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Epidermolysis Bullosa - Why Does a Multidisciplinary Team Approach Matter?

Epidermolysis Bullosa - Multidisipliner Ekip Yaklaşımı Neden Önemlidir?

Abstract

Epidermolysis bullosa (EB) is a rare inherited group of mechanobullous genodermatoses. It is known to be one of the most devastating chronic conditions due to its frequent and detrimental cutaneous and extracutaneous complications. Current treatment is aimed at optimizing the quality-of-life and effectively managing the EB associated complications. In order to provide the best possible care, clinicians need to recognize and appreciate that different subtypes of EB carry different associated co-morbidities. The complexity of medical care in these patients warrants a regular review by a multidisciplinary team experienced in EB. Optimal collaboration and coordination between professionals in the delivery of integrated care is essential for the provision of high-quality care in patients with EB.

Keywords: Epidermolysis bullosa, multidisciplinary team approach, teamwork, complications, management, transition

Öz

Epidermolysis bullosa (EB) mekanik-büllöz genodermatozların nadir kalıtsal bir grubudur. Sık ve zarar verici kutanöz ve ekstra-kutanöz komplikasyonlarından dolayı en harap edici kronik durumlardan biri olarak bilinir. Mevcut tedavi yaşam kalitesini optimize etmeyi ve EB ile ilişkili komplikasyonları etkili bir şekilde yönetmeyi amaçlar. Olası en iyi tedavinin sağlanabilmesi için klinisyenlerin EB'nin farklı alt tiplerinin farklı komorbiditeler taşıyabileceğinin farkında olması ve takdir etmesi gerekmektedir. Bu hastalarda medikal tedavinin karmaşıklığı, EB alanında tecrübeli bir multidisipliner bir ekip tarafından konunun düzenli olarak değerlendirilmesi gereksinimini haklı kılmaktadır. Entegre bakımda profesyoneller arasında optimal düzeyde bir işbirliği ve koordinasyon EB'li hastalarda yüksek kaliteli bakımın sağlanmasında oldukça gereklidir.

Anahtar kelimeler: Epidermolysis bullosa, multidisipliner ekip yaklaşımı, ekip çalışması, komplikasyonlar, yönetim, geçiş

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Introduction

Epidermolysis bullosa (EB) is an umbrella term for a group of inherited bullous skin disorders characterized by skin and mucosal fragility and impaired wound healing. The symptoms and complications experienced by patients with EB can vary widely; however, various extents of blistering from friction, heat or trauma are common in all types of the disease (1). EB is a chronic skin disorder, which has a significant impact on the physical, emotional, social and socioeconomic aspects of lives of the patients. There is currently no cure for EB. As there is progress towards an

effective cure in the form of gene therapy, treatment and management of EB remains symptomatic with skin and wound care, strict surveillance and management of known complications forming a large part of care (2). In order to achieve a comprehensive model of management for patients with EB, a multidisciplinary team model of management is required, especially in cases of managing patients with more severe forms of EB. This article will discuss the coordination of an Australian based multidisciplinary EB service, the common complications associated with severe forms of EB and the required multidisciplinary management.

Epidermolysis Bullosa

EB is classified into four major types of disease; simplex, junctional, dystrophic, and Kindler syndrome; which are further subdivided into 32 subtypes of EB depending on the level of skin cleavage, mode of inheritance and symptoms (1).

The mildest and most prevalent form, EB simplex (EBS), is mostly non-scarring where skin cleavage is superficial in the epidermis. EBS can be subdivided into 12 subtypes depending on the mode of inheritance, genes involved, and clinical manifestation. EBS is predominantly inherited in an autosomal dominant (AD) pattern although severe EBS subtypes such as EBS-muscular dystrophy or lethal EBS are inherited in an autosomal recessive (AR) pattern. Mutated genes associated with EBS are PKP1, DSP, KRT5, KRT14, PLEC1, ITGA6, and ITGB4, producing ineffective proteins such as plakophilin-1, desmoplakin, keratin-5, keratin014, plectin, ectinin-5, keratin014, plectin14, most common type of EBS is EBS-localized, in which blisters frequently form on the palms and soles during early childhood with development of focal keratoderma (1).

