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PRACTICAL DERMATOLOGY

Inherited Epidermolysis Bullosa: From Diagnosis to Reality

A. Hernández-Martín* and A. Torrelo

Servicio de Dermatología, Hospital Infantil del Niño Jesús, Madrid, Spain

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KEYWORDS
Epidermolysis bullosa;
Complications;
Systemic manifestations;
Treatment

Abstract
Inherited epidermolysis bullosa (EB) refers to a group of diseases that is well known to dermatologists. The diagnosis of an EB disease, which is usually straightforward, is devastating for affected families. The manifestations of forms of EB run well beyond the boundaries of dermatology, as patients frequently present a wide range of associated systemic conditions that can be considerably more severe than the skin disease itself. As dermatologists, we must be aware of the potential complications of EB because our intervention is essential for the correct referral of patients and coordination of all the specialists involved in their care.

PALABRAS CLAVE
Epidermólisis ampollosa;
Complicaciones;
Manifestaciones sistémicas;
Tratamiento

Epidermólisis ampollosas hereditarias: del diagnóstico a la realidad

Resumen
Las epidermólisis ampollosas hereditarias (EA) son un grupo de enfermedades que los dermatólogos conocemos bien, y cuyo diagnóstico, habitualmente inmediato, es devastador para las familias afectadas. Las EA son enfermedades que exceden con mucho el ámbito dermatológico, ya que los pacientes afectados asocian con frecuencia una gran variedad de manifestaciones sistémicas mucho más graves que la propia enfermedad cutánea. Los dermatólogos tenemos la obligación de conocer las posibles complicaciones de las EA, porque nuestra intervención es fundamental para derivar adecuadamente a nuestros pacientes y coordinar a todos los especialistas involucrados en su atención.

Introduction

Epidermolysis bullosa (EB) is a group of diseases well known to dermatologists, and their diagnosis, which is usually straightforward, is devastating for affected families. Fortunately, the frequency of EB is low and, with a prevalence

*Corresponding author.
E-mail address: ahernandez_hnj@yahoo.es (A. Hernández-Martín).

of less than 1 case per 2000 individuals, it can be categorized as a rare disease. While severity varies across the different forms of the disease, prognosis is not entirely predictable a priori because the initial clinical picture does not necessarily correspond to the future severity of the condition. In some forms of EB simplex, lesions are generalized at birth but over time become localized exclusively on the hands and feet. By contrast, in some dystrophic forms of EB—a priori the most severe form—lesions may become localized exclusively over bony prominences and have very little impact on the patient's quality of life. Similarly, a case of EB simplex with considerable involvement of the feet may be much more incapacitating than a mild form of dystrophic EB, despite the fact that EB simplex is theoretically a much less disabling disorder.

EB is a genetic disorder, and its treatment goes far beyond the scope of dermatology since affected patients may have systemic manifestations that are much more severe than those affecting the skin. The aim of this article is to provide a general overview of the complications associated with EB rather than an exhaustive review. As dermatologists, we must have a good understanding of these complications because our intervention is crucial in the appropriate referral of these patients and the coordination of the work of all the specialists involved in their treatment.

The Dermatologist

Diagnosis

The diagnosis of the form of EB in each case has no effect on the course of the disease, but is useful in establishing the patient's prognosis and for providing genetic counseling for the parents if they want to have more children. Three consensus classifications have been published to date,[1-3] the most recent in 2008.[1] Our aim in this review is not to provide a detailed clinical study of all the forms of epidermolysis, but rather to summarize the most important changes in the most recent classification.

1. The classic division into EB simplex, junctional EB, and dystrophic EB has been enlarged by the addition of a new group called mixed or dermoepidermal EB made up exclusively by Kindler Syndrome (Table 1).
2. Two new diseases have been added to the EB simplex group, namely, lethal acantholytic EB[4] and ectodermal dysplasia-skin fragility syndrome (Figure 1).[5]
3. An entity called laryngo-onycho-cutaneous syndrome has been added to the junctional EB category. This syndrome was already known, but not previously identified as a form of EB.[6]
4. The new system makes provision for a large number of dominant forms to be classified as dystrophic EB, a form previously thought to be recessive in almost all cases (Figure 2).
5. It proposes the elimination of the descriptive term "transient" from the type of dystrophic EB formerly known as "transient bullous dermolysis of the newborn," since forms have been reported in which the lesions later reappear.

