SEDATION AND PAIN MANAGEMENT IN EPIDERMOLYSIS BULLOSA. PRESENTATION OF 4 CASES

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Summary
Epidermolysis bullosa (EB) forms a group of hereditary bullous disorders in which blisters forms either spontaneously or they are triggered by trauma. Under optical microscopy, EBs present with blisters in the subepidermal region and, seeing this region under electron microscopy, over 16 subtypes were observed and gathered in three main groups. Acquired EB is an auto-antibody-mediated disease, in which these antibodies deposit on lamina and sublamina densa, emerge in adulthood, with formation of blisters in areas submitted to trauma, which heal with atrophic scars and milium.

We report four cases of recessive EB diagnosed after birth and admitted in our Neonatology department. At admittance the patients were with blisters and skin erosions form affecting the hands, feet, knees, and elbows and generalized after few days in response to minor injury. All 4 cases received pain therapy: 2 cases with acetaminophen and 2 cases needed a higher step of pain therapy in the pediatric intensive care unit (PICU) with midazolam and fentanyl. Pain management is very important to bring some relief in patients with EB. Because of the chronic evolution of the disease a specialized pain management is preferred.

Key words: epidermolysis bullosa, pain management, newborn, hereditary disorders, bullous lesion

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Introduction
Epidermolysis bullosa (EB) forms a group of hereditary bullous disorders in which blisters forms either spontaneously or they are triggered by trauma; this denomination have been suggested by Köebner in 1886 (Köebner, 1886).

Basal keratinocytes connect to the dermis through the basal membrane area (dermoepidermical junction), as evidenced by Schiff's periodic acid under optic microscopy as a fine, homogenous linear region. Under electron microscopy, two regions are observed: lamina lucida, which is electron-sparse, below basal keratinocytes, and another, lamina densa or basalis, above the dermal area that binds to the upper portion of the latter by anchoring fibrils, which are electron dense filaments. Under optical microscopy, EBs present with blisters in the subepidermal region and, seeing this region under electron microscopy, over 16 subtypes were observed and gathered in three main groups (Fine et al, 2008):

1. Epidermolysis bullosa simplex - there is an intraepidermal cleavage at the lower portion, owing to cytolytic alterations of basal keratinocytes with defects in cytokeratines 5 (KRT5 gene) and 14 (KRT14 gene). Four subtypes are known: Köebner, Weber-Cockaine, Dowling-Meara and Ogna's variant (Ciubotaru et al, 2003).

2. Epidermolysis bullosa junctionalis – cleavage occurs at lamina lucida or at the central region of the basal membrane area, the ceiling being represented by epidermis and the floor by lamina densa. It is owed to alterations in laminin-5 (LAMA3, LAMB3, LAMC2 genes), integrin-a6b4 (ITGA6 and ITGB4 genes) and transmembrane collagen XVII
(COL17A1 gene), being the same as bullous pemphigoid antigen. Four subtypes are known: Herlitz, non-Herlitz and benign generalized atrophic (McGrath, 2006).

3. Epidermolysis bullosa dystrophica – cleavage occurs at sublamina densa. Epidermis and lamina lucida represent the ceiling of the blister and dermis represents the floor. Alteration is exclusively in COL7A1 gene. Four subtypes are known: Cockaine-Touraine, Pasini, Hallopeau-Siemens and the recessive mitis dystrophic form (Hashimoto, 1999; Horn, 2002).

Researchers have proposed a new category termed hemidesmosomal EB, which produces blistering at the hemidesmosomal level in the most superior aspect of the basement membrane zone (Fine et al., 2008).

Acquired EB is an auto-antibody-mediated disease, in which these antibodies deposit on lamina and sublamina densa, emerge in adulthood, with formation of blisters in areas submitted to trauma, which heal with atrophic scars and milium. In this type of EB there is no mutation, however, immunogenetic studies have demonstrated a connection with HLA DR2 (Almeida, 2002).

