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Mini Review

Screening and Dental Management with the Cystic Fibrosis in North Macedonia

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Abstract

Cystic fibrosis is a genetic disorder in which the mutation of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene that codes the protein forming a chloride channel of epithelial cells results in its distorted functioning. The products of the damaged gene cause irregular transport of water and electrolytes through epithelial cells, leading to chronic diseases of the respiratory and gastrointestinal tract, increase in saliva concentration in the saliva, and damage to reproductive functions.

Oral manifestations are mild and may manifest in the form of enlargement of the lips or erythema, as well as a gingivitis with a concomitant mild dryness in the mouth. Prior to oral surgery, consultations with a doctor who treats the child are necessary, because if there is cirrhosis of the liver then there is certainly a lack of coagulation factor, as well as a disorder in the mechanism of blood coagulation. Dental interventions under general anesthesia should be avoided due to the poor condition of the respiratory system. Nowadays with a modern therapy possibilities is possible to extend patients' life expectancy, although cystic fibrosis remains incurable. The multidisciplinary team of doctors should include a pediatric dentist with the aim to take into consideration the specific prevention and treatment needs of this group of young patients. Knowledge of dentists about clinical signs and characteristics of cystic fibrosis is essential for the successful dental treatment of these patients and the enabling of their better quality of life.

Keywords: *Cystic Fibrosis; Dental Treatment; Sweat Test; Oral Disease*

Introduction

Cystic fibrosis is a genetic disorder in which the mutation of the Cystic Fibrosis Trans membrane Regulator (CFTR) gene that codes the protein forming a chloride channel of epithelial cells results in its distorted functioning [1]. CFTR expression has been shown to be critical for normal function of the of the innate and adaptive immune system [2]. In the patients with cystic fibrosis many systems are affected and disease is characterized by dysfunction of almost all exocrine glands. The disease is inherited and is transmitted autosomal recessively from a gene that is localized to the longer arm of the seventh chromosome. The incidence of the cystic fibrosis is 1: 2000.

In the Republic of Northern Macedonia the screening for cystic fibrosis was introduced in May 2018 as a pilot study, and 3 children with cystic fibrosis were detected. Neonatal screening, early diagnosis, and the treatment of cystic fibrosis as a chronic disease are important for long-term survival and good quality of life for these patients [3].

With the introduction of the newborn screening in May 2018, 12,000 newborns (half of the neonatal population in the country) were included in a pilot study. The concentration of immunoreactive trypsinogen (IRT) in a dry drop of blood taken from the heel of the newborn 48 hours after birth, is determined using an immunofluorimetric DELFIA method. For a period of four months, a total of 4.921 newborns from 16 maternities in the country have been screened, covered by the pilot study. Three newborns with cystic fibrosis have been detected, who have been diagnosed with a sweat test and confirmed by a molecular analysis of the CFTR (cystic fibrosis trans membrane regulator) gene [4].

The nickname of CF is 65 roses. Way back when, children with CF had trouble pronouncing Cystic Fibrosis. So they came up with a nickname with a similar ring: sixty-five roses. Roses certainly evoke a much more lovely image than a life-threatening disease. In fact, the nickname stuck so much that it is still used today and roses have become an unofficial symbol of CF.

The products of the damaged gene cause irregular transport of water and electrolytes through epithelial cells, leading to chronic diseases of the respiratory and gastrointestinal tract, increase in saliva concentration in the saliva, and damage to reproductive functions. Genetically modified protein excreted in children with cystic fibrosis affects the function of the exocrine glands. Micro-structure of the pancreas, and its cystic fibrous degeneration and atrophy, reduces its physiological function, resulting in a reduction in the production of digestive enzymes, causing insufficient absorption of nutrients.

The disease is more common in children in the North European people affecting 90,000 people worldwide [2], and it is much less common in children of the black race. Equally occurs in both sexes, and in males, children often can cause sterility [5]. It is the most common genetic disease that leads to death in white people.

The changes occur on all exocrine glands, except for salivary glands, which are very rarely affected. Clinical manifestations of the disease occur on the pulmonary and gastrointestinal tract, as well as on the sweat glands [6,7]. Singh A., *et al.* investigate the utility of aquagenic wrinkling as screening test for children with cystic fibrosis. A total of 64 children with cystic fibrosis were included in the study. 20 children had sweat chloride values of ≥ 60 mEq/l and diagnosed as cystic fibrosis. Singh A et all concluded that when no facility for sweat test was available, children with phenotype compatible with cystic fibrosis who develop aquagenic wrinkling in 3 minutes may be diagnosed as probable cystic fibrosis and referred for confirmation by sweat test [7].

Clinical symptoms

Symptoms of the disease are manifested with frequent, fat, massive and stinking stools that are caused by dysfunction of the pancreas and ejection of non-digestible foods. Children usually have an appetite and eat, however, they lag behind in the development due to poor nutrition of the nutrients [8]. Also metabolic alkalosis with hypoelectrolytemia is a relatively common manifestation of CF in infancy [9]. Abdominal pain, as well as rectal prolapse often occur, while small fingers appear later.

Diabetes mellitus, as well as cirrhosis of the liver [10], are frequent additional complications that arise as a result of progressive damage to the pancreas [11]. Children with cirrhosis of the liver also experience a disorder in the mechanism of blood coagulation [12,13].

In the study conducted by Fustik S., *et al.* analyzed the all prevalence and the role of possible clinical and genetic risk factors for the development of cystic fibrosis (CF)-related liver disease (LD) in a Macedonian CF population. The conclusion was no significant difference in the pulmonary function, nutritional status, and in the prevalence of meconium ileus. Genetic analysis showed higher frequency of DeltaF508 mutation in the LD group (77.8%) vs. the no LD group (66.2%). All patients with LD had severe mutations: DeltaF508, G542X, N1303K, CFTRdel.21Kb, 1811+1G-->C and Y1092X [14].

