

CHILD CYSTIC FIBROSIS. CASE PRESENTATION.

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Abstract: Cystic fibrosis is a multisystemic disease with an autosomal recessive transmission, being one of the most frequent genetic affection in pediatric pathology. The disease is produced by the mutation of the gene that encodes the protein which regulates the transmembrane conductance, having a large distribution in the epithelial cells of the respiratory tract, the gastro-intestinal tract, in sweat glands, but also in the urinary tract. The consequences are failure in evacuating the mucous secretions, a high level of salt in the glandular secretions, but as well as the others, a limited and chronic infection of the respiratory tract. The authors illustrate the clinical evolution of an infant with record of bronchial obstructive episodes. Further clinical symptoms, including the persistent infection with *Pseudomonas Aeruginosa*, correlated with other investigations, conclude with the diagnosis of cystic fibrosis. For favourable results in therapy, the authors underline the importance of the chronic therapy, which aims at the improvement of the clearance in mucous secretion, controlling the infection, maintaining an optimal state of nutrition, the treatment of complications, as well as psychological retaining of the patient and family. In conclusion, cystic fibrosis remains a severe illness, whose survival rate has risen in the past decade, thanks to progresses recorded in the genetic field and due to the complex approach regarding the therapy.

Keywords: cystic fibrosis, *Pseudomonas Aeruginosa*, thoracic physiotherapy

Rezumat: Fibroza chistică este o boală multisistemică a cărei transmitere este autosomal recesivă, fiind una dintre afecțiunile genetice frecvent întâlnite în patologia pediatrică. Afecțiunea este determinată de mutația genei ce codifică proteina reglatoare a conductanței transmembranare, aceasta având o distribuție largă în celulele epiteliale ale căilor respiratorii, tractului gastro-intestinal, în glande, dar și în aparatul urinar. Consecințele sunt reprezentate de eșecul evacuării secrețiilor mucoase, un conținut crescut în sare al secrețiilor glandulare, precum și infecția cronică limitată la nivelul tractului respirator. Autorii prezintă evoluția clinică a unui sugar cu numeroase episoade bronhoobstructive în antecedente. Manifestările clinice ulterioare, inclusiv infecția pulmonară persistentă cu *Pseudomonas Aeruginosa*, corelate cu investigațiile

paraclinice, au dus la formularea diagnosticului de fibroză chistică. În vederea obținerii unui rezultat terapeutic favorabil, autorii subliniază importanța terapiei cronice combinate, care vizează îmbunătățirea clearance-ului secrețiilor mucoase, controlul infecției, menținerea stării optime de nutriție, tratamentul complicațiilor, cât și susținerea psihologică a bolnavului și familiei. În concluzie, fibroza chistică rămâne o afecțiune gravă, a cărei rată de supraviețuire a crescut în ultimul deceniu, datorită progreselor înregistrate în domeniul geneticii, dar și datorită abordării complexe terapeutice.

Cuvinte cheie: fibroză chistică, *Pseudomonas aeruginosa*, fizioterapie toracică

INTRODUCTION

Cystic fibrosis is one of the most frequent autosomal recessive monogenic affection, with chronic progressive transmission. The typical clinical chart is represented by three symptomatic categories: respiratory, gastrointestinal and deficient. Usually, the diagnosis starts from the typical clinical-anamnestic elements, and it is confirmed by the sweat test and further genetic investigations. The treatment for this disease is complex, associating the administration of certain composites acting on the pathogenetic mechanisms of the disease, with elements of physiotherapy and psychological support for the patient and his family. Nowadays, life expectancy and quality of life in cystic fibrosis have significantly improved; thus, if in the 90's, life expectancy only reached the age of 17-18 years old, today the patients survive until adult age, due to the accomplished progress.

Case presentation.

Patient I.J., female gender, aged 9 months, goes to the IIIrd Pediatric Clinic, Cluj-Napoca, for a bronchial obstructive episode. It is the first child, coming from a pregnancy with physiological evolution, with a normal due date, weighing 3400 grams and with Apgar score 8. The neuropsychic evolution was appropriate for each life stage. Rachitis prophylaxis and the vaccinations have been performed complying with the regulations of the Ministry of Health and Family.

