The dental management of patients with recessive dystrophic epidermolysis bullosa: a case report of two siblings

ABSTRACT

Introduction
Epidermolysis bullosa (EB) is a group of rare inherited disorders uniquely characterised by skin and, in some instances, mucosal blistering. In the most severe form of the disease, recessive dystrophic EB (RDEB), the blister-inducing split occurs below the lamina densa. Extensive scarring of the oral mucosa results in limited mouth opening, making speech and mastication difficult. At the same time, oral mucosal blisters often lead to patients restricting their diets to soft, and generally cariogenic, foods, and battling with oral hygiene practices. This results in poor plaque control, a high caries burden and complex dental management.

Aims and objectives
This paper presents a report on two siblings suffering from generalised RDEB affecting the oral cavity and their extensive dental treatment needs.

Design/Methods
The siblings were referred to the University of Pretoria Oral Health Centre, complaining of painful teeth and oral mucosal discomfort. Their clinical features, dental condition and subsequent management are presented.

Results
Restricted mouth opening, limited personal plaque control and diets limited to soft, carbohydrate-rich foods because of oral mucosal discomfort, resulted in extensive dental decay that required multiple extractions.

Conclusion
The dental and anaesthetic management of patients with RDEB is complex and, due to the friable tissues, requires the most atraumatic care possible. Ideally, patients with this condition need to have early dental intervention where preventive programmes can be implemented to reduce the need for later extensive and complicated dental interventions. Maintenance of the patient's oral health is essential to ensure adequate nutrition, yet also reducing the consumption of soft cariogenic diets which increased their caries risk.

Keywords
Recessive dystrophic epidermolysis bullosa, dental management, general anaesthetic, oral features

Abbreviations
EB: epidermolysis bullosa
DEB: dystrophic epidermolysis bullosa
RDEB: recessive dystrophic epidermolysis bullosa
DDEB: dominant dystrophic epidermolysis bullosa
JEB: junctional epidermolysis bullosa
IFM: immunofluorescence mapping
TEM: transmission electron microscopy
SCC: squamous cell carcinoma
UPOHC: University of Pretoria Oral Health Centre
LA: local anaesthesia
GA: general anaesthesia

INTRODUCTION
Epidermolysis bullosa (EB) is a group of rare disorders uniquely characterised by skin and, in some instances, mucosal blistering. Three main types have been identified based on the level of the epidermis at which the blisters and/or splits develop, namely intra-epidermal (Simplex EB), intra-lamina lucida (Junctional EB) or sub-lamina densa (Dystrophic EB). There is a further subcategory which presents with mixed splits as seen in patients with Kindler syndrome. The diagnosis is determined using transmission electron microscopic (TEM) findings and immunofluorescence mapping (IFM). Further testing with monoclonal antibodies directed against components of the skin and basement membrane zone can be used to subclassify the disease and establish which structural protein is mutated. Each of these inherited disorders is associated with a particular genetic mutation and subsequent altered production of a key structural protein of the epidermis. In RDEB, mutation of COL7A1 results in defective production of collagen type VII. This paper presents case reports, and the subsequent dental management, of two siblings with dystrophic epidermolysis...
bullosa (DEB). This disease can be categorised as dominant (DDEB) or recessive (RDEB) according to the inheritance pattern, while the extent of skin involvement determines if it is generalised or localised. The recessive subtype presents clinically more severely than the dominant subtype, due to the amount and functionality of the anchoring fibril protein that is affected.

The prevalence of DEB and its clinical varieties has not been established in South Africa, but comprehensive registries have been created in Scotland and The Netherlands. The overall prevalence of DEB in Scotland is 24/million, with 68% of cases transmitted dominantly, 13% recessively, and the remainder is undetermined. In the Dutch registry, DEB was the second most common variety of EB (37%), after epidermolysis bullosa simplex (45.7%). The annual incidence of DEB in this population is reported to be 14.1 per million live births, and the point prevalence is 8.3 per million of the population. Dominant DEB (67.1%) appears more frequently than RDEB (32.9%). While both of these registers have been made possible by the countries having robust healthcare systems, the Dutch register is further benefited by well-characterised molecular diagnoses and confirmation in 90% of the cases.

