EPIDEMIOLOGICAL EVALUATION REGARDING THE ROLE OF CYSTIC FIBROSIS AS A RISK FACTOR FOR CHILD MALNUTRITION

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EPIDEMIOLOGICAL EVALUATION REGARDING THE ROLE OF CYSTIC FIBROSIS AS A RISK FACTOR FOR CHILD MALNUTRITION (Abstract): Cystic fibrosis (CF) is the most common monogenic autosomal recessive disorder with progressive chronic evolution which is potentially lethal. Poor growth is a characteristic of children suffering from cystic fibrosis. A poor nutritional status is an independent risk factor for inadequate survival in cystic fibrosis and is associated with disease complications. The appropriate nutritional management is an important part of the treatment so that the patient with cystic fibrosis can achieve normal growth and development and maintain the best possible health status. A balanced diet supplemented with snacks high in fat and calories is necessary to increase the caloric intake in children with cystic fibrosis. Children with cystic fibrosis have higher caloric needs than healthy children of the same age and sex. Malnutrition in CF is multifactorial. Cystic fibrosis is a complex multisystem disorder affecting mainly the gastrointestinal tract and respiratory system. In the past, malnutrition was an inevitable consequence of disease progression, leading to poor growth, impaired respiratory muscle function, decreased exercise tolerance and immunological impairment. A positive association between body weight and height and survival has been widely reported. The energy requirements of patients with CF vary widely and generally increase with age and disease severity. Cystic fibrosis remains a paediatric disorder which is often underdiagnosed but which, if therapeutically managed properly (by means of drug therapy as well as by appropriate physiotherapy techniques), can lead to improved quality of life and, thus, to a bigger life expectancy. Keywords: CYSTIC FIBROSIS, MALNUTRITION, CHILDREN, NUTRITIONAL STATUS

Cystic fibrosis (CF) is the most common lethal inherited genetic condition affecting the Caucasian population. One in twenty-five individuals in the UK are carriers of the gene and the condition is inherited in an autosomal recessive manner, which results in an incidence of one in approximately 2,500 (1, 2). CF is less
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common in Oriental and black populations. It is estimated that 8500 individuals in the UK have CF (2, 3). Cystic fibrosis is one of the genetic disorders commonly seen in the paediatric pathology. It is an autosomal recessive disease whose incidence in Caucasians is $1 : 2000 – 1 : 2500$ in new-borns with a heterozygote frequency from 1 to 25 individuals. The frequency of the disease in the black race is $1/17,000$ live new-borns, in mongoloids is $1/100,000$ live new-borns and in the Republic of Moldova is $1:1,000-1:1,200$ (4).

The study by Farrel combines a variety of methods to determine the prevalence of cystic fibrosis in the European Union. The results of literature reviews, surveys, and registry analyses revealed a mean prevalence of $0.737/10,000$ in the 27 European Union countries, which is similar to the value of $0.797$ in the United States, and only one outlier, namely the Republic of Ireland at 2.98 (5).

Cystic fibrosis is a complex multisystem disorder affecting mainly the gastrointestinal tract and respiratory system. Intestinal malabsorption occurs in approximately 90% of patients. In the past, malnutrition was an inevitable consequence of disease progression, leading to poor growth, impaired respiratory muscle function, decreased exercise tolerance and immunological impairment (3, 4). A positive association between body weight and height and survival has been widely reported. The energy requirements of patients with CF vary widely and generally increase with age and disease severity. For many young adults requirements will be 120–150% of the age-related estimated average requirement. To meet these energy needs patients are encouraged to eat a high-fat high-energy diet with appropriate pancreatic enzyme supplements. Many patients are unable to achieve an adequate intake as a result of a variety of factors including chronic poor appetite, infection-related anorexia, gastro-oesophageal reflux and abdominal pain. Oral energy supplements and enteral tube feeding are widely used.

Improvements in respiratory and nutritional management have led to an impressive increase in life expectancy for individuals with CF. CF, which was once considered a life-threatening disease of childhood is now considered a life-limiting disease of adulthood rather than a terminal childhood illness (1, 2). The median predicted survival is now 35 years and there are now more individuals with CF aged>16 years in the UK than <16 years (2, 3).

Malnutrition in CF is multifactorial. There has been evidence of strong links between improved nutritional status and survival for >30 years. A study that compared patients of two North American CF clinics, one of which treated patients with the then traditional low-fat diet and the second treated patients with a high-fat diet, has found the patients treated with a high-fat diet to be taller and heavier (2, 6). Importantly, this improvement in nutritional status was deemed to be the main reason for a 9-year survival advantage. Since this early study a poor nutritional status has been shown to independently contribute to prognosis (2, 7, 8, 9). Growth failure and wasting are both highly significant independent prognostic indicators of survival. In patients with height < 5th percentile at age 5 years risk of death is significantly increased; this increased risk persists at age 7 years (2, 7, 8). Patients with >85% ideal body weight have a better prognosis at 5 years of age than those with < 85% ideal body weight (2,
There is also a positive association between nutritional status and lung function. Conversely, malnutrition results in poor growth, impaired respiratory muscle function, decreased exercise tolerance and immunological impairment that results in increased susceptibility to infections (2, 10).

