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RARE CASES OF SOFT TISSUE OSSIFICATION SYNDROME IN PEDIATRIC PRACTICE

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Abstract

The article covers the issues of rare genetic syndromes with similar group of symptoms, accompanied by ossification and calcification of soft tissues in children: progressive ossifying fibrodysplasia and progressive osseous heteroplasia. It is shown, that in contrast to the progressive ossifying fibrodysplasia, the progressive osseous heteroplasia is characterized by irreversible changes of the skin in the form of purple or blue coloration appearance, fibrosis, cohesion with the subcutaneous fatty tissue. In progressive ossifying fibrodysplasia ossification is formed avoiding the calcification stage. In progressive osseous heteroplasia pathological process begins with the appearance of calcification transforming into ossification. In osseous heteroplasia the disease progression slows down with age, while in fibrodysplasia ossifying the progression rate of pathological process it is not reduced.

Present study demonstrates the results of clinical observation of a patient with progressive ossifying fibrodysplasia, who was diagnosed a few years after the onset, which resulted in disorders of physical activity, excessive traumatic study and rapid progression of the disease. The clinical observation of the patient with progressive osseous heteroplasia demonstrates an onset of a rare pathology in the neonatal period and the combination of heteroplasia with congenital heart disease, namely, supravalvular aortic stenosis, which was successfully managed by intravascular surgery method. Both cases were confirmed by the results of molecular genetic studies.

The issues of differential diagnosis of progressive ossifying fibrodysplasia and progressive osseous heteroplasia have been studied as well. The frames of a diagnostic search should include rheumatic diseases with soft tissue calcification, such as scleroderma, juvenile dermatomyositis, oncological formations of soft tissues.

Conclusions were made about the need for a comprehensive examination of patients with essential neoplasms such as subcutaneous calcification and ossification, especially combined with malformations of the feet, contractures of joints and limited mobility of the spine, so as to detect the disorders at the genetic level. While dealing with unidentified diagnosis in children with calcifications and/or soft tissue ossification, it is necessary to evaluate the existing congenital changes, malformations of bones and joints before initiating invasive measures or traumatizing conditions (biopsies, surgeries), which may potentiate ossification.

Keywords: *progressive ossifying fibrodysplasia, progressive osseous heteroplasia, ossification, calcification, children.*

Introduction

Pediatricians often have difficulties while dealing with patients who have rare and unusual symptoms, such as soft tissue induration and enlargement, possibly due to calcification or ossification. Moreover, the fact of calcification or ossification itself is not identified immediately, and sometimes not at all identified. Tissue changes are treated as local edema, inflammatory reaction, tumor-like mass, etc.

There are a number of rare genetic abnormalities with signs of ossification, and/or calcification. There are two of them that have similar clinical group of symptoms: progressive ossifying

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fibrodysplasia and progressive osseous heteroplasia [*Shore E, Kaplan F, 2010; Singh G, Verma V, 2011; Garcia-Pinzas J et al., 2013; Faruqi T et al., 2014; Antelava* O *et al., 2015; Lakkireddy M et al., 2015*]. They are characterized by a congenital bone pathology, progressive heterotopic ossification, and/or calcification of muscles, tendons, ligaments and aponeuroses.

The aim of the study was to demonstrate the diagnostic process, to illustrate the similarities and differences in the clinical picture of the two genetic abnormalities, and most importantly, to prepare pediatricians for dealing with a rare case.

So, progressive ossifying fibrodysplasia is a rare autosomal dominant genetic disease characterized by steady progressing and ossification of soft connective tissues (muscles, fascia, tendons) secondary to various congenital bone disorders. The heterotopic ossification processes are preceded by phases of inflammation, fibroblast proliferation, and clinically apparent angioneogenesis. Pathological processes are provoked by mechanical effects (trauma, surgery, and others), infectious agents (usually viruses). Spontaneous onset of the disease with a following progression is possible.

The genetic substrate of progressive ossifying fibrodysplasia is a heterozygous mutation expressed by replacement of amino acid arginine to histidine at position 206 R (206) H in the 23-24 area of chromosome 2 of ACVR1 gene. The mutation occurs, usually, de novo, but familial inheritance is also possible. Metaplastic ossification process develops as a result of intercellular connection disorders, conduction of cellular signaling due to changes in the receptor protein caused by a gene defect.