In contrast, those with rarer junctional EB (JEB) type have a more severe phenotype characterized by absent nails, dysplastic teeth, oral lesions and laryngeal involvement. JEB is inherited as an AR pattern, with skin cleavage at the lamina lucida. The genes LAMA3, LAMB3 and LAMC2 encoding for laminin-332 protein are affected in JEB. These mutations result in abnormal formation of the hemidesmosome-anchoring filament complex (1).

Dystrophic EB is among the most disfiguring types of EB. The subtypes are classified according to their inheritance; dominant or recessive. Dominant dystrophic EB is a more common subtype with patients developing bullae over the limbs, trunk, and bony prominences. Recessive dystrophic EB is characterized by widespread blistering and erosions involving both skin and mucous membranes. Both types of dystrophic EB have gastrointestinal involvement leading to a myriad of complications (1). Widespread blistering and erosions eventually lead to extensive scarring, contractures and, in the recessive form, pseudosyndactyly of the hands and feet. Those with recessive dystrophic EB, have a significantly increased risk of developing aggressive squamous cell carcinoma (SCC) and is one of the major causes of mortality (2).

Kindler syndrome is a rare form of EB inherited in an AR pattern where skin cleavage occurs at various levels. Kindler syndrome is characterized by poikiloderma, photosensitivity, and skin fragility (1).

Multidisciplinary Team Management in Epidermolysis Bullosa

The extensive time and expertise required to care for patients with generalized forms of JEB and DDEB require delivery of health care by a coordinated multidisciplinary care team (3). Interventional studies have shown repeatedly the advantages of multidisciplinary team management of patients with chronic diseases, improving professionals' adherence to guidelines and patients' satisfaction, clinical and health status, and use of health services. The literature

advocates that care teams should include skilled clinicians and educators, coordinated by utilizing a treatment plan individualized for each patient (4). The teams involved in the care of a patient with EB will vary depending on the myriad of complications and symptoms associated with their disease were discussed later in this article. The core team will include an EB trained dermatologist, EB trained nurse, nephrologist, endocrinologist, gastroenterologist, pain specialist and dietician. Supplementary teams often involved include ophthalmology, dental surgery, hand/plastic surgery, urology, social work, psychology, and occupational and physical therapy (Figure 1).

Outline of Service at an Australian Epidermolysis Bullosa Center

The service at St. George Hospital, Sydney, Australia, is an effective and evidence based, chronic illness management program that enterprises on the varied skills of different services, delivered to the patient in a logistically convenient way.

In 1996, Murrell (5) set up a national diagnostic laboratory for immunofluorescence mapping and transmission electron microscopy for EB at St. George Hospital, Sydney and a multidisciplinary team at Sydney Children's Hospital in 1999. In 2010, she established the first formal adults EB center in Australia. At the age of sixteen, pediatric patients who attend the EB clinic at Sydney Children's Hospital, Randwick, Sydney, are transitioned to the care of the St. George department of dermatology which coordinate the multidisciplinary care required for patients with more severe forms of EB.

The team lead by Murrell (5) and her team consisting of an EB nurse (Margaret Norris, RN) and dermatology registrar, develops individual treatment plans for each patient and coordinate three monthly multidisciplinary reviews in ambulatory care. Formal, written, individualized treatment plans for each patient help to organize the work of teams and help patients and carers navigate the complexities of multidisciplinary care of an orphan disease. Milder EB patients are seen in a clinic dedicated to blistering disease patients with the EB nurse and dermatologist (5).

Each severe EB patient is formally reviewed for a day admission to ambulatory care quarterly. The aim is to monitor the patient and surveillance for any known common complications of EB and to address these issues in a coordinated and timely manner. By having multiple issues addressed in one visit, we aim to alleviate the burden of travelling to multiple appointments, improve compliance and patient health outcomes. In conjunction with these formal reviews, sustained clinical follow up is performed by the EB nurse who is available between visits for monitoring the patient on a regular basis via phone or email.

