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Сложный диагностический случай: синдром Бушке—Оллендорф или соединительнотканный невус?

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РЕЗЮМЕ

Дисплазия соединительной ткани, представляющая собой генетически детерминированное нарушение закладки и постнатального развития, является весомой проблемой современной медицины в силу широкого распространения и возможных тяжелых последствий. Клинические проявления дисплазии соединительной ткани варьируют в широких пределах — от повышенной растяжимости кожи до сосудистых аномалий, приводящих к внезапной смерти. Большую группу в пределах дисплазии соединительной ткани составляют различные невусы, изолированные или в составе различных синдромов. Одним из редких генетически детерминированных синдромов является сидром Бушке—Оллендорф, относящийся к орфанным заболеваниям с аутосомно-доминантным наследованием. Основные клинические проявления синдрома — распространенные соединительнотканные невусы кожи, выявляемые в раннем детском возрасте, и остеопойкилия, чаще диагностируемая у взрослых. К редким проявлениям синдрома Бушке—Оллендорф относят различные пороки и поражения нервной системы (от нарушения когнитивного развития до эпилепсии). Диагностика синдрома основывается на совокупности определенных симптомов, главными из которых являются соединительнотканные невусы и остеопойкилия. В случае неполного синдрома диагностика базируется на молекулярно-генетическом исследовании, которое в силу дороговизны доступно не всем пациентам. Данный клинический случай демонстрирует трудность диагностического поиска и неоднозначность получаемых при этом результатов.

Представленный клинический случай был обсужден на общегородском Московском консилиуме при участии дерматовенерологов Москвы и профессоров Н.Н. Потекаева, В.Г. Акимова, В.Н. Гребенюка, А.Н. Львова, Э.А. Баткаева, Н.Г. Короткого, О.В. Жуковой, В.А. Волнухина.

Ключевые слова: кожа, дисплазия соединительной ткани, дерматофиброз, остеопойкилия, диагностика.

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Difficult diagnostic case: Buschke—Ollendorff syndrome or connective tissue nevus?

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ABSTRACT

Dysplasia of the connective tissue, which is a genetically determined disorder of the formation and postnatal development, represents a significant problem for modern medicine due to its high incidence and potentially serious consequences. Clinical manifestations of connective tissue dysplasia vary widely, from increased skin extensibility to vascular anomalies leading to sudden death. Various nevi, in isolated form or as a part of various syndromes, represent a large group within the connective tissue dysplasia. One of the rare genetically determined syndromes is Buschke—Ollendorff syndrome, which belongs to a group of orphan diseases with autosomal dominant inheritance. The main clinical manifestations of the syndrome are common connective tissue nevi of the skin, detected in early childhood, and osteopoikilosis, more often diagnosed in adults. Rare manifestations of Buschke—Ollendorff syndrome include various defects and disorder of the nervous system (from impaired cognitive development to epilepsy). Diagnosis of the syndrome is based on a combination of certain symptoms, the main of which are connective tissue nevi and osteopoikilosis. In the case of incomplete syndrome, the diagnosis is based on molecular genetic study,

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which is not available to all patients due to its high cost. This clinical case illustrates the challenges in the diagnostic search and the ambiguity of the results obtained.
The presented clinical case was discussed at the citywide Moscow Consilium with the participation of dermatovenerologists of Moscow and professors N.N. Potekaev, V.G. Akimov, V.N. Grebenyuk, A.N. Lvov, E.A. Baktaev, N.G. Korotskiy, O.V. Zhukova, V.A. Volnukhin.

Keywords: skin, connective tissue dysplasia, dermatofibrosis, osteopoikilosis, diagnostics.

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Connective tissue dysplasia is genetically determined violation of development of connective tissue in embryonic and postnatal periods. It is characterized by defects in fibrous structures and matrix of connective tissue. These disorders lead to disturbances of homeostasis at various levels and morphofunctional disorders of visceral and locomotor organs with progressive course. According to the most modest data, prevalence of these diseases is similar to that of the main socially significant non-infectious diseases. This group of diseases includes a rare hereditary disease — disseminated lenticular dermatofibrosis (Buschke—Ollendorff syndrome) [1—3]. Abraham Buschke first described the disease in 1902 as "scleroderma adultorum". Heinrich Ernst Albers-Schönberg in 1915 and then Helen Ollendorff in 1928 described two more cases.

