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CASUISTIC PAPER

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Fibrodysplasia Ossificans Progressiva – a presentation of cases and literature review

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ABSTRACT

Introduction. Fibrodysplasia ossificans progressiva (FOP) is a very rare inherited disease leading to progressive ectopic ossification of muscle and soft tissue and resulting in severe immobilisation and premature death. The mutations in *ACVR1* gene that codes the 1A activin receptor which belongs to the family of bone morphogenetic proteins (BMPs) are leading to clinical symptoms.

Aim. In this raport we present 3 cases of paediatric FOP patients presenting varied clinical course of disease.

Description of the cases.

Case 1. A girl, currently 5 years old, was hospitalised for the first time at the age of 10 months with suspicion of a hyperplastic lesion of the left lumbar area. The time period between the first symptom, i.e. subcutaneous oedema, and the correct diagnosis was about 8 months. The symptom with key importance for the diagnosis was congenital deformities of the thumbs and big toes.

Case 2. A 6-year-old girl with a congenital hallux valgus in both feet, a small painless nodular lesion in the area of the distal metaphysis of the femur, limiting the flexion of the knee joint, was diagnosed in the third month of life.

Case 3. A three-year-old girl was diagnosed with congenital defects i.e. hallux valgus of both feet. The first symptoms of the disease occurred during her 14th month when an oedema of the subcutaneous tissue of the nape area was observed.

Conclusion. Until recently, there has been no efficient therapy which could slow down the natural course of the disease and currently the disease is treated as incurable. Of key importance from the perspective of patients is early diagnosis and, more importantly, preventing traumas, surgical procedures, intramuscular injections, sparing dental treatment and ensuring avoidance of airway tract infections.

Keywords. clinical course, diagnostic difficulties, ectopic ossification, fibrodysplasia ossificans progressiva

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Introduction

Fibrodysplasia ossificans progressiva (FOP) is a very rare genetic disease leading to progressive ectopic ossification of muscle and soft tissue. This disease occurs irrespective of sex, race or geographical latitude in 1 per 2 million live births.[1,2] The first case was described more than 250 years ago by a London physician, John Freke, in a report from 1740. The next report that focused on FOP was authored by Jules Rosenstirn from San Francisco in 1918.[1]

Fibrodysplasia ossificans progressiva is inherited in an autosomal dominant manner with a low gene penetration. This mutation, discovered in 2006, occurs in the *ACVR1* gene that codes the 1A activin receptor which belongs to the family of bone morphogenetic proteins (BMPs). The 617G> A (R206H) mutation of the 1A activin receptor gene (*ACVR1, ALK2*) is present in the majority of FOP patients and is regarded as disease specific. There have been incidental reports of the mutation of the *de novo* type e.g. in *ACVR* 1,067 G> A gene (G356D). The 1A activin receptor is present in all body tissues including muscle and chondral tissue in which it helps to control development and growth of bones and muscles and ossification of chondral elements.[2, 3] A consequence of this mutation is excess BMP-4 protein produced in white blood cells that is responsible for normal osteogenesis in the fetal stage. Additionally, a low level of the BMP-4 antagonist noggin, which inhibits bone growth and development, is noticed in patients affected with the disease.[4,5] Currently, intensive studies are concerned with the following: an examination of the BMP-signalling pathway, a search for activin receptor inhibitioning proteins, evaluation of toll-like receptor-bone morphogenetic protein (TLR-BMP) signalling, the role of the innate immune system, including monocytes, macrophages, mast cells, natural killer (NK) and dendritic cells as well as T and B lymphocytes and proinflammatory cytokines. The research question posed in these studies is whether FOP is an autoinflammatory or autoimmune disease. The answer to this question will determine the search for efficient treatment methods.[6-8]

The main clinical manifestation of this disease is ectopic ossifications which usually occur in a specific sequence moving vertically downwards in the body, gradually leading to patient immobillity in their 2-3rd decade of life. The outcome of this process is premature death at approximately 40 years of age. Death occurs as a result of circulatory and respiratory insufficiency, frequently complicated with pneumonia.[10,11]

There are no specific tests allowing for a quick diagnosis, apart from the determination of a typical genetic mutation. The symptoms which might be helpful in a correct diagnosis are congenital defects of the toes and fingers.

