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Escobar syndrome (multiple pterygium syndrome) associated with osteogenesis imperfecta: a case report

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A clinical case of a unique combination in a patient of a combination of rare genetic diseases — imperfect osteogenesis and Escobar syndrome is presented. Imperfect osteogenesis (osteogenesis imperfecta, congenital fragility of bones, periosteal dystrophy, intrauterine rickets, osteopsaturosis, Lobstein-Wolff disease, «crystal» disease) [Q 78.0] — heterogeneous hereditary disease, with a frequency in the population from 1–7.2:10 000 to 1:20 000. Characterized by a violation of the synthesis of type I collagen. Clinically manifested by multiple fractures and the development of progressive deformities of long bones of extremities, some variants of the disease are accompanied by the presence of blue sclera and progressive deafness. Escobar syndrome (multiple pterygium syndrome, Multiple pterygium syndromes, OMIM 265 000) is an orphanic hereditary disease, the incidence is unknown. Clinical manifestations — cervical, antecubital, popliteal pterygiums, multiple contractures of joints, excessive skin folds in the axilla and between the fingers, congenital or early manifested scoliosis or kyphoscoliosis, the presence of hemivertebra, partial fusion of vertebral bodies, cryptorchidism and hypogonadism in boys, fetal akinesia, low hair growth at the back of the head, deformity of the feet as a «rocking-stop», intrauterine growth retardation, small growth, craniofacial dysmorphisms (micrognathia), antimonyholoidal incision of the eyes (displacement of the medial edges of the optic gaps upwards) with epicanthus or without it, ptosis, arachnodactyly, respiratory distress syndrome (due to hypoplasia of the lung tissue), cleft hard and soft palate, low set eyes. Intellectual development, as a rule, does not suffer. Treatment is complex: correction of metabolic disorders, surgical interventions to eliminate deformities of limbs, cleft palate, pterygium. Key words: Escobar syndrome, imperfect osteogenesis, bone fractures and deformations, hereditary diseases.

Представлен клинический пример уникального сочетания у пациента комбинации редких генетических заболеваний — несовершенного остеогенеза (НО) и синдрома Эскобара. НО (osteogenesis imperfecta, врожденная ломкость костей, периостальная дистрофия, внутриутробный рахит, остеопсатироз, болезнь Лобштейна-Вролика, «хрустальная» болезнь) [Q 78.0] — гетерогенное наследственное заболевание, с частотой в популяции от 1–7,2:10 000 до 1:20 000. Характеризуется нарушением синтеза коллагена I типа. Клинически проявляется множественными переломами и развитием прогрессирующих деформаций длинных костей конечностей, некоторые варианты заболевания сопровождаются наличием голубых склер и прогрессирующей тугоухостью. Синдром Эскобара (синдром множественных птеригиумов, Multiple pterygium syndromes, OMIM 265 000) — орфанное наследственное заболевание, частота встречаемости неизвестна. Клинические проявления — шейный, антекубитальный, подколенный птеригиумы, множественные контрактуры суставов, избыточные кожные складки в подмышечной впадине и между пальцами, врожденный или рано проявившийся сколиоз или кифосколиоз, наличие полупозвонков, частичное слияние тел позвонков, крипторхизм и гипогонадизм у мальчиков, фетальная акинезия, низкий рост волос на затылке, деформация стоп по типу «стопа-качалка», задержка внутриутробного развития, небольшой рост, черепно-лицевые дизморфизмы (микрогнатия), антимонголоидный разрез глаз (смещение медиальных краев глазных щелей вверх) с эпикантом или без него, птоз, арахнодактилия, респираторный дистресс-синдром (в связи с гипоплазией легочной ткани), расщелина твердого и мягкого неба, низко посаженные глаза. Интеллектуальное развитие, как правило, не страдает. Лечение является комплексным: коррекция метаболических нарушений, хирургические вмешательства для устранения деформаций конечностей, расщелины неба, птеригиумов. Ключевые слова: синдром Эскобара, несовершенный остеогенез, переломы и деформации костей, наследственные заболевания.

