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Original Research Paper

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EPIDERMOLYSIS BULLOSA- A NARRATIVE REVIEW

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KEYWORDS :

INTRODUCTION

The term Epidermolysis Bullosa (EB) was proposed in 1886 and refers to mechanobullous diseases which are caused by mutations in various structural proteins of skin and presents as blistering of skin following minimal mechanical trauma.[1] The disease severity varies and there are some types that affect only limited areas on body, whereas others can be severe enough to cause involvement of generalized skin surface along with mucosa, badly affecting the quality of life of patients as well as their families.[2]

Since there is lack of curative treatment at present, management of EB is centered on routine skin care, prevention and timely recognition and management of complications. Wound care, infection control, pain relief and enhancing nutritional level play an important role in raising their quality of life. The nutritional care in EB encloses tackling malnutrition and nutritional deficiencies and promoting growth and pubertal development. This multitier approach should also manage bowel function, immune status and wound healing.[3]

Pathogenesis of EB

EB occurs due to mutation in the genes encoding several structural proteins present at the dermoepidermal junction (DEJ). Based on the level of split in the skin, EB is divided into 4 major types - EB simplex (EBS, split at the level of basal cells), junctional EB (JEB, split at the level of lamina lucida), dystrophic EB (DEB, split at the level of anchoring fibrils and sub lamina densa) and Kindler syndrome (multiple levels of split). About 30 phenotypes with 18 candidate genes are already known with new subtypes being increasingly recognized.[4] The classification along with inheritance pattern is summarized in Table 1.[5]

Table 1. Classification and inheritance pattern in EB.

Type	Subtype	Inheritance	Defective antigen
EB simplex (EBS)	**Suprabasal**		
	Lethal acantholytic EB	AR	Desmoplakin
	Plakophilin deficiency	AR	Plakophilin 1
	EBS superficialis (EBSS)	AD	?
	Basal		
	EBS – localized	AD	Keratin 5, Keratin 14
	EBS – Dowling-Meara	AD	Keratin 5, Keratin 14
	EBS- Generalized non Dowling-Meara	AD	Keratin 5, Keratin 14
	EBS with mottled pigmentation	AD	Keratin 5
	EBS – migratory circinate	AD	Keratin 5
	EBS – Ogna	AD	Plectin
	EBS with muscular dystrophy	AR	Plectin
	EBS with pyloric atresia	AR	Plectin
	AR-EBS	AR	Keratin 14
	AR-EBS (new subtype)	AR	BPAG1-e
Junctional EB (JEB)	Herlitz JEB	**AR**	Laminin 332
	Non Herlitz JEB		
	Localized	AR	Type XVII collagen (BPAG 2)
	Generalized	AR	Laminin 332, Type XVII collagen (BPAG 2)
	Pyloric atresia	AR	Alpha 6 beta 4 integrin (α 6 β 4 integrin)
	Inversa	AR	Laminin 332
	Late onset	AR	?
	LOC syndrome	AR	Laminin 332, alpha 3 chain
Dystrophic EB (DEB)	**Dominant (DDEB)**	AD	Type VII collagen
	DDEB-Generalized	AD	
	DDEB-Acral	AD	
	DDEB-Nails only	AD	
	DDEB-Pretibial	AD	
	DDEB-Pruriginosa	AD	
	DDEB-Bullous dermolysis of new born	AD	
	Recessive (RDEB)	AR	Type VII collagen
	RDEB - generalized	AR	
	RDEB-Localized	AR	
	RDEB-Pretibial	AR	
	RDEB-Pruriginosa	AR	
	RDEB-Inversa	AR	
	RDEB-Centripetalis	AR	

	RDEB-Bullous dermolysis of new born	AR	
Kindler syndrome		AR	Kindlin 1

AD- autosomal dominant, AR- autosomal recessive

Diagnosis of EB:

As clear from above classification, different types of EB are inherited differently hence their clinical features, course, complications, extracutaneous involvement, treatment and final outcome in terms of survival are also different.[6] This diagnosis can be established using clinical features and laboratory tools. When arrived at a correct/most probable diagnosis, mutational screening for the most probable altered antigens can be requested for which gives final clinical diagnosis and predictability for future generations of the same/ related families to have same/related disorders, thereby helping in genetic counselling of frightful parents after they have had one child that is affected with a severe type of EB.

Clinical approach is immensely important in resource poor settings. Also, severity scores named Birmingham EB severity score (BEBs)[7] and Instrument for scoring Clinical outcomes of research for Epidermolysis Bullosa (iscorEB)[8] have been developed. It helps to stratify the clinical features according to severity and helps in monitoring improvement in severity.