CASE PRESENTATION

Permission was obtained from the University of Pretoria, Faculty of Health Sciences, Research Ethics Committee clearance number 750 2022, following informed consent of the participants.

Case 1

A 14-year-old boy was referred to the Oral Medicine clinic at the University of Pretoria Oral Health Centre (UPOHC) with a diagnosis of DEB. His dentist has asked for help with his complex dental needs and treatment. His condition was diagnosed clinically, at birth, based on the fact that his older sister suffered from the same condition. No special investigations had ever been performed. His affected skin areas were treated with silbecor dressings (silver sulfadiazine). The patient was otherwise healthy, had no allergies and on no medication except for a daily multivitamin supplement.

His oral hygiene practices had been severely limited due to the extreme fragility of the oral mucosa, and pain when brushing. He had only been rinsing with a 0.2% chlorhexidine formulation as prescribed by his dentist. His diet was restricted to soft foods and liquids which may have limited its variety and nutritional value. His small stature was a further suggestion of likely malnourishment.

The visual extra-oral examination revealed both current blisters as well as evidence of past lesions which had resulted in scarring (Figure 1) and a ‘mitten hand’ deformity (pseudosyndactyly) in both hands (Figure 2). The skin lesions were accompanied by pruritus. Oral and peri-oral examination revealed limited mouth opening (Figure 3) and mucosal fragility, both of which prevented the clinician from performing a detailed intra-oral examination. He had numerous broken down teeth that may have aggravated the oral blisters, causing even more soft tissue damage and pain. He was unable to protrude his tongue due to scarring. Dental crowding of the anterior maxilla was also noted.

Intra-oral radiographs could not be obtained due to his microstomia and ankyloglossia. A panoramic radiograph revealed extensive caries (Figure 4), which would require extraction of teeth 36, 46, 26, 16, 21, and root rests of 14 and 63. This was carried out under general anaesthesia (GA) where it was hoped that the amount of soft tissue damage and pain could be managed better. Access and vision during the surgery was complicated by the severe microstomia, which also prohibited use of standard lip and cheek retractors. The commissures of the lip were protected with petroleum jelly, and dental extractions were performed carefully using dental forceps where possible and elevators in the more posterior areas. Despite all attempts to limit mucosal trauma, sheets of epithelium detached during the procedure (Figure 5). This complication has been reported by others and was anticipated. A hydrocortisone ointment (1g/100g) was prescribed to reduce mucosal inflammation.

Figure 1: Scarring and crusting of the patient’s skin.

Figure 2: Pseudosyndactyly of the patient’s right hand.

Figure 3: Microstomia, dental crowding and decay that is visible of the anterior maxillary teeth.
as well as a combined suspension of paracetamol (250mg), ibuprofen (200mg) and codeine phosphate (10mg/10ml), taken as 10ml every 4-6 hours for postoperative pain control.

Prophylaxis and desired maintenance of the patient’s remaining dentition will rely on chemical plaque control, through the use of a 0.12% chlorhexidine mouthwash with cetylpyridinium chloride in an aqueous solution, and fluoridated toothpaste which he can rub onto the tooth surfaces. However, the mechanical plaque control shall be limited due to the fragility of the oral mucosa and his inability to hold a toothbrush. He was also given a sucralfate (1g/5ml) suspension to apply when new blisters develop, and topical glucocorticoid syrup (betamethasone 0.6mg/5ml) which can be used in a diluted form as a mouth rinse to help reduce inflammation.

**Case 2**
The patient’s older sister also then came for dental treatment. She presented with a similar clinical picture as her brother (Figure 6, Figure 7, Figure 8) and used the same therapy for her skin lesions. She also had no other diseases, allergies or habits of relevance.

