

## OSTEO-ARTICULAR DISORDER IN CHILDREN WITH CYSTIC FIBROSIS

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### ABSTRACT

Osteo-articular disorder in cystic fibrosis is considered a common complication of this pathology. The most efficient strategies used for bone health maintenance in patients with cystic fibrosis are early recognition, prevention and correct treatment. The purpose of this study was the clinical and paraclinical evaluation of patients hospitalized in the 3<sup>rd</sup> Clinic of Pediatrics, "Sf. Maria" Children's Emergency Hospital Iasi, diagnosed with cystic fibrosis that exhibited also symptoms of osteo-articular manifestation. The results from this study support the idea that the association of treatment, calcium, multimineral supplements with appropriate hygienic-dietary regimen and with the background therapy of the disease can contribute significantly to better health and wellbeing. Also, non-compliance to treatment among patients and their families significantly contributes to early installation of the complications, including the osteo-articular ones (even from the age of 6 years).

**Keywords:** cystic fibrosis, osteo-articular complication, child

### INTRODUCTION

The cystic fibrosis (CF) is the most frequent monogenic autosomal recessive disorder found in Caucasian populations, characterized by clinical pleomorphism and progressive chronic evolution, potentially lethal (5).

The osteo-articular complication was first described in 1979 and in present it is considered a common complication in which the quantity and quality of the bone mineral is diminished. The most efficient strategies used for bone health maintenance in patients with cystic fibrosis are early recognition, prevention and correct treatment (2).

### OBJECTIVES

The identification, clinical and paraclinical evaluation and the response to the specific treatment of the osteo-articular manifestations that accompany CF.

### MATERIALS AND METHODS

A retrospective study was performed on a lot of 43 patients aged between 2 days and 18 years diagnosed with CF in the 3<sup>rd</sup> Clinic of Pediatrics, "Sf. Maria" Children Emergency Hospital Iasi.

The study protocol included:

- the criteria on which the CF diagnostic was based.
- the medical history, i.e.: age, sex, anthropometric indices-height, weight.
- the clinical and biological evolution resulting from the laboratory tests.
- the causes of the osteo-articular complications.
- the clinical symptoms (the severity of the malabsorption, respiratory symptoms, symptoms of osteo-articular disorder and the onset age).
- the correlation between the osteo-articular manifestations and the frequency of the respiratory infections.

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- the investigation of the bone disorder: calcium, phosphorus, alkaline phosphatase, serum 25-hydroxy-vitamin D concentration, osteodensitometry, long-bone radiographs, thoracic spine radiograph or fist radiography.
- investigations needed to rule out other forms of arthritis,
- the treatment (background therapy for CF, corticotherapy, anti-inflammatory, vitamin D) and treatment adherence.
- the evaluation of the response to therapy.
- the education and conciliation of the patients and their families.

## RESULTS

The age distribution of the patients from the lot studied showed that the majority of patients with CF were between 9-18 years of age (51%) and only 5% were infants. Regarding gender distribution, a higher frequency of the disease was found in boys (67%).

Bone manifestations were present at 7 from the 43 patients: initial signs were characteristic to rickets, then demineralization of the bone progressed up to osteoporosis in advanced stages. Also, postural defects such as dorsal kyphosis, asthenic chest, lordosis, painful muscular contractures, monoarthritis/oligoarthritis and digital clubbing were identified, Table 1.

**TABLE 1.** Osteo-articular manifestations in the studied lot

Signs and symptoms of the osteo-articular disorder	Number of cases	Percentage
Kyphoscoliosis	5	12%
Painful muscular contractures	5	12%
Monoarthritis	1	2%
Oligoarthritis	1	2%
Limb paresthesia	3	8%
Tooth decay	6	15%
Rosary rib	5	13%
Breastbone in hull	3	8%
Chest flared at the bottom	2	5%
Micrognathia	1	3%
Craniofacial dysmorphism	2	5%

The articular manifestations varied from mild arthralgia (5 cases) to arthritis (2 cases), usually with symmetric distribution (5 cases) that interested the following articulations: ankles – 2 cases, knee – 3 cases, fist – 1 case, elbow – 1 case, metacarpophalangeal – 2 cases. The onset was insidious, like a dull pain (5 cases) or an episodic joint pain. The symptoms recur when the respiratory function deteriorates (2 cases). In these 2 cases we

observed the aggravation of the symptoms during the exacerbation of the pulmonary infection with *Pseudomonas aeruginosa*. Five patients from the lot studied presented digital clubbing, characteristic sign of OAHP.