There were some vomiting episodes mentioned in the personal pathologic clinical record at the age of 2

CLINICAL ASPECTS

weeks, interpreted as part of the gastroesophageal reflux disease, for which prokinetic medication had been administered. Up to the age of 9 months, the ponderal index had an unsatisfying evolution. Starting with the age of 5 weeks, the child presented repeated bronchial obstructive episodes, expressed through productive cough, difficult and hissing breathing. The first hospitalization in our clinic took place at the age of 9 months, for a bronchial obstructive episode. The objective examination revealed a patient with a ponderal index of 0.7, denoting a second degree protein-caloric malnutrition, pale teguments, wet cough and subcrepitant bilateral rales. The diagnosis of bronchial obstructive syndrome is derived from this. There were several affections taken into consideration in its etiology: recurrent wheezing (pleaded for by the continual bronchial obstructive episodes), cystic fibrosis, gastroesophageal reflux disease (pleaded for by the vomiting episodes, lack of growing, and respiratory symptoms), obstructions of the tracheobronchial tract through extrinsic compression (vascular ring, tumours, adenopathy). The performed paraclinical investigations revealed the presence of a minimum inflammatory syndrome, and the thoracic radiography showed a bilateral pulmonary hyperinflation, thickened and reticulonodular interstitial pulmonary image, and a hydro-aerial level in the right cardiophrenic angle. The bronchoscopy and the baritate transit of the esophagus have revealed a normal aspect. The cystic fibrosis has been assumed due to the fact that during bowel tracking period it had the aspect of steatorrea and because the chronic pulmonary disease was associated with the lack of growing. There were further investigations. The sweat test revealed much higher values than the normal ones (chlorine 108 mmol/l at the first quantification and 120 mmol/l at the second quantification). The diagnosis has been confirmed by the deceleration of the genetic mutation Δ F508/G 542X.

The molecular confirmation of the cystic fibrosis diagnosis led to the beginning of the appropriate chronic therapy. The beholders have been trained in order to assess works of pulmonary physiotherapy (thoracic tapotage and postural drainage). Pancreatic enzymes have been associated to this therapy, 10 000 U/day divided according to meals, and also products meant to decrease the viscosity and the flexibility of the saliva – Pulmozyme (alpha-dornase) 2500 U/day in aerosols. Inhalatory corticotherapy was administered in order to diminish the inflammatory process present at branchopulmonary level (fluticasone 200 μ g/day).

In its evolution it presented episodes of exacerbation manifested through paroxystic cough and mucopurulent saliva. *Pseudomonas Aeruginosa* has been relieved in the culture assessed through laryngeal-tracheal aspiration. Taking into consideration the presence of *Pseudomonas Aeruginosa* superinfection, a parenteral therapy followed according to the Imipenem antibiogram, as well as Tobramycin-type aminoglycoside aerosol therapy. This therapy helped sterilizing the cultures.

Nowadays, the patient has a normal weight for her age and even if she still coughs every day, the bronchial obstructive exacerbations occur less and less, 2-3 times/year. The chronic therapy is represented by a nourishment diet rich in calories, proteins, pancreatic enzymes (20 000U/day divided for each meal), Pulmozyme (2 500 U/day, in the morning in aerosols), thoracic physiotherapy, inhalatory glucocorticoids and liposoluble vitamins (vitamin A, D and E).

DISCUSSIONS

Cystic fibrosis is one of the most frequent genetic affections in pediatric pathology. It is an autosomal recessive transmitted disease whose incidence reaches 1: 2000 - 1: 2500 newborns. According to the National Centre of Mucoviscidosis in Timișoara, the incidence of the disease in Romania is of 1: 2054 newborns. Regarding the survival rate, one can notice that due to the accomplished progress, there is a big difference from the 90's, when life expectancy was around the age of 17- 18 as against today when patients may survive until adult age (1).

The gene for cystic fibrosis is placed on the long arm of chromosome no. 7, where the regulatory protein of the transmembrane conductance is coded (CFTR). The gene may suffer multiple mutations (about 1300) and may present over 300 polymorphic variants, the most common being Δ F 508 mutation, also met in this case study. CFTR is located at the level of the apical membrane of the epithelial cells, providing a transporter for chloride, bicarbonate and glutathione. Gene mutation leads to CFTR mutation, resulting in a disturbance of the sodium, chloride and water transport at cellular level. The result will be a viscous mucus and thus, the diffuse obstruction of the small airways. The persistence of the obstruction leads to infection and pulmonary inflammation. The inflammatory process leads on one side to the spreading of enzymes which split the DNA and close the vicious circle of viscous secretion emergence and on the other side the inflammation leads to the progressive destruction of the pulmonary tissue and the emergence of breathing insufficiency. This physiopathologic mechanism does not occur only at pulmonary level, but also at pancreatic, intestinal, hepatobiliar and different vessels levels.