Description of the cases

Case 1.

A girl, currently 5 years old, was hospitalised for the first time at the age of 10 months with suspicion of a hyperplastic lesion of the left lumbar area. The results of diagnostic laboratory tests were inconclusive. The CT and MRI examinations revealed a well-defined abnormal soft-tissue structure adjacent to the dorsal muscles, measuring 11×94×123 mm, not exceeding the dorsal fascia and not penetrating the spinal canal. The lesion was qualified for surgical resection. The findings from the physical examinations performed one day before the surgery revealed significant growth of the lesion to such an extent that surgery was abandoned. A physical examination, performed at the age of 18 months, revealed a hard oedema of subcutaneous tissue involving the neck, nape, back and the lumbar area and, in the projection of the right scapula – an elevated nodular lesion was observed. The oedema restricted the mobility of the entire spine and right shoulder joint. Only then was particular attention paid to the shortening of the thumbs in both hands and the *hallux valgus*, observed immediately after birth of the child and qualified as a congenital defect of the bone system. The laboratory tests revealed only a slight increase of alkaline phosphatase activity. The imagining diagnostics, comprising an ultrasound and X-ray performed at that stage, did not reveal any significant abnormalities with the exception of extensive oedema of the subcutaneous tissue. The differential diagnostics took into consideration systemic diseases of the connective tissue, fasciitis and oncological diseases of soft tissues. The presence of anatomical anomalies of the thumbs and large toes aided in a correct diagnosis, as on the basis of these symptoms, a suspicion of FOP was noted and a typical *ACVR1* gene mutation was confirmed. The child was subjected to chronic ibuprofen and anti-leukotriene therapy. In periods of exacerbations and after traumas, the treatment also included glucocorticosteroids (GCs). Moreover, for 2 years, the child was treated with pamidronate in intravenous infusions for 3 consecutive days every 3 months. From the time of pamidronate introduction, a significant decrease in the frequency of exacerbations was observed. Despite the applied therapy, within a 3.5 year follow-up period, a significant progression of the disease occurred with numerous ossifications and a silhouette deformity. A significant reduction of the mobility of the entire spine, frozen shoulder and elbow joints, hard palpable lumps and multiple ossifications within the chest (Fig. 1.) and abdominal cavity reaching the iliac wing (Fig. 2.) were observed. An X-ray of the spine revealed ossifications of the cervical vertebrae (Fig. 3.), numerous perispinal ossifications in the thoracic and lumbar spine, massive additional calcifications and ossifications within the nape soft tissues to the level of Th-6. In other areas, surplus

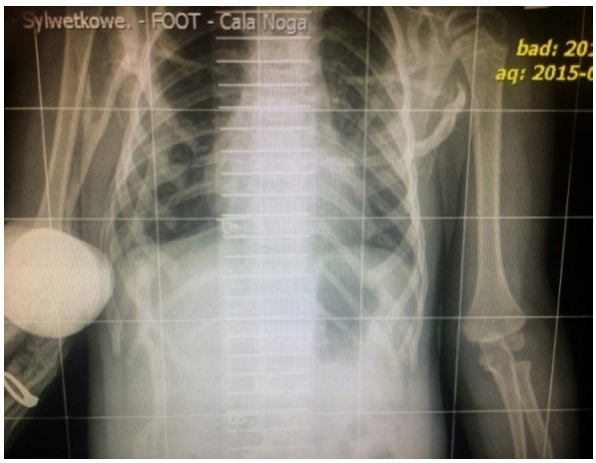

Fig. 1. Chest X-ray examination of Patients 1 showing multiple ossifications within the chest

