Original Article

A Cephalometric Analysis of Patients with Recessive Dystrophic Epidermolysis Bullosa

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Abstract: Patients diagnosed with Recessive Dystrophic Epidermolysis Bullosa (RDEB) suffer from severe growth inhibition due to reduced food intake as a result of severe oropharyngeal and esophageal blistering. This investigation examined the patterns of facial growth in a group of 42 children with RDEB for whom lateral skull radiographs were available. The differences between RDEB patients and patients with normal cephalometric values were also assessed. Lateral skull radiographs were digitized and a number of orthodontic indices were compared to the published normal values.[1] The RDEB patients examined demonstrated smaller maxillae than normal (length 41.3 ± 2.9 mm compared to 47.4 ± 2.5 mm) and smaller mandibles than normal (length 82.3 ± 6.1 mm compared to 93.1 ± 4.2 mm). This impaired growth may result from reduced food intake or severe orofacial scarring associated with RDEB. This contributes significantly to dento-alveolar disproportion and dental crowding and puts patients at increased risk of dental caries. (*Angle Orthod* 2002;72:55–60.)

Key Words: Cephalometric analysis; Oral scarring; Calorie restriction

INTRODUCTION

Epidermolysis Bullosa (EB) describes a mixed group of hereditary, chronic, noninflammatory skin diseases. All types of this disease are characterized by exceptional skin fragility and share the common feature of reduced resistance to shearing and frictional injury. Mild to moderate trauma even from everyday wear and tear can cause large bullae and ulcers of the skin and mucous membrane. In some cases bullae develop spontaneously.[2] Epidermolysis Bullosa is a rare skin disease that affects all populations and racial groups and equally afflicts males and females.

The classification of EB is on the basis of genetic modes of inheritance, anatomic location, lesion distribution, and morbidity associated with the illness. Epidermolysis bullosa is classified into 4 main groups and at least 23 subtypes.[2] This report is confined to children and adolescents affected by the very severe form of EB which has an autosomal recessive inheritance pattern—Recessive Dystrophic Epidermolysis Bullosa (RDEB).

Recessive Dystrophic Epidermolysis Bullosa is characterized by sub lamina dura separation, due to blistering below the lamina densa of the basement membrane zone. It is associated with the absence of Type VII collagen fibers.[2] As with all forms of EB, there are widespread bullae involving the skin and mucosa that heal with atrophic scarring (Figure 1). There are also defects resulting in retardation of bone growth.[2] In RDEB, the teeth are not directly affected although severe anterior crowding is common (Figure 2).

Dental management of these cases is difficult. There is repeated blistering and ulceration from eating normal consistency foods. These ulcers heal with scarring leading to microstomia and limited oral opening. The buccal and vestibular sulci are eliminated and there is a marked tongue atrophy or ankyloglossia.[3] Routine preventive care such as tooth brushing may lead to bullous formation on the lips, gingivae, and oral mucosa, causing severe pain and discomfort. The scarring leads to trismus. The severe oropharyngeal and esophageal scarring requires that food is liquefied and even then there can be marked dysphagia (Figure 3). Scarring of the fingers and hands (Figure 4) makes it difficult for children to brush properly. The discomfort of