Buschke—Ollendorff syndrome is a combination of connective tissue nevi and osteopoikilosis (OMIM 166700). Incidence of this disease is 1 per 20—30 thousand live newborns with equal frequency among boys and girls. This pathology is inherited in an autosomal dominant manner with high penetrance and variable expressiveness. The disease is caused by LEMD3 gene mutation. This gene is located in chromosome 12q14.3 and encodes one of the structural proteins of connective tissue. This mutation is followed by excessive dermal accumulation of elastin [4].

Buschke—Ollendorff syndrome usually manifests early, the first symptoms may be diagnosed immediately after birth. Symptoms are often different as in any hereditary disease and divided into cutaneous and extra-cutaneous **(Fig. 1)**.

The first symptom is skin lesion by connective tissue nevus. Rashes are usually localized on the lateral surfaces of the body, upper third of the abdomen, back, lower back, thighs and buttocks and represented by flesh or yellowish papules, nodules and plaques. These elements are slightly elevated above the skin, often have reticular, linear or herpetiform orientation and can merge with each other. Rash is usually symmetrical, but one-sided arrangement is described in children. Consistency of the elements is soft. Palpation is painless. There are usually no subjective sensations from efflorescences. Other skin lesions include anetoderma, palm-plantar keratosis, morphea and periarticular pads.

The second common symptom is skeletal system lesion due to focal calcium deposition (osteopoikilosis). Synonyms are congenital multiple sclerosing osteopathy, congenital maculous multiple osteopathy [3, 5]. Signs of osteopoikilosis are mainly found in bones of limbs and shoulder girdle. There are no clinical complaints, but these changes are important for differential diagnosis. X-ray examination of bones reveals small round or oval consolidations of spongy structures in osseous tissue **(Fig. 2)**.

Less common manifestations of disease are various malformations of the heart, ribs, teeth, facial skull, eyes, etc., endocrine disorders (diabetes), neurological disorders (epilepsy, mental retardation).

Diagnosis of syndrome is based on a combination of typical clinical symptoms and requires mandatory instrumental confirmation (morphological, radiological, genetic). Signs of connective tissue nevus including local proliferation of elastic structures and dermal accumulation of mucin are observed by histological examination. Additional staining of specimens by Weigert, Van—Gieson, toluidine blue and comparison with healthy skin specimens are necessary to confirm Buschke—Ollendorff syndrome **(Fig. 3)**.

Molecular genetic diagnosis aimed at searching for LEMD3 gene mutations is used if routine methods are failed to determine the diagnosis. The course of disease is usually benign. However, unfavorable variants with development of malignancies within the areas of osteopoikilosis are possible.