Table 1 Classification of Epidermolysis Bullosa (EB).[a]

EB simplex (EBS)
Suprabasal Subtypes
Lethal acantholytic EBS
Ectodermal dysplasia-skin fragility syndrome
Superficial EBS
Basal Subtypes
EBS, localized
EBS, Dowling-Meara or herpetiform
EBS, generalized (non Dowling-Meara)
EBS with mottled pigmentation
EBS with muscular dystrophy
EBS with pyloric atresia
Autosomal recessive EBS
EBS, Ogna
EBS, migratory circinate
Junctional EB (JEB)
JEB, Herlitz type
JEB, non-Herlitz type
JEB, non-Herlitz, localized
JEB with pyloric atresia
JEB, inversa
JEB, late onset
Laryngo-onycho-cutaneous syndrome
Dystrophic EB (DEB)
Recessive DEB (rDEB)
rDEB, severe generalized
rDEB, generalized other
rDEB, inverse
rDEB, pretibial
rDEB, pruriginosa
rDEB, centripetalis
rDEB, bullous dermolysis of the newborn
Dominant DEB (dDEB)
dDEB, generalized
dDEB, acral
dDEB, pretibial
dDEB, pruriginosa
dDEB, nails only
dDEB, bullous dermolysis of the newborn
Mixed EB
Kindler Syndrome

[a]Adapted from Fine JD et al.[1]

6. Antigenic mapping is recommended as the diagnostic method of choice rather than electron microscopy because it is considered to be more accessible, cheaper, and easier to interpret than the ultrastructural study.
7. It proposes the elimination of proper names from the classification of these diseases, except for Dowling-Meara EB simplex in the case of EB herpetiformis, and junctional EB of the Herlitz and non-Herlitz types.

Management

EB is currently an incurable disease. Management takes the form of preventative and symptomatic treatment of skin lesions and systemic complications. Early intervention

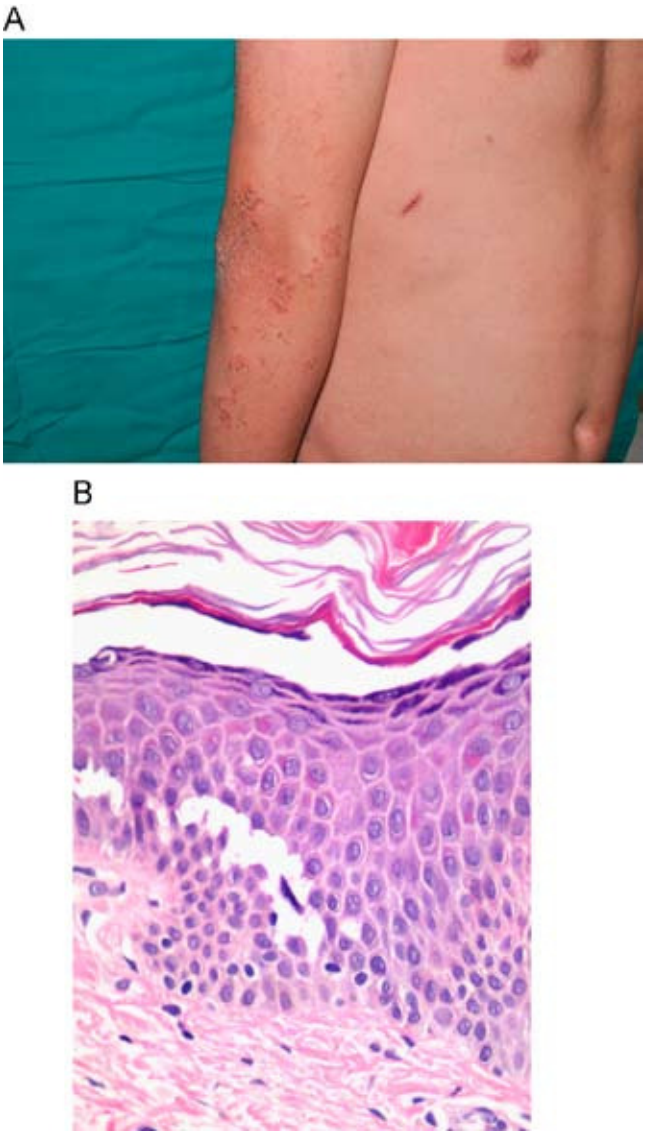

Figure 1 A, Erosive and crusted lesions on the arm of a patient with ectodermal dysplasia-skin fragility syndrome. B, Histological image of the same disease showing suprabasal epidermal acantholysis. Hematoxylin-eosin, original magnification ×80.

Figure 2 Dominant dystrophic epidermolysis bullosa. Mainly ungeal involvement and small white dystrophic scars on both legs (pretibial regions).

is crucial because the patient's quality of life and even their life expectancy depends on adequate and timely management.

Skin Care. Nursing Care

Since the role of the nurse is vital in the care and follow-up of cutaneous lesions in these patients, the availability of experienced and specially trained nursing staff is of great benefit. Unfortunately, the Spanish health care system makes little provision for the specialization of nurses and we generally have to depend more on the willing and positive attitude of these professionals than on specific training programs. Nurses are responsible for educating family members about how to manage and handle their children. They provide guidance to caregivers on the most appropriate dressings and topical treatments and generally stay in close daily contact with the affected families, developing a relationship more easily than would be possible in the case of a physician. Nurses also monitor the patient's lesions over time, identifying foci of infection, ulcers that are not resolving, and other possible local or systemic complications.

