The eye in epidermolysis bullosa

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Abstract

Aims—To describe the ophthalmic findings in a large cohort of epidermolysis bullosa (EB) patients managed in one large specialist centre.

Methods—A case note review of consecutive patients seen at Great Ormond Street Children’s Hospital. Data on the dermatological disease, ophthalmic history, and examination were collected and coded onto a data sheet.

Results—181 patients: 50 (28%) simplex EB; 15 (8%) junctional EB; 28 (15%) autosomal dominant dystrophic EB; 72 (40%) autosomal recessive dystrophic EB; nine patients (5%) with dystrophic EB whose inheritance could not be ascertained; and seven cases (4%) of EB that could not be classified. Ocular problems were found in 12% (n=6) of simplex patients and 40% (n=6) of those with junctional disease. One patient (of 28) in the autosomal dominant dystrophic group had ocular involvement and 51% (37/72) of patients in the autosomal recessive dystrophic group had ophthalmic complications: corneal (25/72), lid ectropions (3/72), lid blisters (5/72), and symblepharon (3/72).

Conclusion—Ophthalmic complications are common in EB overall but the incidence varies widely with subtype. Ophthalmic complications are the most severe in the dystrophic recessive and junctional subtypes where there is a need for extra vigilance. The major treatment modality was use of ocular lubricants.

Epidermolysis bullosa (EB) is a term for a group of conditions associated with abnormalities of the basement membrane zone of skin and mucous membranes. Most frequently it is genetically determined and congenital although there is an acquired variety. The characteristic features are skin and mucosal fragility starting during infancy with a tendency to blister after even minor trauma. The involvement of the eye with conjunctival and corneal blistering can lead to progressive scarring with reduced vision and even blindness.1 There are several genetic subtypes: dystrophic (autosomal recessive and autosomal dominant), junctional, and simplex. Even within these subtypes clinical variability has been recognised and further subcategorisation has been applied.2 Many of the subtypes of EB have now been characterised by mutations of various genes affecting different elements of the basement membrane zone.

Subsequent tissue involvement is different in each subtype of EB. Simplex disease involves the basal cells, junctional disease the lamina lucida. Dystrophic affects the dermis below the lamina densa at the level of the anchoring fibrils. Among the different subtypes there is considerable variation in the severity of systemic disease and ocular involvement. Ocular features previously described include corneal abrasions (three), corneal scars (two), corneal pannus (two), eyelid blisters (two), eyelid ectropion (two), conjunctival blisters (two), and symblepharon (two). Other ocular associations reported in EB include cataracts (11), cornea plana and sclerocornea (12), refractive errors, amblyopia, lacrimal duct obstruction, strabismus, lens subluxation, posterior vitreous detachment, and Graves’ disease.4

This study aimed to describe the ophthalmic findings in a large cohort of EB patients who have been carefully and systematically examined in one large specialist centre. This is, firstly, to compare the incidence of complications with another large series and, secondly, to indicate which patients are most at risk and therefore to assist in the management of these patients.

Methods

Consecutive patient names and hospital numbers were located from the database kept by the specialist dermatology EB team coordinator. Between 1980 to 1996 at the Hospital for Sick Children, Great Ormond Street, London, 181 patients were seen. Records were located in all cases. All patients had been seen by a consultant dermatologist and had undergone a standard clinical examination consisting of: general examination by the dermatologist, nutritional assessment by a dietician, dental assessment, physiotherapy assessment, and blood tests to check nutritional status. Where indicated, biopsy of unaffected skin was done and immunohistochemistry and electron microscopy of the specimens performed.

All patients had also been seen by an ophthalmologist of at least senior registrar level. Full ophthalmic examination was performed consisting of: vision (visual acuity where possible); refraction, ocular alignment and ocular motility; slit lamp examination and tear film assessment. Details of the results of this examination were recorded on to a data sheet. The presence or absence of the following lesions was coded together with their duration if known: punctate keratitis, corneal abrasion, pannus or scar, conjunctival blisters or symblepharon, eyelid ectropion or entropion. A history suggestive of corneal erosions (recent red eye with photophobia) was also noted.
Table 1 Comparison of the results from Lin et al2 with the current study