A panoramic radiograph revealed extensive caries, which necessitated the removal of teeth 13, 14, 15, 37, 36, 46, 23, 24, 25 and 26 (Figure 9). There was also evidence of a dental abscess on the 37. Unfortunately, the long theatre waiting list prevented immediate dental treatment, necessitating the need for antibiotics to manage the existing dental abscess. The extent of debilitation associated with this condition became starkly evident as she was unable to swallow tablets due to oesophageal stenosis, and required suspension formulations. During the consultation, the patient had high aesthetic desires and requested to have her teeth restored with aesthetic crowns and veneers.
Unfortunately, given access limitations, badly broken down dentition, and questionable future oral hygiene maintenance that this disease imposes, this was not possible.

She was given a similar maintenance and therapeutic programme as her brother.

**DISCUSSION**

**Diagnosis**

Both patients were diagnosed with RDEB, based on the fact that neither parent had evidence of the disease, yet both siblings suffered from the disease. The diagnosis was largely based on the clinical history, including the age at the time of the onset of the bullae, the distribution of the lesions and eliciting factors of bullae formation.²

Ideally, the diagnosis should be confirmed through TEM, and/or IFM, and/or genetic testing (mutation analysis) of the patients and parents to type and subtype the EB variant.²,⁶,⁹ However, the literature reports on many cases diagnosed purely on clinical features, with less than 20% confirmed by molecular analysis.⁵

Given the longstanding nature of the presumed diagnosis and dermatological care that the patients have received, it was not considered necessary to subject the patients to further special investigations.

**Clinical features**

The RDEB variants usually have an onset at birth where patients present with generalised skin involvement. These are characterised by blisters, milia, atrophic scarring, dystrophic or absent nails, pseudosyndactyly and scalp abnormalities.¹,¹⁰ Blisters are easily induced, and may also involve the mucosa of the oral cavity, eyes and gastrointestinal tract where recurrent blisters and healing result in scarring. In addition, patients may also suffer from anaemia and growth retardation with a significant risk of squamous cell carcinoma (SCC) by the age of 30.¹

Blisters may also affect any oral mucosal surface, and although they may be common to all EB subtypes, they are more severe in RDEB,¹⁰ occurring in 92% of patients, and most frequently affecting the tongue.¹⁵ In neonates, blisters may interfere with the child’s ability to suckle.⁴ Pacifiers can also induce blistering and parents should be advised to avoid using them.¹³

The continuous process of blister formation, healing and scarring leads to changes in the oral architecture with loss of the buccal vestibule, palatal rugae and tongue papillae. The tongue frequently becomes bound down to the floor of the mouth (ankyloglossia) and mouth opening loss of the buccal vestibule, palatal rugae and tongue papillae. The tongue frequently becomes bound down to the floor of the mouth (ankyloglossia) and mouth opening is most likely due to chronic inflammation, especially in the absence of other known risk factors.⁴

**Pathogenesis of skin disease and mucosal blistering**

Mutations that result in loss of function in the COL7A1 gene result in abnormal or absent collagen type VII protein synthesis. This protein is normally produced by keratinocytes and fibroblasts, and is instrumental in anchoring the epidermal basement membrane to the dermis. Thus, abnormalities in these anchoring fibrils result in blister formation.¹⁰,¹⁷-¹⁸ The mutation of COL7A1 can occur along any of the 118 exons, but several hotspot mutations are associated with particular ethnic groups.¹⁸

Repeated blistering leads to protracted wound healing, especially at sites that are routinely exposed to mechanical stress. The near-continuous cycles of blistering and altered healing result in persistent ulceration that is characterised by incomplete epithelialisation, frequent infections and pariesional inflammation which eventually results in chronic ulcers with fibrosis and scarring. The sequelae of these events are seen as syndactyly, mitten deformities and limb ankylosis, oesophageal strictures and multiple SCCs of the skin.¹⁷

