

ABSTRACT

Fibrodysplasia ossificans progressive (FOP) is a very rare, genetically determined, severe disease leading to progressive skeletal ossification and premature death.

The clinical course is characterized by the occurrence of exacerbation periods, so-called flares. During this period, the subcutaneous tissue swells in the form of tumors, which progressively ossify forming heterotopic bones, leading to reduced mobility of affected body region. As a result, patients become disabled physically and prematurely die, because of respiratory failure. The correct diagnosis of the disease is extremely difficult. Cancers are often misdiagnosed and the performed surgical resection results

in an increased ossification. The basis for making the correct diagnosis is finding valgus of toes, and confirming diagnosis with positive result of genetic testing. Currently, effective treatment for patients with FOP, which could prevent the formation of new ossifications does not exist. In the process of ossification, an important element is

the initial phase - the inflammatory process. In order to stop the inflammatory process, glucocorticoids, non-steroidal anti-inflammatory drugs, leukotrienes' inhibitors are used.

Focusing treatment on the initial stage of HO development, i.e. inflammation, can result in numerous benefits, stopping or slowing down the course of the disease. Increasing availability of biological drugs is the significant opportunity for patients with FOP,

and the use of biological therapy may be effective in inhibiting HO formation

and be beneficial to existing presently options.

The aim of this study was to perform the first in Poland analysis of the population of children with FOP. What is more, the research project also aims to assess the serum concentrations of biologically active mediators, which are involved in the induction of inflammation and local tissue destruction regarding current clinical activity and stage of the disease.

The entire Polish population of children with FOP participated in the research. The examined group consisted of 9 patients, including 8 girls and 1 boy. Medical history was carried out using surveys. The FOP advancement level was assessed by using the Katz scale, CAJIS and the clinical staging of FOP. The blood sample taken from children to assess the levels of biologically active substances, cytokines, chemokines and metalloproteinases was assessed by using the multi-parameter Luminex method. Statistical analysis was performed using appropriately selected methods according to the distribution of variables.

In the Polish population of children with FOP, female patients were in majority and it differs from data from other countries. An important observation is confirmation of a significant delay in correct diagnosis despite pathognomic symptoms. Although this period seems shorter than in other countries, it still does a significant proportion of patients underwent surgery that exacerbated the symptoms of the disease.

The very interesting observation is confirmation of the increased concentration of cathepsin S. A relationship between serum cathepsin S concentration and disease severity was demonstrated. A statistically significant and strong correlation was noticed between serum cathepsin S concentration and the score obtained during the patient's assessment

according to the Katz and CAJIS scale. A statistically significant negative and very strong correlation was found between the concentrations cathepsin S, and bone mineral content. The concentration distribution of the studied chemokines was relatively homogeneous. The next statistically significant correlation was observed between the score in a Katz scale, and myeloperoxidase level. Furthermore, a relationship between serum concentration of MMP-2 and results obtained during evaluation, using the CAJIS scale, was demonstrated. On the other hand, serum concentration FGF1 strongly positively correlated with the value of mineral bone density. Obtained results and established relationship requires further complex research.

Conclusions:

1. Despite the occurrence of a pathognomic symptom, which is a congenital defect of toes and typical clinical symptoms, making the correct diagnosis poses difficulties, hence there is a need to spread knowledge about FOP among medical practitioners.
2. Performing a patient assessment with the use of Katz's scale, CAJIS scale and clinical staging allows to monitor disease progression and treatment effectiveness during follow-up visits.
3. A different response to GKS treatment may indicate a clinical variety of patients with FOP.
4. The obtained BMC value of patients with FOP, may be an objective indicator of the physical activity of patients.
5. Low serum cytokines of tested children, are probably associated with the prolonged use of anti-inflammatory treatment.

6. Correlation between serum concentration of MMP-2 and score in CAJIS or Katz scales, are probably associated with ongoing bone remodeling during clinical remission.
7. Correlation between serum concentration MPO, and a score in a CAJIS scale, may be associated with a persistent, active, chronic inflammatory process, without the clinical manifestation of exacerbation.
8. Increased level of cathepsin S in the serum, and its correlation with disease activity, obtained in the CAJIS and Katz scale, may be related to formation of HO.
9. Our study suggests the presence of chronic inflammation, hence chronic anti-inflammatory and immunosuppressive therapy may be beneficial in the treatment of FOP.
10. A long-term study with the participation of control group, untreated patients, and patients in the acute phase of the disease is needed.