The osteo-articular manifestations were debuted after 5-10 years from the diagnostic of CF.

The analysis of nutritional status showed that 14 patients exhibited different degrees of dystrophy (3 cases – dystrophy 1<sup>st</sup> degree, 5 cases- dystrophy 2<sup>nd</sup> degree, 6 cases– dystrophy 3<sup>rd</sup> degree) and 23 cases – ponderal hypotrophy. Seven patients with CF and osteo-articular manifestations presented the alteration of nutritional status and 4 of them presented signs of severe malabsorption.

The causes of vitamin D deficiency were malabsorption, insufficient intake and insufficient exposure to the sun, Table 2.

**TABLE 2.** The causes of vitamin D deficiency in the studied lot

The cause of vitamin D deficiency	Number of cases	Percentage
Malabsorption	4	44%
Insufficient intake	3	33%
Insufficient exposure to the sun	2	22%

The analysis of the serum levels of calcium, phosphorus and alkaline phosphatase at all the patients with CF showed: hypocalcemia at 34% of patients, hypophosphatemia at 31% of patients and increase of alkaline phosphatase at 26% of the patients.

The level of vitamin D was determined at 29 from the 43 patients (the optimal serum concentration of 25-hydroxivitamin D is between 30-50 ng/mL), Table 3.

**TABLE 3.** Serum concentration of 25- hydroxivitamin D in the studied lot

Serum concentration of 25-hydroxivitamin D	Number of cases	Percentage
Under 10 ng/mL	1	3%
10-20 ng/mL	8	28%
20-100 ng/mL	20	69%

The measurement of the bone density was performed using osteodensitometry. This is an accurate method for the diagnose of osteoporosis, and also an accurate estimator for the risk of fractures. Table 4 presents the results of the studied lot.

All 7 patients with osteo-articular manifestations showed diminished levels of Z-score: 4 patients – osteopenia, 3 patients – osteoporosis. The 3 patients with osteoporosis presented severe osteo-

**TABLE 4.** The modifications of osteodensitometry in the studied lot

Results of osteodensitometry	Number of cases	Percentage
Normal	10	56%
Osteopenia (score Z between -1 and -2,5)	6	33%
Osteopenia (score Z $\geq$ -2,5)	3	11%

articular symptomatology and increased levels of alkaline phosphatase and decreased levels of calcium and phosphorus in comparison with the patients with osteopenia. Table 5 indicates the radiologic modifications of the lot studied.

**TABLE 5.** The radiologic modification identified in the studied lot

Radiologic modification	Number of cases	Percentage
Periostitis of distal ends of long bones	5	18%
Metaphyses of long bones, dilated appearance, in cup	6	22%
Metaphyseal concave line with irregular edge	6	21%
Lateral spikes	4	14%
Delay in the ossification of the nucleus	4	14%
Kyphosis	3	11%

The 2 cases with arthritis showed multiple radiologic modifications: metaphyses of long bones, dilated appearance, in cup, delay in the ossification of the nucleus and lateral spikes. All patients had radiologic modifications, including patients with cystic fibrosis, apparently normal, without obvious clinic osteo-articular manifestations.

The treatment of the bone disorder targeted first the correction of malabsorption and malnutrition, the supplementation with vitamins, minerals and oligo-elements. (4,16,17)

The medical treatment included:

1. substitution treatment with pancreatic enzymes (Kreon®).
2. treatment of pulmonary infections according to the antibiogram.
3. treatment of the vitamin D deficiency, of the rickets, osteopenia or osteoporosis by:
  - administration of supplements with vitamin D, in the form of drops/tablets containing cholecalciferol or in injectable form for the patients with severe malabsorption.
  - administration of supplements with calcium in association with vitamin D or in the form of multimineral complexes (Ca + Mg + Zn + vitamin D) 5-10 ml x 2-3 times per day.