A multistage pathogenesis of skin disease is proposed in RDEB and is defined by defects in the inflammatory response, skin proliferation and skin remodelling. Fibrosis predominates during healing due to persistent inflammation, reduced myofibroblast removal and excessive ECM deposition, and ultimately results in hand and foot deformities as well as aggressive SCC.¹⁷,¹⁹ Fibrosis creates a permissive tumour microenvironment, with fibroblasts adapting a carcinoma-associated fibroblast behaviour, being able to promote the development of cancer themselves.¹⁹ IL-6, an inflammatory cytokine responsible for fibrosis, which directly correlates with the severity of the disease, also regulates the growth and metastatic behaviour of epithelial malignancies.¹⁹ The absence of COL7 enhances epithelial migration, invasion and vascularisation, and impairs epithelial differentiation, resulting in aggressive malignant behaviour.²⁰

Early detection is a clinical and histologic challenge because SCC occurs within chronic wounds and scars, where it is hard to distinguish it from granulation tissue and other reactive changes.¹⁹ Subsequently, cutaneous SCC has a very poor prognosis in DEB and represents the first cause of death in these patients.⁶,¹⁹

Although cutaneous SCC may also occur among other EB subtypes, the majority (69.2%) is found among patients with RDEB, where the median age of diagnosis is 36 years, and results in death in 41% of patients.⁸ The majority of SCC develop on the upper and lower extremities, particularly over bony prominences, and typically (99% frequency) in areas of chronic non-healing ulcerations, and only unusually appears on sun-exposed skin. Aggressive surgery, including partial limb amputation, may be supplemented with chemo- and/or radiation therapy, but radiation therapy toxicity and low skin tolerance limits its use. Relapse is common (36.1%) due to the difficulty of establishing tumour margins in the altered field.⁹

**Oral mucosal treatment considerations**

RDEB present with the most extensive oral mucosal involvement among the EB subtypes, characterised by
blistering, erosions and scarring, yet the treatment of these oral lesions has seldom been reported. Individual reports were found to support the use of sucralfate, low-level laser therapy (LLLT) with cord blood platelet gel, and gentamycin, and, most recently, stem cell therapy. Effective treatment of oral mucosal lesions is necessary to improve plaque control, and therefore reduce caries experience and gingival inflammation, as well as to improve nutrition.

The topical use of sucralfate was shown to relieve pain and reduce the number of oral blisters experienced by DEB patients. Sucralfate creates a viscous, adhesive coagulum to coat areas of damaged mucosa, effectively providing protection against local irritants such as toothpaste, toothbrush and food, favouring the re-epithelialisation of the ulcer bed. Hopefully, by reducing the number and size of oral blisters, scarring and the resultant microstomia and ankyloglossia can also be prevented. Sucralfate may also be compounded with diphenhydramine hydrochloride and lidocaine, which is commonly known as magic mouthwash, to manage oral discomfort.

Sindici et al., 2016 used cord blood platelet gel in combination with LLLT in the treatment of persistent oral ulcers in seven patients with DEB, resulting in the healing of lesions. However, lesions recurred shortly thereafter and continued to develop over untreated surface areas. Admittedly, the combined treatment protocol does not allow us to measure the individual treatment effects, and either one of these therapies may have been effective.

A twice-daily oral rinse with 0.3% gentamycin resulted in clinical and symptomatic improvement with healing of oral lesions and a reduced number of new blisters. The authors propose that topical gentamycin effectively treats skin wounds because of its antisepctic activity and by repairing the nonsense mutation so that the collagen type VII protein is fully synthesised.

More recently, attention has turned towards correcting the gene defect responsible for the disease. Regenerative treatment approaches include stem cell therapy and gene therapy.

A functional copy of the affected gene can be added through retroviral and lentiviral vectors to epidermal keratinocytes and fibroblasts to transduce and correct the keratinocytes of RDEB patients. The transgenic keratinocytes are then used to generate autologous epidermal sheets which are grafted onto patients.