Laboratory tools in diagnosis of EB:

Although clinical features of different EB subtypes are different and definitely contribute towards an accurate diagnosis, final diagnosis can be ascertained after certain laboratory investigations that help to locate the site of blistering. Light microscopy is not very helpful in diagnosing types of EB as it fails to identify alterations at molecular level but it helps to differentiate EB from other acquired autoimmune disorders. In order to make an accurate diagnosis, it is essential that a freshly induced blister is biopsied, from a clinically uninvolved area using either a punch or shave biopsy.[9]

Electron microscopy: EM still remains the gold standard for diagnosis of EB. This technique allows locating level of split in EB skin and semi-quantitative assessment of the specific structures such as keratin intermediate filaments, desmosomes, hemi-desmosomes, anchoring fibrils etc. In EBS, blister formation is seen at the level of basal cells. EBS Dowling-Meara variant shows clumping of tonofilaments in basal cells. In JEB, blister formation is through lamina lucida of BMZ. Hemidesmosomes are small and rudimentary in severe Herlitz variety. In DEB, split is below lamina densa and anchoring fibrils are either reduced (DDEB) or absent (RDEB).[10]

Immunofluorescence Antigen mapping: IFM is a modified indirect immunofluorescence technique. Antibodies to BP antigen (hemidesmosomes), laminin (lamina lucida) and type IV collagen (lamina densa) are used. The level of split is determined by noting which antigens are seen on roof and floor of blister. In EBS, all the three antigens will be located on the floor of blisters whereas in DEB, all three will be located on the roof of blister. In JEB, BP antigens will be in the roof and laminin and type IV collagen will be on the floor side.[11]

Sensitivities and specificities of EM on comparing with genetic testing were 71% and 81% and those of IFM were 97% and 100% respectively.[12]

Immunohistochemistry[13]: Immunohistochemistry involves the use of specific monoclonal antibodies against various proteins. The advantage of this test is that this can be done on formalin fixed and paraffin embedded sections. It can be performed in any of the routine pathology laboratories. By this technique one can find out the presence or absence of the specific target proteins involved in EB.

Onion skin approach for diagnosis of EB: Onion-skin approach refers to a holistic approach for ascertaining final diagnosis in a patient affected with EB. Like layers/ skin of onion, we go from superficial to deep i.e. use clinical, laboratory and finally genetic tools in that order to identify the mutation in an individual EB patient and manage accordingly.[5]

Treatment of EB:

Supportive management, excellent nursing care and adequate and timely referral to other specialities is the cornerstone for treating every EB patient. Various medical therapies like phenytoin, minocycline, vitamin E, retinoids, cyclosporine, tetracyclin, cotrimoxazole etc. have been tried but without conclusive benefit. Specific newer options consist of gene therapy, protein therapy and fibroblast therapy.[14,15](Table 2)

Table 2–Newer therapeutic modalities for epidermolysis bullosa.[16]

Sl. No.	Therapies with curative aim	Investigational Drug	EB Type
1.	**Gene therapy**	Transplantation surgery of genetically corrected cultured epidermal autograft	JEB with COL17A1 mutations
		Genetically corrected cultured epidermal autograft	RDEB
		FCX-007, Genetically modified autologous human dermal fibroblasts	RDEB
		KB103, a non-integrating, replication-incompetent herpes simplex virus vector expressing human collagen VII protein	DEB
2	**Antisense oligonucleotide**	QR-313, an antisense oligonucleotide	DEB with mutations in exon 73 of COL7A1
3	**Premature termination codon read-through**	Gentamicin, intravenous	RDEB
4	**Cell therapy**	Serial mesenchymal stem cell infusions from a related donor	All EB types
		Allogeneic stem cell transplantation and "off-the-shelf" mesenchymal stem cells	All EB types
	Symptom-relief therapies		
5	**Anti-fibrotic**	Losartan, systemic	RDEB
6	**Anti-inflammatory**	Diacerein, topical	EBS
		Oleogel, topical	All EB types
		BPM31510 3.0% Cream, topical	All EB types
		Sirolimus, topical	EBS

Care of EB patient:

Care of EB patient primarily involves thoroughly educating the

parents/ caretakers.

The primary goals are:

1. Prevention of trauma to skin
2. Wound care and avoiding infection
3. Ensuring adequate nutrition and preventing dietary complications
4. Reducing deformities and contractures
5. Promoting a positive attitude and a strong support system.

Protection of the skin against trauma: (Table 3)

Table 3- Do's and don'ts while taking care of Epidermolysis bullosa.