The Pre-Planning Epidermolysis Bullosa Meeting Before the Multidisciplinary Team Review

Four weeks before the quarterly review, the EB patient has their routine panel of bloods performed (Table 1). The registrar evaluates the data and prepares an updated PowerPoint presentation with those flow charts and previous clinical photography (5). The week prior to the

review of a patient, an one-hour planning meeting is held to discuss the patient, review the investigation results and highlight active medical and social issues that need to be addressed (Figure 2). This is in the form of the updated PowerPoint presentation covering each aspect and problem needing addressing. A written individualized patient update and management plan with action points is developed with an action slide at the end and e-mailed to each consultant involved in the patients care. Consulting teams are notified the week prior to the pending EB review and an appropriate time slot is allocated. All required investigations, such as echocardiogram, bone mineral density (BMD) scans or X-rays are pre-booked for the day of review. The patient is informed about the plan, allowing them to also appropriately prepare for the day.

What Happens on the Day of the Multidisciplinary Team Visit?

On the morning of the review, the patient meets the EB nurse and dermatology registrar in the EB bathroom equipped with a hydraulic bath and heater (Figure 3). The patient bathes in a saline and bleach bath. Then the patient's dressings are removed and the dermatologist performs a full skin examination and quantitatively scores the disease using

the EB Disease Activity and Severity Index score. Previous photographs printed out are compared with current lesions to determine which wounds and lesions are non-healing and may require biopsy. Adherent scales are gently debrided using forceps as SCCs may occur (Figure 4). The patient is then dressed and moved to ambulatory care to await the review of other consulting teams and to have any relevant investigations performed to survey and manage the complications listed below.

In addition to getting involved in the multidisciplinary care of EB patients in Australia, Debra Australia provides educational and supportive interventions directed at helping patients and carers to acquire skills to bolster patients' motivation and their confidence in managing their condition.

Complications of Epidermolysis Bullosa

Different EB centers worldwide have different practices and follow-up routines. The EB subtype, patient's age and comorbidities should be factored when determining the frequency of the follow-up. Some of the common and life-threatening complications of EB are reviewed.

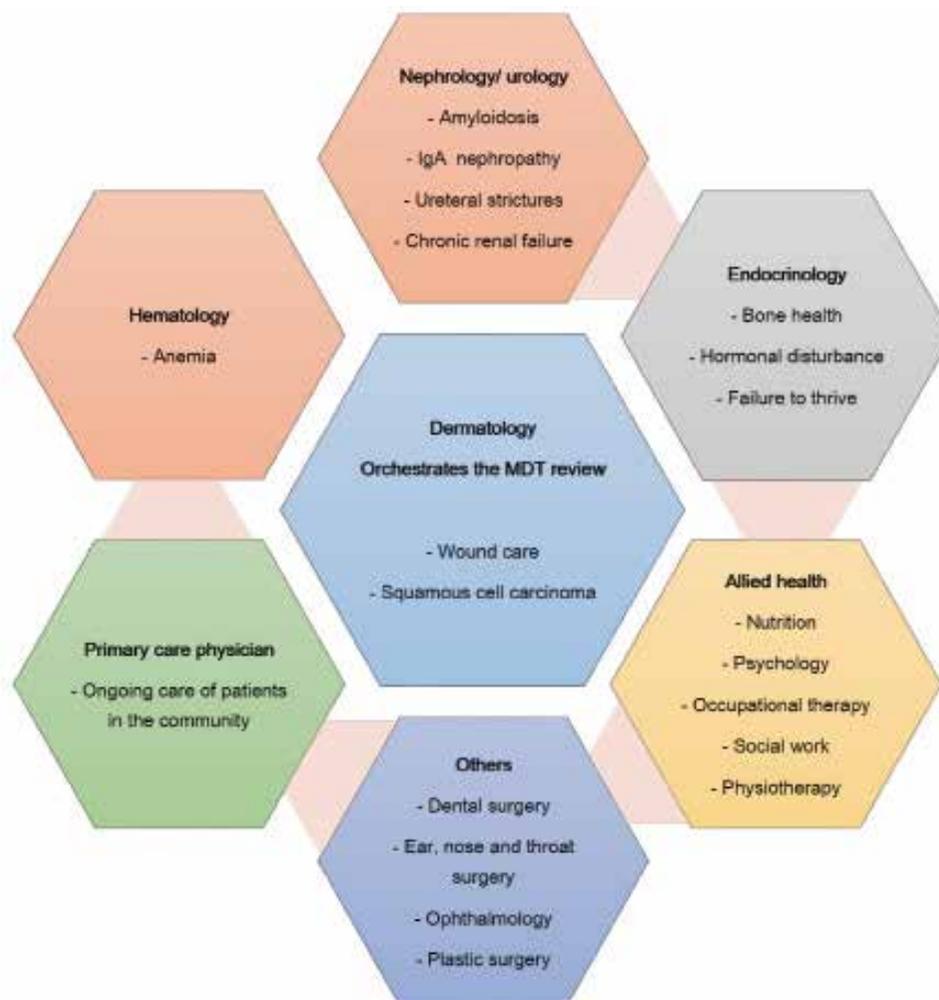


Figure 1. Dermatology team orchestrating the multidisciplinary review for epidermolysis bullosa patients