<table>
<thead>
<tr>
<th></th>
<th>Lin et al2</th>
<th>This study</th>
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<tbody>
<tr>
<td>Total number of EB patients</td>
<td>204</td>
<td>181</td>
</tr>
<tr>
<td>Number of male EB patients</td>
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<td>Number of female EB patients</td>
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<tr>
<td>Number of simplex EB patients</td>
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<td>Number of functional EB patients</td>
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<td>Number of recessive dystrophic EB patients</td>
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<td>Number of dominant dystrophic EB patients</td>
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<tr>
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<td>9</td>
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<tr>
<td>Number of unclassified EB</td>
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<tr>
<td>Ocular complications in simplex EB patients</td>
<td>2 (3%)</td>
<td>6 (12%)</td>
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<tr>
<td>Ocular complications in junctional EB patients</td>
<td>14 (39%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Ocular complications in recessive dystrophic EB patients</td>
<td>31 (51%)</td>
<td>37 (51%)</td>
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<tr>
<td>Ocular complications in dominant dystrophic EB patients</td>
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<td>1 (4%)</td>
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<td>Ocular complications as a whole</td>
<td>53 (26%)</td>
<td>50 (28%)</td>
</tr>
<tr>
<td>Corneal pannus in recessive dystrophic EB patients</td>
<td>24 (39%)</td>
<td>17 (24%)</td>
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<tr>
<td>Corneal pannus in recessive dystrophic EB patients</td>
<td>12 (20%)</td>
<td>13 (18%)</td>
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<td>Country of study</td>
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*Not reported.

Results

Records were found on all patients in the study group (n=181). The study population included 100 males—55% (mean age 9.6 (SD 5.6) years) and 81 females—45% (mean age 10.5 (6.0) years). The subtypes of EB were 50 (28%) simplex EB; 15 (8%) junctional EB; 28 (15%) autosomal dominant dystrophic EB; 72 (40%) autosomal recessive dystrophic EB; nine patients (5%) with dystrophic EB of uncertain inheritance; and seven cases (4%) of unclassified EB.

Autosomal dominant dystrophic EB (n=28): only one patient (4%) had significant ocular involvement consisting of conjunctival blistering without eyelid or corneal disease.

Autosomal recessive dystrophic EB (n=72): 14% (n=10) reported symptoms of recurrent erosions but were normal on examination while 51% (n=37) had eye complications on examination. Ocular involvement consisted of: 25/37 (68%) had corneal complications, including three cases of corneal abrasion, 13 cases of corneal scarring and nine cases of corneal pannus; 8/3 (3%) had exposure keratitis associated with upper and lower eyelid ectropions; 24% (9/37) of the patients had conjunctival complications; 14% (5/37) of the patients had eyelid blisters.

Junctional EB (n=15): 40% (n=6) had eye complications. Three had corneal scarring, two had severe exposure keratopathy, and one had corneal abrasion. None of these patients had symblepharon or conjunctival blistering.

Simplex EB (n=50): no ocular disease was found in 88% (n=44) of these patients. Peripheral corneal vascularisation was seen in 12% of patients, all of whom had the Dowling subtype.

Binocular vision was 6/12 or greater in 175 patients at their last visit. Unioocular testing and refractive correction were not always possible in the clinic as many had been admitted because of a flare up of their illness and were very unwell when seen. Vision was obtained using a variety of techniques including Sheridan–Gardiner, Cardiiff cards, and linear Snellen. There was one case of significant hypermetropia, four cases of myopia, and three cases of marked astigmatism that required correction with glasses. Amblyopia was detected in only four cases (2%) and was not associated with any particular subtype of EB. Special precautions were taken with the pressure points for glasses with sponge padding and for patches soft tie on occlusion was used. Using this technique few problems were encountered in treatment of the amblyopia by occlusion or spectacle correction. Three patients had squints, including one with an A pattern and facial asymmetry. Among these, one patient had an alternating convergent squint of 80 prism dioptres without glasses and 30 prism dioptres with glasses of +6.0 DS right and left. Subsequent squint surgery was uneventful.

Miscellaneous features noted were lacrimal punctal occlusion (one patient); punctal papilloma on the eyelid (one patient); recurrent subconjunctival haemorrhage (one patient); pseudopterygia (four patients); microphthalamos (one patient); anterior polar cataract with astigmatism (one patient).