Stem cell therapy, of mesenchymal and hematopoietic origin, results in improved healing of chronic wounds and decreased mucocutaneous blister formation. But the origin, results in improved healing of chronic wounds and stem cell therapy, of mesenchymal and hematopoietic cells from patients with RDEB into functional hematopoietic cells.

Dental disease

Children with RDEB tend to have more caries, gingivitis and higher plaque scores. A study has shown that the prevalence of dental caries, scored as DMFS (decayed, missing, filled surfaces), was significantly higher in JEB (mean 58.6) and RDEB (mean 37.6) than in controls (mean 23.2). This correlates with the enamel defects in JEB, but is not directly proportional to the degree of oral soft tissue involvement in RDEB, emphasising the multifactorial aetiology of caries.

Unlike JEB, in which the enamel is structurally compromised, the tooth structure in RDEB is chemically and mechanically sound because the COL7A1 gene is not expressed by ameloblasts, and the eruption and maturation patterns match healthy controls. Neither can the caries be attributed to salivary gland dysfunction, as both flow rates and antibody titres are comparable with controls. However, plaque control is complicated by a very small mouth opening, painful blisters that develop upon the slightest mechanical trauma such as tooth brushing, and a physical inability to hold a toothbrush. Yet, tooth brushing is possible, and can be simplified with the following adaptations: using a small headed, soft bristle brush which may even be shortened; and adapting the handle to the hand impairment of the patient. Others suggest the use of oral irrigators and a soft electric toothbrush. Daily exercises can maintain, and hopefully improve, mouth opening.

A soft, high carbohydrate diet may be favoured due to dysphagia from oesophageal strictures, the fragility of the oral mucosa, and to increase calorie intake. Although total daily sugar intake may still be similar to healthy controls, it is possible that reduced oral clearance, and slow and frequent eating patterns, increase carbohydrate contact time and therefore caries risk. Meals should be accompanied by fluids to improve oral clearance, and dietary advice should be given.

It is also likely that dental care may take a back seat due to the complexity of the medical condition, the hesitancy by patients and caregivers to approach dentists, and dentists’ reluctance to manage this rare disease. Microstomia is the biggest obstacle in dental management, followed by ankyloglossia and the risk of trauma during dental procedures.

Given these factors, it is essential that all possible attempts be made to preserve the dentition, with early referral to a multidisciplinary team and regular follow-up. Preservation of the dentition is key to maintaining nutrition and improving aesthetics, self-esteem and phonetics. The tooth structure should be protected by systemic and topical fluoride applications, together with chemical plaque control, as this combination can successfully maintain the dentition. Neutral sodium fluoride applications, as well as fluoride varnishes, may be used. Chlorhexidine (0.12% to 0.2%) solutions may be difficult to manipulate due to limited oral movement; therefore, the solution or gel can either be applied with a cotton bud or sprayed on the tooth surfaces. In all cases, alcohol-free preparations should be used.
In cases with extensive dental decay where extractions are needed, it may be better to perform them under GA. However, routine dental treatment may be tolerated by some patients, and even extractions may be performed under local anaesthesia (LA).

However, it may be possible to carry out endodontic therapy under LA up to the second premolar, by using short files, making use of a vestibular or palatal access cavity, an apex locator (to avoid using intra-oral radiographs) and using diluted 1% sodium hypochlorite due to the risk of mucosal injury. The literature reports that root canal-treated teeth have been restored with prosthetic crowns, and missing teeth have successfully been replaced with a removable partial denture. However, impression-taking will be complicated by limited mouth opening and the fragility of the oral mucosa, and this may also complicate denture wearing.