1. Squamous Cell Carcinoma

1.1 What is Known about Squamous Cell Carcinoma in Epidermolysis Bullosa?

Since the first reported case in 1913, cutaneous SCC in EB remains the most devastating and fearful complication with a high morbidity and mortality (6,7). The risk of developing SCC begins to increase at adolescence and is the highest in recessive dystrophic EB (RDEB). More than 55% of RDEB patients die from SCC before the age of 40. SCCs mostly develop on sun-exposed areas in EBS whereas the most

common sites involved in RDEB are within chronic skin wounds and chronic cutaneous scars. Although rare, some cases of extracutaneous SCC, such as SCC of the hard palate and esophageal SCC, have been reported as well (8,9).

Although the exact pathogenesis of SCC in EB is still not well understood past studies have failed to demonstrate that RDEB SCC and non-RDEB SCC are distinct. Recent studies suggest that the tumor microenvironment may be the main driver of tumor pathogenesis and aggressiveness in RDEB (10,11).



Figure 2. The pre-planning epidermolysis bullosa meeting before the multidisciplinary team review



Figure 3. Specific hydraulic bath for epidermolysis bullosa patients

Table 1. Routine investigations for patients with severe types of epidermolysis bullosa

	Investigations	Frequency	Special instructions
Haematology (serology)	Full blood count with differentials C-reactive protein Erythrocyte sediment rate Red cell folate	Every 3 months	Minimum of 4 mls of blood is required for accurate testing of red cell folate.
Chemical pathology (serology)	Urea, electrolytes, creatinine Calcium, magnesium, phosphate Liver function test Iron studies Soluble transferrin receptor Parathyroid hormone Vitamin A, B1, B2, B3, B12, C, D Zinc, copper, silver, selenium, manganese	Every 3 months	Sera for vitamins need to be protected from light, collected on ice and delivered to lab urgently.
Urine tests	24 hour urine collection protein excretion creatinine clearance urine albumin: creatinine ratio	Every 3 months	Nil.
Ultrasound	Transthoracic echocardiogram	Annually	Nil.
Radiology	lumbar spine x-ray with lateral and anteroposterior (AP) view Dual-energy x-ray absorptiometry	Annually	Nil.
Others (serology)	Luteinizing hormone Follicle stimulating hormone Oestradiol Prolactin	Every 3 months	For female patients only

Flagellated gram-negative bacteria in colonized and infected EB wounds can promote SCC via the Toll-like Receptor-5 (12).

1.2 Monitoring and Management of Squamous Cell Carcinoma in Epidermolysis Bullosa

It is difficult to identify SCC in EB clinically due to its high resemblance to areas of non-malignant EB ulceration and wounds. Clinicians should have a high suspicion for SCC if patients have atypical and non-healing wounds associated with altered sensation relative to normal EB wounds. SCC in EB often grows under areas of hyperkeratosis. Best practice guidelines for EB-associated cutaneous SCCs suggest that patients with RDEB need to have a full skin examination every 3-6 months starting from age of 10 and other types of EB starting from age of 20 (13). There should be a low threshold for diagnostic biopsies in the presence of a lesion clinically suspicious for SCC. As tumor grade is not a good indicator of SCC prognosis in EB, patients should be urgently referred to a plastic surgeon for a surgical excision. Further staging for distant metastases may be required for some patients with a primary SCC larger than 5 cm in maximum diameter or those with signs and symptoms suggestive of metastatic spread. A wide local excision is considered first-line treatment for the majority of SCCs in EB. Other options include amputation, radiotherapy, conventional chemotherapy, and biological therapy, such as epidermal growth factor receptor (EGFR) antagonists (13).

