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EDITORIALS

Adult cystic fibrosis

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ABSTRACT

Adult cystic fibrosis is a new topic in internal medicine and intensive care units assistance. The numbers of individuals with cystic fibrosis (CF) aged 18 years and older has increased with increasing of predicted survival in the last ten years.The gender difference in the death rate is also disscused. After presenting the Guide for the positive diagnosis of CF (Consensus Conference Program, 1998), the authors introduce the two separate groups of CF adult patients.

The first group has the diagnosis of CF from their early childhood and presents in adolescent and youth life the most severe disease complications (nutritional deficiency, pulmonary chronic infections with Ps. aeruginosa*, severe haemoptisia, and end stage lung disease which recommend the patient for lung transplantation, CF bone related disease, CF related diabet etc.).*

The second group are the CF patients diagnosed in the adulthood with atypical CF. These patients have a higher mean age, a better nutritional status, rare chronic bronchial colonization with Ps.aeruginosa*, pancreatic sufficiency. These cases may have unique presentation such as congenital bilateral absence of the vasa deferent, chronic sinusites, nasal polyps, recurrent pancreatitis.*

The last topic discussed is the sensible subject regarding the way to transfer the CF patients from paediatric to adult care, a new medical team, and ethical and empathic implications in these cases.

Cystic fibrosis (CF) is a genetic autosomal recesive disease with multisystem clinical manifestations, primary by chronic pulmonary infection and bronchiectasis, pancreatic exocrine insufficiency in 80% of the cases, and elevated sweat chloride. In the last decades median predicted survival in CF patients is older than 35 years. This increased survival has resulted in a dramatic increase in the number of adult CF patients and in consequence, new problems for the adult medicine.

Since the early 1970's, the number of individuals with CF aged 18 years or older has increased by more than 400%, and currently in the western countries 43% of all CF patients will be older than 18 years, majority of them between 18 and 30 years and 10% being older than 40 years (1).

The growing number of adults with CF move the interest of the adult pneumologyst to a specific pediatric disease (in the classical view of medical praxis).

This increase in predicted survival has been aided by a greater appreciation of the potential variability in the severity and clinical aspect in the presentation, resulting of mild cases unrecognized before. The diagnosis of CF is now being put in an increasing number of adults (2).

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The phenotypic abnormalities in CF are caused by dysfunction of the protein cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel present in the epithelia with a significant role to sodium and water balance. More than 1500 mutations have been identified which lead to disfunction of CFTR, with variable phenotypic aspects, from very severe with clinical manifestations in the newborn and infants to mild cases. The majority of individuals with CF are diagnosed before age 3, but 5% are diagnosed after the age of 16 years. A large number of CF patients do not demonstrate all the classic symptoms of CF. In this situation the internist has to keep in mind CF when considering the differential diagnosis of adults with bronchiectasis, chronic sinusitis or male infertility.

Gender differences in the death rate of patients with CF have been documented for years. In 2000 Annual Report of Cystic Fibrosis Foundation (CFF) is presented a median survival rate of 32 years for a group of approximately 23,000 patients, with a 5.3 years difference between male (34.4 years) and female (29.1 years) (3). We need to elucidate the causes of this differences. Probably there are fundamental cellular difference, differences in response to chronic infection and inflammation, earlier onset of pubertal development in girls, psychosocial factors as body size, body image, physical activity, differences in the pulmonary or nutritional care. Individuals with CF manifest an increase in energy expenditure that is sex dependent with female having a significant greater resting energy expenditure (REE). The greater REE in female with CF may explain their difficulty in maintaining normal growth and contribute to the their shorter life expectancy (4).

Positive diagnosis

In 1998 The Consensus Conference Program initiated by CFF had the goal to establish guidelines for CF diagnosis and patient care (5, 6).

It is essential to confirm or exclude the diagnosis of CF with high degree of accurency and to avoid unnecessary testing. In the consensus of the panel the diagnosis of CF should be based on one or more characteristic of phenotypic feature (**Box 1**), a history of CF in a sibling, a positive newborn screening test result plus laboratory evidence of a CFTR abnormally as documented by: elevated sweat chloride concentration or identification of the mutation in CFTR gene known to cause CF or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium.

