DOI: 10.17816/PTORS3451-59

DYSTROPHIC EPIDERMOLYSIS BULLOSA ASSOCIATED WITH CONGENITAL CONTRACTURES OF THE UPPER AND LOWER LIMBS: LITERATURE REVIEW

Agranovich O.E., Buklaev D.S., Tikhonenko T.I.

The Turner Scientific and Research Institute for Children's Orthopedics, Saint-Petersburg, Russian Federation

Epidermolysis bullosa (EB) is a rare hereditary disease. Its main feature is vesication and weeping sores (erosions) of the skin and mucous membranes, resulting from a minor injury. Clinical manifestations of the disease may vary from localized vesicles on the hands and feet to a generalized rash of the skin as well as lesions of the mucosa of the inner organs. At present, there are four main groups of EB: simple, intermediate, dystrophic, and Kindler syndrome. Mutations cause changes in the structure of the proteins responsible for the adhesion between layers of the dermis, leading to vesication. Treatment of EB is a challenge because of the lack of opportunities for the direct influence on the disease process, and its main purpose is to correct the existing cutaneous manifestations and prevent the occurrence of new elements. This article describes the main types of EB, methods of current diagnosis, and treatment of the disease as well as a clinical case of a rare combination of two severe disorders: 1) dystrophic EB and 2) arthrogryposis with upper and lower limb involvement.

Keywords: Epidermolysis bullosa, arthrogryposis, flexion contractures of extremities.

The term "epidermolysis bullosa" (EB) was first used in 1886 to describe a disease characterized by increased skin trauma followed by bulla formation. Today, EB is classified as a rare genetic disease caused by mutations in the genes encoding the structure of keratinocyte proteins and the dermoepidermal junction. These mutations result in alterations in the structure of proteins responsible for adhesion between dermal layers, which results in formation of bullae [1, 2].

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Normal skin has an outer layer known as the epidermis, a main layer or the dermis, and a basement membrane between these two layers, which consists of the lamina lucida and lamina densa. According to the Third International Consensus Meeting on Diagnosis and Classification of Epidermolysis Bullosa [3], four main groups of EB have been currently categorized and depend on the positions of target proteins and the level affected by bullae: 1) epidermolysis bullosa simplex (epidermolytic); 2) junctional EB (lucidolytic); 3) dystrophic EB (dermolytic); and 4) Kindler syndrome (Fig. 1).

EBS has an autosomal dominant pattern of inheritance; however, in some rare cases of families, particularly the consanguineously related ones, it can be inherited in an autosomal recessive pattern. Mutations localized in the structure of keratins 5 and 14, plectin, and α6β4 integrin induce lysis of keratinocytes and subsequent intraepidermal formation of bullous elements. Today, EBS is subdivided into two main types (local and generalized) and 12 subtypes. Clinical manifestations can vary from the mild local form (with bullae mostly affecting hands and feet) to the severe and lethal generalized form [1, 4–7].

Junctional epidermolysis bullosa (JEB) is inherited in an autosomal recessive pattern and includes mutations in the genes encoding synthesis of plectin, type XVII collagen, α6β4 integrin, or one of three chains of laminin 332; these mutations lead to the disruption of hemidesmosome formation and fixation of connective fibers. Bullae affecting large skin regions can be clinically diagnosed. The typical feature of this type of EB is the formation of granulation tissue on a patient's face, back, and armpits. There are three main subtypes of JEB: 1) Herlitz JEB; 2) non-Herlitz JEB; and 3) JEB