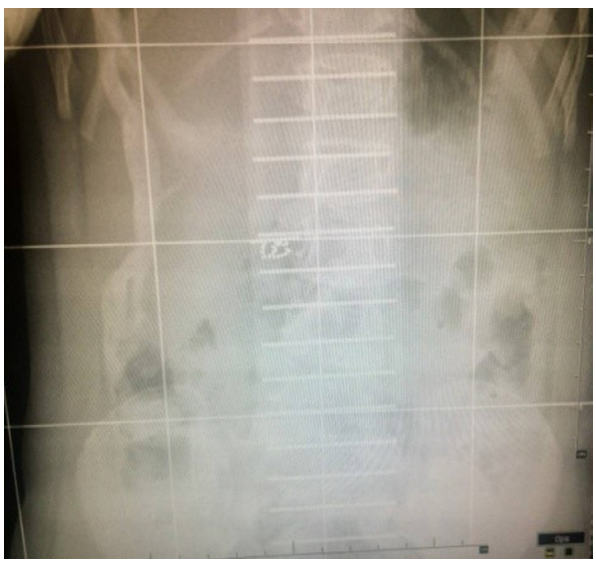

Fig. 2. X-ray examination of Patients 1 showing ossification in abdominal wall reaching the iliac wing

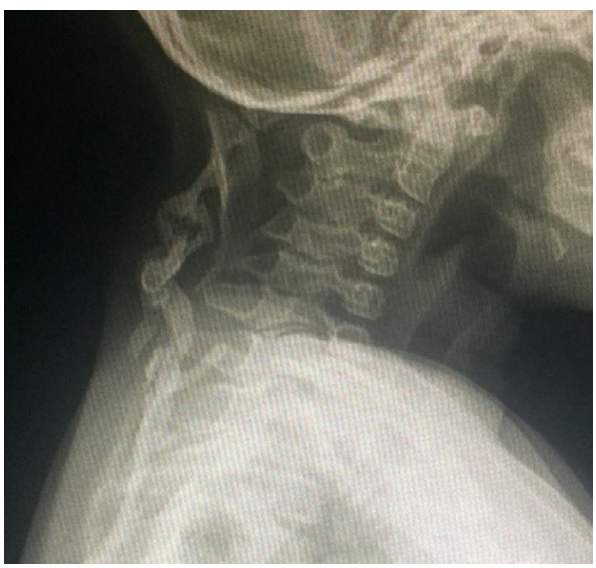

Fig. 3. X-ray examination of Patients 1 showing ossifications of the cervical vertebrae

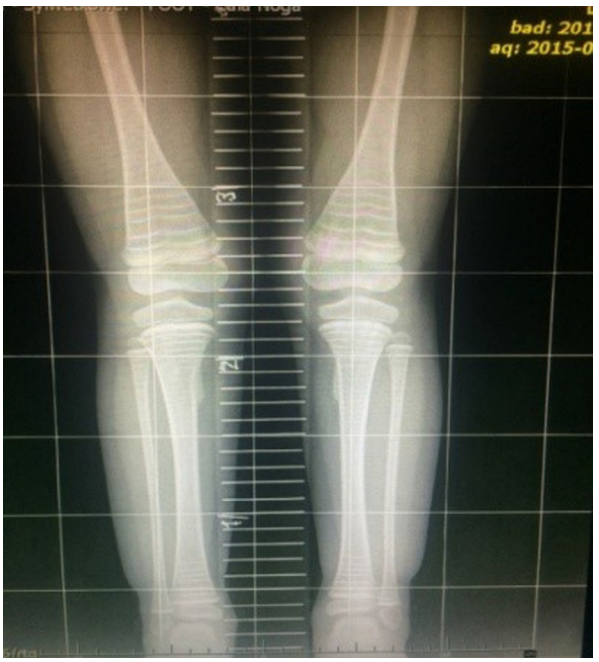

Fig. 4. X-ray examination of Patients 1 showing surplus bone in both proximal tibial metaphyses