1. Chronic sinopulmonary disease manifested by:
a. Persistent colonization/infection with typical CF pathogen including:
Staphylococus aureus, Haemophilus influenzae, mucoid or nonmucoid
Pseudomonas aeruginosa and *Burkholderia cepacia.*
b. Chronic cough and sputum production.
c. Persistent chest radiograph abnormalities (bronchiectasis, atelectasis, infiltrates, hyperinflation).
d. Airway obstruction manifested by wheezing and air trapping.
e. Nasal polyps; radiographic and computered tomographic abnormalities of the paranasal sinuses.
f. Digital clubbing.
2. Gastrointestinal and nutritional abnormalities including:
a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse.
b. Pancreatic: pancreatic insufficiency, reccurent pancreatitis.
c. Hepatic: chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis or multilobular cirrhosis.
d. Nutritional: failure to thrive, hypoproteinemia and edema, complications secondary to fat-soluble vitamin deficiency.
3. Salt loss syndrome: acute salt depletion, chronic metabolic alkalosis.
4. Male urogenital abnormalities resulting in obstructive azoospermia (CBAVD).

BOX 1. Phenotypic features consistent with a diagnosis of cystic fibrosis (1998, The Consensus Conference Programe of Cystic Fibrosis Foundation) (5)

Evidence of CFTR abnormality

Dysfunction in CFTR can be demonstrated in one of three ways (5):

1. Sweat test: measurement of chloride concentration in sweat after ionophoresis of pilocarpine, using standardized methods.

A sweat chloride concentration of more than 60 mmol/l is consistent with the diagnosis of cystic fibrosis. For infants younger than 3 months old of age, the sweat chloride concentration of more than 40 mmol/l is highly suggestive of a diagnosis of CF. A sweat chloride concentration of more than 160 mmol/l is physiologically

impossible and suggest an error in collection or analysis. The borderline sweat test results should be repeated. Sweat chloride test should not be used as the sole criteria for exclusion of the diagnosis of CF because some patients have normal values (correlated with the functional class of CFTR gene mutation).

2. Mutation analysis

CFTR genotyping has to demonstrate the presence of two known CF mutations in the same patient. The sensitivity of the test depends entirely on the number of mutation tested. The most common mutation in our population is Δ F 508 (70%). Costs considerations limit yet (not only in our country) genotyping to be the first line of screening with a suggestive phenotype.

3. Direct in vivo measurement of CFTR function in nasal epithelium (nasal potential difference) (7).

Respiratory epithelia including nasal epithelia transport ions as sodium (Na+) and chloride (Cl-). This active transport generates a transepithelial electrical potential difference wich can be measured in vivo. In CF patients it is a different pattern of nasal potential difference (PD), used for positive diagnosis as high basal PD and a greater inhibition of PD after nasal perfusion with Na + channel inhibition (amiloride).The PD equipment emplies in a high impedance voltmeter but the interpretation of PD measurements must ensure adequate rigor of the technique, not simple at all. Nasal PD has a potentially useful role in the diagnosis of CF, particulary when uncertainly exists with current diagnostic methods. However this test is technically very difficult to be performed and is not currently to routine clinical use.

Pancreatic function

More than 98% of the pancreatic capacity to secrete enzymes has to be lost to have evident symptoms of maldigestion (5).

Measurement of serum cathionic trypsinogen is the only usefull test after age of 7-8 years as a direct methods of diagnosis. Among indirect test, fecal fat analysis with a 72 hours stool collection is most informative, but is not the ideal test.

The patients are classified into pancreatic insufficient or pancreatic sufficient phenotypes.

Respiratory chronic disease

Respiratory disease in CF would be investigated by chest radiography, computed tomography, ciliary biopsy (differential diagnosis for immobile ciliary syndrome).

Lung function would be tested by spirometry (flow volume curve), to measure baseline FEV 1, bronchial hyperreactivity and hyperresponsivenes, pulseoxymetry and complementary, plethismography (5).

Chronic pulmonary infection would be demonstrated with positive culture from bronchoalveolar fluid lavage, sputum, oropharingeal swab, sinus aspirate. The presence of mucoid or nonmucoid phenotypes of *Pseudomonas aeruginosa* in the respiratory tract is highly suggestive for CF diagnosis but also persistent presence of *Staphilococcus aureus, Haemophilus influenzae* or *Burkholderia cepacia*, may support the diagnosis of CF. Some researchers speek about the protective effect of *Staphilococcus aureus* infection due to active competition between *S. aureus* and more harmful *Ps. aeruginosa* in the airways of CF patients.