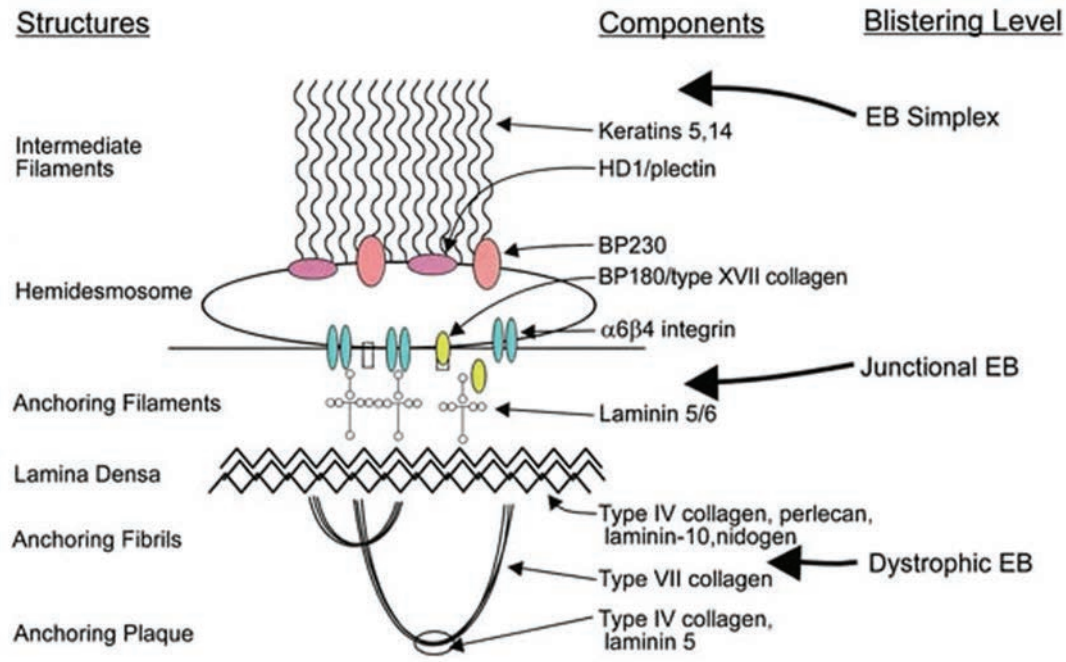

Fig. 1. Classification of EB depending on the level of skin lesions (PathologyOutlines.com, Inc., 2012)

with pyloric atresia [4, 6, 7]. The Herlitz subtype is the most severe generalized type of epidermolysis bullosa. Since birth, children have extensive wound defects that cause frequent septic complications, severe protein–electrolyte disturbance, dehydration, and severe hypotrophy. The presence of extracutaneous bullae (in the esophagus, stomach, respiratory tract, intestine, and urogenital system) causes severe multiple organ failure, and children often die before the age of 2 years.

In addition to generalized bullae, patients with non-Herlitz EB have rough thickened nail plates, atrophic cicatrices, tooth enamel malformations, and scarring alopecia. However, extracutaneous manifestations, except for laryngeal and tracheal stenosis, are extremely rare.

Dystrophic epidermolysis bullosa (DEB) is inherited both in autosomal dominant (DDEB) and autosomal recessive patterns (RDEB). In both cases, the disease is caused by a mutation in the gene responsible for synthesis of type VII collagen (*COL7A1*). Bullae are formed between the basement membrane and the dermis [1, 3, 7–9].

DDEB is characterized by the presence of confluent bullae in children right after birth. The course is usually generalized; however, bullae localize only on the lower limbs, elbows, or knees because of mechanical trauma. The recurrent course causes the formation of milia, atrophic cicatrices (especially affecting the limbs), onychodystrophy, and eventual nail loss. However, severe secondary deformities of the upper and lower limbs as well as extracutaneous manifestations are rare.

Recessive generalized (Hallopeau–Siemens) EB is characterized by a severe clinical course with the generalized formation of bullae and erosion, followed by the formation of atrophic cicatrices, onychodystrophy, nail loss, and severe pseudosyndactyly of the hands and feet. Furthermore, with age, patients develop contractures of elbow and knee joints and hands and feet. Involvement of the gastrointestinal mucosa causes the formation of secondary microstomy, damage to the esophageal mucosa, the formation of cicatricial esophageal stenosis, and swallowing disorders; the combination of these disorders aggravates nutritional insufficiency and causes chronic anemia, growth retardation, and osteoporosis. There is an extremely high risk for patients with this subtype of EB for aggressive squamous-cell cancer development.

Non-Hallopeau–Siemens generalized RDEB is characterized by bullae localized on arms, legs, knees, elbows, sometimes on knee and elbow bends, and on the trunk. The course of the disease is less severe than that of severe generalized RDEB; healing is scar-free.

Kindler syndrome is an extremely rare recessive genodermatosis that includes mutations in the gene encoding the structural protein Kindlin-1 [7]. Bullae are formed in any skin layer. Patients with Kindler syndrome have generalized skin and gastrointestinal lesions, including those involving the formation of anal stenosis. These patients have an increased risk of developing oral mucosal squamous cell cancer.

DIAGNOSIS OF EPIDERMOLYSIS BULLOSA

Taking into account the similarity of clinical presentations for different types of EB, the greatest mistake is made in determining the type and subtype of EB during the neonatal period without performing proper tests. In patients carrying the same mutation, the clinical presentations may differ even for the same subtype of EB. Diagnostic testing can be performed in the prenatal or postnatal periods.

Skin biopsy. Examination of skin biopsy specimens by transmission electron microscopy and/or immunofluorescent visualization of antigen antibodies are two of the methods for diagnosing DEB. It is very important that biopsy sampling is performed properly. Biopsy specimens should be sampled from the anterior edge of a fresh (<12 h) or an opened bulla; some intact adjacent skin needs to be sampled as well because the altered bullae may fail to provide a clear morphological diagnosis.