The extreme fragility of the skin of children with EB is evident from birth, and measures to prevent blistering must be implemented from that moment on (Table 2). The child must be handled with extreme care, avoiding even very minor trauma, such as rubbing one leg against the other. Padding should be used to protect the areas where blisters most easily occur, such as the heels, knees, elbows, and hands. Despite protective measures, blisters frequently form even without any apparent triggering trauma. Blisters should be drained as soon as the lesion appears, leaving the roof intact except when the contents are purulent, in which case it should be removed. The roof should also be

Table 2 The Ten Commandments of Skin Care in Infants With Epidermolysis Bullosa[a]

1. Lift the infant by placing one hand beneath the buttocks and the other beneath the head. Avoid lifting the baby from under the arms.
2. Dress the infant in soft loose-fitting cotton clothes. Avoid folds.
3. Bathe the infant without soap and very gently apply moisturizing lotion.
4. Dry the body by patting gently. Never rub the skin.
5. Drain blisters using a sterile needle, leaving the blister roof intact.
6. Be meticulous about keeping the skin clean and use chlorhexidine 0.5% as an antiseptic.
7. Do not use antibiotics except when infection is suspected or has been confirmed.
8. The choice of dressing should depend on the degree of exudate and whether or not the lesion is infected.
9. Use non-adherent, non-occlusive dressings.
10. Even before lesions develop, pad bony prominences and areas of the body likely to suffer trauma.

[a]Adapted from the guidelines for the care of newborn infants. (http://www.debra.es/epidermolisis-bullosa/informacion/index.html)

Table 3 Types of Dressings Used in Epidermolysis Bullosa

Primary dressing (silicone or hydrocolloid dressing in contact with the wound)
Superficial erosion/low level of exudation: Mepitel, Urgotul
Deep wounds/exudation ++: Mepilex/Mepilex Lite
Infection: Urgotul SAg, Mepilez Plata

Secondary dressing (placed on top of the primary dressing to protect skin from trauma)
Velband (cotton dressing)
Tubifast/Tubitón (tubular net bandage)

removed from crusted lesions to ensure that the crust does not conceal or promote infection.

A wide range of dressings is available on the market, and the choice of dressing will depend on the depth of the lesion, the volume of exudate, and whether infection is suspected (Table 3). Dressings must always be nonadherent and nonocclusive to ensure that exudate that might act as a culture medium for microorganisms is wicked away from the wound. When an adhesive dressing is required (for example, for monitoring or to secure an intravenous line), a little white petrolatum should first be applied to the area to minimize tension when the dressing is removed.

While bacterial colonization and infection delay and prevent wound healing, the use of topical antibiotics is not indicated unless infection has been confirmed. *Staphylococcus aureus* is the microorganism most commonly isolated. Currently, the staphylococcal strains found in this group of patients are not methicillin resistant, but the incidence of methicillin-resistant strains may increase in the future, following the trend seen in the rest of the population. Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas* are occasionally isolated. However, their presence is often contaminant rather than pathogenic.[7] Uninfected wounds can be cleansed with antiseptics, such as chlorhexidine 0.5% and hydrogen peroxide, or by using small quantities of vinegar or even very dilute bleach in the bath water (the use of povidone iodine is contraindicated in small children and not recommended in adults with extensive erosions).[8] The application of bactericidal or bacteriostatic preparations before dressings are applied is a controversial practice. The bactericides most often used are polymyxin B, bacitracin, and silver sulfadiazine. However, in patients with extensive erosions the risk of percutaneous absorption must be taken into account. For example, cases of systemic argyria secondary to the application of topical sulfadiazine have been reported.[9,10] Several studies have shown that the topical application of honey to wounds reduces unpleasant odor, facilitates debridement, and that the honey even has analgesic properties owing to its antimicrobial and anti-inflammatory effects.[11] The routine use of mupirocin is not recommended because bacterial resistance can develop.[12] In selected cases, when a local infection has been confirmed and the infected wounds are extensive, specific oral antibiotics may be given. Systemic infections are rare and usually caused by catheters or the indiscriminate use of topical or systemic corticosteroids.[8]

Wound care is usually associated with intense pain during the removal of dressings and the application of new ones. In most hospitals, these procedures are performed under sedation, but it is much more difficult to manage pain when dressings are changed in the home. The child should be placed in a bath to soak the dressings so that they can be removed without difficulty. Paracetamol or a nonsteroidal anti-inflammatory drug can be given a few minutes before a dressing change to alleviate the pain caused by manipulation of the wounds.