The method of treatment in all our patients was conservative with frequent ocular lubricants, such as preservative-free hypromellose drops in the daytime, which were as frequent as hourly, and eye ointment at night.

Discussion

We have reviewed the dermatological diagnosis and ophthalmic examinations in a large group of patients with EB seen at one specialist British centre. Previously McDonnell10 studied a series of 11 patients with dystrophic EB and reported 73% of patients were noted to have eye changes. In the largest series of patients published to date from the United States, ocular complications were seen in 26% of the 204 patients. The results of this study by Lin et al2 agree closely our results (Table 1).

Simplex EB

Simplex EB has various subtypes such as Weber–Cockayne, Koebner, and Dowling, which differ in their clinical features. In our study no ocular involvement was found in patients with Weber–Cockayne and Koebner subtypes. Simplex patients with ocular involvement (eyelid blistering and corneal abrasion) belonged exclusively to the Dowling–Meara subtype in which the skin disease is normally more severe.11–12

Simplex EB is caused by mutations in the keratin 14 gene on chromosome 17 or keratin 5 gene on chromosome 12. Keratin abnormalities lead to dysfunction in the intermediate filaments.13 These keratins are not restricted to ocular tissue but are expressed by basal keratinocytes in the skin elsewhere as well, hence explaining the skin involvement of this condition. On the other hand, mutations of cornea specific keratins (K3 and K12) as in Meesmann’s corneal dystrophy only result in disease in the cornea, without concurrent systemic disease.14

Junctional EB

Junctional EB is a heterogeneous group, being conventionally subdivided into lethal and non-lethal types. Ocular lesions were found in 40% (6/15) of our patients with corneal scarring in 20% (3/15) and exposure keratopathy in 33%
The eye in epidermolysis bullosa

(\(n=5\)). These figures are very similar to those reported by Lin et al.\(^2\) although they reported many more cases of corneal abrasion among this group.

Considerable molecular heterogeneity underlies cases of junctional EB. Mutations in six different gene/protein systems have been described including the three genes that encode lamin 5 (LAMA3, LAMB3, and LAMC2)\(^{12-18}\) the gene for the 180 kDa bullous pemphigoid antigen (BPAG2/ COL17A1) and the alpha 6 beta 4 integrin genes (ITGA6/ITGB4).\(^{19-21}\)

**DYSTROPHIC EB (AUTOSOMAL RECESSIVE)**

Autosomal recessive dystrophic EB is the most common type of EB in our series (\(n=72\)). Ocular complications occurred in 51% with a further 14% reporting symptoms suggestive of recurrent corneal erosions but without signs at examination. The ocular complications ranged from punctate keratitis, corneal pannus, corneal scarring, eyelid blisters, and symblepharon to eyelid ectropion. Symblepharon was found in this group of patients but not in other genetic types of EB. The recessive dystrophic type of EB results from mutations in both alleles of the collagen VII gene on the short arm of chromosome 3.\(^9\)

To some extent it is possible to explain the clinical phenotype by examining the specific mutation in dystrophic EB. Although both the recessive and dominant types of dystrophic EB are caused by mutations of the collagen VII gene, different domains of the gene can be affected. As a result the abnormality may affect the function of the anchoring fibrils of the basement membrane to different extent. For example, an amino acid substitution of methionine to lysine in position 2798 in the non-collagenous domain-2 affects the intermolecular disulphide bonding during assembly of the fibrils but clinical phenotype is mild (called the mitis/inversa type recessive dystrophic EB) because partial assembly of the fibrils can take place. In patients with premature termination codons of translation in the collagenous domain (from single base pair deletion or insertion) the resulting collagen polypeptides become truncated, this results in no functioning fibrils and the severe clinical phenotype called the Hallopeau–Simens type of recessive dystrophic EB is manifested.

Dystrophic EB may be complicated by cutaneous squamous cell carcinomas\(^6\) although, as far as we are aware, there have been no documented case of squamous cell carcinomas reported in the conjunctiva or eyelid of these patients. The tumorigenesis may be related to expression of mutant p53 gene in EB patients.\(^9\) Mutant p53 protein may be expressed in 26% of the squamous cell carcinomas from recessive dystrophic EB patients, and it was believed that this expression correlated with poor tumour differentiation.