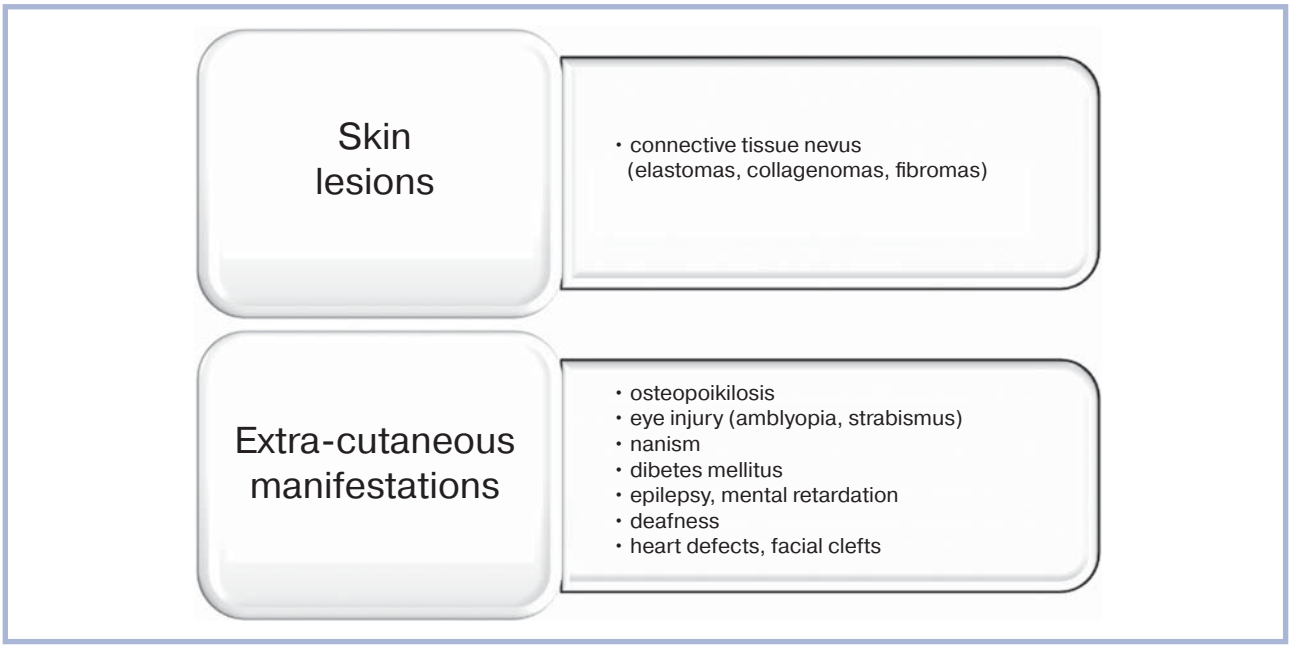

Fig. 1. **Clinical manifestations of Buschke—Ollendorff syndrome.**

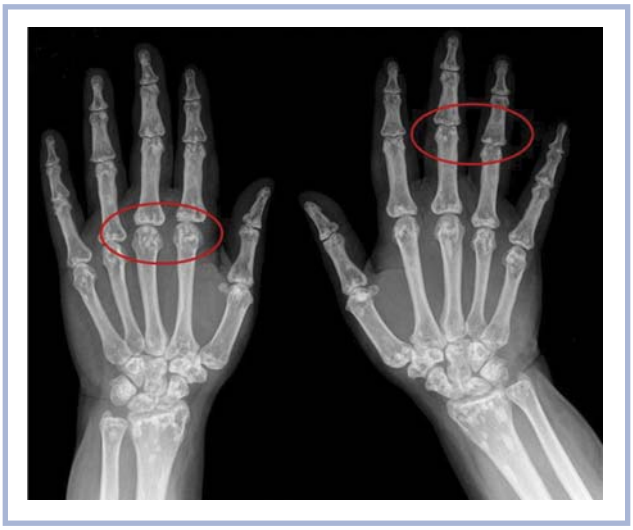

Fig. 2. **Osteopoikilosis.**

We present case report in order to demonstrate complexity of diagnosis and differential diagnosis of hereditary dermatoses.

Clinical case

Patient A., 5 years old. This pregnancy was the sixth (the 1st — missed abortion, the 2nd and the 5th — full-term boy, the 3rd — medical abortion, the 4th — miscarriage) and followed by anemia, ARVI, threat of miscarriage. The third births was through emergency caesarean section at the 36th week due to failure of uterine scar. Body weight at birth was 2630 g, height 48 cm, weight-height index 55 (reference range 60–80), Apgar score 7–8. Early development had no any features. Breastfeeding was up to 18 months. Vaccination corresponded to national immunization schedule. Family history was burdened by the mother — allergic diseases (atopic dermatitis, pollinosis), Wolf — Parkinson — White syndrome (WPW), arthropathy. Older sibs had pauciarticular juvenile arthritis, annular granuloma; younger one — pollinosis, food allergy.