While pruritus is a symptom characteristic of all forms of EB, it is particularly associated with recessive dystrophic forms of the disease and with EB simplex Dowling-Meara.[13] Pruritus is probably caused by dryness of the skin in the affected area, chronic local inflammation, and the continuous formation of scar tissue. All of these factors trigger the release of itch-mediators and give rise to a self-perpetuating scratch-erosion-itch cycle, which is exhausting for the patient. Therapeutic measures range from simple cold water baths and standard antihistamine treatments to the use of immunosuppressive therapy and immunomodulators, such as ciclosporin[14,15] and thalidomide. However, the efficacy of such treatments is very variable.[16]

A number of researchers are currently investigating the production of artificial skin for wound treatment, but access to such therapies is still exclusively experimental.[17]

General Medical Care

Patients with EB are normal individuals who, apart from the many complications associated with their disease, are also susceptible to contracting any other disease. Children with

EB should be vaccinated as normal in accordance with the standard immunization schedule, standard preventative protocols should be followed, and they should have all the normal pediatric examinations. A certain degree of growth retardation is common but may not necessarily be related to the disease. When applicable, premature birth should be taken into account, as well as the height of the child's parents, and even the possibility of a delay in physical development due solely to reduced mobility. Puberty is delayed in many patients with EB, probably owing to chronic inflammation and nutritional deficiencies among other factors. Delayed puberty frequently has a psychological affect on the patient and may also further exacerbate preexisting osteopenia and osteoporosis, making hormone replacement therapy necessary in some cases.[7]

When these patients require surgery (for example, an appendectomy), meticulous care must be taken to protect their skin. Peripheral venous lines can be inserted in the normal way, but the surrounding area must be protected to prevent contact between the line and the skin (for example, by placing a silicone or hydrocolloid dressing under the cannula). Endotracheal tubes should be somewhat smaller than anticipated for age and well lubricated so that they will slide easily. Before monitoring electrodes are placed, a small amount of petrolatum should be applied to the area to facilitate their later removal. Care must be taken to properly protect and cushion all the weight-bearing areas of the body, and normal skin care measures should be resumed once the intervention is completed (Table 4). Although all of the above recommendations might seem relatively easy to implement, the care of patients with EB usually produces a degree of apprehension in the health care personnel charged with their care. This issue is not easy to resolve when the staff lack the necessary training and experience.

Table 4 Care of Patients with Epidermolysis Bullosa during Surgical Interventions[a]

Preoperative Care
Correct anemia and fluid, electrolyte and protein imbalance
Assess the state of the patient's mouth for intubation (microstomia, unstable dentition)
Assess the heart (echocardiography) in patients at risk for heart disease
Perioperative Care
Make the care protocol known to the patient and all the personnel involved in the procedure
Avoid all accidental trauma during transfer to the operating theater (patients should move themselves where possible)
Do not place identification bracelets on the patient's wrist or ankle. Labels should be affixed to clothing
Do not use adhesive tape to keep eyelids closed
Place padding under blood pressure cuffs
Never use adhesive pulse oximeter sensors (use clip-on sensors)
Make sure intravenous lines are well secured and protect the skin under the line
Lubricate skin before attaching electrodes
Lubricate all tubes before insertion (endotracheal, nasogastric, etc)
Lubricate the perioral zones in contact with the mask, and place the mask carefully over the face
Use bipolar diathermy to obviate need for a dispersive plate
Disinfect the area of intervention without excessive rubbing

[a]Adapted from Fine JD et al[7]

Systemic Complications of Epidermolysis Bullosa

Gastrointestinal Complications

Involvement of the gastrointestinal tract is common in EB and gives rise to considerable morbidity, including growth retardation, refractory anemia, hypoalbuminemia, malabsorption, and malnutrition. While disorders related to gastrointestinal abnormalities are found in every type of EB, they are usually more severe in recessive dystrophic forms of EB. The fragile digestive epithelium is subject to repeated blistering, erosion, and detachment leading to the development of complications (Table 5).

Growth Retardation

Growth retardation is almost universal in patients with recessive dystrophic EB. In a study of patients from the British National Epidermolysis Bullosa Registry, the cumulative risk of growth retardation was 79.4% by 20 years of age in those with severe forms of recessive dystrophic EB.[8] Although less frequent, growth retardation

Table 5 Gastrointestinal Manifestations of Epidermolysis Bullosa[a]

Impaired swallow motility
Dysphagia
Esophageal stenosis
Esophageal folds
Esophageal perforation
Vomiting of detached esophageal epithelium
Gastroesophageal reflux
Esophageal motility disorders
Hiatus hernia
Peptic ulcer
Pyloric atresia or stenosis
Malnutrition and growth retardation
Protein-losing enteropathy
Constipation
Fecal impaction
Rectal stenosis
Rectal fissure
Hemorrhoids
Chronic diarrhea
Megacolon/megarectum
Sigmoid perforation
Diverticulitis
Irritable bowel
Inflammatory bowel disease

[a]Adapted from Fine JD et al.[7]

is also found in severe forms of EB simplex, especially the Dowling-Meara subtype, and in recessive forms of EB simplex. While in some cases retardation is caused by the involvement of the oral and gastric mucosa, in others it occurs despite the lack of any such mucosal lesions.