bone in both proximal tibial metaphyses (Fig. 4.) and bilateral deformities with widening and shortening of the femur were found. The cause of the last hospitalization was diffuse hard nodules in the subcutaneous tissue reaching from the mandibula to the manubrium of the sternum which occurred during an infection of the upper respiratory tract. The treatment was comprised of pulses of methyl-prednisolone leading to a fast regression of the lesions. In the described case, the time period between the first symptom, i.e. subcutaneous oedema, and the correct diagnosis was about 8 months. The symptom with key importance for the diagnosis was congenital deformities of the thumbs and big toes.

Case 2.

A 6-year-old girl with a congenital hallux valgus in both feet, a small painless nodular lesion in the area of the distal metaphysis of the femur, limiting the flexion of the knee joint, was diagnosed in the third month of life. On the basis of a typical X-ray image, a chondro-osteophyte was diagnosed, which was then surgically removed at the age of 11 months. In the post-operative period, a formation of hematoma was observed in the scar, which then limited the mobility of the joint. Within a four-month follow-up period, the lesion had increased 2-3 fold. The diagnosis was of a recurrence of the chondro-osteophyte, measuring then 3.4 cm × 2.4 cm with adjacent calcifications. The child underwent revision surgery. The histopathological report described alteration of the chondro-osteophyte morphology with hyaline cartilage and a wide band of enchondral ossification; under a connective tissue layer there was also

a band of metaplastic myxoidal cartilage. Three weeks after the revision surgery, a painful and tender oedema of the scar reaching the proximal part of the femur was observed and, after another 6 months, a follow-up X-ray revealed some other numerous chondro-osteophytes along the entire length of the scar on the medial side of the proximal segments of both tibias. Another surgery was proposed, but the parents did not consent. Two and half years after the first symptom, on the basis of a clinical picture, and on the current big toes anomaly, a suspicion of FOP was made. The presence of a heterozygotic p.R206h mutation in the sequence coding the *ACVR1* gene was dertermined in a genetic examination. Currently, in the physical examination, some shortening and *hallux valgus* of both big toes was found (Fig. 5); moreover, on the lateral side of the left femur under the post-operative scar, some irregular bone masses reaching the mid-thigh and an immobilisation of the left knee joint with a progressive hyper-extension, and thickening of the medial surfaces of both tibias was found. The imaging diagnostics revealed band-like calcifications in the iliotibial band with a length of approx. 40-50 mm which, segmentally, was connected with the bone, stretching mainly in the lateral and medial vastus muscle; the calcifications in the deep surface of the tendon reached the suprapatellar recess. In the distal part of the left femur, there was an irregularly shaped chondro-osteophyte on a wide base, originating from its antero-lateral surface, along a segment of 7.5 cm long as well as calcifications in the soft tissues (Fig. 6, 7). The patient's treatment comprised a chronic application of indomethacin. After one of the many episodes of falls, causing long-term immobilisations, prednisone was included in the therapy, and after its introduction no additional ossifications were observed.

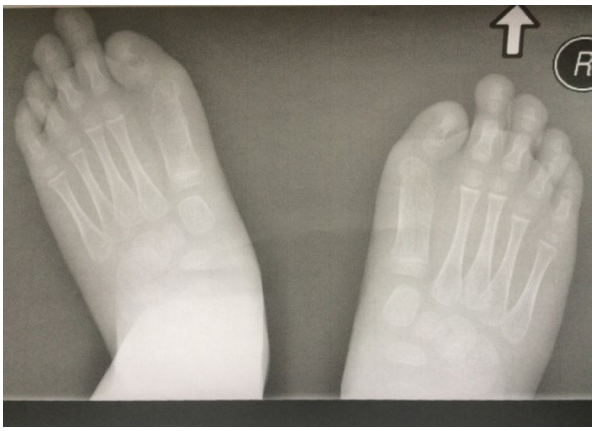

Fig. 5. X-ray examination of Patients 2 showing shortening and hallux valgus of both big toes