The first symptoms of progressive ossifying fibrodysplasia usually appear in childhood in the form of tumor-like knots in the soft tissues of the neck, head and back, followed by ossification. These symptoms may be accompanied by fever. Joint and spine contractures gradually develop near the site of ossification. Laboratory assessment of inflammation activity is usually absent.

Patients with progressive ossifying fibrodysplasia have a congenital bone abnormalities, usually presented with short thumbs, finger synostosis, joint surfaces of the cervical vertebrae, costal-vertebral joints; short neck of the humerus. The main and essential diagnostic sign of bone anomaly is a congenital deformation of the big toes in the form of shortening or clinodactyly (Fig. 1).

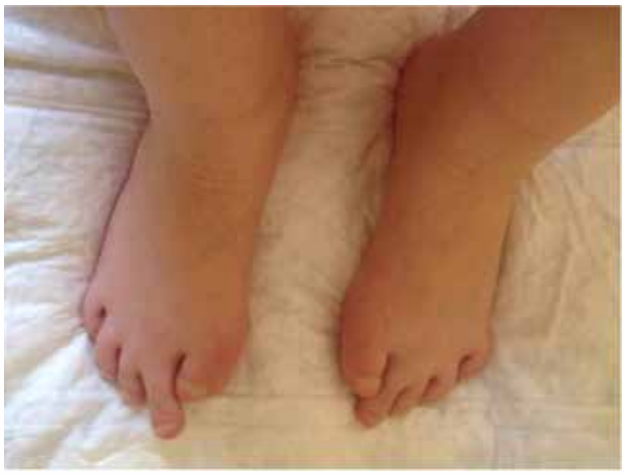

Figure 1. *Shortening and valgus deformity of big toes in a patient with progressive ossifying fibrodysplasia*

Progressive osseous heteroplasia is an autosomal dominant disease, which, in contrast to the progressive ossifying fibrodysplasia, is characterized by spontaneous ossification of the connective tissue neoplasms preceded by calcification. An apparent trigger factor is often missing. Some authors point out that the progress of the disease slows down with age, whereas the ossification is progressing steadily in the progressive ossifying fibrodysplasia [*Murray J, Favus M, 1990; Singh G, Verma V, 2011*]. Progressive osseous heteroplasia is often accompanied by hormonal disorders (most often by hypofunction of the adrenal and thyroid glands).

In progressive osseous heteroplasia GNAS gene mutation occurs. The mentioned gene is located on chromosome 20 and contains 13 coding exons. It encodes the production of G protein, which plays a major role in the intercellular interaction between the cells. Gene defect leads to its deficiency, resulting in intercellular communication disorders. Heterotopic calcification and the following ossification of the connective tissues (skin, muscle, fascia, ligaments, tendons) are explained by disorders

in conduction of cell signaling that regulate the differentiation of immature cells.

There are 6 subtypes of the disease associated with this gene mutation [*Ringel M et al., 1996*]:

1. Albright's osteodystrophy (or Albright's syndrome)
2. Pseudo-pseudohypoparathyroidism
3. Pseudohypoparathyroidism type Ia
4. Osteoma cutis
5. Progressive osseous heteroplasia
6. Combined forms.

The reasons, determining a clinical picture of a patient having a gene defect, are unknown. As a rule, defective alleles in progressive osseous heteroplasia are paternally inherited. Clinically, the disease often begins with subfebrile temperature, appearing of painful indurations in the dermis, in subcutaneous fatty tissue and muscles followed by calcification, and then ossification, stiffness and limitation of movement. Osseous tissue appears in inappropriate sites of the body [*Berezhnoi V et al., 2014*].

It is worth mentioning, that in contrast to the progressive ossifying fibrodysplasia, the progressive osseous heteroplasia is characterized by irreversible changes of the skin in the form of purple or blue coloration appearance, fibrosis, cohesion with the subcutaneous fatty tissue. Patients with progressive ossifying fibrodysplasia always retain intact skin. In the presence of overt clinical symptoms rapid and accurate diagnosis is almost always absent due to the rarity of these diseases, low awareness of pediatricians, orthopedists, oncologists, rheumatologists, i.e. the professionals who are often the first to encounter children with progressive ossifying fibrodysplasia and progressive osseous heteroplasia.