Growth retardation is influenced by a variety of factors, including insufficient food intake, the increased energy consumption associated with chronic erosive lesions, and malabsorption caused by detachment of the gastric mucosa.[19] Chronic constipation and the development of painful anal fissures aggravate the condition because they give rise to an unconscious rejection of food.[19]

Children with recessive dystrophic EB often reject food, and it is difficult for their parents to know how to deal with this behavior because they do not know whether the child is really experiencing pain or whether the rejection is merely normal childish behavior unrelated to any real physical problem. To prevent growth problems in these patients, their diet should be planned with a view to making sure that they achieve the necessary intake of calories, vitamins, and micronutrients. Oral energy supplements are a useful complement to food intake, and a gastrostomy may also be helpful.[20] Gastrostomy appears to be particularly useful when it is performed before growth retardation is clinically apparent.[18,20] Conversely, prolonged use of nasogastric tubes is not recommended because the chronic friction on the mucosa may cause erosions and scarring. Likewise, parenteral nutrition should only be used in extreme cases because of the risk of septicemia caused by the catheter.[19]

Esophageal Stenosis

Esophageal stenosis caused by repeated episodes of mucosal detachment and subsequent scarring is one of the most important gastrointestinal complications of EB. Stenosis of the esophagus is found in up to 64.9% of patients with recessive dystrophic EB.[18,21] Although the prevalence of this manifestation increases with age, stenosis may develop during the first decade of life.[21] In most cases, stenosis affects the upper third of the esophagus and may involve solitary or multiple strictures measuring anything from a few millimeters to several centimeters.[22,23] Severe stenosis must be corrected, and balloon dilatation is the method preferred by a number of authors.[24,25] In refractory or very severe cases, more aggressive surgical methods may be used, including partial resection or colon interposition, but these are complex procedures associated with high morbidity and mortality.[18,26]

Constipation

Constipation is the most common digestive tract symptom in all forms of EB. Difficulties chewing and swallowing, iron supplements, and pain associated with lesions of the anal mucosa all give rise to fecal retention and a series of associated complications, such as megcolon, mucosal tears, anal fissures, hemorrhoids, intussusception, etc.[18] These patients should eat a fiber-rich diet. Osmotic laxatives and motility stimulants may be given. Enemas and suppositories should be avoided because of the risk of trauma to the anal mucosa.[7]

Pyloric Atresia

Pyloric atresia is observed in a very rare form of EB simplex associated with plectin deficiency[27] and, more frequently, in certain forms of junctional EB associated with $\alpha 4\beta 6$ integrin deficiency.[28,29] In the latter form, systemic involvement is generally very severe and the patient dies in the first few years of life.[29,30] Surgical reconstruction of the pylorus is only undertaken when the child has reasonable possibilities of survival.

Ocular Complications

The ocular epithelium is often affected, and the patient's vision may be irreversibly damaged if early treatment is not received. Severity varies (Table 6); ocular complications may be transient and self-limiting, such as watering eyes and conjunctival erythema, or permanent and scarring, such as ectropion and symblepharon. In the case series recorded in the British National Epidermolysis Bullosa Registry, the most common findings were corneal vesiculation and erosions.[19] Most of the patients with eye involvement have junctional EB or recessive dystrophic EB, but ocular abnormalities have also been reported in severe cases of EB simplex Dowling-Meara.[31] Given the importance of early treatment, it is very important to refer these patients to an ophthalmologist as soon as there is any indication of ocular involvement.

Complications Involving the Oral Cavity and the Laryngotracheal Mucosa

All forms of EB can give rise to bullous, erosive, and scarring lesions of the oral mucosa, but the clinical repercussions will depend on the severity of the lesions and the type of EB (Table 7). During acute erosive phases, patients reject food because of pain. Subsequent scarring may lead to the occasional loss of teeth and give

Table 6 Ocular Complications of Epidermolysis Bullosa[a]

Red watering eyes
Photophobia
Ocular pain
Conjunctival injection and/or edema
Subconjunctival hemorrhage
Blepharoconjunctivitis
Exposure keratitis
Corneal erosions, abrasions, and blisters
Corneal opacities and scarring
Corneal neovascularization
Reduced visual acuity
Pseudopterygium
Symblepharon
Ankyloblepharon
Ectropion
Blocked tear duct
Eyelash thinning
Blisters on periocular skin (eyelids)

[a]Adapted from Fine JD et al.[7]

Table 7 Complications Affecting the Oral Cavity in Epidermolysis Bullosa[a]