2. Osteoporosis

2.1 What is Known about Osteoporosis?

A reduced BMD has been reported in severe forms of EB, such as JEB and RDEB. A retrospective study of 39 patients with EB concluded that mobility level is the best predictor of BMD in EB (14). Other contributing factors for the poor BMD for these patients include reduced weight-bearing activities, nutritional imbalance, pubertal delay, low vitamin D level from reduced UV exposure, and increased osteoclastic activity in the presence of chronic inflammation and recurrent infection (15). Bruckner et al. (16) demonstrated that short stature, a greater extent of skin blistering, and anemia also correlate



Figure 4. Gentle debridement of adherent scales using forceps

with lower BMD in RDEB. A subset of patients with RDEB also suffers from liver and/or renal complications, resulting in impaired activation of vitamin D.

2.2 Monitoring and Management of Osteoporosis

Major EB centers worldwide recommend that regular monitoring of bone health is mandatory, especially for those at high risk, to maximize bone density and to prevent fractures. Bone health should be monitored with blood tests and radiographic imaging. Regular serological testing should include calcium, phosphate, 25-OH vitamin D, and alkaline phosphatase levels. Plain x-rays and dual-energy x-ray absorptiometry (DEXA) scans are commonly used imaging modalities for assessing radiographic evidence of osteoporosis and occult pathologic fractures. Although there is no consensus regarding the frequency of routine DEXA, many centers perform scans every 1-2 years. Plain x-rays are indicated when patients complain about bone pain. At our EB center, a DEXA scan and a lumbar spine x-ray with lateral and anteroposterior (AP) views are performed annually for adult patients with JEB and RDEB. It is imperative to further investigate the underlying etiology when abnormal findings have been identified.

The evidence for effective management of osteoporosis in EB is lacking. Tailored treatments for patients with JEB and RDEB who have other complications, such as end-stage renal failure, tertiary hyperparathyroidism and esophageal strictures, can be challenging. Bisphosphonates are contraindicated in patients with an eGFR<30. Denosumab has a risk of profound hypocalcemia in dialysis patients without proven benefit as a treatment for osteoporosis. Increased weight-bearing activity and better nutritional support can be of benefit. Pharmacological options for treating osteoporosis include oral/subcutaneous cholecalciferol, oral/ intravenous bisphosphonates and denosumab injection.

3. Dilated Cardiomyopathy

3.1 What is Known about Dilated Cardiomyopathy in Epidermolysis Bullosa?

Patients with RDEB are at a higher risk of developing dilated cardiomyopathy compared to other types of EB. A few cases have also been reported in patients with JEB. According to the National EB Registry (NEBR) data, the cumulative risks of developing dilated cardiomyopathy after the age of 20 in severe generalized RDEB (RDEB-SG), JEB and intermediate generalized RDEB (RDEB-O) were 4.5%, 1.1% and 0.4%, retrospectively (16). Despite a low incidence, dilated cardiomyopathy is a fatal complication with high mortality. Selenium and carnitine deficiency, concomitant viral illness, chronic anemia, iron overload from repeated transfusions, and medications are thought to contribute to the development of dilated cardiomyopathy (15,17).

3.2 Monitoring and Management of Cardiomyopathy

Micronutrients were routinely monitored for patients with JEB and RDEB. In addition, annual echocardiography was recommended. It is vital for clinicians to acknowledge that EB patients may not necessarily exhibit the usual signs and symptoms of dilated cardiomyopathy, as many patients with JEB or RDEB have limited mobility and are sometimes wheelchair-bound.

4. Anemia

4.1 What is Known about Anemia in Epidermolysis Bullosa?

Anemia is a common complication of EB. It commonly affects patients with JEB and RDEB, and a subset of these patients become blood transfusion-dependent. The overall prevalence of anemia among EB patients in Australia is 27.8%, which is much higher than the estimated prevalence of 4.5% in the general population (18). Anemia in EB is thought to be multifactorial in origin. Chronic blood, iron, and protein loss from multiple cutaneous and gastrointestinal wounds, nutritional imbalance from increased metabolic requirements and poor absorption, chronic inflammatory status, and blunted bone marrow response to the elevated levels of erythropoietin (EPO) are potential contributing factors (19-21). Patients with anemia often experience chronic lethargy, dizziness, reduced exercise tolerance, dyspnea, and impaired wound healing. Such signs and symptoms of anemia have a substantial impact on a patient's daily life and their quality of life.