Key words: Escobar syndrome, osteogenesis imperfecta, bones' fractures and deformations, hereditary diseases

Introduction

Escobar Syndrome (Multiple pterygium syndromes, OMIM 265000) is a hereditary disease, it was first described by J. A. Bussiere [1] and later — by American geneticist V. Escobar. [2] It is a rare abnormality, therefore the disease incidence is unknown. There are two types of this pathology: lethal variant and non-lethal (Escobar type). Autosomal dominant, more frequent autosomal recessive and X-linked (chromosome II, part 2q37.1) types of inheritance are described in papers [3].

System disorders of skeletal development are congenital pathological processes appearing just after birth or during postnatal period. Osteogenesis imperfecta (congenital bones' fragility, periostal dystrophia, osteopsatirosis, Lobstein-Vrolik disease, «fragile» disease) [Q 78.0] is the heterogeneous hereditary disease associated with mutation of gene COL1A1 and COL1A2, has frequency between 1–7,2:10000 and 1:20000 [4, 5]. In 1979 D. O. Sillence described four basic types of disorder according to clinical, radiologic and collagenous molecular signs [6]. Furthermore, osteogenesis imperfecta is the one of constituent elements of some hereditary syndroms (Bruk's syndrome, Levin's syndrome etc.).

Diagnostics of these lesions is based on complex clinical, radiologic and genetic investigations. The knowledge about the nature of these diseases can affect treatment planning and further prognosis for the patients.

Case report

The parents of a three-year-old male patient complained of frequent low-power fractures of upper (11) and lower (20) limbs; progressive cranium deformity, cleft of hard and soft palate, ptosis, decreased muscle strength and hypotrophy of extremities, limitation of the right elbow joint and both knee joints extension, spine, chest and feet deformity, speech disorder. The child was born in gestation term 39 weeks; his mother suffered from toxicosis in first half of pregnancy and a long waterless period during the delivery.

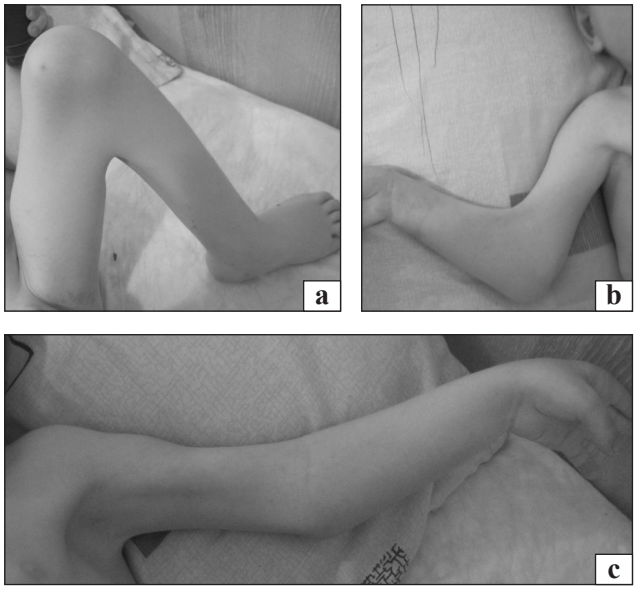

Fig. 2. Multiple pterygiums of popliteal (a), elbow (b) and axillary (c) regions

On examination, the boy isn't able to walk (fig. 1), his lower limbs are with extensive knee and elbow contracture, severe muscle hypotrophy and bones' deformation of limbs. The patient's weight is 9400 kg. Moreover, funnel-shaped chest deformation, plane and valgus feet deformation, multiple pterygiums of elbow, axillary and popliteal regions are revealed. (fig. 2). Cleft of hard and soft palate (fig. 3), mandible hypoplasia, ptosis present. Patient has unarticulated speech and is able to contact.

The complex clinical, radiologic and laboratory investigation was performed. The patient was consulted in the genetics center.