Mom considers that the child is sick since birth. Pink rounded spot up to 1 cm with clear contours was found on anterior surface of right thigh immediately after discharge from the maternity hospital. A pediatrician described the rash as a manifestation of food allergy during the first patronage and recommended a diet. Two-three months later, erythemal-squamous eruptions occurred on the cheek, body and shins and were associated with errors in mother's diet. Spot on the thigh was still considered as a manifestation of food allergy. Allergist examined 6-month-old child for the first time due to eruptions. Atopic dermatitis was diagnosed and hypoallergenic diet was recommended.

The progression of eruptions began after 1.5 years. ARVI was followed by occurrence of new elements with changed color (yellowish) and consistency (elevation above skin surface and induration). An allergist prescribed topical glucocorticosteroids (Advantan) and the 1st generation of antihistamine drug (dimetindene, Fenistil). The effect of therapy was not observed. Augmentation of the number of the elements was noted at the age of 3 years after catarrhal tonsillitis and then in 5 months after intestinal infection (Fig. 4). For the first time, a child began to complain of pain in legs.

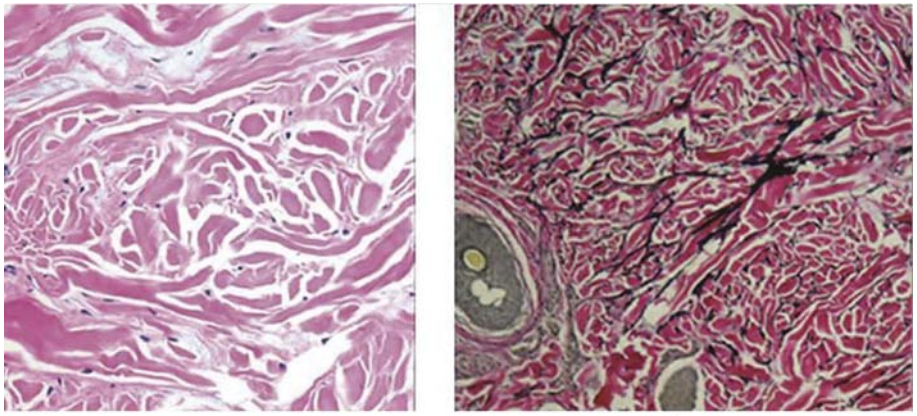

Fig. 3. **Morphological study of the biopsy (skin of the anterior abdominal wall) of a patient with Buschke—Ollendorff syndrome.**
a — areas of consolidation of collagen fascicles with no signs of hardening (stained with hematoxylin and eosin; ×40); b — thickened fascicles of elastic fibers, oriented in different directions (Van Gieson stain, ×40).

Various specialists repeatedly consulted the child and patient underwent difficult and expensive examinations during 1.5-year period **(Table 1, 2)**.

Child's condition was satisfactory at admission. Non-inflammatory local symmetric skin lesion was localized on the anterior, lateral and posterior surfaces of the right thigh. Yellowish-pink subcutaneous nodes 0.5 — 1.5 cm had clear contours, hemispherical shape, smooth surface, elastic consistency and tendency to merger (Fig. 6). Palpation of the elements was painless; subjectively, the was an itching after contact with a heat source. Skin outside the lesions was intact with moderate xerosis. Skin appendages and mucous membranes were also intact.

Routine examination including blood test, urine analysis, biochemical blood test and immune status did not reveal any changes. Rotation of both kidneys was diagnosed by ultrasound examination of abdominal cavity and retroperitoneal space. A neurologist diagnosed hyperactivity syndrome, an allergist — food allergy. There was no evidence of Buschke—Ollendorff syndrome during examination. Final dermatological diagnosis was connective tissue nevus.

The recommendations consisted of follow-up, photofixation and ultrasound examination of efflorescences on the right thigh every 6 months. Surgical excision of lesions may be advisable in adulthood. Follow-up is necessary since other clinical signs of Buschke—Ollendorff syndrome can occur in delayed period and aggravate prognosis for recovery. The main causes of death of these patients are cancer (osteosarcoma, chondrosarcoma), cardiac malformations and complicated diabetes mellitus. Timely diagnosis, correct differential diagnosis and adequate management are necessary to prevent complications.