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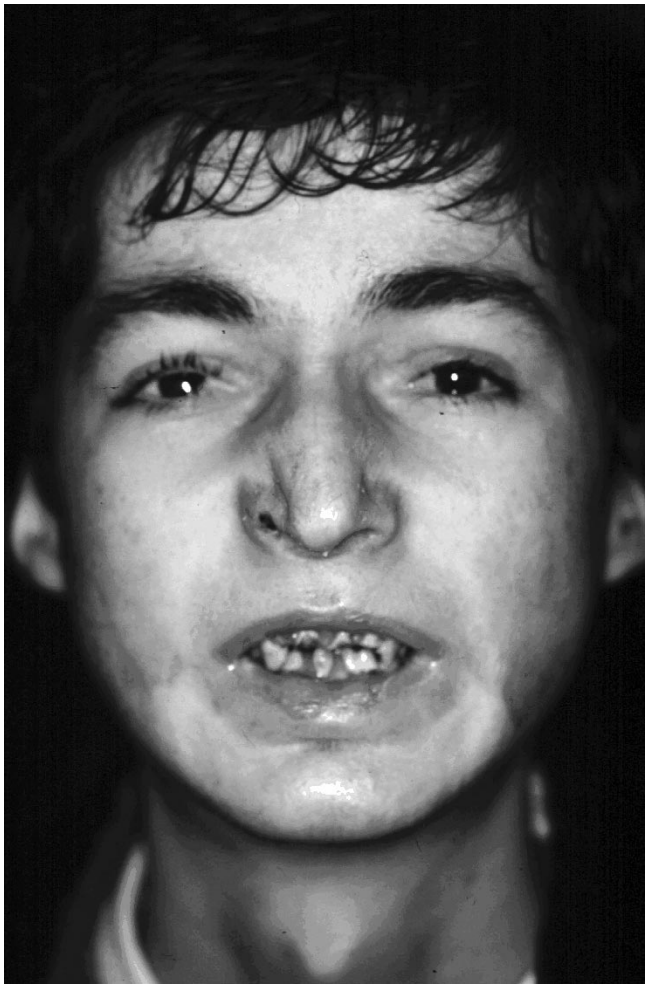

FIGURE 1. Facial view of 14-year-old male with RDEB showing microstomia, severe angular cheilitis, and ulcerated lesions on the cheeks. There is also scarring from ocular and palpebral blistering.

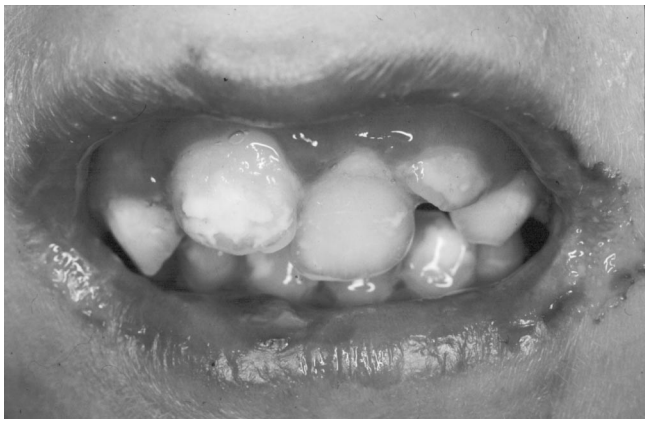

FIGURE 2. Anterior view of teeth of 10-year-old male with RDEB and severe dentoalveolar crowding. There is a healing blister on the upper lip, generalized gingivitis, and crusting in the angular area.

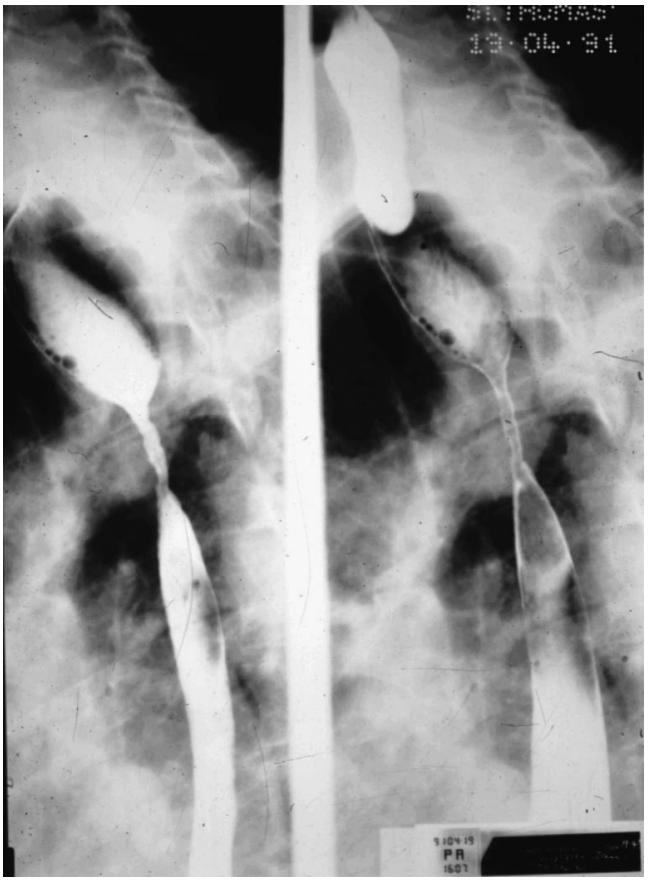

FIGURE 3. A barium swallow showing scarring and stricture within the esophagus.