Blisters and erosions
Soft tissue scarring
Ankyloglossia
Microstomia
Tooth enamel defects
Caries
Loss of teeth
Difficulties moving food bolus

[a]Adapted from Fine JD et al.[7]

rise to ankyloglossia (impaired tongue mobility), making chewing and movement of food boluses difficult. Caries are particularly characteristic of junctional EB and also very common in recessive dystrophic EB.[32] They are caused by the factors mentioned above in addition to genetic abnormalities affecting the formation of dental enamel (in which type XVII collagen plays a role),[33,34] the high calorie content of food supplements, and the difficulty of ensuring adequate oral hygiene because the patients are unable to open their mouths properly and cannot energetically brush inside the mouth without trauma to the oral mucosa. Microstomia, particularly common in recessive dystrophic EB, makes eating and dental hygiene even more difficult and also makes it very difficult to perform surgical procedures to repair and replace teeth; commissurotomy and other mouth reconstruction techniques may become necessary in some cases.[35] Finally, involvement of the aural epithelium may cause recurrent otitis and ultimately hearing loss, while erosions of the nasal, laryngeal, and tracheal mucosas can cause potentially fatal airway stenosis.[36]

Musculoskeletal Complications

The most important musculoskeletal complication of EB is the loss of hand function. Pseudosyndactyly may develop at a very early age—even during the first few months of life—and in all forms of EB, including the severe forms of EB simplex Dowling-Meara.[37] Webbing of the fingers is common, even at a very young age, shortening their overall length. When extensive erosions develop on the sides of the fingers, the digits may fuse along their whole length if they are not kept well separated during reepithelization. Obviously, fusion of the fingers will reduce the patient's ability to execute fine movements and, in extreme cases, will result in the mitten deformity seen in severe forms of EB in which the fingers are encased in a hyperplastic skin with a stratum corneum as much as 5 times thicker than normal (Figure 3).[38] The same process causes foot deformities that may limit the patient's mobility or even make standing and walking impossible.

Muscle contractures are another common complication that can sometimes be severely disabling. Contractures can affect any joint, but are particularly common around the shoulders, elbows, and knees.[37] Musculoskeletal alterations generally require surgical correction, and repeated interventions are necessary in many cases because recurrence is common.[39,40] When repair procedures are not performed in time, the underlying muscles atrophy and the phalanges are reabsorbed. However, the ideal age to begin such reconstruction has not yet been determined.

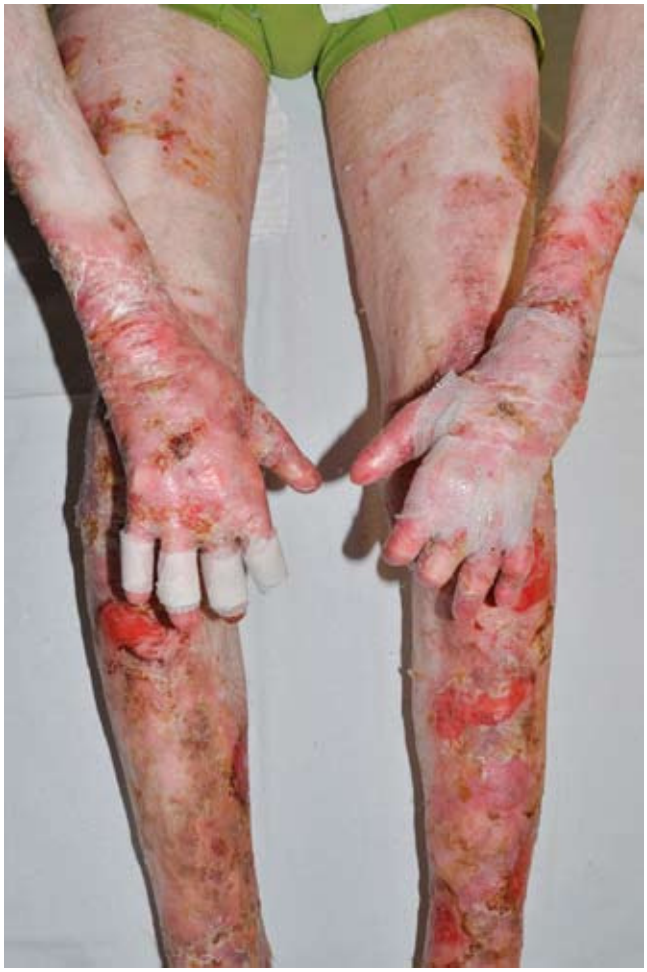

Figure 3 Severe dystrophic scarring on upper and lower limbs with loss of the distal portion of the fingers in a patient with a severe form of recessive dystrophic epidermolysis bullosa.

The development of blisters on the hands and feet should be prevented insofar as this is possible. In some cases, the best solution is to bandage or cushion the distal parts of the limbs even when no blisters are present. Other patients use special bandages or custom-made orthopedic devices to keep the fingers separate during the night in order to prevent the appearance or progression of these complications (Figure 4).