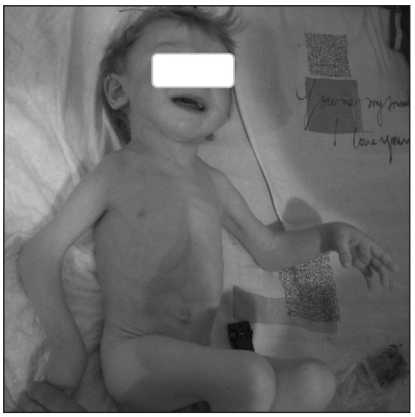

Fig. 1. Patient's appearance

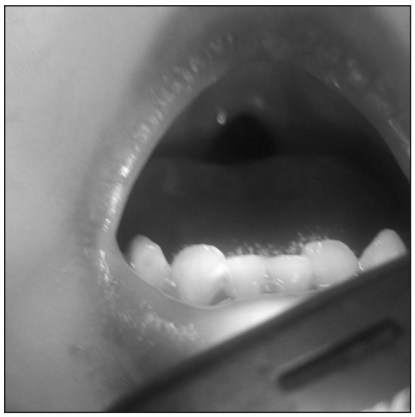

Fig. 3. Cleft of hard and soft palate

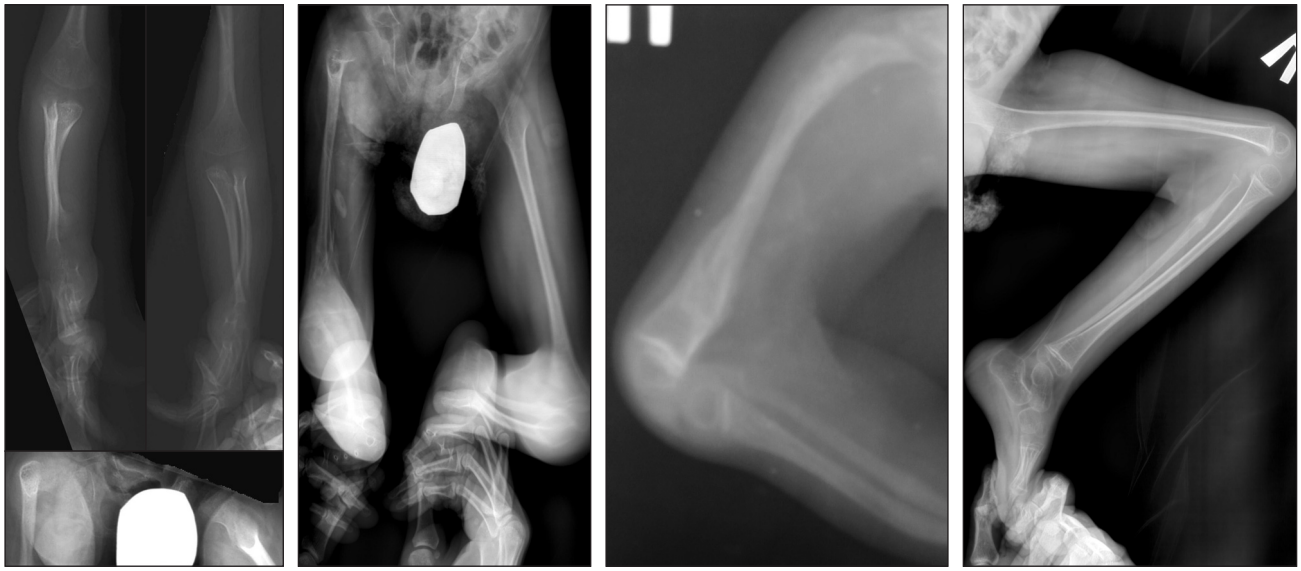

Fig. 4. Upper and lower limbs radiographs

An X-ray of upper and lower limbs shows long bones and pelvis hypoplasia, fractures of the right thighbone and shin bones during different stages of bones consolidation, combined axial deformations of extremities segments (fig. 4). Moreover, the left-side C-like thoracic and lumbal scoliosis was diagnosed I–II degree, deformation of vertebral bodies C_{III}–C_V with angle kyphosis (fig. 5). Shape and structure of other vertebrae aren't changed. Results of dual-photon bone densitometry show that Z-score of lumbal spine is –3.3. Data of the laboratory examination demonstrate the twice-increase in bone metabolism markers. Markers of general and ionized calcium and 1,25-OH D3 are decreased.