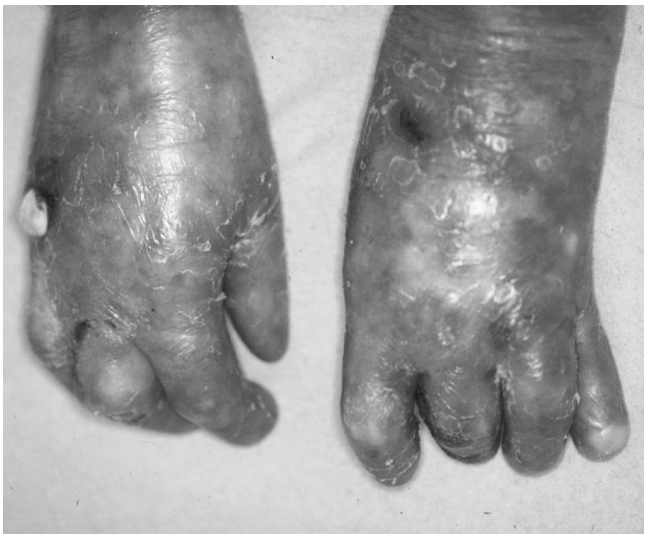

FIGURE 4. Scarring of hands leads to severe contracture making it difficult for RDEB patients to hold and manipulate a toothbrush.

brushing results in poor oral hygiene that leads to advanced periodontal disease that can result in early loss of primary and permanent teeth. There is also an association with the occurrence of premalignant lesions with some studies demonstrating positive predisposition to oral carcinoma such as squamous cell carcinoma.[4] Dental caries is common and may be mild or rampant[5] and poor oral hygiene is one contributory factor. The other factor is a diet rich in sugar and carbohydrates that is necessary to provide sufficient caloric intake to maintain growth. Because of the oropharyngeal blistering, food is consumed in small amounts frequently throughout the day.[6]

There is no quantitative data on the craniofacial pattern of these children. It is unlikely that craniofacial development will have remained unaffected by this condition. Growth is a particular problem in children with RDEB and is thought to be secondary to inadequate nutrition.[7] The effects include retardation in skeletal growth and development affecting the entire body and the cranial and facial bones. A recent report detailed the development of the teeth in RDEB and showed that there was a small, but significant delay in dental maturation.[8] There is no data on growth and development of the craniofacial skeleton.

This investigation was undertaken to determine the magnitude and pattern of craniofacial growth in RDEB patients. Lateral cephalometric radiographs were used to estimate craniofacial development.

MATERIALS AND METHODS

The RDEB patients for this study attended the multidisciplinary EB clinic at The Great Ormond Street Hospital for Children, London, United Kingdom. This hospital is a tertiary referral unit and receives patients only from specialists or consultants. These patients attended at yearly intervals from all parts of the United Kingdom. Many of the patients attend as part of the shared care ongoing between the EB clinic at The Great Ormond Street Hospital for Children and the local Pediatric Unit close to the child's home. The lateral skull radiographs were taken as part of the dental assessment for all RDEB children attending the multidisciplinary clinic. Not all RDEB patients were radiographed as some were too young or had received a full dental assessment in a dental clinic near to the child's home.