In EB, both dominant and recessive inheritance patterns are found, up to this date with no association with histocompatibility antigens (HLA) (Hashimoto, 1999; Horn, 2002; Almeida, 2002). According to epidemiological data from the United States of America, epidermolysis bullosa occurs in 50 cases out of 1,000,000 born alive, 92% of them with simple EB, 5% with dystrophic EB, 1% with junctional EB and 2% non-classified. Patients with hemidesmosomal EB probably constitute much less than 1% of total EB cases (Risser, 2009). In Romania there are no epidemiological data.

Hallopeau-Siemens' dystrophic epidermolysis bullosa (DEB) corresponds to a severe form, usually lethal in childhood. It presents with hands and feet synechia, esophageal stenosis, anemia, growth retardation, dysplastic teeth and atrophic scars on the scalp. Mitis subtype is characterized by more discrete alterations, which may vary according to genetic inheritance (De Benedittis, 2004).

**Cases report**

We report four cases of recessive EB diagnosed after birth and admitted in our Neonatology department. At admittance the patients were with blisters and skin erosions form affecting the hands, feet, knees, and elbows and generalized after few days in response to minor injury (Figure 1).

Figure 1: Blisters and skin erosions affecting the feet in a 2 days old newborn

In 2 cases mucous membranes such as the moist lining of the mouth and digestive tract were severe affected leading to feeding difficulties (Figure 2).

Figure 2: Ulcerating lesions involving mucous membrane in dystrophic EB
As the blisters heal, they result in severe scarring. Additional complications of progressive scarring: fusion of the fingers and toes, loss of fingernails and toenails has been observed in the 2 cases (Figure 3).

![Figure 3: Fusion of the fingers and toes, loss of fingernails in dystrophic EB](image)

In all 4 cases the family history indicated an autosomal recessive mode of inheritance. Based on clinical features diagnosis of Hallopeau-Siemens type has been established. No skin biopsy and histological exam have been performed.

Because treatment of EB is primarily preventive and supportive we tried to avoid unnecessary trauma to the skin. Intensive topical therapy with epithelisation cream and drying lotions have been tried to accelerate the healing process and to prevent secondary infections. Also a treatment with phenitoin has been tried without considerable improvement of the skin manifestations. Unfortunately one patient died at 4 months due to pneumocystis carinii pneumonia.

All 4 cases received pain therapy. Psychomotor agitation was improved in two cases by controlling pain with acetaminophen. In the other 2 cases pain could not be controlled only with acetaminophen and a higher step of pain therapy was needed in the pediatric intensive care unit (PICU).

Epidermolysis bullosa lesions behave as those from burns. The essence of lesions management is avoidance of trauma to the skin. For wound dressing changes our patients were admitted in PICU and received pharmalogic analgesia on reducing pain and anxiety during exacerbation of the skin lesions. Respiratory and heart rate were monitoring using only pulse-oximetry, avoiding chest leads. Pre-oxygenation with a high flow of oxygen was achieved with a mask held just over the face without actually touching it. Analgesia and sedation was obtained with midazolam 0.1 mg/kg and fentanyl 2 mcg/kg intravenously. Respiration was spontaneous.

One patient, 4 month old was admitted in PICU with pneumocystis carinii pneumonia for respiratory support on mechanical ventilation. A 3.5 oral endotracheal tube was gently inserted. A nonadhesive endotracheal tube locker was initially used, but because of high risk of accidental detubation during manipulation a thin strip was used to secure the endotracheal tube. Sedation during mechanical ventilation was achieved with continuous infusion of midazolam 0.1 mg/kg/hr and fentanyl 2 mcg/kg/hr. For skin cleansing and wound dressing change on this mechanically ventilated patient we used neuromuscular blockade agents (rocuronium 0.6 mg/kg). Skin cleansing was made with betadine soap and we put Sea buckthorn (*Hippophae Rhamnoides*) ointment on bullous lesions. Rough and stiff clothing were avoided. For the blisters and bullae themselves protective dressings were useful. Antibiotics were used for treating secondary infections of the skin.

**Discussion**

Clearly, the cause of the pain cannot be eliminated. An attempt must be made to protect the skin from injury. This can be accomplished through gentle handling, applying lubricants to reduce friction, and using protective dressings that help prevent friction. Bandages are secured with rolled gauze and tubular retention dressings because using tape and adhesives causes further blistering and skin loss.