The typical clinical picture is generally based on three types of symptoms: respiratory, gastrointestinal and deficient. The respiratory semeiology begins with cough, initially a dry cough and predominant at night, afterwards becoming productive and persistent during the entire day, joined by the elimination of ample bronchial secretions. The early gastrointestinal transit changes with steatorrhea. In its evolution, it usually displays an unsatisfying weight curve, with failure in growing, despite a good appetite and an adequate nutritional share.

The diagnosis can be assessed based on the sweat test, which represents the gold standard, and it estimates the concentration of chloride and sodium ions from the sweat. It is recommended to make 2 estimations in order to confirm the diagnosis. The positive values are

CLINICAL ASPECTS

those over 60 mmol/l chloride. The values between 40 and 60 mmol/l chloride are ambiguous and require test recurrence and result interpretation in clinical framework. A percentage of up to 5 - 10 % teenagers and healthy adults may display values of the sweat test over 60 mmol/l chloride, but the molecular diagnosis is negative, infirming the presence of the disease.

The certain diagnosis of cystic fibrosis is the molecular one, which identifies the pathological signs. The genetic estimation should ideally be performed for all the sick people with positive sweat test. It is also performed for patients with typical clinical picture, but with balanced or negative sweat test, and for those with atypical clinical picture and positive sweat test.

A study achieved by Stanke et al. on a group of 255 patients with cystic fibrosis, emphasizes the fact that there is no connection between the electrolytes' value in sweat and the prognosis (2). In most of the developed countries, the identification of cystic fibrosis cases occurs through newborn screening. The protocol requires, in the first phase, the assessment of an immunoreactive test of the trypsinogen in the feces, thus identifying the newborn children with high risk of cystic fibrosis. Afterwards, the samples are subject to a double DNA test in order to identify the cystic fibrosis gene (3).

Cystic fibrosis therapy is complex, requiring the administration of products which act especially upon the pathogenetic mechanisms of the disease, but also the association with physiotherapy, psychological support provided for both the patient and his family.

The thoracic physiotherapy is the most important factor in the prevention of the respiratory infections, due to the mobilization and elimination of bronchial secretions. It includes techniques of respiratory clearance, physical exercise and aerosol therapy. The different respiratory clearance techniques are associated with taking postural drainage positions, adequate for each segment and pulmonary lobe, thus favouring secretion elimination and semeiology improvement (4). The percussion is just a help for the postural drainage. Most of the assessed meta-analyses have proved that there is no substantial advantage regarding a certain technique, as long as the patient begins the therapy (5, 6). In order to optimize the effectiveness of these tests it is vital to provide the best adherence of the patient to a therapy, and it seems that this adherence is best related to the patient's satisfaction regarding the chosen technique (7). Thus, the most adequate approach in choosing the respiratory clearance technique sits perhaps in the presentation to the patient and his family of the entire set of therapy possibilities, so that the choice will be done according to the patient's lifestyle, and his fondness for a certain technique (8). The new respiratory clearance techniques include high frequency oral oscillation therapy and high frequency thoracic compression therapy. The physical exercises are an important part of those patients' physiotherapy, with the following objectives: maintaining muscular force, a good mobility, as well as gaining a good physical condition.

Another important element in those patients' therapy is the aerosol therapy, used for the administration of antibiotherapy, mucolytic therapy (alpha dornase - Pulmozyme) and anti-inflammatory therapy.

One of the most common complications of cystic fibrosis is the chronic infection of the respiratory tract, with a very important role in the disease's evolution and prognosis. The etiology is generally bacterial, with frequent complication, such as *Pseudomonas Aeruginosa*, *Staphilococcus aureus*, *Aspergillus fumigatus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. The effect upon the respiratory tract produced through the obstruction of the airways will implicitly lead to the slackness of the viscous mucus and the adherent emergence of chronic infection which will finally lead to the emergence of respiratory insufficiency.

Antibiotherapy must be aggressive and targeted at the beginning, according to the isolated germ. Antibiotic therapy will be administered for a period of 3-4 weeks. In case of disease exacerbation, the anti-infectious therapy will be performed parenterally.