The study material comprised lateral cephalometric radiographs of RDEB patients collected over a period of 6 years. The comparison was made with published longitudinal data. The radiographs were analyzed by the Jiffy Orthodontic Evaluator (JOE Version 4.0, Rocky Mountain Orthodontics, San Francisco, Calif). The points digitized are shown in Figure 5. The cephalometric landmarks used for computation of the outcome variables are shown in Table 1. A pilot investigation confirmed that JOE produced statistically similar results as conventional hand tracing. The outcome variables from the sample radiographs were

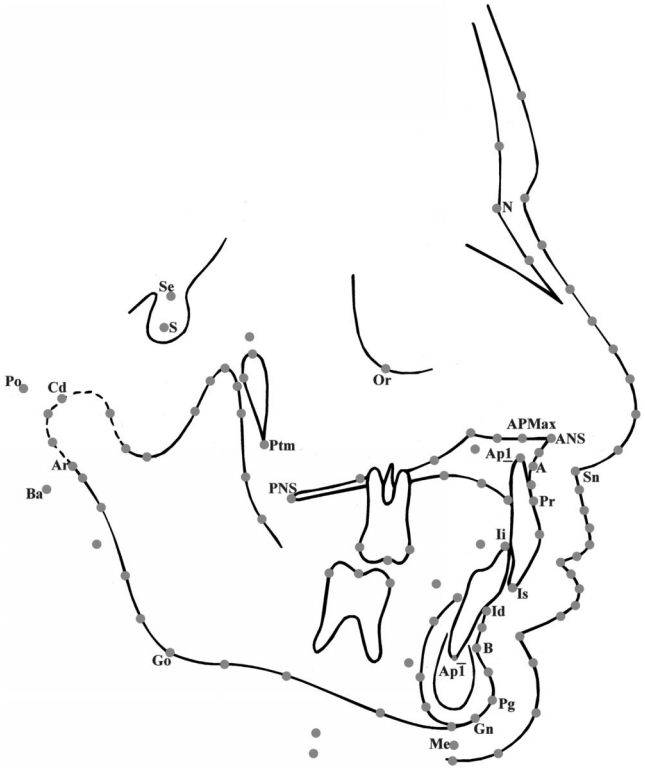

FIGURE 5. Cephalometric points traced.

matched up with the same variables from the published normal values of Bhatia and Leighton.[1] In addition, each outcome variable was matched with the mean normal value for age and gender. Ethnicity was not recorded in the Bhatia and Leighton study (the control sample) so subjects could not be matched by this criterion. These data were then subjected to statistical analysis using the Mann Whitney test as the data were nonnormally distributed when subjected to the Shapiro Wilk test for normality. Variables that give significantly different results are shown in Table 2.

Intra-examiner repeatability was assessed on 10 radiographs selected randomly and recoded by one of the principal investigators (Dr Shah). In addition, a further investigator (Dr McDonald) assessed 10 radiographs in order to estimate inter-examiner reproducibility. This data was also analyzed by the Mann Whitney U test ($\alpha = .05$).

The institutional review boards of The Great Ormond Street Hospital for Children and The Eastman Dental Hospital gave approval for the project.

RESULTS

The 42 RDEB patients (25 males, 17 females) were compared with 42 controls matched for age and gender from the normal standards. The age ranged from 4 years 1 month to 18 years 4 months. On statistical testing, maxillary length, mandibular length, middle facial height, lower facial height, and the distance from lower lip to esthetic plane were significantly reduced in the RDEB group compared to

TABLE 1. Cephalometric Landmarks Used in Recessive Dystrophic Epidermolysis Bullosa Radiographs

N	Nasion	Anterior point on the frontonasal suture. If it was not possible to reliably identify this, the deepest part of the concavity at the site of the suture is used instead.
S	Sella	Center of the sella turcica
Se	Midpoint of sella entrance	Midpoint of line connecting the posterior clinical process and the anterior opening of the sella
Sn	Subnasale	Point at which the nasal septum merges with the integument of the upper lip
A	Point A	Deepest point on the concave outline of the upper labial alveolar process extending from the anterior nasal spine to the prosthion
APMax	Anterior maxillary landmark	Perpendicular from point A to palatal plane
Pr	Prosthion	Crest of the upper labial alveolar process
Is	Incisor superius	Tip of the crown of the most anterior mandibular central incisor
AP*1*	Apicale *1*	Root apex of the most anterior maxillary central incisor
Ii	Incisor inferiorius	Tip of the crown of the most anterior maxillary central incisor
Ap1	Apicale 1	Root apex of the most anterior mandibular central incisor
Id	Infradentale	The most antero-superior point on the labial crest of the mandibular alveolar process
B	Point B	The deepest point on the bony curvature between the crest of the alveolus (infradentale) and the Pogonion
Pg	Pogonion	The most anterior point on the mandibular symphysis
Gn	Gnathion	The most antero-inferior point on the mandibular symphysis
Go	Gonion	The midpoint at the angle of the mandible
Me	Menton	The lowest point on the lower border of the mandibular symphysis
Ar	Articulare	Point of intersection of the posterior margin of the ascending ramus and the outer margin of the cranial base
Cd	Condylion	Most superior point on the head of the condyle
Or	Orbitale	Lowermost point of the orbital border
ANS	Anterior Nasal Spine	The tip of the anterior nasal spine
PNS	Posterior Nasal Spine	The tip of the posterior nasal spine
S′	Landmark	The perpendicular dropped from point S onto a line extending the palatal plane. Used for assessing the length of the maxillary base
Ba	Basion	Lowest point on the anterior border of the foramen magnum
Ptm	Pterygomaxillary fissure	Contour of the fissure projected onto the palatal plane