Immunofluorescence is currently used for preliminary diagnosis to determine at what skin level a lesion has occurred and what proteins are involved in the process. The method is based on binding of monoclonal antibodies to proteins (antigens) that are present in normal specimens. If no specific antigens are present, no staining will occur. It will be possible to determine what proteins are missing, thereby allowing one to identify the type and sometimes the subtype of EB. Hence, in patients with DEB, antigen staining of collagen VII is reduced or absent. Staining of collagen VII can be normal for the mild form of EB; however, visualization may show splitting of the plane of dermal structures as bullae or micro-bullae below the lamina densa and stained collagen VII. Meanwhile, normal staining for other antigens (such as laminin 332, collagen XVII, plectin, α6β4 integrin, and keratins 5 and 14) confirms the diagnosis of DEB [10, 11].

Nevertheless, particularly in patients with mild forms of EB, indirect immunofluorescence data are insufficient to make a diagnosis because antigen levels are almost normal and no splitting of layers is observed.

Transmission electron microscopy, the gold standard EB diagnosis, is performed in these cases. Electron microscopic examination of a skin biopsy specimen visualizes the structures of the basement membrane zone and, in particular, can determine the number and morphology of anchoring fibrils, the presence and morphology of hemidesmosomes, and keratin intermediate filaments. Thus, in patients with all forms of EBS, splitting is visualized at the level of lamina lucida of the epidermal basement membrane or slightly above the basement membrane at the level of hemidesmosomes of the lower epidermis. In patients with Herlitz DEB, examination shows the reduced number of hemidesmosomes, hemidesmosome hypoplasia, and a significant decrease in the number of anchoring fibrils. For non-Herlitz DEB, hypoplastic hemidesmosomes can be observed, and the number of anchoring fibrils is reduced. During infancy, in some forms of DEB, type VII collagen can be intracellularly retained in the basal epidermis instead of being transported to the basement membrane zone.

Genetic testing. With four main types of EB known at present, there are up to 24 genetic subtypes of the disease. The inheritance type is identified and the DNA structure is analyzed to determine the mutation location and its type, which is important for predicting the prognosis of the disease and assessing the risk of giving birth to a child with EB for parents who either already have children with EB or have this disease themselves. After the genetic mutation has been identified in the family, prenatal diagnosis can be performed from the 11th week of gestation by performing amniocentesis, a biopsy of chorionic villi. Pre-implantation genetic diagnosis can be performed for families having EB and undergoing in vitro fertilization [12, 13].

Gene mapping also plays a crucial role in designing specific therapy using genetically engineered drugs, which is the most promising method for pathognomonic therapy at present.

TREATMENT

The treatment of epidermolysis bullosa is a combination of measures aimed at eliminating the existing symptoms and preventing the occurrence of new bullae. Fresh vesicular elements should be opened and drained to prevent the process from further spreading because of the pressure exerted by the fluid [6, 10]. In most cases, dressings applied to the bullae consist of 3 layers: 1) The first (main) layer should loosely adhere to the skin surface to prevent additional trauma and damage to the upper epidermis. The primary layers can consist of dressings impregnated with an emollient (petroleum-based mesh) and topical antiseptics (Adaptic® or Xeroform®) and exhibit antiadhesive properties (e.g., Telfa® or N-terface®). Nonadherent silicon dressings (e.g., Mepitel® or Mepilex®) are also used. Epithelialization ointments (Solcoseryl, Panthenol) and agents containing zinc oxide with antiseptic properties (antibiotics, silver) can be used to prevent and treat the infection as well as to accelerate wound healing in the main layer. Topical glucocorticoids may aggravate the local status and should be used only for a short time in patients with severe EB. 2) The second layer ensures fixation of the main layer and contributes to the multilayer effect to increase patient's activity without mechanical traumatization. 3) The third layer usually exhibits elastic properties, providing the integrity of the dressing (such as Tubifast® and Coban®). However, in patients with EBS, as opposed to other EB types, excessive bandaging may increase the number of bullae, probably because of higher local temperatures and increased sweating rate. Adhesive dressings with the minimal number of additional layers should be used for these patients [6].

Another significant problem is manufacturing orthopedic footwear for patients with EB, which needs to be atraumatic and comfortable to prevent bulla formation. Clothing containing silver fiber has been designed, which makes it possible to reduce infection of the damaged areas (when walking as well). All children with EB require life-long rehabilitation treatment, which includes various types of physical therapy procedures. Adequate rehabilitation treatment allows one to effectively reduce chronic joint contractures, thereby decreasing the number of surgeries on the upper and lower limbs. However, it is very difficult to fix the treatment outcomes achieved using orthotic devices in this group of children because of increased skin traumatization when using rigid fixation; that is the reason for the high rate of deformity recurrence [12].

The British Association of Dermatologists has reported the use of botulinum toxin injected into feet to reduce pain syndrome in patients with extensive bullae on the plantar surface. The effect lasted for an average of 3 months. Electron microscopy examination has shown the elimination of intraepidermal splitting due to botulinum toxin therapy [14]. However, topical use of aluminum-based agents is currently the most widespread method to reduce plantar sweating.