After complex research osteogenesis imperfecta associated with Escobar syndrome was diagnosed.

Discussion

Molecular and genetic cause of Escobar syndrome is mutation in CHRNG gene (Cholinergic receptor, nicotinic, gamma polypeptide) encoding gamma-subunit of the acetylcholine receptor (AchR). Gamma-subunit is found only in the fetal AchR producing up to 33 gestation weeks. Further gamma-subunit changes to the epsilon — subunit forming an adult's AchR. The fetal AchR establishes a connection between a muscle and akson and takes part in the neural and muscular organogenesis. The letal type of disease is characterized be mutations in CHRNA1 and CHRND genes encoding alfa1- and beta-subunit AchR [7, 8].

Basic clinical signs of Escobar syndrome are multiple pterigiums in different grades and localization. Except that, joint contractures (particularly, contractures of interphalangeal joint, so-called camptodactilia), enlarged skin folds in the axilla and between the fingers, congenital scoliosis or kyphoskoliosis, semivertebrae, partial vertebra concrescence, cryptorchism and hypogonadism, low growth of hair at the nape, prenatal development's delay, cranium and facial dysostosis, epycantus, ptosis, respiratory distress-syndrome caused by lungs hypoplasia, cleft of hard and soft palate, low-set eyes take place. Intelligence, as a rule, is normal.

The osteogenesis imperfecta is characterized by quantitative or qualitive disorders of the first type collagen synthesis; in particular, precollagenious fibers that do not undergo maturity are produced. Histochemical examination shows that collagenious fibers in osteogenesis imperfecta have excessive amount of prolin which causes disorder of the bone calcification. A large amount of osteoblasts with high proliferative activity produces a little bone substance, transforms to osteocytes rapidly.

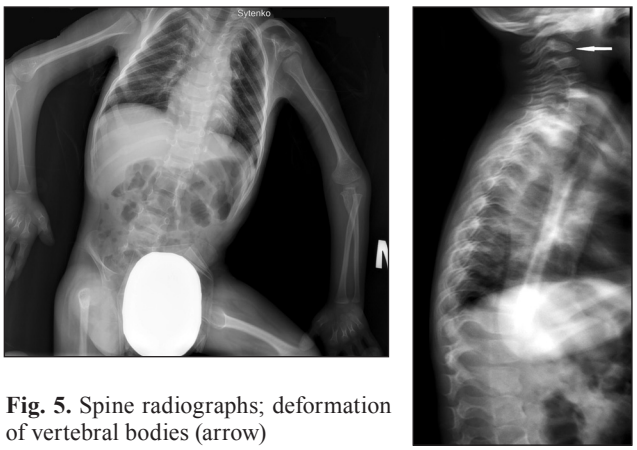

Fig. 5. Spine radiographs; deformation of vertebral bodies (arrow)

However, high proliferative activity of osteoblasts determines a good fractures consolidation. Clinical study reveals multiple fractures and progressive long bones' deformations. Some variants of disease are accompanied by blue scleras and progressive hearing loss [9, 10].

Treatment of the described congenital pathology is complex. Conservative methods are directed to metabolism correction; surgical intervention is performed with the aim to correct limbs deformities, palate clift and other morphological disorders. The prognosis depends on genetic variant of the abnormality: letal forms are inconsistent with life in most cases, whereas life quality in non-letal types can substantially increase providing effective and well-timed treatment.

Conclusions

Escobar syndrome associated with osteogenesis Imperfecta in one patient is a rare clinical observation. Imaging methods are important for the diagnostics of bone structure and analyses different defects of the skeleton. Correct diagnosis enables to plan an adequate treatment. Diagnostics of the above mentioned diseases is complex and genetic examination is also necessary.

Conflict of interest. The author declare the absence of conflict of interest.

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НЕСОВЕРШЕННЫЙ ОСТЕОГЕНЕЗ И СИНДРОМ ЭСКОБАРА: УНИКАЛЬНОЕ СОЧЕТАНИЕ ОРФАННОЙ ГЕНЕТИЧЕСКОЙ ПАТОЛОГИИ У ПАЦИЕНТА (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

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