Urogenital evaluation

Obstructive azoospermia is finding present in 98-99% of affected individuals, as result of absent vasa deferents. The vital prognosis of such patients is excellent, if this phenotype is unique presentation (5).

The diagnosis of CF patients with atypical clinical feature is not easy to be made. There are great difficulties confirming or rebutting the diagnosis in such patients with normal chloride sweat values, persistently in the normal range. CF is traditionally diagnosed by the presence of at least one major clinical feature (typical pulmonary or gastrointestinal manifestation or familiary history of CF associated with positive sweat test (> 60 mmol/l Cl^-) or demonstrating two CF genes mutation in the same patient.

Cystic fibrosis in adult patients

The adults patients with cystic fibrosis can be classified in two groups:

- one group has the diagnosis of CF from childhood and present in adolescent and youth life with disease complications.
- the second group are new patients, with mild or atypical CF who are diagnosed in youth or adult life.

We have to explain the clinical aspects of these two groups of patients, very different as evolution, median survival and quality of life (8).

CYSTIC FIBROSIS COMPLICATIONS IN THE ADULT LIFE

Pulmonary complications

The typical complication of adult CF are bronchiectasis, chronic infection with *Ps.aeruginosa*, or *S.aureus*, permanent deterioration in lung function (decline by 3-4% annually in patients with established pulmonary infection) and haemoptisia. Bronchial artery embolization is effective in acute control of recurrent or major haemoptysis in adult CF (9). Some researchers speak about the protective effect of *S.aureus* infection due to active competition between *S.aureus* and more harmful *Ps.aeruginosa* in the airways of patients with CF. Chronic infection and inflammation have the responsibility for morbidity and mortality in CF. The results of chronic pulmonary infection is not only local inflammatory process but also, the secondary systemic complications (10).

End stage lung disease causes about 80% of all death among patients with CF and so they are placed on the waiting list for lung transplantation (11).

Bilateral lung transplantation is actually considered a valuable optimal treatment for patients with end stage lung disease related to CF, and CF is the major reason for listing the patient on the heart-lung transplantation list (58% of cases). The indications for lung or heart-lung transplantation are those recorded by International Society for Heart and Lung Transplantation (ISHLT) Registry (12). The most important are: positive six minute walking test, FEV1 (forced expiratory volume in 1 minute) </=28%, Pa CO2 >45, pulmonary arterial hypertension (>35 mmHg), supplemental O^2 requirement. Guidelines for timing transplantation incorporate these data.

The risk of death awaiting lung transplantation is high for CF patients. At some transplant centres 15-40% of CF patients died before operation. A multivariant analyses revealed that three are significant independent risk factors for death on the waiting list for transplantation: a shorter six-minute walk distance, a higher arterial pulmonary hypertension and CF related diabet. The adverse effect of diabet is still under discussions (13).

Regarding the international experience with lung or heart-lung transplantation in CF patients, adults and children, we are able to presents the next data.

In 1998 in Lancet (14) was accepted that the clearest survival benefit for lung transplantation occurred in the CF patients group, according with the experience of International Society for Heart and Lung Transplantation Registry between 1992-1994.

The Report of Eurotransplant International Foundation (1999) considered that patients with CF had the highest chance of a successful lung transplantation and the type of end stage lung disease is a distinction factor for predicting survival after lung or heart-lung transplantation (15).

An other study published in 2002 reviewed the experience of a North Carolina Centre in lung transplant in CF patients in an over 10 years period. 123 CF patients have undergone 131 lung or lobar transplant procedures, including from live donors.

Survival at 1 year was 81%, at 5 years was 59%, and at 10 years 38%. Lobar transplant was associated with o poorer survival. CF patients colonized with *B. cepacia* have an worse outcome (16).

In 2002 was reported a Washington study (17).190 children (<18 years old), majority (121) 10-18 years old, underwent lung transplantation in St. Louis Hospital Missouri. CF represents 89 cases. The average age at the time of transplant was 9,5+/-5,9 years. Survival at 1 year was 77 %, and at 5 years was 55%. The most common cause of early death was bronchiolitis obliterans. Conclusion was that in children lung transplantation is a high risk treatment for end-stage pulmonary disease.