Thus, diagnostics and differential diagnostics of progressive ossifying fibrodysplasia and progressive osseous heteroplasia can be a significantly difficult task for a doctor. In this regard, it is important to demonstrate two cases with these genetic abnormalities.

MATERIAL AND METHODS

Clinical observation No 1

Female patient B., 13 years of age, was admitted to the University Hospital with complaints of the tumor-like, mildly painful, hen egg-size neoplasms which appeared 6 months ago in the right infrascapular and posterior cervical regions.

In the community hospital the patient was diagnosed with "recurrent angioedema" and "myositis". The suspicion of possible cancer genesis of the tumoral neoplasms led to biopsy of hypodermic changes, the results of which were not informative because of poor technical quality of the examination. Prior to her visit to the clinic, the girl was consulted by pediatricians, allergist, dermatologist, oncologist.

During the initial outpatient examination of the patient, the rheumatologist focused his attention on the deformities of the big toes (shortening and clinodactyly), synostosis of cervical vertebrae (according to the cervical spine X-ray study made at the community hospital), which allowed to suspect progressive ossifying fibrodysplasia immediately. The diagnosis was confirmed by the follow-up molecular genetic investigation: "The DNA patterns showed Arg206His mutation in the ACVR1 gene in the heterozygous state".

By the time of the first visit to the rheumatologist the following questions had arisen:

- Whether the child has other symptoms of progressive ossifying fibrodysplasia, in addition to the mentioned complaints.
- When the patient manifested the true onset of progressive ossifying fibrodysplasia.

During the objective examination a similar subcutaneous neoplasm was discovered in the left axilla. The investigation also revealed significant limitation of mobility of the spine (Fig. 2), the left shoulder joint and interphalangeal joint of the little finger.

The patient and the parents did not see the limitation changes in the movement of large joints (the girl even attended physical education classes), which indicated a gradual and long-time process of the contracture formations. Stiffness of interphalangeal joint was formed at the age of 7 after the traumatic arthritis of the little finger. The found changes were not reflected in any of the medical document. Mother drew the pediatrician's attention to the peculiar structure of the big toes of the child, but to no avail.

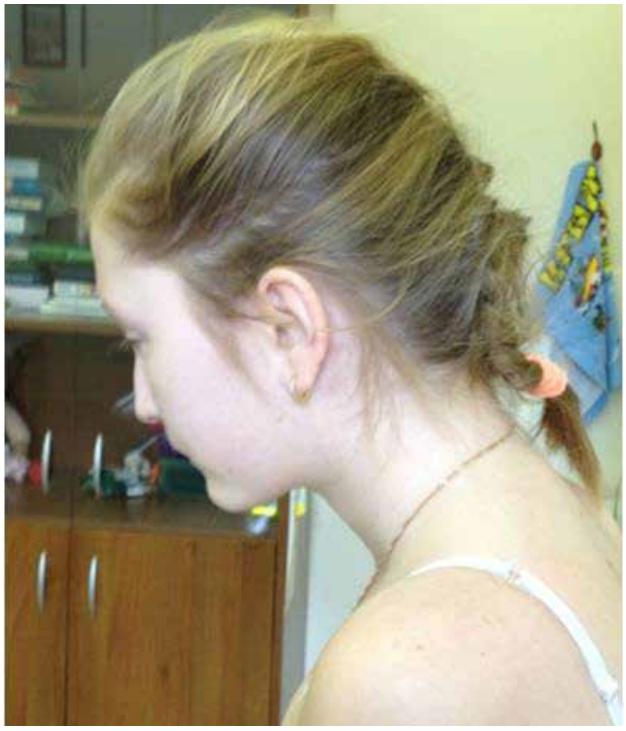

Figure 2. *Restriction of movement in the cervical spine in a patient with progressive ossifying fibrodysplasia (cannot touch the chin to chest)*

Thus, the main reasons of late diagnostics of progressive ossifying fibrodysplasia (supposedly after 6 years since the debut) were incomplete physical examination of the girl and unawareness of specialists consulting the patient. In this case, early diagnosis would have promoted the appointment exercise mode with limited physical activity and would have helped to avoid the traumatic examination of biopsy.