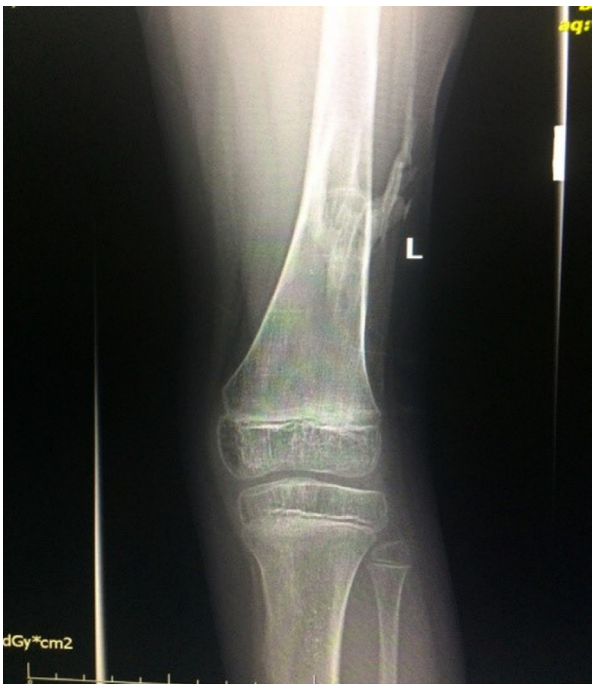

Fig. 6. X-ray examination of Patients 2 showing ossifications in distal part of the left femur

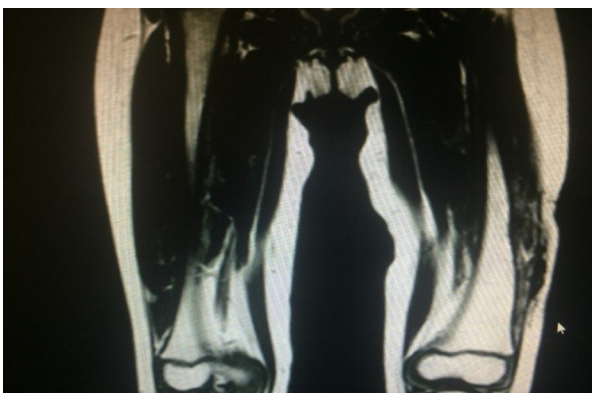

Fig. 7. MRI scan of Patients 2 showing ossifications and calcifications in the soft tissues

Case 3.

A three-year-old girl born from first gestation, with an uneventful family history, was diagnosed with congenital defects i.e. hallux valgus of both feet. The first symptoms of the disease occurred during her 14th month when an oedema of the subcutaneous tissue of the nape area was observed. Immobilisation in a Schanz collar brace and NSAIDs were applied in the therapy. Two weeks after the onset of treatment, the lesion had significantly increased. A physical examination revealed a significant limitation in cervical spine and shoulder joint mobility, as well as a massive oedema covering the nape, neck and the chest, reaching down to the lumbar area. Additionally, an inflammation of the medium lobe of the right lung was diagnosed. The laboratory tests showed an increase in inflammatory protein concentration and an increase in alkaline phosphatase activity. Imaging diagnostics (X-ray and CT) did not show any abnormalities with the exception of the subcutaneous oedema. The ap-