Cardiac Complications

Cardiomyopathy is associated primarily with severe forms of recessive dystrophic EB, but has also been reported in some patients with junctional EB.[41] The most common cardiac complication is dilated cardiomyopathy. The etiology is multifactorial and includes exogenous iron overload, micronutrient deficiencies (especially carnitine[42]

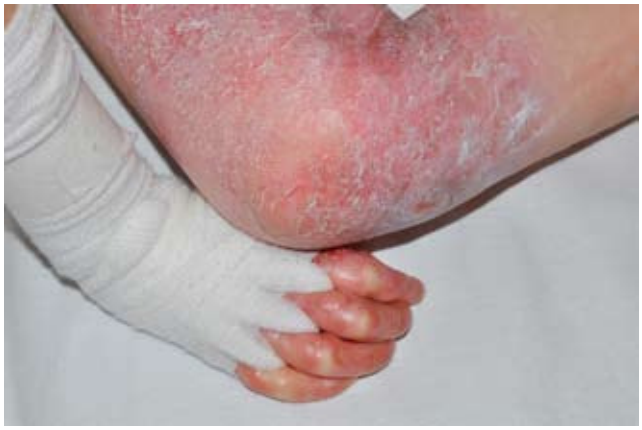

Figure 4 Proximal separation of fingers with cotton bandages to prevent proximal fusion of the fingers (webbing).

and selenium[43]), chronic anemia,[44] the use of cardiotoxic medications, such as amitriptyline and cisapride,[45] and in some cases concurrent viral infections.[46] Cardiac complications can appear during the first decade of life and are more common in patients with chronic renal failure. Fine et al reported that 30% of patients with severe recessive dystrophic EB in whom a cardiac complication was detected died as a results of the heart condition.[41] Heart disease must be diagnosed in its early stages so that all the aggravating factors listed above can be modified insofar as is possible.

Renal and Urological Complications

EB is associated with a wide variety of genitourinary complications, which are chiefly the result of scar retraction.[47] The risk of chronic kidney disease is greater in the severe forms of EB, and contributing factors include hydronephrosis secondary to ureteral stenosis, amyloidosis caused by chronic inflammation, and concomitant poststreptococcal glomerulonephritis caused by bacteremia secondary to skin infection.[48] Chronic renal failure is the cause of death in 12% of these patients, usually those having a severe form of recessive dystrophic EB.[49] Urological complications require surgical treatment in most cases.

Anemia

Anemia is a common finding in these patients and in severe forms of EB it may affect the patient's general state of health, leaving them feeling tired, asthenic, and with little appetite. The causes of anemia are diverse, but iron deficiency and chronic inflammation are determining factors. In addition, it appears that chronic inflammation triggers the release of inflammatory cytokines that inhibit erythropoiesis and negatively affect the efficient use of circulating iron.[50] Correcting iron deficiency by way of oral supplements is difficult because the most bioavailable forms are difficult to swallow and are poorly absorbed in the gastrointestinal tract.[20,51,52] Intravenous iron has been shown to increase hemoglobin levels, improve the patient's general state of health, and reduce the need for blood transfusions.[51,53] It appears that the ferric formulas that minimize anaphylactic reactions are the iron hydroxide-sucrose complex and ferric gluconate,[53,54] and that these formulas are preferable to the intramuscular administration of iron dextran. In any case, the decision about whether to use erythropoietin injections, blood transfusions, or both, and the type of iron supplement and regimen chosen will depend on the characteristics of each case.

Cancer and Epidermolysis Bullosa

Patients with EB have a high risk of developing skin cancer but, fortunately, do not have a increased risk for any internal malignancy. While the risk of developing skin cancer is highest in patients with severe junctional and recessive forms of dystrophic EB, cases of squamous cell carcinoma have also been reported in patients with dominant dystrophic EB and basal cell carcinoma in adult patients with EB simplex Dowling-Meara.[55] Although melanoma is not common in this population, these tumors may appear even in young patients and outside of the areas affected by EB.[7]

Psychological Problems

Children with EB obviously face severe difficulties with social relationships. This is not only because of their physical appearance, which is more or less disfigured depending on their symptoms, but also because they must wear bandages and padding even when they have no lesions, and because they can never take part in the same physical activities as other children. For better or for worse, children with EB have normal intelligence and are aware of their limitations and the rejection their disease provokes in others. They need psychological support to raise their self-esteem and to help them to understand the implications and repercussions of their disease.[56]

The initial psychological support received by the family is also crucially important. Families are often facing for the first time the reality of a severe disease that they have never heard of before and a great psychological effort is needed on their part to understand and adapt to the situation. In fact, the divorce rate and the incidence of other family problems is very high in couples who have a child with EB.[57]