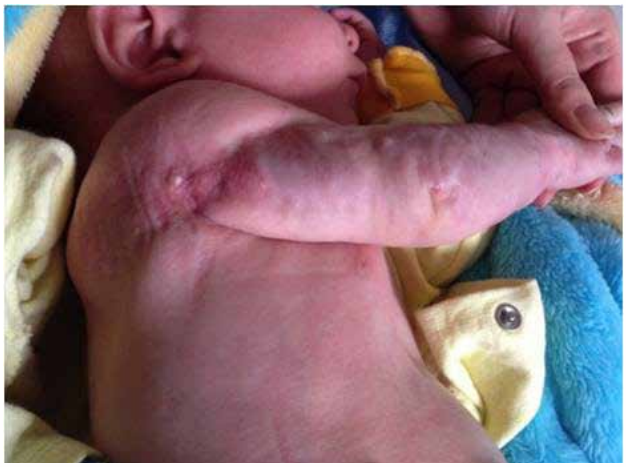

Figure 3. *Patient with progressive osseous heteroplasia. Focal lumps (calcifications) in the region of the right shoulder and arm. Fibrosis, skin cohesion with underlying tissues*

Clinical observation No 2

The patient, 6 months of age with congenital heart disease, presented with supravalvular aortic stenosis. Since the 1st month of life the child had multiple painless progressive focal knots, which appeared in the right shoulder, arm, neck, back, abdomen. This led to contractures of the right elbow, shoulder joints. The skin over the knots had a purple tint, no atrophy, presence of fibrosis, skin cohesion with the underlying tissues (Fig. 3).

Since birth the child was under supervision at the Institute of Cardiovascular Surgery after Bakulev as a candidate for surgical correction of the congenital heart disease. According to the specialists of the Institute of Cardiovascular Surgery, the soft tissue changes were assessed as manifestation of common scleroderma.

Perinatal history of the boy: born from 2nd pregnancy proceeding with interruption threat, 2 births by emergency caesarean section at the 36th week, weight at birth – 1770 *g*, length – 42 *cm*. The parents and 2-year-old brother are phenotypically healthy.

On admission to hospital the 6-month-old patient's condition was satisfactory, weight 5044 *g*, length 56 *cm*, psychomotor development without defects, the scleroderma symptoms were absent. In addition to the soft tissue and joint changes, multiple dysembryogenesis stigmas were found, well-marked systolic murmur over the entire heart, no signs of heart failure.

The laboratory data showed a slight increase in blood calcium, Ca ionized 1.34 *mmol/l* (normal range – 1.03-1.29 *mmol/l*). The level of blood parathyroid hormone was 24.2 *pg/ml* (normal range – 15-65 *pg/ml*). According to X-ray and echographic studies of soft tissue, the subcutaneous changes were seen as calcifications. The patient underwent investigation to rule out two genetic diseases manifested by ectopic calcification and ossification, i.e. progressive ossifying fibrodysplasia and progressive osseous heteroplasia. According to DNA study, mutation c. 565_568del GACT (CD0920862) was found in exon 10 of GNAS gene in the heterozygous state, which allowed to confirm the diagno-

sis of progressive osseous heteroplasia.

The boy underwent a successful intravasal surgical correction of congenital heart disease. He tolerated the surgery satisfactorily, but intravenous manipulations on the left hand potentiated the development of calcifications in the left fore arm and a decrease of motion range in the left elbow and left wrist joint.

Present observation illustrates the hardships of diagnosis identification of a rare genetic disease combined with the congenital heart disease, which had an early debut.

Discussion

The differential diagnostic search in suspicion of progressive ossifying fibrodysplasia and progressive osseous heteroplasia usually includes oncological diseases [*Matveeva I, 2003*], rheumatic diseases, accompanied by soft tissue calcification, joint contractures, acquired shortening of the fingers due to osteolysis.