The aims of the nutritional management of CF are that children and adults should be adequately nourished, have normal weight, height, body composition and pubertal development and have optimal vitamin, antioxidant and essential fatty acid status. With increased life expectancy there are constantly new nutritional challenges emerging (2, 11). Pancreatic insufficiency usually develops in infancy and approximately 92% of individuals with CF are pancreatic insufficient by 1 year of age. Approximately 95% of patients in northern Europe will eventually be pancreatic insufficient as a result of an inadequacy of their own pancreatic enzyme secretions (2, 12).

With the introduction of newborn screening within the UK and the early identification of milder mutations the percentage of patients with pancreatic sufficiency may increase. In individuals with CF malabsorption is secondary to pancreatic insufficiency. In patients with CF a host of other factors contribute to malabsorption, including a deficiency of pancreatic bicarbonate that reduces duodenal pH an increased loss of bile salts in the stool, an imbalance in the type of bile salts produced, abnormal ion transfer in the gut as a result of the basic defect in the CFTR (Cystic fibrosis transmembrane conductance regulator) impaired mucosal uptake and transport of long-chain fatty acid across the gut wall and altered gut motility (2, 13, 14, 15).

Growth failure is a common presentation of patients with pancreatic insufficient cystic fibrosis. However, full blown kwashiorkor is extremely rare. Cystic fibrosis is also considered to be rare in the South Asian population.
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Protein energy malnutrition results in a group of disorders, including marasmus and kwashiorkor. Kwashiorkor, caused by decreased protein availability, results in oedema, muscle wasting, skin and hair changes, irritability, and anorexia (16, 17). In developing countries it occurs mainly as a result of primary protein calorie malnutrition. However, in developed countries, it usually arises as a result of chronic disease rather than primary nutritional deprivation (16, 18). Cystic fibrosis is frequently presents in infancy with failure to thrive. CF is the most common inherited autosomal recessive disease in the Caucasian population, but is considered rare in the Indian subcontinent population (16, 19) and in North Africa.

Epidemiological aspects. According to the National Centre for Cystic fibrosis in Timisoara (where a pilot study was conducted in the 2nd Paediatric Clinic of Timisoara in the ‘80s, on a number of 10,000 live births), the incidence of the disease in Romania is 1 : 2054 newborns. In terms of survival rate, it can be noted that, in Western Europe, life expectancy was situated around the age of 17-18 in the 70s, in 2005 it increased to about 32, and, at present, due to scientific progress, the patients who were the newborns with CF at the beginning of the 90s can survive well over 40 years of age (4).

The gene for cystic fibrosis is located on the long arm of the 7th chromosome, which encodes the regulatory protein of the cystic fibrosis trans membrane conductance regulator (fig. 1). The gene can undergo multiple gene mutations (about 1300) and it may have more than 300 polymorphic variants, among which the most commonly found in Europe is the Δ F 508 CFTR mutation. (20) F508del accounts for 70% of the cases worldwide3 and for 52–54% of CF cases in Greece. Frequencies vary from a maximum of 100% in the isolated Faroe Islands of Denmark, to a minimum of about 20% in Turkey.

In the last two decades, CF has been increasingly diagnosed in Latin America, the Middle East, and populations derived from the Indian subcontinent that have emigrated to Western Europe, thus implying the presence of CF in significant numbers among the citizens of India and Pakistan who have remained in their homelands (21).

In South Africa alone, it is expected that over 110 African CF babies are born annually. With an overall infant mortality rate of 52 per 1000, CF would only make up between 0.12 and 2.5% of the total.

In India, the CF incidence is estimated to be 1 in 40,000 to 100,000 live births. In Japan, the estimated incidence is 1 in 100,000 to 350,000 live births, but is likely to be higher than anticipated.

The incidence of CF in the Middle East varies according to the ethnic background and the degree of consanguinity. Consanguinity is claimed to be about 65% in the Arab world. Estimates range from 1 in 2,560 to 1 in 15,876 (20, 22). A few mutations in the Middle East are shared with many other regions in the world, i.e. F508del, N1303K, W1282X and 3120+1G >A.

In Uruguay, Ecuador, Colombia, Venezuela and Brazil, the presence of descendants of African origin is important, although its percentage does not exceed 10%. The incidence of CF ranges respectively from 1/3,900 to 1/8,500 neonates in Cuba and Mexico (23).