Discussion

Coughing is the most common symptom of lung infection. In the lungs there is retention of the mucus that causes obstructive lung disease and increased susceptibility to infection. The changes in the lungs are of varying degrees. Frequent occurrence of acute respiratory infections are accompanied by coughing, bronchopneumonia, bronchiectasis and lungs abscess. Recurrent pulmonary infections occur due to decreased resistance of respiratory epithelium, accumulation of sticky and thick mucus, as well as the inability of the child to absorb vitamin A [15]. Due to the accumulation of mucus in the lungs, the small bronchioles are blocked and collapses of their distal parts

occur. Many trials in the world are being conducted to find appropriate therapy for frequent pulmonary infections with Pseudomonas aeruginosa [16]. Pulmonary magnetic resonance imaging using hyperpolarised 129Xe gas (XeMRI) can quantify ventilation inhomogeneity by measuring the percentage of unventilated lung volume (ventilation defect percent; VDP) [17]. Rayment JH., *et al.* in their study included 15 cystic fibrosis patients age 8 - 18 years underwent XeMRI, spirometry, plethysmography, and multiple breath nitrogen washout at the beginning and end of inpatient treatment of a pulmonary exacerbation. Rayment concluded that further investigation of XeMRI as a tool to capture treatment response in cystic fibrosis lung disease should be done. MRI, as a non-ionizing imaging technique, may be particularly attractive in CF care for longitudinal evaluation, providing a new imaging biomarker to detect early ventilator abnormalities [18].

Studies have now established that neutrophil cytotoxins, extracellular DNA, and neutrophil extracellular traps (NETs) are associated with increased mucus clogging and lung injury in cystic fibrosis [19]. Khan MA., *et al.* in their study concluded that clarifying the role of neutrophils and NETs in CF lung disease and identifying therapies that preserve the positive effects of neutrophils are essential in achieving innovative therapeutic advances [19]. All of this can lead to the emergence of so-called „bursts of chest", deformations that result from hypertrophy of the auxiliary respiratory muscles, which is intensively involved in breathing. The progressive development of the lungs diseases results in their enlargement.

Pulmonary infection (*Staphylococcus aureus, Pseudomonas aeruginosa* and *Hemophilus influenza*), extensive bronchiolitis, atelectasis, haemoptysis, pneumothorax, and cor pulmonale are common complications in children with cystic fibrosis. Approximately 60% of CF patients are infected with *Aspergillus fumigatus*, a ubiquitous environmental fungus, and its presence has been associated with accelerated lung function decline [2].

Dental aspects

Oral manifestations are mild and may manifest in the form of enlargement of the lips or erythema, as well as a gingivitis with a concomitant mild dryness in the mouth. A large percentage of children in the past had tetracycline tooth discolorations because in the treatment of the disease, this antibiotic has been used for many years. The pathophysiology and clinical manifestations of cystic fibrosis are relevant for dental practitioners and in this article relevant recommendations are given for dentists to ensure optimal treatment planning for these patients.

The incidence of caries in children with cystic fibrosis is low [20], which is explained by the long-term use of the antibiotic, as well as the increased saline buffer capacity due to the presence of large amounts of calcium. In these children the prevalence of malocclusion has increased, especially the open bite, as a result of breathing trough the mouth due to chronic and sinus obstructions.

Before the discovery and application of the antibiotic, children with cystic fibrosis died very early, and the cause of death was most commonly pneumonia and anoxia due to a long period of respiratory infection. Today, with early diagnosis and timely therapy, many patients can experience the third, and even the fourth decade of life. In addition to the use of adequate drugs, it is also necessary to take physical and therapeutic measures aimed at eliminating the accumulated secretor content in the lungs and the release of the obstructed bronchioles.

The European cystic fibrosis registry that was dedicated to collection of demographic data, and assess whether the resources available in countries with and without European Union (EU) membership affects care and survival of patients [21].

The new therapy requires dietary modification, as well as intake of pancreatic enzymes [22] and vitamins A, D, E and K. If patients are unable to maintain normal weight, it is necessary to be feed with nasal-gastric probe or to start with parenteral nutrition. Antibiotics are essential to prevent the occurrence of infections and their inhalation application significantly improved the health condition of diseased children.

Dental treatment of children with cystic fibrosis should not be treated in a lying position, but in a sitting position, and the head of the patient should be slightly tilted forward to make it easier to get rid of the secret. The using of the sedatives in patient should be avoid, because sedatives influence lung function. A variety of changes in the oral cavity environment of the cystic fibrosis patients may occur,

like mineralization disorders of hard dental tissues, gingivitis and the change in the content and properties of saliva [1]. Specific dental manifestations of the disease may result from the condition itself or complications of treatment [23].

Prior to oral surgery, consultations with a doctor who treats the child are necessary, because if there is cirrhosis of the liver then there is certainly a lack of coagulation factor, as well as a disorder in the mechanism of blood coagulation.

Dental interventions under general anesthesia should be avoided due to the poor condition of the respiratory system. Nowadays with a modern therapy possibilities [24] is possible to extend patients' life expectancy, although cystic fibrosis remains incurable. The multidisciplinary team of doctors should include a pediatric dentist with the aim to take into consideration the specific prevention and treatment needs of this group of young patients.

Conclusion

Knowledge of dentists about clinical signs and characteristics of cystic fibrosis is essential for the successful dental treatment of these patients and the enabling of their better quality of life.

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