Surgical management is employed to correct secondary deformities (pseudosyndactyly) and contractures of the upper and lower limbs and to close extensive skin defects, including the use of hybrid skin grafts containing keratinocytes from the patient and fibroblasts from a donor [9, 15]. The future of treating this difficult group of patients lies in EB gene therapy, which is currently and actively being developed. Replacement of the defective gene with the normal functioning one is one of the main goals of gene therapy. Thus, recessive DEB is an ideal model for gene therapy because all its variants are caused by mutations in the same gene, *COL7A1*, which encodes type VII collagen, the key component of anchoring fibrils that connect the epidermis to the dermis.

The introduction of mesenchymal stem cells (MSCs) to patients with RDEB is one of the new directions of cell therapy. According to recent studies, the use of MSCs improves and accelerates wound healing by stimulating the secretion of angioprotective factors (such as endothelial growth factor XVII). Using MSCs also has a mediating immunosuppressive effect via the activation of tumor necrosis factor, which in turn reduces the local inflammatory reactions. However, the mechanisms of MSC cell migration toward the affected zone(s) have not yet been studied; the rate of development of severe adverse effects (graft versus host disease) also needs to be assessed.

The investigation of injecting wild-type (WT) fibroblasts into patients with dystrophic EB performed by the Dystrophic Epidermolysis Bullosa Research Association (DeBRA) has now entered

the third phase of clinical trials. According to these data, subcutaneous injection of fibroblasts induces the formation of new deposits of type VII collagen and total regeneration of the previously affected layers [15, 16, 17]. Despite the fact that EB has predominantly cutaneous signs, it is equally important to correct its extracutaneous manifestations. Oral ulcers, microstomy, esophageal stenosis, and disturbed digestion and absorption with a concurrent and constantly increasing demand for energy and nutrients slow down skin repair and induce inflammatory and infectious processes. Hence, the treatment of protein and nutritional deficiencies, correction of water–electrolyte imbalances in children of early age, osteoinductive therapies (vitamin D3 and calcium supplements), and surgical management of secondary GI strictures are the key components of combination therapy for EB [18].

Therefore, there is no unified approach to EB diagnosis and treatment. The challenging nature of differential diagnosis of its subtypes makes specific treatment too late and results in early development of severe complications.

Case report

Patient X., 5 months old, was admitted to the Arthrogryposis Clinics of the G.I. Turner Scientific Research Institute for Children's Orthopedics from an orphanage with a diagnosis of recessive dystrophic epidermolysis bullosa and arthrogryposis involving the upper and lower limbs. According to the past medical history data, it was the fourth pregnancy of the child's mother (the first three children were healthy girls) from a consanguineous marriage; the baby was in the cephalic presentation and had a timely delivery. At birth, the child had flexion contractures of the right elbow joint and both knee joints up to 90° and equinovalgus deformity of both feet. Based on these manifestations, the child was diagnosed with arthrogryposis affecting the upper and lower limbs. Extensively macerated tissue (glove type) was observed on the palmar surface. On day 9 after his birth, the child was transferred to the Children's City Hospital No. 1 for further treatment. Erosions were formed in the plantar and palmar areas with signs of infection; the child received topical conservative treatment. The dermatologists at St. Petersburg State Pediatric Medical Academy diagnosed him with recessive dystrophic EB. At discharge, the lower limbs were fixed with plastic foot orthotic devices in the maximally achievable proper position; however, pronounced skin trauma made it impossible to wear them for a long time. The child was admitted to the Arthrogryposis Department for conservative the treatment of lower limb deformities. Clinical examination revealed numerous bullous elements of irregular shape on hands; fresh bullae on the right hand and opened bullae on the left hand without any pronounced inflammatory signs were also observed (Fig. 2). Flexion contracture of the right elbow joint up to 130° was also observed.

Flexion adduction contractures of the hip joints and 140° flexion contractures of the knee joints were observed for the lower limbs (Fig. 3).

The patient had persistent equinovalgus foot position with the maximum dorsal flexion angle of 20°. The first toes on both feet also had flexion abduction contractures (Fig. 4).

X-ray data showed abduction of the anterior part of the foot and pronation of the posterior part (Fig. 5).

Opened bullae, up to 1.5 × 0.5 cm in size, with moderate hyperemia were detected on the plantar surface of the toes. An extensive surface vesicular element in the epithelization phase was visualized on the plantar surface of the left heel.

Taking into account the presence of open wound surfaces on the patient's feet, treatment was started with applications of multilayer dressings with wound-healing ointments, including zinc-containing agents. Physical therapy (application of polarized light onto de-epithelized tissues) was prescribed. After skin manifestations had been stabilized, the child was subject to serial casting of the equinovalgus foot deformity with bilateral achillotomy. He received nutritional support with protein drugs and intensive therapy using microelements containing zinc oxide and calcium, phosphorus, and manganese ions. The combination therapy also included vitamin D3 at an age-specific dosage.