The OAHP treatment of the patients from the studied lot consisted in rest, administration of non-steroidal anti-inflammatory (Acetaminophen, Ibuprofen 20-40 mg/kg/day, corticotherapy, 7 days), simultaneously with the treatment of the respiratory affection (18).

After establishing the diagnostic and the establishment of the therapeutic measurements, the evolution of the patients with osteo-articular disorder was:

- persistency of a certain degree of osteopenia going up to severe osteoporosis in the cases of persistent malabsorption.
- exacerbation of AFC and OAHP associated with the deterioration of the pulmonary function in one case.

It has been also made the prophylaxis of exacerbations and relapses

## DISCUSSIONS

The arthritis from CF was first described by Ansell and Newman. The main types of arthritis that appear in CF are arthropathy from cystic fibrosis (ACF) and hypertrophic pulmonary osteoarthropathy (OAHP), which represent important causes of morbidity (13,14).

The arthropathy from cystic fibrosis (ACF) – the most frequent form of arthritis from CF, clinically manifested as a recurrent asymmetric mono- or polyarthritis that affects especially the knees (3). The prevalence of ACF is between 2-8,5%, 13,6 years old being the average age of onset of the illness, but this could be overrated because of the possibility of undiagnosed cases (6). There is no formal definition of the arthritis from CF, but this disease has distinct symptoms such as: recurrent episodes of joint pain and tumefaction, especially at the knee and ankle joints, sensitivity and movement limitation, which are disabling for the patient. The pain develops in 12-24 hours and lasts between 5-7 days and the symptoms may disappear completely between the exacerbations (8).

Hypertrophic pulmonary osteoarthropathy or Bamberger-Marie osteoarthropathy is less frequent than ACF, with a prevalence between 2-7%. It mainly affects males (12). The clinic symptoms include: digital clubbing (deformation – “drummer fingers”), bone and articular manifestations and cutaneous manifestations (15,22).

In our study the prevalence of the joint manifestations was of 16.27%. The disease was more frequent in boys, confirming the dates from the literature. However, in the medical literature the male

gender is considered a more favorable factor than the female gender.

Several studies support the idea that the patients with cystic fibrosis have a decreased risk to damage the balance of calcium that affects bone health, the finding being confirmed also by this study (34%) (1). The recommended calcium intake varies between 500 mg/day for patients aged between 1-3 years, 800 mg/day for children between 4-8 years and 100 mg/day for children between 9-18 years (7,9), this intake will increase the absorption of calcium.

It is recommended, at least one time per year, to determinate the serum concentrations of vitamin D and calcium. The ideal time is at the end of the winter because the values of vitamin D vary according to the season (20,11). If this is not possible at least the interpretation of the results should be made depending on the season when the analyses was taken, the degree of sun exposure and if the patient uses sunscreen (10).

The radiography had an important role in the evaluation of the osteo-articular disorder, considering the fact that radiologic signs appear early, they are present in the state in which clinical signs are

rare or absent and they are considered pathognomonic (21).

The exacerbations of the pulmonary infections must be treated rapidly in order to minimize the adverse effects of the inflammation on the bone.

## CONCLUSIONS

The treatment with vitamin D, calcium and multi-mineral supplements associated with hygiene-dietary regimen and the background therapy of the disease have significantly contributed in some cases to a better health condition, determining a better quality of life and an improvement in the osteo-articular disorder.

Also, in some cases the patient's non-compliance with the treatment, the interruption of the therapeutic schedule, the failure to respect the recommendations contribute to the appearance of early complications, especially the osteo-articular ones (even from the age of 6).

Osteodensitometry must be performed for all the patients with CF starting at the age of 10, once a year or every 1-3 years, but at least one test until 18 years (23).

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