in CF and additional three CF patients with prominent heart involvement early in life that hampers the therapy and follow up.

Methods: By studying the data from the registry and medical charts of CF patients in Bulgaria we found two children and three adults with end stage lung disease and cor pulmonale and we identified three with other main cardiac problems. The classical cor pulmonale in adult CF due to long term progression of the disease is very well described, especially in articles regarding lung transplantation, thus we will not describe these adult patients. Interesting fact was that in both children with cor pulmonale there was late diagnosis and long term denial of the parents, leading to very poor therapy compliance almost noncompliance at all.

Results: Due to the similarity of both child cases with cor pulmonale we are describing only one of them. We are describing the rest three very challenging cases-boy and an adult lady with dilative cardiomyopathy and a boy with supraventricular tachycardia.

Conclusion: The cardiovascular system besides in the end-stage lung phase in CF is relatively rarely affected but when it is this poses challenges for interdisciplinary team approach with careful consideration of drug interactions. Regular monitoring of the heart condition, proper nutrition and enzyme replacement with the supply of the necessary microelements and vitamins are necessary for the prevention of cardiac damage in patients with CF.

Keywords

Heart; Cystic fibrosis; Cor pulmonale

Introduction

Cystic fibrosis (CF) is a complex, autosomal-recessive disorder, affecting the functions of respiratory system, gastro-intestinal tract and all exocrine glands [1]. It's the most common fatal inherited disease in Caucasian. For the CF lung disease is known, that it involves self-perpetuating cycles of airway obstruction, infection and inflammation [2]. The chronic infections and inflammation, leading to bronchiectasis and respiratory failure are the leading cause for morbidity and mortality. In the last decades survival of CF patients has been drastically improved due to newer therapeutically regimens, but still there is no a definite cure. Although with significantly improved survival and quality of life, compared to data 20 years ago, the cost for this achievement is substantial for both society and the patients [3]. Daily adequate treatment is very costly and time-consuming. It usually consists from more than 30 pills per day, multiple nebulized sessions and hours of respiratory cleaning techniques [4]. Cardiovascular impairment in CF is well-known, with cor pulmonale being the most serious cardiovascular complication, but also the heart could be affected as a primary myocardial damage with necrosis or as in associated heart conditions [5].

We present four cases of classical phenotype CF patients [6] with heart involvement. Out of 140 CF patients in Bulgaria (aged from 0 to 64 years) we found two children (aged 17 and 9 years) and three adults with end stage lung disease (aged 27, 29 and 31 years, all diagnosed early in infancy) and cor pulmonale and we identified three with other main cardiac problems. The classical cor pulmonale in adult CF due to long term progression of the disease is very well described, especially in articles regarding lung transplantation, thus we will not describe these adult patients. Interesting fact was that children were at that stage due to late

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diagnosis and long term denial of the parents, leading to very poor therapy compliance almost noncompliance at all. Due to the similarity of both cases we are describing only one of them. We are describing the rest three very challenging cases-boy and an adult lady with dilative cardiomyopathy and a boy with supraventricular tachycardia.

Patient's Summaries

Case 1

First case is a girl born with moderate asphyxiation, intrauterine infection and anaemia. Postpartum, she required oxygen support, antibiotics and blood transfusion. In infancy the baby produced very smelly fatty stools-upto 10 daily especially after greasy food and she presented with failure to thrive and bloated belly. At 2 years of age she had prolapse of the rectum. In relation to these symptoms at 2 years and 10 months of age she was diagnosed with cystic fibrosis by two positive sweat tests and genetic conformation (compound heterozygous for F508del/R1162X). Never the less the mother refuses the specific therapy as she found every medication either "not working" (pancreatic enzyme supplements) or "causing side effects" (i.e. purpura on the legs due to ursodeoxycholic acid). When the girl turned 4 years she started to cough regularly. First pulmonary exacerbation for which the family sought respiratory specialist occurred when the patient was 7 years. Almost 16 months later second pulmonary exacerbation treated in the hospital revealed *B.cepacia complex* infection. A year later at the third exacerbation in the hospital we noted the presence of bradycardia and cor pulmonale (with cardiac catheterization) with severe irreversible changes in the left lung (Figure 1).