Buschke — Ollendorff syndrome may be excluded despite similar skin manifestations if typical mutations in LEMD3 gene are absent. It is necessary to continue diagnostic searching (immunohistochemical study of connective tissue nevus, whole exome sequencing of skin fibroblasts) for determination of the prognosis and differentiation of relatively benign diseases (collagen or elastin types of multiple dermal nevi) from severe melorheostosis followed by disability.

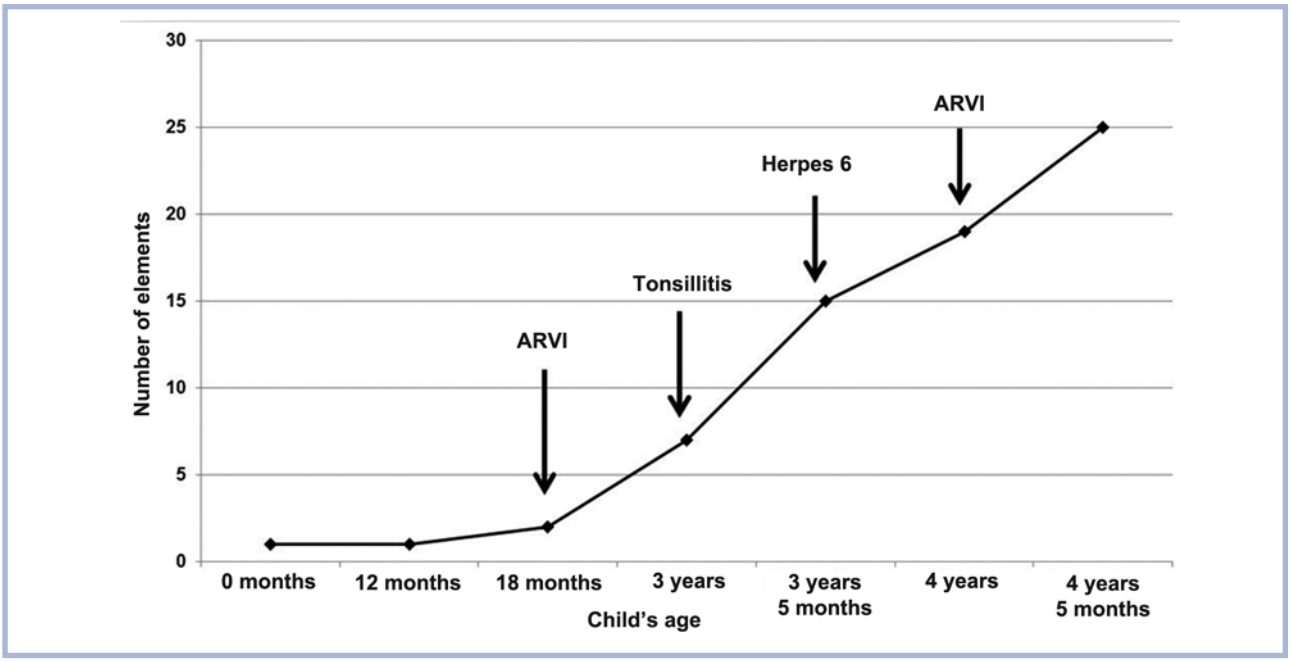

Fig. 4. **The dynamics of the skin process.**

Table 1. **Specialists' advice**

Date	Specialist	Suspected diagnosis
August 2016 (3 year and 5 months)	Sechenov University Children's Clinical Hospital, rheumatologist	Connective tissue disorders are excluded
September 2016 (3 year and 6 months)	State Research Center for Dermatovenerology and Cosmetology of the Ministry of Health of Russia, dermatologist	Connective tissue nevus? Buschke – Ollendorff syndrome?
September 2016 (3 year and 6 months)	Filatov Municipal Children's Clinical Hospital №13, geneticist	Epidermal nevus
September 2016 (3 year and 6 months)	National Medical Research Center of Children's Health, Ministry of Health of the Russian Federation, dermatologist	Buschke – Ollendorff syndrome
October 2016 (3 year and 7 months)	National Medical Research Center of Children's Health, Ministry of Health of the Russian Federation, orthopedist	Bone pain in growth period. There are no data for bone damage.
November 2016 (3 year and 8 months)	Center of Dermatovenerology and Cosmetology of the Ministry of Health of Russia, dermatologist	Buschke – Ollendorff syndrome
December 2016 (3 year and 9 months)	Morozov Children's City Clinical Hospital, geneticist	Disseminated dermatofibrosis – Buschke – Ollendorff syndrome