plied treatment was comprised of parenteral antibiotics and ibuprofen. The picture of the disease at that time allowed for diagnosis of FOP, which was confirmed by the presence of the heterozygotic p.R206h mutation in the sequence coding of the A*CVR1* gene. Further observation of the child revealed frequent exacerbations, not only after traumas or infections, but also spontaneous ones, consisting of repetitive episodes of soft tissue oedemas followed by consecutive ossifications of the areas of the nape, neck, scapula, chest and both upper extremities (Fig. 8, 9). A physical examination at the age of 20 months, revealed an antero-flexion of the trunk with a limitation of cervical spine mobility, alleviation of the mobility in the shoulder joints and a limitation of flexion to 90 degrees. Moreover, hard nodular infiltrations and additional ossifications in the frontal, suprascapular and intrascapular areas, on the nape, as well as along the thoracic spine, the left lumbar area, and along the arms and forearms in addition to shortening and valgus of the toes and discreet shortening of both thumbs were observed. The chest and extremities X-ray revealed calcifications and ossifications within the soft tissues, and along the humeral bones joining the chest in the upper medial section of the back and nape. The treatment consisted of chronic administration of the NSAIDs, antileukotriene agents and D3 vitamin supplementation. After episodes of disease exacerbations before dental and laryngological interventions, prednisone was administered. Within the next few months, the dynamics of the occurrence of the lesions was exceptionally pronounced. Numerous exacerbations of the disease were observed which led to the necessity of frequent use of prednisone. At the age of 2.5 years, the girl lost the ability to walk independently and a physical examination showed additionally a hard oedema in the subcutaneous right lumbar area descending to the area of the buttocks and into the proximal part of the right thigh. Laboratory tests revealed increased levels of alkaline phosphatase with other results being within the normal range. An X-ray revealed calcium-saturated bands in the soft tissues of the upper part of the lumbar spine, the area of the buttocks and the sacrococcygeal area and deformities of the necks of both femur and the head of the left femur (Fig. 10). With regard to gait limitation, a decision was taken to administer GCs in the form of Solu-Medrol pulses, according to the 1-3-5 day regime, which allowed for a very rapid improvement of the patient's condition shortly after the first dose of the drug. The girl started to walk the following day. Yet, still some repetitive "flashes" were observed leading to oedemas both in the subcutaneous level of the chest and in the abdomen and extremities, which resulted in the necessity of periodic use of prednisone, ranging from 4 to 5 times per month. At that time, a decision to introduce pamidronate was made. After the administration of the drug, within a 6-month follow-up period, a significant reduction of disease progression was observed. In this case, despite of the quick diagnosis, the lack of effective treatment resulted in continual progress of the disease and consequent disability. The fulminant course of the disease, with a limitation of the mobility of the entire spine, chest, upper and lower limbs, occurring in such a short period of time, are indicative of an extremely aggressive course of the disease.