Pseudomonas Aeruginosa is the most common pathogen agent associated with cystic fibrosis patients' morbidity and mortality. This bacterium causes a chronic infection at pulmonary level, hard to root out even with an accurate antibiotherapy (9). The early infection is with nonmucoid *Pseudomonas* stem from the environment, with a quick growing rhythm and sensitive to antibiotherapy (10). This phase is temporary and the airways become permanently colonised with *Pseudomonas Aeruginosa* for most of the patients. During the chronic infection, the bacterial population adapts to the environment from the patient's airways. This process correlates on one side with the genetic adaptability of the microorganism, but also with the presence of some mutant genes which lead to the loss of bacterial functions (11). In a study accomplished at the Centre for Cystic Fibrosis in Copenhagen, Lars Jelsbak et al. have examined the initial colonization with *Pseudomonas Aeruginosa* and the chronic infection with this bacterium. The patients with cystic fibrosis have been dynamically watched, and the results showed a high level of *Pseudomonas Aeruginosa* genotypic diversity for all patients with cystic fibrosis who presented intermittent colonization. It has also been proved that the patients with cystic fibrosis and *Pseudomonas Aeruginosa* intermittent or chronic infection are characterized by genotypic diversity. This suggests that *Pseudomonas Aeruginosa* acquires unique independent connections in patients with cystic fibrosis, probably due to the different types of *Pseudomonas Aeruginosa* in the outer environment (12). In the case presented by us, we have identified 2 episodes of *Pseudomonas Aeruginosa* infection, from the age of 1 ½, but early and long-drawn antibiotherapy, administered both parenterally, and in aerosols (Tobramycin), led to the quick sterilization of the samples.

Pulmozyme is a product of genetic engineering used in order to decrease saliva's viscosity and mobility. The administration takes place every day, as nebulization,

CLINICAL ASPECTS

the recommended dose is of 2500 U Pulmozyme a day. The maximum therapeutic benefit comes from its daily administration in aerosols. There are studies which assert that the intermittent administration determines a slow improvement of the pulmonary function compared to the continuing administration.

Because the inflammation is the central spot of the physiopathologic mechanism in cystic fibrosis, the limitation of inflammation mediators' release is the key therapeutic strategy leading to the deceleration of the pulmonary function decline and to the improvement of life expectancy (13). Thus, glucocorticoids are used for their anti-inflammatory effect, and also for their effect upon neutrophils (14). Even if it is beneficial, the systemic use of glucocorticoids presents several side-effects which limit their use (15, 16). Inhalant glucocorticoids give the opportunity to deposit at the level of the airways, and together with the low systemic effects, this explains their frequent use in cystic fibrosis therapy in the past years (17). Still, there are debates regarding the efficiency of the therapy with glucocorticoids in the patients with cystic fibrosis. Recently, Balfour-Lynn et al. made a multicentric study regarding the test of the hypothesis according to which giving up inhalant glucocorticoids therapy wouldn't produce semeiology exacerbation (18). The study's results supported the Cochrane conclusions which asserted that this therapy has no benefits, and still it does no harm, and that most probably, certain subgroups of patients with cystic fibrosis may take advantage of the use of inhalant glucocorticoids (15). The variability of the pulmonary inflammatory process as well as the variable effect of the glucocorticoid therapy suggest the hypothesis according to which the genetic polymorphism of the glucocorticoid receptor might influence its sensitivity in different used therapeutic methods, and implicitly it might contribute to the variability of the inflammatory answer. Harriet Corvol et al. proved in their study on 255 young patients diagnosed with cystic fibrosis, a possible association between the glucocorticoid polymorphism of the receptor's gene and the progression of the pulmonary disease for these patients. Identifying the elements involved in the answer to the glucocorticoid has been an important factor in predicting the therapeutic answer, and this pharmacologic process could help optimizing the therapy for the patients with cystic fibrosis (13).

Another aspect of the therapeutic process is the management of the pancreatic pain; the patients may evolve towards complications such as pancreatic calculus, cysts and pancreatic pseudocysts, recurrent pancreatitis and even pancreatic insufficiency. Pancreatic enzymes are administered in order to prevent this from happening, in doses which vary according to the patient's age, from 500–700 UI/kg/meal for nurslings up to maximum 10 000 UI/kgc/day for children over 6. The administered dose should be correlated with the aspect of the patient's feces, because increased doses might lead to complications, such as fibrosing colonopathy. Another consequence of an unappropriate pancreatic enzyme

secretion is that of an insufficient absorption of liposoluble vitamins. That is why these vitamins will be associated with the patient's basic therapy.

For patients with cystic fibrosis, the evolution might be accompanied by a series of complications, such as the osteoarticular ones with changes like fibrosing hypertrophic osteopathy and arthritis, but also a late puberty or even infertility due to obstructive azoospermia.

CONCLUSIONS

Cystic fibrosis remains one of the affections typical for the pediatric age, usually under-diagnosed, but which can lead to a better quality of life and a higher life expectancy if the adequate therapy is chosen (both in medicamentation, and by choosing the appropriate techniques in physiotherapy).

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