Figure 1-CT of the chest-Not visible pulmonary parenchyma in the left, where highly over dilated segmental and subsegmental bronchi were found. The loss of volume in the left lung has led to the displacement and rotation of the entire mediastinal "shadow" so that the contour of the left of the heart is directly placed to the left thoracic wall distal to truncus pulmonalis which is expanded up to 22 mm. There is also visible emphysema of the entire right lung, the medial contour of which also reaches the left chest wall.

Currently the girl has BMI 12.5, delayed growth velocity, 2 years delay in bone age, impaired liver function, with chronic *Paeruginosa* infection and her last measured FEV₁ was 23% (before her last exacerbation). At least, although late at that moment the mother accepted the diagnosis of CF and agreed to follow strict CF regimen. She is now in a process for evaluation for lung transplantation, on oxygen support and therapy for cor pulmonale added to her CF therapy.

Case 2

The second case is a boy who was diagnosed with dilative cardiomyopathy at the age of 3 months due to repetitive respiratory infections. He is followed closely by cardiologist but at the age of 1 years and 8 months two positive sweat tests hinted for possible CF, but definite genetic confirmation was done 2 years later (the patient is homozygous for DF508). The patient follows strict regimen and is followed by cardiologist and pulmonologist. Currently the boy has BMI of 17.84, normal growth velocity, no delay in bone age, normal liver and kidney function, normal biochemistry tests, and FEV 105% (at age 7). He didn't require any in hospital treatment for the last 5 years, no pulmonary exacerbations and no chronic lung infection

either. Despite careful consideration for drug interactions the case is not posing any difficulties in monitoring.

Case 3

The third case is a boy who at the age of 1 year and 3 months after a pneumonia developed severe supra ventricular tachycardia. He is also followed strictly by cardiologist and despite having presented with typical CF symptoms since infancy he was diagnosed with CF at the age of 7 years, genetic analysis confirmed heterozygous for 2184insA/L571S. The patient has a chronic *Paeruginosa* infection and with growing older he exhibits signs of recurrent bronchial obstructions, but the heart condition prevents us from using beta2 agonists. Currently the boy has BMI of 17.64, normal growth velocity, no delay in bone age, normal liver and kidney function, normal biochemistry tests, and FEV 63% (at age 16). He didn't require any in hospital treatment for the last 3 years, and had no pulmonary exacerbations for this period. The patient remains therapeutic challenge.

Case 4

The fourth case is a lady diagnosed with CF since infancy-homozygous for DF508, she had followed very rigorous therapy for CF. She survived pulmonary embolism at the age of 30 with underlying pulmonary hypertension. After myocarditis at the age of 33 yrs she developed severe dilative cardiomyopathy, couple of cardio-surgical interventions and for 6 years was in a heart-transplant waiting list. The challenges posed by the patient were her chronic *Paeruginosa* infection and very low lung function, classifying her since last year also in a lung-transplant waiting list. Her last known BMI was 17.96, she had anemia (Hgb 92-106 g/l); gout; impaired glucose tolerance; hypothyroidism; chronic pyelonephritis; drug allergy and impaired liver function, her last FEV₁ was 38% (in June 2018, aged 42) she required in hospital treatment every month due to her heart problems and intravenous antibiotics. The patient died with severe multiple organ system failure couple of months ago.

Discussion

Pulmonary hypertension is characterized by a chronic increase in pulmonary artery pressure, overloading the right ventricle with hypertrophy and dilation of the right ventricle, which can progress to heart failure. Over 50 years have passed since the publication of Moss et al., in which the squeeze of the pulmonary vasculature had been attributed to hypoxemia and cor pulmonale, its sequelae, had been recognized as a major cause of death for patients with cystic fibrosis. The authors had found that the only method able to properly confirmed the presence of cor pulmonale is the gold standard even for now - cardiac catheterization [7]. The etiology of right ventricular disease in CF is thought to be raised pulmonary artery pressure secondary to chronic or acute-on-chronic hypoxia from the progressive lung destruction. In 2015 Giacchi et al. found that patients with CF may show signs of potential heart impairment such as an increase of pulmonary pressure in paediatric age, and an impaired systolic function of right ventricle in adult age, while a poor pulmonary function is a risk factor for the development of pulmonary hypertension [8]. The under standing of pulmonary hypertension in CF has progressed, yielding an understanding of the chronic systemic inflammation and pulmonary vascular bed remodeling that occurs in these patients to create the phenomenon of pulmonary hypertension.