In a very recent study (2007) (18) who reflects the last United States experience in CF lung transplantation, is presented the effect of lung transplantation on the survival and quality of life in children with CF. The conclusion is uncertain (19). Improved survival was detected only in 5 of 248 patients who underwent lung transplantation. Between 1992-2002, from 31,394 patients with CF (117 CF centres in USA), 3364 CF patients were placed on the lung transplantation waiting list, 602 of these patients were younger than 18 years of age. 141 patients

died on the waiting list and 120 after undergoing transplantations (60% of them from primarily allograft rejection). The retrospective study showed that the patients who underwent lung transplantation in childhood did not have a significant estimated benefit.

CF related bone disease (CFRBD) is an important systemic complication and is very similar to osteoporosis, increasing bone fragility and susceptibility to fractures (Z score less -2 SD the age) (20). The prevalence of CFRBN is 30-38% in adults (21). It was attributed to systemic inflammation as a very important factor in the development of CFRBD. In adult patients with CF bone metabolism may be altered by multiple mechanisms such as abnormal calcium homeostasis, malnutrition, chronic inflammation and inactivity in the course of respiratory failure (10). In a group of CF patients (mean age of 32 years) Lang (22) found 32% osteopenia 29% osteoporosis. Screening of adult CF is recommended to evaluate the prevalence of osteoporosis, non- vertebral fractures, and change in bone mineral density. Bone disease in CF is probably multifactorial owing a combination of malnutrition (vitamine D and calcium), circulating cytokines (chronic inflammation) inadequate androgen and estrogen level and use of glucocorticoids for control of the pulmonary involvement. *Proinflammatory cytokines stimulate osteoclasts activity and increase bone resorbtion in CF adult patients.*

CF related diabetes (CFRD) develops on average around 24% of the cases at the age of 20, and increases to 74% at 30 years old CF patients, in individuals with long standing pancreatic exocrine insufficiency (exclusively) (23). CFTR dysfunction has as result precipitation of protein hyperconcentration and obstruction within pancreatic ducts. The subsequent parenchymal damage aids the development of diabet: ductal blocage and dilatations, fatty and fibrotic replacement of tissue, severe loss β cells, and significant amyloid deposition. There are some evidence between alteration in insulin secretion, independent of β cell distruction. Progressive distruction of pancreatic islet is the common explanation for CFDR. Pulmonary function may decline few years prior the development of this specific kind of diabet. Decline of patients' clinical status and worsening glucose intolerance is found in these CF patients. A new study (2006) (24) found that the subgroup of CF patients with diabetes had a poorer lung function (50% of mean % predicted FEV 1), poorer bone mineral density and a greater number of *Ps.aeruginosa* pulmonary exacerbations. CFRD differs in many ways from classical type I and type II diabetes. Ketoacidosis is very rare, microvascular complications are also rare (diabetic retinopathy is found in 16-23% of CFRD cases). CFRD is associated with poorer outcome in people with CF and female CF are particulary vulnerable to the impact of diabetes. Glucose intolerance is more common than before suspected in CF. CFRD is one insulinopenic condition and insulin treatment is the choice for the management, but also the alimentary intake.

Systemic vasculitis and CF arthropathy (10)
Recurrent episodes of distal purpuric vasculitic rash are related with systemic infection with immune complex deposition in skin capillaries.The cause of CF arthropathy and arthritis is not determined. The main cause is systemic inflammation secondary to lung inflammation and infection.

CF related liver disease (CFRLD)
Is found in 30% of adult CF, but a minority of patients develops cirrhosis (biliary cirrhosis Bodian) (10).

Distal intestinal obstruction syndrome in adults with CF (DIOS)
Among 171 CF adults (mean age 29 years), 15.8% reported 43 episodes of DIOS, all occurred in adulthood. All the cases had pancreatic insufficiency, the majority with severe genotype (25).

Pancreatitis
Only the patients with CF and pancreatic sufficiency (mild mutation) have an increased risk of developing recurrent acute pancreatitis. All patients with idiopathic chronic pancreatitis or acute recurrent pancreatitis should be screened for CFTR mutation (26).

Vitamine K deficiency in CF is common, and is particulary important in CF patients with liver disease or haemoptysis. Supplementation with vitamine K is very effective for the treatment in this cases. Vitamine K has also an important role in maintaining normal bone health and is correct to add vitamine K to all people with CF (10).