January 2017 (3 year and 10 months)	Veltishchev Research Clinical Institute of Pediatrics, Department of Congenital and Hereditary Diseases	Buschke – Ollendorff syndrome, osteoporosis, scoliotic posture, plano-valgus foot, kidney rotation, neurotic reactions, bruxism, food allergy, hyperopia
March 2017 (4 years)	Morozov Children's City Clinical Hospital, geneticist (once again)	Buschke – Ollendorff syndrome? Exome sequencing is recommended to search for LTMD3 gene mutations in specimen (skin from the right thigh)
January 2018 (4 years and 10 months)	Federal Bureau of Medical and Social Expertise, orthopedist	Generalized osteoporosis
January 2018 (4 years and 10 months)	Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, dermatologist	Other specified diseases of skin and subcutaneous tissue

Table 2. Conducted examinations

Date	Examination	Conclusion
September 2016	National Medical Research Center of Children's Health of Ministry of Health of the Russian Federation — morphological examination of specimen (skin of the right thigh)	Histological pattern of connective tissue nevus most characteristic for Buschke – Ollendorff syndrome
April 2017	"Genomed" — full excome sequencing:	No significant changes including in LEMD3 gene
October 2017	Veltishchev Research Clinical Institute of Pediatrics, Department of Congenital and Hereditary Diseases — X-ray examination of hands, legs and feet	Moderate signs of osteoporosis
December 2017	Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology — morphological examination of specimen (skin of the right thigh)	Histological pattern is not specific. Differential diagnosis between connective tissue nevus, morphea and other connective tissue diseases is not possible in this volume of specimen.
January 2018	Pediatric polyclinic №10, branch №1 in Moscow — densitometry	Bone mineralization at the lower normal limit **(Fig. 5)**