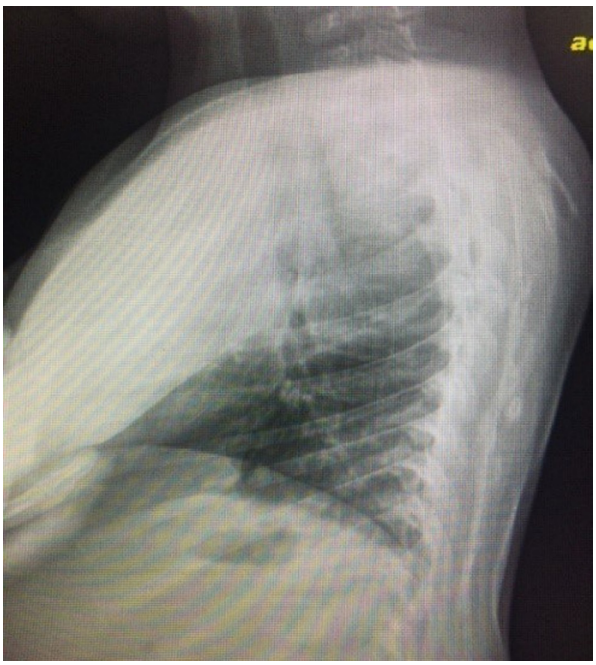

Fig. 8. X-ray examination of Patients 3 showing ossifications in trunk area

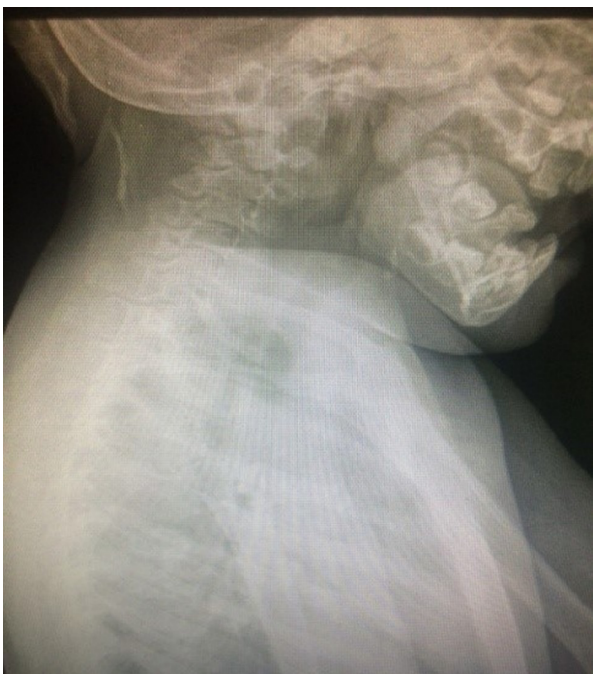

Fig. 9. X-ray examination of Patients 3 showing ossifications in neck area

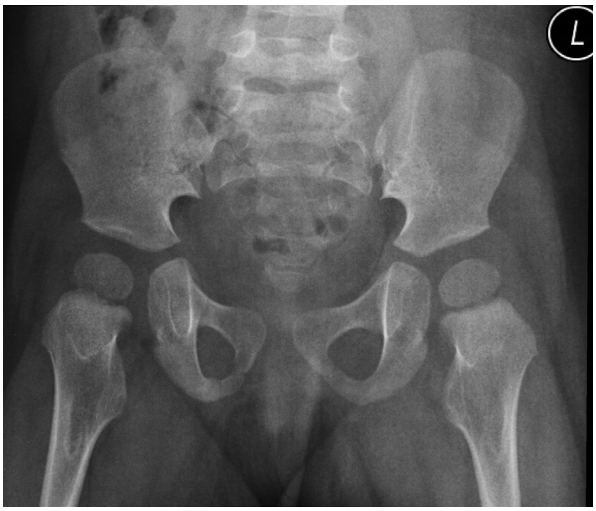

Fig. 10. X-ray examination of Patients 3 showing calcium-saturated bands in the soft tissues of the upper part of the lumbar spine, the area of the buttocks and the sacrococcygeal area and deformities of the necks of both femur and the head of the left femur

Discussion

The above-described cases allow us to conclude that the correct diagnosis at the stage of oedema, before additional ossifications are formed, is associated with several difficulties and the time period between the occurrence of the first symptoms and the establishment of the diagnosis ranged between 3 months and 2.5 years, the latter being the case with an atypical course. New bony tissue was formed outside the skeleton, mostly in the muscles, ligaments, fascia and tendons, avoiding the muscles of the diaphragm, tongue, heart, eye and smooth tissues, which agrees with published reports.[9] There were erroneous suspicions of cancer, including sarcoma, osteosarcoma, lymphomas and desmoid tumours. In consequence, the decision to perform surgery was made, after which usually the ossification process was intensified, which was observed in two of the described cases.[12] Positive support for the diagnostic process was the presence of typical phenotype defects, observed immediately after birth, the presence of which was found in each of the described cases. These defects comprise microdactylia and valgus of the big toes occurring as a result of the deformity of the first metatarsal bone and lack of formation of the interphalangeal joint, and, sometimes also clinodactyly of the fifth toe.[13-16] In two children, a shortening of the thumbs was observed, yet this defect occurred less frequently. Additionally, in all the described cases, an X-ray revealed deformities of the vertebral bodies in the cervical spine, together with a bony adhesion of C2-C7, short and wide femur necks and chondorosteophytes within the proximal tibia, which is a feature frequently reported in many publications.[14,16-19]