4.2 Monitoring and Management of Anemia

Many patients with EB have chronically elevated inflammatory markers (erythrocyte sediment rate and C-reactive protein), most likely as a result of chronic wound healing. Ferritin is not a useful indicator of iron stores in EB, as chronic inflammation results in falsely elevated ferritin levels. Measuring soluble transferrin receptor (STR) levels in such patients may be helpful in determining whether the patient is truly iron deficient or not. It is important to rule out thalassemia trait in patients with chronic anemia, as iron overload in patients with thalassemia can result in organ damage (22). Patients with ongoing anemia of unknown etiology warrant more extensive investigations with radiographic imaging modalities, pill-cam, upper endoscopy and colonoscopy to rule out an internal source of bleeding.

Iron-rich foods and iron supplements can be helpful in preventing and treating mild anemia (15). Patients may require aperients, as oral iron supplements can cause constipation. Concurrent intake of vitamin C can increase absorption of iron. A number of case reports have demonstrated the beneficial role of iron infusion and EPO in EB patients with moderate-to-severe anemia. Regular use of EPO can be especially accommodating in treating anemia for patients with chronic renal failure and impaired EPO synthesis. Iron sucrose and ferric gluconate complex formulations are favored over iron dextran, as the risk of anaphylaxis is much less. Packed red blood cell transfusions are indicated for patients with severe anemia.

5. Renal and Genitourinary Complications

5.1 What is Known about Renal and Genitourinary Complications in Epidermolysis Bullosa?

EB patients have recurrent skin infections from chronic wounds. Subsequently, post-infectious glomerulonephritis resulting from streptococcal or other infections are frequently observed in EB. IgA nephropathy is the most common type of glomerulonephritis in EB, evidenced by microhematuria, proteinuria, and the presence of IgA deposition on IF. Up to 30% of patients with IgA nephropathy develop end-stage

renal failure (23,24). Renal amyloidosis has been documented in JEB, DEB and RDEB, with chronic inflammation and antigen stimulation thought to be responsible. Patients with renal amyloidosis have proteinuria, edema and hypoalbuminemia.

Urinary tract involvement in EB was first reported in a 3-year-old patient with RDEB in 1973 (25). According to a study with 3,280 patients with EB, genitourinary complications were found in all EB subtypes (26). These complications were most frequently observed in RDEB (31.1%) followed by JEB (30.2%), DDEB (19.5%) and EBS (16.6%). Severe dysuria is sometimes experienced by EB patients when blisters and erosions develop within the urethral orifice. Urethral meatal stenosis, urinary retention and bladder hypertrophy are more commonly observed in patients with JEB and RDEB. Some cases of hydronephrosis secondary to ureteral strictures requiring ureteral dilation, nephrostomy tube placement and ureteral sigmoidectomy have also been documented (26).

5.2 Monitoring and Management of Renal and Genitourinary Complications

Collective literature reports about 1 in 8 patients with RDEB-GS will likely die due to chronic renal failure (20). Renal amyloidosis due to secondary amyloidosis is also deemed disastrous in RDEB, with 7 deaths out of 8 reported cases. Rapid progression of nephropathy, delayed diagnosis, and extremely difficult blood access for hemodialysis in patients with RDEB are thought to contribute to this high mortality (27). Dialysis using a central venous catheter carries a high risk of sepsis due to catheter infection, but it may be the only available option for some patients. It is imperative to routinely screen at-risk patients for any early signs of subclinical renal impairment. Patients with JEB and RDEB should have routine investigations to monitor renal function. There are no guidelines for the frequency in which urinalysis and renal function tests should be completed. RDEB patients should be regularly screened via urinalysis and serum amyloid A protein levels for the early diagnosis of renal amyloidosis. At our EB center, we perform serological investigations including electrolytes, urea, creatinine, calcium, magnesium and phosphate for patients with JEB and RDEB at 3-month intervals. A 24-hour urine collection is also requested to calculate protein excretion, creatinine clearance and urine albumin: creatinine ratio.