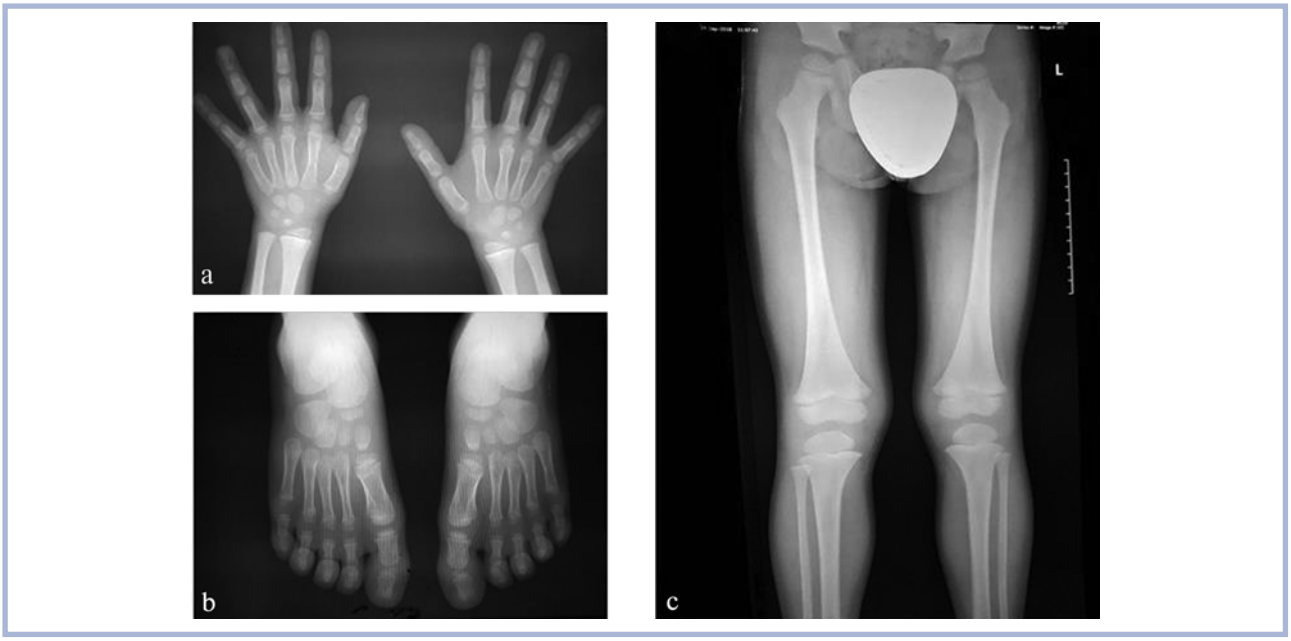

Fig. 5. **X-ray examination of patient *A.*, 5 years.**
a — hands; b — feet; c — knee and ankle joints.

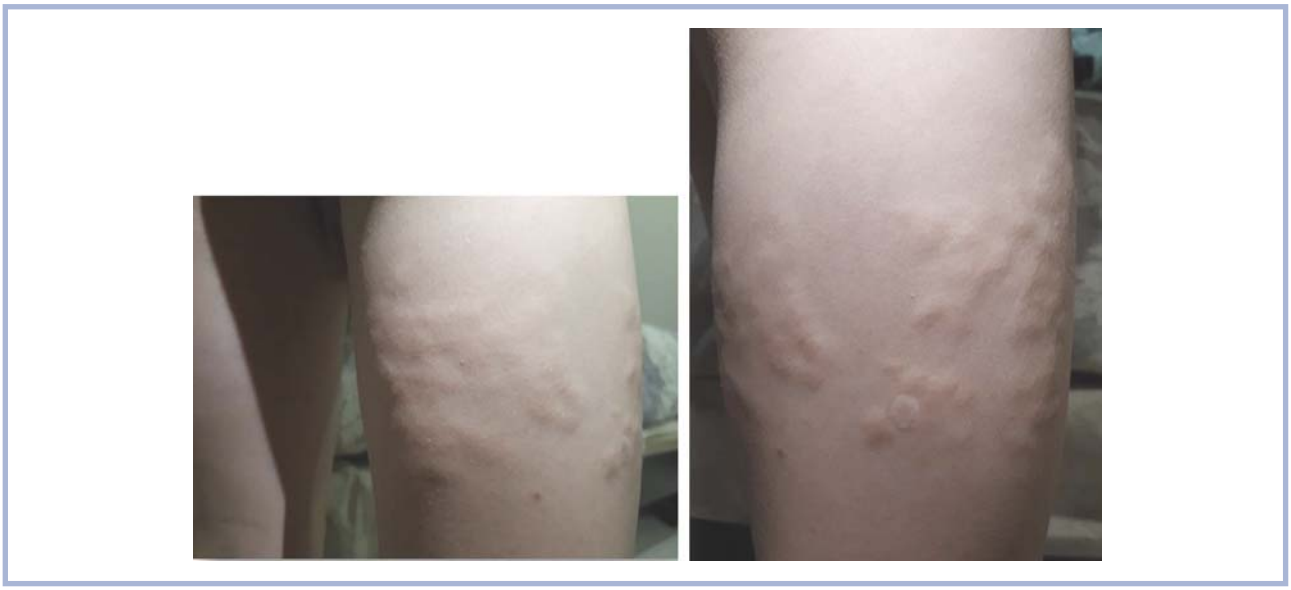

***Fig. 6*. Skin process in the child *A.*, 5 years.**
The posterior and lateral surface of the right thigh.

Authors' contributions:
Guidance and Review — N.G. Korotkii
Collection and processing of material, writing of the manuscript — A.S. Botkina

The authors declare no conflicts of interest.

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