Cystic fibrosis patients diagnosed in adulthood (=> 16 years age), atypical CF

There is a new identified group of CF patients. The anthropometric parameters, respiratory and digestive clinical abnormalities, chest radiological exam, sputum bacteriology, respiratory function and genetic mutants are different as in the previous described group. The mean age of the group is higher, the patients had a higher weight, pancreatic sufficiency, rare hepatic disease, rare chronic bronchial colonization with *Ps.aeruginosa* (27). This individuals have two CF mutations but they do not develop the classical phenotype and may not have any symptoms at all. There are also cases who had one or few features traditionally associated with CF but in whom the sweat test are equivocal or negative. That is possible in a disease with more 1500 mutations recorded for the CFTR gene. These mutations have been classified into six classes: severe (I, II, III) and mild mutations (IV, V, VI). It has been an unexpected discovery to find a such wide range of clinical phenotype. The most atypical CF cases may present the clinical features as in the **Box 2** (28).

- sinopulmonary disease, pancreatic sufficiency and positive sweat test
- sinopulmonary disease, pancreatic sufficiency and normal sweat test
- disseminated brochiectasis and positive sweat test
- male infertiliy only
- severe sinusitis and congenital bilateral absence of the vasa deferens (CBAVD)
- chronic pancreatitis only
- allergic bronchopulmonary aspergillosis
- positive sweat test only
- no clinical features including normal sweat chloride

BOX 2. Range of clinical features in atypical CF patients (two mutation in CF gene)

The World Health Organization has recognized a category of CF patients with atypical phenotype, often with a single organ disease ("unique presentation" is the used term !) (29).

In contrast with chronic complications presented in the first part of the chapter of this compilation, unique presentation of CFTR-related disease in adults such congenital bilateral absence of the vasa deferents (CBAVD), chronic recurrent pancreatitis, chronic sinusites and nasal polyps can also be indicative for CF diagnosis. It can be suggestive for the idea that vasa deferents, pancreas and paranasal sinusis are the tissues very sensitive in decreasing CFTR function. Between 800 men with isolated CBAVD, 71% had two CFTR mutations (class IV or class V), that means CFTR function estimated to be about 10% of normal. We must conclude that the mesonephric and paramesonephric ducts are one of the most sensitive tissue to CFTR dysfunction.

An interesting relation between mutation of cystic fibrosis gene and idiopathic pancreatitis was described by Cohn in 1998 (30). These data suggest that pancreas is also particularly sensitive to CFTR dysfunction. In a group of 27 patients with chronic idiopathic pancreatitis,37% of them had at least one CFTR mutation and 11 % had two CFTR gene mutations. The decrease of CFTR levels to 10% of functional normal level induce o high risk for pancreatitis and a low level CFTR activity (<1%), leading to exocrine pancreatic insufficiency, as in classical type of CF phenotype, is not associated with recurrent pancreatitis.

Moderate decrease of CFTR function induces also isolated chronic sinusitis and nasal polyposis, and Wang (31) found an increased number of CF mutations in such cases. The same considerations for the patients with unusual presentation as allergic bronchopulmonary aspergillosis (32) or idiopathic diffuse bronchiectasis.

Transition from pediatric to adult care

What will be the best way for transferring known paediatric CF patients to adult medical assistance? This problem is not easy to be solved anywhere, but is a great discuss in our country. Cystic Fibrosis Centres joining clinics for children and adults with this disease will be the best way for medical assistance of CF patients (33).

The transfer to the adult centre with a medical letter is to simple in such a complicated disease with medical, social, genetic, psychological, and financial implications. It will be not cruel to transfer a very sick patient who will die in the next months or in the next year in a new, unfamiliar medical team? The methods of transfer must be flexible and empathic. This problem is not yet solved and is in debate. Medical Insurance has its rules and financial implications are important (33).

We must admit that not all adult pneumologyst from our country are familiar with complications in CF adults and is correct to offer to

such patients a multidisciplinary team, well informed to assist and to provide a good compliance to the complex treatment of this special disease. Some years from now, Romanian doctors will be put face to face with this very complicated medical situation, because CF is not at all only a pediatric disease as in the last ten years period.

Since 1990, in our country is very active the "Romanian Association of Mucoviscidose" (AMR-Asociatia Romana de Mucoviscidoza), organized in Timisoara, under the supervision of Prof. Dr. Ioan Popa. Since 2001 cystic fibrosis is in attention of Health Ministry of Romania with a special programme and special financial facilities (34). In November 2004 Romanian Society of Pneumology started the activity of a new working group "Cystic fibrosis in adults" (35). It is also not surprising that in 2003 the adults CF patients joined into "Association of Adults with Cystic Fibrosis" in Focsani, Vrancea County (34).

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