The incidence of CF, based on derivative populations, is about 1 in 3,500 in North America.
There are no accurate CF prevalence figures for northern African countries bordering the Mediterranean, although small CFTR mutation detection studies have been done in Algeria and Tunisia, showing largely European mutations such as F508del, G542X and N1303K, albeit at different frequencies. Some unique mutations were identified in these populations (20).

Reports from South Africa show the presence of CF in persons of pure African descent, thus demonstrating that the earlier observation of the presence of CFTR mutations in African Americans was not simply due to a mixture of European genes. A small proportion of CF patients (<3%) remains undiagnosed until adulthood (24, 25).

CF affects both females and males in all racial and ethnic groups, but it is common among Native American and Latino populations, particularly in areas of Pueblo and Zuni (Colorado). In France, for example, there is a very high incidence of CF in Northwest Brittany and a lower incidence in the South Ethnic. Specific mutations are observed in some populations such as the Nordic mutation 394delTT, the 3905insT mutation in Switzerland, the R1162X mutation in Northeast Italy, and the Eastern Slavic CFTRdele2, 3 (21kb) mutation (20, 26).

**Therapeutic aspects.** Malnutrition may be aggravated by the presence of anorexia, resulting from gastro-oesophageal reflux and/or cough, respiratory infections and chronic psychosocial stress. The role of dietary treatment is to improve or maintain adequate nutritional status of the patient and break the vicious malnutrition-infection cycle (27). Despite CF being the most common lethal inherited genetic condition affecting the Caucasian population, it remains relatively rare, with approximately 8,500 individuals with CF in the UK (2, 3). Nevertheless, increasing numbers reach adulthood and go through the transitional process. Ensuring a seamless transfer is one of the greatest challenges facing both children’s and adult services. Poor growth is a characteristic of children suffering from cystic fibrosis. A poor nutritional status is an independent risk factor for inadequate survival in cystic fibrosis and is associated with disease complications (28).

The appropriate nutritional management is an important part of the treatment so that the patient with cystic fibrosis can achieve normal growth and development and maintain the best possible health status.

A balanced diet supplemented with snacks high in fat and calories is necessary to increase the caloric intake in children with cystic fibrosis. Children with cystic fibrosis have higher caloric needs than healthy children of the same age and sex for the following reasons: higher energy consumption during respiration; energy use in fighting fevers and infections; few energy-producing foods are properly digested and absorbed into the body even if the treatment is optimal. In patients with cystic fibrosis what is recommended is the high calorie and high protein diets, which are rich in fats, and have a normal amount of carbohydrates as well as supplements of fat-soluble vitamins. The hyper-caloric diet can be achieved by: spontaneous intake, nutritional supplements (orally, by nasogastric gastrostomy tube) and parenteral nutrition (4, 16).

The recommended calorie needs is: 1,700–1,950 calories/day for preschool children; 2,300–3,000 calories/day for school children; 2,900–4,500 calories/day for adolescents. Dietary supplements are recom-
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Recommended to malnourished patients with cystic fibrosis and to patients with suboptimal dietary intake despite all the measures taken. Consumption is recommended after meals or at bedtime. Dietary supplements available for patients with cystic fibrosis are: Frebini (special, energy enriched food for children between 1-12 years old), Nutren junior (especially designed for a nutritionally balanced diet and suitable for children between 1-10 years old), Nutridrink (a ready-made nutritional, liquid supplement with milk flavour and other 8 different flavours for increased compliance), Infatrini (a high-energy formula in a small volume, with an optimal ratio between macronutrients and micronutrients, and with prebiotics), Cystilac (nutritionally complete special formula with prebiotic blend).

CONCLUSIONS
Cystic fibrosis remains a paediatric disorder which is often under diagnosed but which, if is therapeutically managed properly (by means of drug therapy as well as by appropriate physiotherapy techniques), can lead to improved quality of life and, thus, to a bigger life expectancy.

REFERENCES

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16. ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1719610/***
21. ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1867536/***

**HP1404 - A NEW ANTIMICROBIAL PEPTIDE**

Antimicrobial peptides are active against a variety of microbes including antibiotics resistant strains. In a study by Li Z *et al.* a novel cationic antimicrobial peptide Hp1404 was identified from the scorpion *Heterometrus petersii*. It is an amphipathic α-helical peptide with inhibitory activity against gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*. At low concentration, it is able to penetrate the membrane of *S. aureus*, and at high concentration it disrupts the membrane directly. The bacterium does not develop drug resistance after multiple treatments at sub MIC concentration. Hp1404 has low toxicity to mammalian cells and balb-c mice and it can improve the survival rate of the MRSA infected balb-c mice in the peritonitis model. In conclusion, Hp1404 can be considered to have potential applications as an antibacterial agent (Li Z, Xu X, Meng Let al. Hp1404, a New Antimicrobial Peptide from the Scorpion Heterometrus petersii. *PLoS One.* 2014;9(5):e97539. doi: 10.1371/journal.pone.0097539).

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