In spite of the presence of the typical p.R206h homozygotic mutation in the sequence coding of the ACVR1 gene, disease development may be varied. A typical picture is characterized with periods of exacerbations, within which new bone is usually formed. Also, the reports declare that the flashes are mainly triggered by traumas, surgeries, biopsies, intramuscular injections, muscle overloads and infections, but can also be spontaneous.[20,21]

In two of the children described above, progressive heterotrophic ossification had a specific course, involving first the areas of the nape, neck, spine area, back and shoulder girdle, extending then to the distal segments of the upper extremities, chest, and through the abdominal integuments to the lower limbs. Initially, the lesions formed nodular subcutaneous infiltrations, above which the skin was unchanged and sometimes with vessels visible through the skin. Gradually, these lesions hardened forming a new bone located in the muscles and around the joints and were followed by limitation of mobility, stiffness and sometimes, subluxations of the joints.[19,22,23] Incidentally, differences in the ossification sequence are observed in spite of the presence of a typical mutation , as seen in Case 2. Each of the described cases, presented different dynamics in symptoms development and involvement of the motor organ: beginning with a very aggressive course impairing physical activity in a very short period of time (Case 3) ending with a latent form, without flashes even at large traumas, the onset of which had an atypical location (Case 2).[24] The results of laboratory tests were normal, apart from an elevation of alkaline phosphatase activity in the periods of exacerbation in Cases 1 and 3.[25] The diagnosis may be facilitated by conventional X-rays in which the foci of heterotopic ossification may be visualised. Such examinations as CT or MRI are pointless in the early stage of the disease. For a correct diagnosis, it is enough to diagnose typical big toe anomalies and to confirm the mutation of the *ACVR1* gene.[26,27]

Currently there is no efficient therapy of FOP, which could prevent the formation of new ossifications. Attempts to the resect a new bony tissue result in an even larger and more intensive ossification in the locations of an intervention, which happened in Case 2. The guidelines for a symptomatic treatment are presented on the IFOPA website. The application of GCs in the periods of exacerbations seem to be the most effective in treatment. In the case of the involvement of large joints, the head and the neck, mega-doses of GCs, administered parenterally are recommended. This treatment might lead to the fast regression of oedematous lesions and alleviate strong pain while at the same time improve joint mobility – as was observed in 2 cases. As a standard supportive therapy, non-steroid anti-inflammatory drugs, leukotriene inhibitors and agents stabilizing mast cells are used, yet they do not affect disease activity. Attempts of long-term immunosuppression, according to

the published data, render positive results in some cases, yet the general use of drugs from this group is not recommended. Some significant improvement was made after the application of bisphosphonates, which were administered in 2 of the 3 described cases, obtaining a decrease in the number of flashes and the reduction of the applied doses of GCs.[12,28,29] Some hopes have been placed in a procedure of allogenic bone marrow transplantation, which lead to the elimination of lymphocytes which are genetically programmed to produce an excess of BMP-4. The studies performed on an animal model revealed that an allogenic bone marrow transplantation followed by immunosuppressive therapy reduced extra-skeletal ossification, although it did not result in remission of the disease.[8] High hopes have also been placed in the use of palovarotene, the efficiency of which is currently being evaluated in clinical studies.[30]

Conclusion

Until recently, there has been no efficient therapy which could slow down the natural course of the disease and currently the disease is treated as incurable. Of key importance from the perspective of patients is early diagnosis and, more importantly, preventing traumas, surgical procedures, intramuscular injections, sparing dental treatment and ensuring avoidance of airway tract infections.

Acknowledgments

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