DO's	DON'T
Aspiration of blisters with sterile needles to prevent the fluid pressure to increase blister size. making the blister larger.	After aspiration, blister should not be rubbed as the roof of the freshly popped blister serves as natural protection or a covering for the area.
Soft, non-abrasive materials like satins, silk, soft cotton should be preferred for bedding and clothing. Wearing clothing inside-out prevents friction against child's skin.	Adhesive bandages or tapes should always be avoided.
Loose-fitting and lightweight clothes reduce friction; eventhough, snug tights or leggings help to hold bandages in place and protect the limbs.	Avoid lifting child from under his/her armpits and sites where his/her wounds are, and prefer to lift from bottom or upper thighs and across back.
Apply bandages to pad the child's feet.	Avoid firm or poorly-fitting shoes
For newborn babies, preferably lay them on an absorbent pad rather than use a diaper.	

Prevention of infection and care of erosions:

Despite routine care, it is difficult to prevent formation of blisters. Utmost skin care, with special attention to erosions should be provided. Adequate wound management helps to control pain, enhances healing and decreases risk of infections.

Minimizing deformities and contractures:

Contractures are due to tightening of skin, ligaments, and tendons causing decreased range of movement at the joint. Regular physiotherapy should be advised to prevent muscle atrophy.

Ensuring adequate nutrition and preventing dietary complications:

Similar to patients with burns, extra protein and calories are required to help in wound healing. However, increasing food intake in EB children is challenging owing to painful blisters and erosions in the mouth and throat. Hence close monitoring of fluid and protein loss, early initiation of breast feeding. Soft, pureed foods, frequent feedings and snacks should be encouraged to meet the nutritional needs.

Management of extracutaneous complications

The spectrum of EB ranges from mild to severe based on extent and depth of involvement of cutaneous and extra-cutaneous structures. Involvement of oral mucosa, teeth and gastrointestinal system, eyes, respiratory system, genitourinary and musculoskeletal systems may be seen.[17]

THINC (Tool to Help Identify Nutritional Compromise) is a scoring system which evaluates factors interfering with dietary intake. Factors like growth, gastrointestinal involvement and dermatologic manifestations are considered. Higher scores indicate poor nutritional status.[3]

Gastrointestinal system involvement includes gastresophageal reflux disease, strictures of oesophagus, peptic ulcer disease, protein-losing enteropathy, inflammatory bowel disease, anal fissures and constipation.

Management of each complication is as follows:

1. Esophageal stenosis- Dietary modifications in the form softer food with a high calorie content is preferred in children with mild strictures. For those with severe strictures, Periodic fluoroscopy-assisted pneumatic balloon dilation is the best procedure of choice provided minimal instrumentation, is done to avoid mechanical trauma.[18]
2. Constipation - Recommended fibre intake in EB children is calculated as- age of the child (in years) + 5-10 g/day; this is similar to European Food Safety Authority requirements.[19]
3. Anemia - Oral and parenteral iron administration is advised. Transfusion is indicated in symptomatic patients not responding to iron supplements and in patients having persistent low hemoglobin levels (< 8g/dl).[20]
4. Malnutrition- In EB children and adolescents, Supplementation of 100% to 150% of the Estimated Energy Requirement (EER), a component of DRI (Dietary reference intake) is recommended. On regular growth monitoring if growth is found to be inadequate, a stepwise increase in calorie supplementation should be advised. For protein demands, 115-200% of estimated average requirement for respective chronological age according to RDA, a part of DRI. Supplementation of 150-200% of normal recommended intake of micronutrients through a prescribed vitamin supplement.[21]
   Eventhough the nutritional intervention is not known to prevent formation of new blisters; it has been observed that it enhances immunity, visceral proteins, accelerates healing of wounds and prevents secondary infections. Earlier the age at which nutritional intervention is started, the greater is the probability of recovery from malnutrition.
5. Bone involvement- Annual DEXA scan and plain radiographs of spine and calcaneum has been proposed in RDEB and JEB patients from 5 years of age for diagnosing these complications earlier. Encouraging mobility and weight bearing, physiotherapy, calcium and vitamin supplementation, bisphosphonates may be tried.
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CONCLUSION

Epidermolysis Bullosa is a group of inherited diseases characterized by varying degrees of skin fragility due to mutations in genes that code for the structural proteins of epidermis and DEJ. Since EB is not curable and studies on gene therapy are currently under trial, management of impairment of growth and nutrition in EB patients is of utmost importance. Meanwhile, symptomatic treatment and multidisciplinary collaboration are necessary for effective disease control and providing palliative care.

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