In progressive ossifying fibrodysplasia, the recurrent soft tissue formations can be reduced in size, apparently because of the disappearance of the initial edema, which is not possible in case of tumor-like growths. The oncological pathology is not accompanied by the above-described osseous anomalies. In scleroderma, the "plus-tissue" phenomenon is always accompanied by changes in the skin in the form of dyschromia and/or fibrosis, skin atrophy, which is not observed in progressive ossifying fibrodysplasia. Minor calcifications (not ossification) may appear in acrosclerotic forms of scleroderma with periarticular localization on the fingers (Fig. 4).

Often they get lanced and the soft tissue around them becomes inflamed and infected, which is never observed in progressive ossifying fibrodysplasia. The myopathy symptoms, increased levels of muscle enzymes in the blood are not found in progressive ossifying fibrodysplasia either. Joint contractures developing in scleroderma and juvenile dermatomyositis, are associated with fibrosis of periarticular tissues, with their long-term functional impairment; to a certain extent, these contractions are reversible. Limitation of joint mobility in progressive ossifying fibrodysplasia and progressive osseous heteroplasia is due to steadily progressive irreversible ossification [*Kaplan F et al., 2011*].

Thus, present observations illustrate the difficulties of diagnosis identification of rare genetic diseases.

Conclusion

Thus, it can be concluded, that even on the first appeal of patients with multiple formations, such as subcutaneous calcification and ossification, especially combined with malformations of the feet, with contractures of the joints, limited

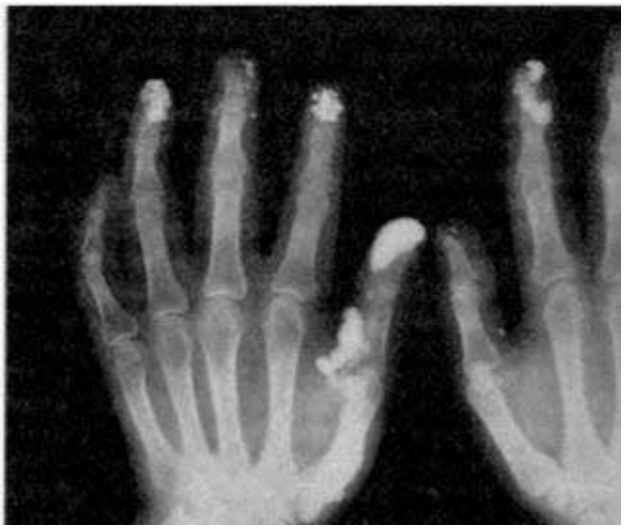

Figure 4. *Periarticular calcification in scleroderma*

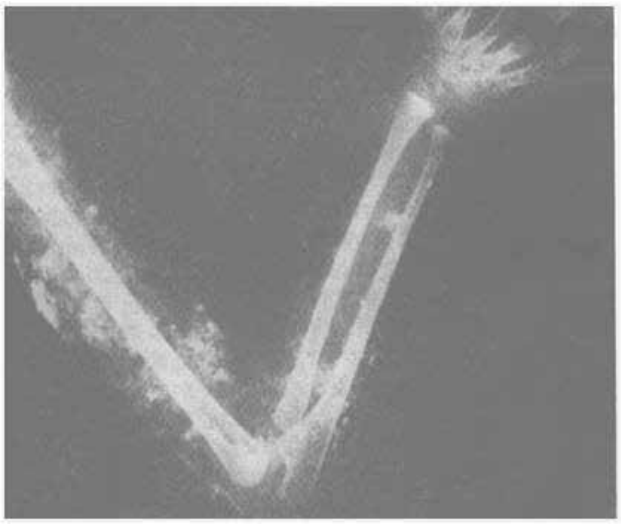

Figure 5. *The soft tissue calcification in a patient with juvenile dermatomyositis*

spinal mobility, it is necessary to conduct complex investigation in order to detect disorders at the genetic level.

While dealing with unidentified diagnosis in children with calcifications and/or soft tissue ossification, it is necessary to give evaluation to the existing congenital changes, malformations of bones and joints before initiating invasive measures or traumatizing conditions (biopsies, surgeries), which may potentiate ossification.

The differential diagnostics of progressive ossifying fibrodysplasia and progressive osseous heteroplasia should be carried out with benign, malignant tumors of the soft tissue, scleroderma, juvenile dermatomyositis, and other rheumatic and genetic abnormalities.

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