Special precautions should be taken during dental treatment, such as: covering all metal instruments and retractors with hydrocellular foam dressing and with soft silicone sleeves; liberally coating all mucosal surfaces and equipment with petroleum jelly or hydrocortisone ointment; always positioning the suction tip on a hard tooth surface; using paediatric size instruments and a laryngeal mirror; always positioning the suction tip on a hard tooth surface; using paediatric size instruments and a laryngeal mirror; depositing LA deep to prevent separation of tissue layers; and moistening cotton rolls before use. The fact that even topical anaesthetic application or the use of an air syringe can result in blistering explains why extensive sloughing of the skin and oral mucosa may be experienced despite these precautions being taken. If bullae form, they should be drained to avoid further expansion. Surprisingly, the healing of blisters and extraction sites is uneventful and remarkably painless. Antibiotic cover has been restored with prosthetic crowns, and missing teeth have successfully been replaced with a removable partial denture. However, impression-taking will be complicated by limited mouth opening and the fragility of the oral mucosa, and this may also complicate denture wearing.

Anaesthetic management

General anaesthesia is generally preferred in the dental management of patients with RDEB, but is extremely challenging. Some suggest that all mucosal surfaces and equipment used during induction and intubation be liberally coated with petroleum jelly. Yet even this may be difficult to perform due to restricted access.

A further challenge in patients that are malnourished may be electrolyte abnormalities, hypalbuminemia, deranged renal function and anaemia. In addition, certain diseases associated with EB, such as porphyria cutanea tarda, diabetes mellitus, amyloidosis, multiple myeloma and hypercoagulable states, can impact GA. The clinician should also consider the pre-operative use and dosage of disease modifying drugs such as corticosteroids. Intra-operative corticosteroid replacement should be given in cases of steroid use within the last 12 months.

During examination of the airway, oral scarring or microstomia will indicate difficult passage of the laryngoscope during intubation. Scarring of the skin and the pseudosyndactyly will make placement of an intravenous cannula very challenging. With induction of anaesthesia, the face mask should be applied with as little pressure as possible to prevent blister formation of the face. The use of an oro-pharyngeal airway to maintain patency during bag mask ventilation is discouraged due to risk of mucosal damage. Intubation (which may be complicated with bullae formation or bleeding into the airway) should be done with extreme caution as not to damage the friable mucosal surfaces. Since dental surgery requires nasal intubation, it is recommended that a preformed nasal endotracheal tube (north facing RAE) with the smallest circumference, but that still has adequate length, be used. Fortunately, the mucosa of the larynx is rarely involved, so endotracheal intubation is considered safe as long as the cuff of the tube is carefully inflated to provide just enough resistance to leakage during positive pressure ventilation. The endotracheal tube is fixed so that there is no traction on the nostril through which it is placed. Over the course of the tube from the nose to the forehead, the skin under the tube must be protected by means of pressure absorbent material such as a small sponge. To prevent trauma or development of life threatening oro-pharyngeal bullae at extubation, the airway is suctioned under direct vision before careful removal of the endotracheal tube.

The application of any adhesive material, such as standard eye patches, adhesive NEC electrodes, transparent fixation material for IV cannulas and endotracheal tube fixation tape, will cause bullae formation, and as such must all be avoided. IV cannula should rather be fixed by means of a gauze wrap or suture, while the endotracheal tube can be attached with a broad elastic material wrap around the head. Antibiotic eye ointment is placed in the eyes to prevent drying, rather than closing the lids with eye patches. If needle ECG electrodes are not available, ECG is generally not monitored during the procedure, and pulse oximetry and capnography are used to monitor circulation. The non-invasive blood pressure cuff is applied to the selected limb only after loosely wrapping the area in orthopaedic wool to eliminate friction. The patient should be positioned on the table as to avoid any pressure-related bullae formation.

CONCLUSION

The dental and anaesthetic management of patients with RDEB is challenging, mostly due to the microstomia and mucosal fragility. Unfortunately, this population also often has extensive dental disease and endotracheal tube fixation, and frequently requires multiple dental extractions. This paper outlines strategies for prevention and treatment of oral disease and maintenance of the dentition in this vulnerable population.

REFERENCES