Although it is unclear whether an earlier diagnosis of pulmonary hypertension in CF and subsequent intervention will impact clinical outcomes, the study of Hayes et al. demonstrated that patients with severe pulmonary hypertension still have lower survival rates than those with mild hypertension, but that the existence of pulmonary hypertension does not affect post-transplant survival [9]. The authors hypothesis that such cardiac impairments may gradually arise due to preceding chronic inflammation related to prior degeneration of lung function and thus it is very important to keep patients clinically stable and address chronic inflammation as early as possible in the progression of CF [9]. The same result was drawn from a metaanalysis of Li et al. suggesting that the presence of pulmonary hypertension was strongly correlated with worse blood-gas parameters and worse

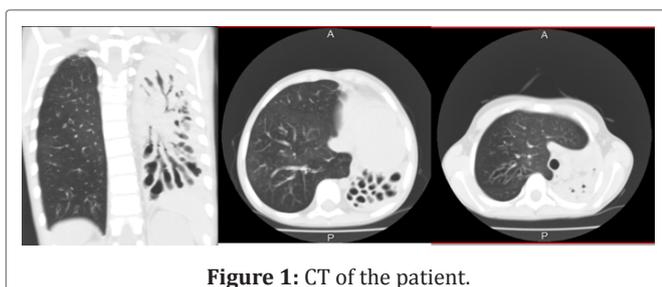


Figure 1: CT of the patient.

lung function, but had no significant prognostic value on survival among patients with CF [10]. Even in some publications pulmonary hypertension in CF is referred as a “mild comorbidity” [11].

Pathological, experimental, and clinical evidence suggest the existence of specific myocardial involvement in cystic fibrosis, influencing systolic and diastolic function of both ventricles at rest and/or during exercise [12]. The clinical relevancy of these heart abnormalities is still unclear. The role of CFTR in the heart remains to be clarified. Some studies have demonstrated that the transmembrane conductance of the CFTR gene intervenes in regulation of contraction of cardiomyocytes by means of maintenance of a resting potential of the membrane, preventing an intracellular calcium overload, which could lead to myocardial hypercontraction. As such, the CFTR gene in the myocardium protects against necrotic myocardial injury induced by ischemia. Therefore, in patients with CF regulation of the activity of the myocardium, which should be reduced by the CFTR gene, does not take place, explaining the right ventricle dysfunction and development of disproportional elevation of pulmonary artery blood pressure in some individuals [13,14].

Chronic infections complicate also the natural disease course [1]. And if our 1st and 4th cases could represent the expected changes in poorly controlled or long term CF, in the other two cases we can think of comorbidity in CF. Comorbidity is clinically important for three reasons. First, some types of comorbidity complicate diagnosis because presenting complaints are a mix of symptoms of different comorbid conditions. Second, some types of comorbidity complicate treatment because standard therapies for one disorder in a comorbid set are contra-indicated for patients with another disorder in the set. Third, some types of comorbid disorders can magnify the functional impairment and adversely influence the course of other conditions.

As the longevity increases, further studies are required to precise the impact of these cardiac abnormalities on survival, quality of life and transplant candidacy. These patients will require a comprehensive approach and multidisciplinary team evaluation.

Conclusion

The cardiovascular system in CF is relatively rarely affected but when it is this poses challenges for interdisciplinary team approach with careful consideration of drug interactions. Regular monitoring of the heart condition, proper nutrition and enzyme replacement with the supply of the necessary microelements and vitamins are necessary for the prevention of cardiac damage in patients with CF.

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