The presence of concurrent EB necessitated replacing casting bandages more frequently. At first, the bandages were replaced every 4 days because his skin condition worsened abruptly in case of longer immobilization; the number of fresh bullae increased and extensive maceration areas were formed. Hence, eight plaster bandages were required to completely correct the foot position (Fig. 6).

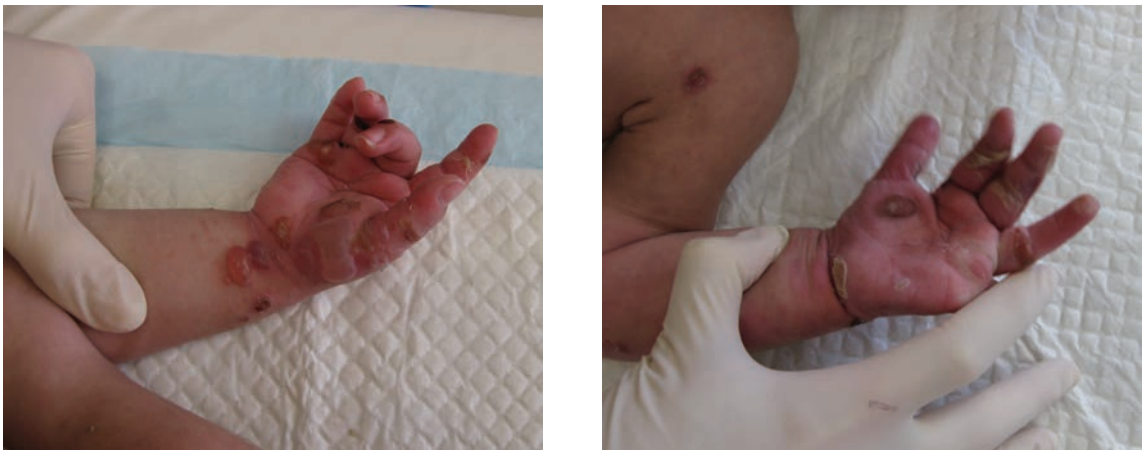

Fig. 2. Appearance of the patient's hands upon admission

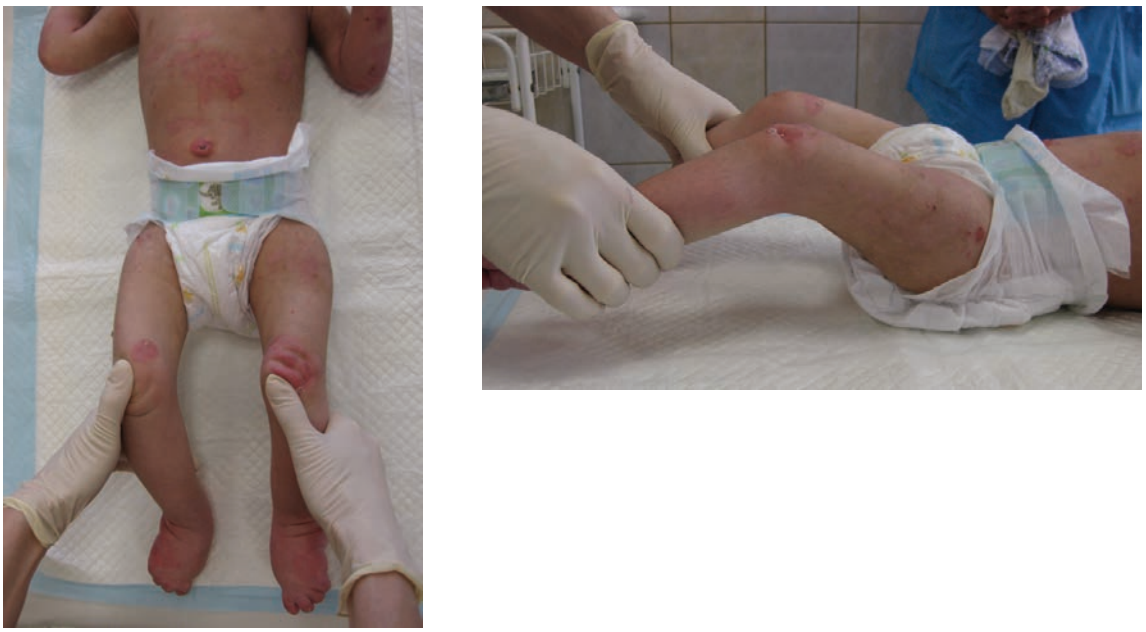

Fig. 3. Appearance of flexion contracture of the knee joints upon admission

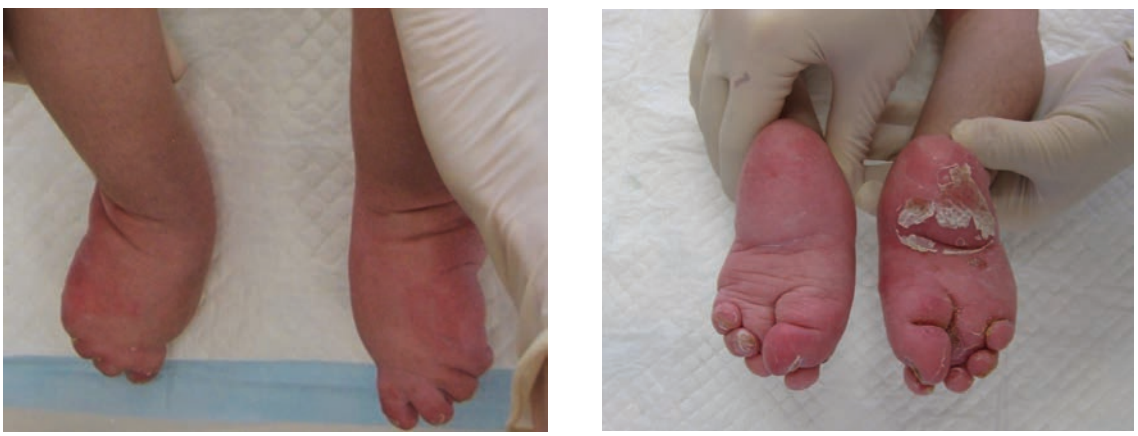

Fig. 4. Appearance of feet upon admission

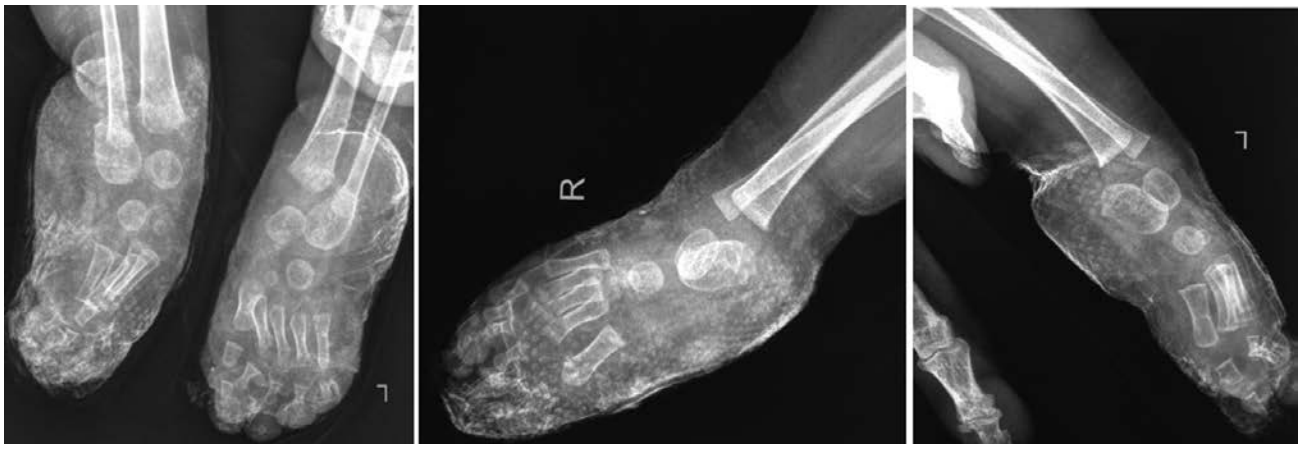

Fig. 5. X-ray of feet upon admission (lateral and front views)

Flexion contractures of the right elbow joint and knee joint also require serial casting. However, we believe that it is reasonable to perform this when the patient gets older because pronounced protein and nutritional deficiency facilitates the formation of new bullae even without mechanical impact. Meanwhile, the need for long-term application of plaster bandages will increase the risk of formation of extensive epidermal defects and, therefore, the development of generalized skin infection. It is also worth mentioning that flexion contractures of knee joints can be treated only after stable correction of foot deformity is achieved.

DISCUSSION

As discussed earlier, further orthotic control to prevent deformity recurrence poses a serious challenge. The situation is aggravated by concomitant arthrogryposis when wearing a rigid orthosis and does not prevent the recurrence of chronic deformity. Unfortunately, even the most modern orthotic devices are not intended for the combination of such complex diseases.