**DYSTROPHIC EB (AUTOSOMAL DOMINANT)**

Ocular complications were rare with only one patient (4%) having any involvement while Lin et al.\(^2\) reported 3/17 with ocular involvement.

There is no statistical difference between these findings and both confirm the low level of ocular involvement.

The patients who wore glasses (\(n=7\)) did not develop major problems despite the expected difficulty at the contact points on the nose and ears. All our glasses were fitted by a specialist fitter within the department able to make adaptable frames and use various amounts of additional sponge. No patient in this series wore contact lenses and no patient required the use of soft bandage contact lenses for stubborn corneal ulcers as has been reported.\(^1\)

Despite 29 patients in our series having corneal scars or pannus, no patient required corneal surgery. Lin et al.\(^2\) reported three patients who underwent lamellar keratectomy with some visual improvement although this required many regrafts. This may reflect an overall more conservative approach or alternatively greater success with conservative treatment. There was one patient who underwent squint surgery that was not associated with any problems. There was no precipitation of excessive conjunctival or lid blistering and no excessive scarring.

**MANAGEMENT**

**General**

Children suffering from EB, in particular those with the recessive dystrophic variety, benefit from a multidisciplinary approach to care. Regular short admissions to a specialised centre aim to encourage the child to reach his full potential and minimise disability. During such admissions emphasis is placed on nutritional review, physiotherapy assessment, ophthalmic and dental examinations and adjustment of skin care regime.

Intermittent surgery includes insertion of gastrostomy buttons for those failing to thrive or having severe dysphagia, plastic hand surgery to release contractures and dental surgery. Excellent healing and recovery has been observed following surgery for conditions not arising from EB, such as appendicectomy, orchidopexy and squint surgery. The main prognostic criterion for good healing after surgery appears to be satisfactory nutritional status.

**Ophthalmic**

The management of the EB patient should be based on the severity and type of ocular complication presented. The method of treatment in the majority of patients is conservative with regular ocular lubricants. Care needs to be taken not to hold the lids when applying the drops in children as this may damage the skin.

Patients with minimal disease, especially those with the simplex EB (except the Dowling–Meara subtype) do not need regular ophthalmic review, as long as the parents have been advised what symptoms to look for and to seek the advice of an ophthalmologist when required. After the initial ophthalmic evaluation and advice on ocular lubricants, they can be referred to the eye department again if further problems occur.
Patching using a soft tie on a patch and spectacle wear is not impossible but the practitioner needs to monitor the patient carefully for skin complications. Dispensing opticians should be aware of the problems and be ready to use large padded arms where necessary. Ideally a person used to dealing with these types of problems would be best. Other methods of amblyopia therapy such as penalisation can be considered; empirically, preservative-free drops should be used to minimise the risk of problems.

Patients with exposure keratitis are most difficult to manage and require the most frequent follow up. Both ectropion and severe symblepharon can cause exposure or lagophthalmos. Some patients with blistering and induration of the upper lid have a mild lagophthalmos nocturnally. Once a dense corneal scar is formed little improvement can be obtained with lubricants. Lamellar keratoplasty can be considered although its role has not been proved here and management should be aimed to prevent the development of this complication. Tarsorrhaphy and ectropion surgery may be performed with the usual indications.

We conclude that ocular complications are necessary. Ideally a person used to dealing with these patients with blistering and induration of the upper lid have a mild lagophthalmos nocturnally. Once a dense corneal scar is formed little improvement can be obtained with lubricants. Lamellar keratoplasty can be considered although its role has not been proved here and management should be aimed to prevent the development of this complication. Tarsorrhaphy and ectropion surgery may be considered; empirically, preservative-free drops should be used to minimise the risk of problems.

Patients with squint and problems with extraocular muscles should be assessed as for other patients and surgery may be performed with the usual indications.

We conclude that ocular complications are common in EB overall although the incidence in the different subtypes varies enormously. Ophthalmic complications are most severe in the dystrophic recessive (46%) and junctional group (40%) where there is a need for extra ophthalmic vigilance.