6. Ophthalmological Complications

6.1 What is Known about Ophthalmological Complications in Epidermolysis Bullosa?

Embryonically, the skin and the ocular surface are both derived from the surface ectoderm (28). As such, there are ultrastructural similarities in the interface between the basal epithelium and underlying connective tissue in both the skin and the cornea (29). Since the first documentation of ophthalmic involvement in EB in 1904, a number of case studies have reported the ocular manifestations of EB (30). Some of the findings included corneal erosions, corneal blisters, corneal scarring, symblepharon, blepharitis, ectropion, lacrimal duct obstruction, impaired vision and blindness. Patients with RDEB and JEB experience eye complications more frequently than patients with EBS (31). Amongst the

listed complications, corneal blisters and erosions were the highest occurrences. Ocular involvement is more common in childhood and the frequency gradually diminishes over time. As in the cases with cutaneous blisters, patients can develop corneal blisters and erosions from rubbing/friction of the eye and from minor trauma.

6.2 Monitoring and Management of Ophthalmological Complications

Prophylactic preservative-free artificial tears or lubricants may be needed to reduce friction of the lids over the eye. Antibiotic ointments are used in patients with erosions. Eye surgery is indicated in patients with ectropion (32). In our center, patients with JEB and RDEB are reviewed by an ophthalmologist annually.

7. Oral Disease

7.1 What is Known about Oral Disease in Epidermolysis Bullosa?

Ankyloglossia, microstomia, disappearance of gingival fornices, enamel defect, dysplastic teeth, excessive caries and premature loss of teeth are observed in patients with RDEB, DDEB and JEB (20). The frequency of enamel defects and dental caries in EBS is similar to that of the unaffected population. According to a cross-sectional study performed by Fortuna et al. (33) in 2015, 62.2% of the patients with DEB had gingival involvement with erythema being the most common clinical manifestation, followed by erosions and ulcers. The affected anatomical sites were equally distributed and no gender difference was observed. The frequency of caries development is higher in patients with JEB and RDEB compared to those with EBS or DDEB. Compromised oral hygiene due to microstomia, pseudosyndactyly and fear of applying adequate force on tooth brushing predispose patients to dental plaque accumulation and caries formation (34). Enamel defects are most frequently observed in JEB.

7.2 Monitoring and Management of Oral Disease in Epidermolysis Bullosa

Sucralfate powder has been successfully used on the oral mucosa in patients with DEB. It is thought to prevent oral blisters and reduce discomfort. Oral hygiene with regular gentle tooth brushing is important to prevent caries development. Many studies have proposed the use of fluoride and chlorhexidine as a preventative measure against oral disease in EB (35). Caries prevention, professional plaque removal, dietary advice, and topical fluoride application by a dentist have been proven to be useful in maintaining dental health in these patients. In our center, we recommend patients with JEB, DDEB and RDEB to be reviewed annually by a dentist experienced in EB.

8. Mental Health

Psychological and psychiatric conditions, including depression and altered perception of body image, are commonly observed in patients with severe forms of EB (22). Chronic pain, worsened wound healing, and development of EB-related complications may be contributing factors. It is also well-known that parents of a severely affected EB child are more likely to get divorced. Disease-related financial burdens

and lack of social support have a significant impact on the psychological well-being of EB patients and their families. In our center, patients' quality of life (QOL) is routinely monitored using QOLEB questionnaire (36). Social service, psychologist and psychiatrist review should be provided when necessary.

Conclusion

Caring for patients with EB can be a real challenge as patients with severe types of EB frequently develop a myriad of cutaneous and extracutaneous complications. Clinicians need to recognize and appreciate that different subtypes of EB carry different risks and associated comorbidities. A multidisciplinary approach is crucial to delivering comprehensive, quality care to these patients.

Ethics

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Minhee Kim, Anes Yang, Dedee F. Murrell, *Concept:* Minhee Kim, Anes Yang, Dedee F. Murrell, *Design:* Minhee Kim, Anes Yang, Dedee F. Murrell, *Data Collection or Processing:* Minhee Kim, Anes Yang, Dedee F. Murrell, *Analysis or Interpretation:* Minhee Kim, Anes Yang, Dedee F. Murrell, *Literature Search:* Minhee Kim, Anes Yang, Dedee F. Murrell, *Writing:* Minhee Kim, Anes Yang.

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