CONCLUSIONS

All children with suspected epidermolysis bullosa need to undergo accurate diagnostic verification using gene mapping to choose the optimal treatment strategy and make the general prognosis. The combination of severe epidermolysis bullosa and arthrogryposis requires the use of a special approach to conservative and surgical treatments for this group of patients. It necessitates meticulous preparation of serial casting and

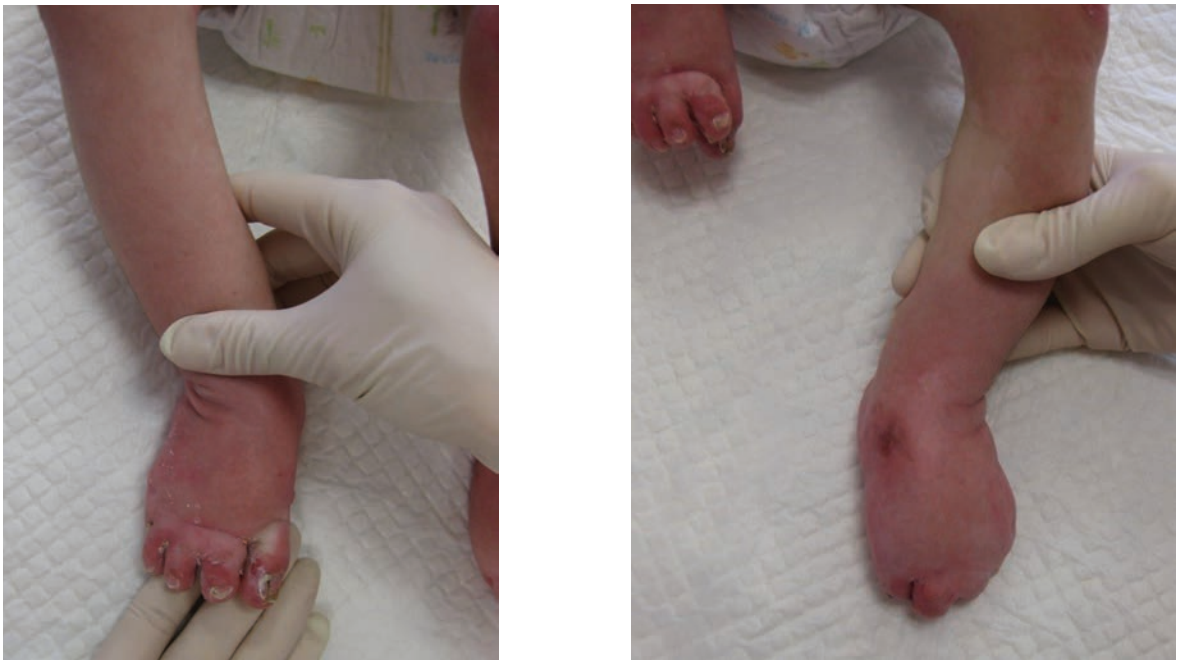

Fig. 6. The result of step therapy of valgus position of the feet

other conservative measures. Designing the next-generation fixation orthotic devices and planning customized rehabilitation programs are expected to improve patients' quality of life and their social adaptation.

References

1. Intong LR, Murrell DF. Inherited epidermolysis bullosa: new diagnostic criteria and classification. *Clin Dermatol.* 2012;30:70-7. doi: 10.1016/j.clindermatol.2011.03.012.
2. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa. *J Am Acad Dermatol.* 2009;61:387-402. doi: 10.1016/j.jaad.2009.03.053.
3. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol*. 2008;58:931-950. doi: 10.1016/j.jaad.2008.02.004.
4. Bolling MC, Lemmink HH, Jansen GH, Jonkman MF. Mutations in KRT5 and KRT14 cause epidermolysis bullosa simplex in 75 % of the patients. *Br J Dermatol*. 2011;164:637-44. doi: 10.1111/j.1365-2133.2010.10146.x.
5. Pfendner EG, Bruckner AL. Epidermolysis Bullosa Simplex. Initial Posting: October 7, 1998; Last Update: September 1, 2011. doi: 10.1007/springerreference_35076.
6. Pope E, Lara-Corrales I, Mellerio J, et al. A consensus approach to wound care in epidermolysis bullosa. *J Am Acad Dermatol*. 2012;67:904-17. doi: 10.1016/j.jaad.2012.01.016.
7. Fine JD, Bruckner-Tuderman L, Eady RA, et al. Inherited epidermolysis bullosa: Updated recommendations on diagnosis and classification. *J Am Acad Dermatol*. 2014;70:1103-26. doi: 10.1016/j.jaad.2014.01.903.
8. Murrell D. Epidermolysis Bullosa: Part I – Pathogenesis and Clinical Features. 1 ed. Vol. 28-1. *Dermatologic Clinics*. Elsevier, 2010. doi: 10.1016/j.det.2009.10.020.
9. Woodley DT, Chen M. Recessive Dystrophic Epidermolysis Bullosa: Advances in the laboratory leading to new therapies. *J of Investigative Dermatology*. 2015;135:1705-1707. doi: 10.1038/jid.2015.149.
10. Bruckner-Tuderman L. Dystrophic epidermolysis bullosa: pathogenesis and clinical features. *Dermatol Clin*. 2010;28:107-114. doi: 10.1016/j.det.2009.10.020.
11. Soro L, Bartus C, Purcell S. Recessive Dystrophic Epidermolysis Bullosa: A eview of disease: Pathogenesis and update on future therapies. *J Clin Aesthet Dermatol*. 2015;8(5):41-46. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4445895/
12. DEBRA International. Available from: http://www.debra-international.org/debra.html
13. Liu N, Guo H, Kong X, Shi H, et al. COL7A1 gene mutation analysis of dystrophic epidermolysis bullosa and prenatal diagnosis. *Exp Dermatol*. 2015;95(4):277-82. PMID: 25877244.
14. Swartling C, Karlqvist M, Hymnelius K, et al. Botulinum toxin in the treatment of sweat-worsened foot problems in patients with epidermolysis bullosa simplex and pachyonychia congenita. *Br J Dermatol*. 2010;163(5):1072-6. doi: 10.1111/j.1365-2133.2010.09927.x.
15. Wong T, Gammon L, Liu L, et al. Potential of fibroblast cell therapy for recessive dystrophic epidermolysis bullosa. *J Invest Dermatol*. 2008;128:2179-89. doi: 10.1038/jid.2008.78.
16. Woodley DT, Wang X, Amir M, et al. Intravenously injected recombinant human type VII collagen homes to skin wounds and restores skin integrity of dystrophic epidermolysis bullosa. *J Invest Dermatol.* 2013;133:1910-3. doi: 10.1038/jid.2013.10.
17. Hovnanian A. Systemic protein therapy for recessive dystrophic epidermolysis bullosa: how far are we from clinical translation? *J Invest Dermatol.* 2013;133(7):1719-21. doi: 10.1038/jid.2013.137.
18. Zidorio APC, Dutra ES, Leão DOD, Costa IMC. Nutritional aspects of children and adolescents with epidermolysis bullosa: literature review. *An Bras Dermatol.* 2015;90(2):217-23. doi: 10.1038/jid.2013.137.