Other Professionals Involved in the Care of Patients with Epidermolysis Bullosa

Genetic Counselors

Each form of EB is caused by the mutation of a particular gene and has a known hereditary pattern. This means that there is an exact genetic diagnosis in every case that can be used to counsel affected patients and their families. Geneticists provide genetic counseling, that is, they explain to those affected the molecular mechanisms that give rise to the particular disease affecting their family and provide them with information concerning the possibility of transmission of the disease to further

offspring. Naturally, the perception of the risk of having an affected child varies enormously depending on the type of EB in question. The perception of risk is not the same in a couple who have lived with a child affected by a mild form of recessive dystrophic EB as it is for a family member of a patient with junctional EB. Geneticists also provide information concerning prenatal diagnosis, which can only be made on the basis of an embryonic tissue sample.[58-60] Apart from ethical considerations beyond the scope of this article, under the current Spanish abortion legislation (the Ley Orgánica de Interrupción voluntaria del embarazo de 5 de julio de 1985), evidence of EB in a fetus is considered sufficient reason under the law to perform a eugenic abortion.

Rehabilitation Specialists, Physiotherapists, and Occupational Therapists

Early and prolonged intervention on the part of rehabilitation specialists, physiotherapists, and occupational therapists is essential. Continuous work on muscles and joints will prevent contractures and deformities and improve the functional capacity of the joints. It will also enable the patient to become independent and will stimulate their integration into society and in some cases even the workplace. Static (preventive) and dynamic (corrective) orthoses, therapist-directed exercises, and games, and certain forms of physical therapy, such as hydrotherapy, are all highly effective tools.[61]

Domiciliary Care Professionals

EB is a chronic incurable disease and patients require continual care and regular and meticulous monitoring. After the first few years, patients and their families and caregivers tend to tire of an exercise that they perceive as "visiting the doctor for nothing." Moreover, at every visit patients are obliged to undress completely and reveal their bodies, which are covered with lesions and scars. In hospital, these examinations are often carried out in areas that lack adequate privacy, and this experience may eventually lead the patient to abandon such visits. Most Spanish hospitals lack appropriate facilities for attending to these patients. Lack of space and, even worse, lack of time to dedicate to a proper examination also contribute to an understandable rejection of consultant visits on the part of the patients. Some countries, such as the United Kingdom, have an effective network of outreach services that monitor these patients in their homes. This monitoring service includes dermatological examination and assessment of the psychological and social factors that may influence the course of the disease. This model of care is extremely effective and it would be advantageous to implement a similar service in Spain.

Pain Management. Palliative Care

Besides the acute pain discussed above in relation to dressing changes, some patients also experience severe chronic pain.[62] Pain may be due to multiple factors, including blisters, chronic ulceration, oral mucosal involvement, corneal erosions, stenoses of the digestive tract, constipation, anal fissures, and muscle spasms caused by contractures. Patients who suffer chronic pain may need to attend a pain clinic or palliative care unit where they can obtain information on the appropriate analgesics for each particular complaint. The life expectancy of patients with junctional forms of EB is, in most cases, very short,[63] and during their brief lives these infants suffer extreme pain and require aggressive analgesic treatment. In the United Kingdom, where the prevalence of this disease is considerably higher than in Spain, such patients can be admitted to palliative care facilities (hospices) where analgesia can be properly administered in a hospital setting. The most radical country is the Netherlands, where euthanasia has been legalized and where, in one case, the parents of an infant with a dystrophic form of EB received legal authorization to terminate their child's life.[64]

Patient Support Associations. Debra Spain

The Spanish branch of the Dystrophic Epidermolysis Bullosa Research Association (Debra) is very active and provides a great deal of support to families (http://www.debra.es). This non-profit organization informs, educates, and supports affected individuals and their families as well as social workers and health care professionals. The organization employs nurse specialists who visit patients at home or in health care centers, regardless of where they live, to explain and demonstrate how dressings should be changed and to provide psychological support. Debra Spain also holds national meetings, fund-raising events, and, above all, works to improve the social and healthcare conditions of these patients in Spain, Portugal, and some 30 other countries.[65]

National Epidermolysis Bullosa Registry

In 2005, the Instituto de Salud Carlos III (a national public research organization) set up a Spanish national registry for EB (http://www.registroraras.isciii.es). The purpose of the registry is to collect information on a large number of patients, both to gather valuable clinical data and to provide affected patients with pertinent information about their disease. Registration is entirely voluntary and highly recommended. In conclusion, the various forms of EB have manifestations that go far beyond the skin disease itself, and these have an enormous impact on the patients' quality of life and in some cases their survival.

Diagnosis is only the first step taken by the dermatologist, and although the skin involvement may eventually cease to occupy center stage, these patients will always need us both as experts in their disease and coordinators of their overall treatment.

Conflict of interest

The authors declare that they have no conflicts of interest.

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