All forms of epidermolysis bullosa (EB) are characterized by skin fragility and cutaneous injury. Hence, wound healing is the dominant issue of disease management in all types of EB. Due to ongoing blistering, persistent inflammatory activity,
polymicrobial colonization with frequent infections, poor nutritional status, and oxygen supply, EB lesions often become chronic, non-healing wounds. This causes considerable pain, daily extended wound dressings with costs to the patient, family, and healthcare providers (Mellerio et al., 2005).

Pain and discomfort are universal features in all forms of EB, and their management is central to the well-being and quality of life of the patient (Weiner, 2004). Chronic pain can be a burden for children and families and can impair social functioning and school attendance. During the last decades researchers have discovered much about the causes, mechanisms, and treatment of pain. Additionally, much more is now known about the safe and effective management of pain in infants and children. However, bridging the gap between this knowledge and everyday clinical practice in patients with EB remains a major difficulty.

The sources of pain in patients with EB are multiple and often difficult to treat. Pain may be acute (e.g. from cutaneous or oral cavity blisters and wounds, gastrointestinal reflux, esophageal stenosis or spasm, tooth disease, corneal erosions, or anal fissures), chronic (e.g. from persistent inflammation of the skin, neuropathic pain, bone pain, constipation, or contractures) or procedural (e.g. related to dressing changes or bathing) (Mellerio et al., 2005). Even the milder variants of EB may cause considerable suffering and limitation of normal childhood activities. EBS is often considered to be the mildest subtype of EB but Horn et al. showed that, in her Scottish cohort, EBS had a more marked negative effect on the quality of life than the non-Hallopeau-Siemens variants of DEB (Horn, 2002).

At present, no specific therapy is available for DEB. The approach to the management of patients with DEB must be multifactorial and be based on a series of principles. Therapy should be directed toward prevention of skin trauma to avoid new blister formation, prevention of secondary bacterial infection, aggressive treatment of infection when it occurs, measures to improve wound healing, maintenance of good nutrition, treatment of all correctable complications and, finally, rehabilitation (Bello, 2003).

Severe pain is usually not a major clinical problem, despite the extent of skin denudation. Although pain reduction is appropriate, narcotic analgesics should be avoided whenever possible in order to decrease future risk of narcotic dependency. Topical analgesics are ineffective for control of pain when applied to skin lesions but are helpful in the management of painful anal fissures and erosions (Culpepper, 2001). Fine reported the findings of a study in which 425 patients with inherited EB were sampled to assess the presence of and possible differences in cutaneous pain scores. This study reported that fewer than 10% of individuals with recessive DEB and 12% to 13% of individuals with EB simplex, jonctional EB, and dominant DEB say they are pain-free. Moderate to severe pain frequency was most often noted in patients with clinically more extensive disease involvement. This study demonstrates that cutaneous pain is the norm in all major types of EB - the alarming realization is that approximately 90% of individuals with EB report experiencing pain on an average day (Fine, 2004).

Although many medications on the market treat pain, they are not without significant side effects for the patient. Due to the chronicity of the disease and the prevalence of ongoing pain in this population, a reasonable goal is to determine alternatives to the use of pain medications, which include opioids. While opioids clearly provide pain relief, many of the side effects - constipation, pruritus, tolerance, and central nervous system (CNS) depression - actually may worsen the overall condition of EB (Breslow et al, 1993).
Infants and young children with EB present an even greater treatment challenge. Medications causing CNS depression and sedation frequently result in feeding difficulties and weight loss in the infant. Feeding difficulties in infants with EB may cause a life-threatening downward spiral, as their fluid and protein requirements are already higher due to the presence of wounds and denuded areas. Inadequate nutrition slows wound healing, decreases immunocompetence, and increases susceptibility to infection (Hamilton, 1995).

Conclusion
Living with EB is living with pain. Until a cure is found, patients, parents, and practitioners working with EB maintain a constant quest for alternative, successful methods of wound healing and pain control. Pain management is very important to bring some relief in patients with EB and because of the chronic evolution of the disease a specialized pain management is preferred.

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