ДИСТРОФИЧЕСКИЙ БУЛЛЕЗНЫЙ ЭПИДЕРМОЛИЗ В СОЧЕТАНИИ С ВРОЖДЕННЫМИ КОНТРАКТУРАМИ ВЕРХНИХ И НИЖНИХ КОНЕЧНОСТЕЙ

© Агранович О.Е., Буклаев Д.С., Тихоненко Т.И.

ФГБУ «НИДОИ им. Г. И. Турнера» Минздрава России, Санкт-Петербург

Буллезный эпидермолиз (БЭ)— это редкое наследственное заболевание, его главный признак — образование пузырей и мокнущих ран (эрозий) на коже и слизистых оболочках, возникающих при незначительном травмировании. Клинические проявления заболевания могут варьировать от локализованных пузырей на руках и стопах до генерализованных высыпаний по всему кожному покрову, а также с поражением

слизистой оболочки внутренних органов. В настоящее время выделено четыре основные группы БЭ: простой, промежуточный, дистрофический и синдром Киндлера. Мутации вызывают изменения в структуре белков, ответственных за адгезию между слоями дермы, что и приводит к образованию везикул. Лечение БЭ представляет собой сложную задачу вследствие отсутствия возможности прямого воздействия на патогенез заболевания, и его основной целью является купирование существующих кожных проявлений и предотвращение появления новых элементов. В статье приводится описание основных типов БЭ, видов современной диагностики и лечения заболевания, а также представлен клинический случай редкого сочетания двух тяжелых патологий — дистрофического буллезного эпидермолиза и артрогрипоза с поражением верхних и нижних конечностей.

Ключевые слова: буллезный эпидермолиз, артрогрипоз, сгибательные контрактуры конечностей.

Information about the authors

Agranovich Olga Evgenievna — MD, PhD, professor, head of the department of arthrogryposis. The Turner Scientific and Research Institute for Children's Orthopedics. E-mail: olga_agranovich@yahoo.com.

Buklaev Dmitry Stepanovich — MD, PhD, chief of the department of arthrogryposis. The Turner Scientific and Research Institute for Children's Orthopedics. E-mail: dsbukl@mail.ru.

Tikhonenko Tatiana Ivanovna — MD, PhD, leading research associate of the department of arthrogryposis. The Turner Scientific and Research Institute for Children's Orthopedics. E-mail: Tikhonenko_turner@mail.ru.

Агранович Ольга Евгеньевна — д. м. н., руководитель отделения артрогрипоза ФГБУ «НИДОИ им. Г.И. Турнера» Минздрава России. E-mail: olga_agranovich@yahoo.com.

Буклаев Дмитрий Степанович — к. м. н., заведующий отделением артрогрипоза ФГБУ «НИДОИ им. Г.И. Турнера» Минздрава России. E-mail: dsbukl@mail.ru.

Тихоненко Татьяна Ивановна — к. м. н., ведущий научный сотрудник отделения артрогрипоза ФГБУ «НИДОИ им. Г.И. Турнера» Минздрава России. E-mail: Tikhonenko_turner@mail.ru.