TABLE 2. Normal Values vs. RDEB Values for Variables Showing Significant Differences

Variable	Normal Values Mean (SD)	RDEB Values Mean (SD)	Significance
Maxillary Length (mm)	47.4 (2.5)	41.3 (2.9)	$P < .001$
Mandibular Length (mm)	93.1 (4.2)	82.3 (6.1)	$P < .001$
Middle Facial Height (mm)	65.2 (2.4)	54.1 (5.7)	$P < .001$
Lower Facial Height (mm)	56.5 (3.5)	42.7 (4.9)	$P < .001$
Lower Lip to Aesthetic Plane (mm)	2.6 (0.4)	−2.6 (4.3)	$P < .001$
Nasiolabial angle (degrees)	110.1 (1.1)	141.1 (16.4)	$P < .001$
Saddle Angle (degrees)	130.7 (0.8)	123.7 (9.8)	$P < .001$

the group of normal standards ($P < .001$). Saddle and nasolabial angles were significantly larger in the RDEB group compared to the group of normal standards ($P < .0001$). This data is summarized in Table 2. The radiographic appearance of a normal child and a severely affected RDEB child are shown (Figures 6 and 7).

There were no statistically significant differences in measurements recorded when inter- and intra-examiner reproducibility was assessed (Mann Whitney U test, ($P > .05$).

DISCUSSION

It is well established that the feeding problems in RDEB patients lead to a significant reduction in height and weight.[7] It appears that this inhibitory effect on bone growth occurs also in the craniofacial skeleton. The use of gastrostomy has overcome some of these problems by enabling the caloric intake of RDEB patients to be greatly improved. The subjects in this study had the lateral skull radiographs taken before the gastrostomy was placed.

The lack of contemporaneous lateral skull radiographs from healthy children for the age range of subjects studied is a shortcoming of this study. This is because such radiographs are no longer taken as a routine for orthodontic diagnosis especially in the younger ages. The comprehensive data from the standards published by Bhatia and Leighton[1] were used. A shortcoming of this approach is that these published standards did not record ethnicity. Although this is a potential problem the differences noted between RDEB

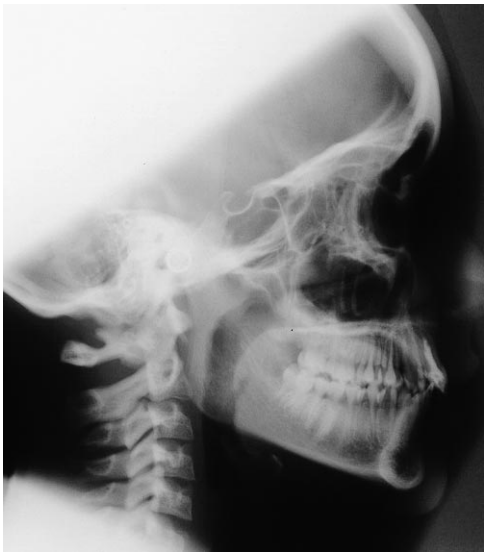

FIGURE 6. Lateral cephalometric view of a normal child aged approximately 10 years.

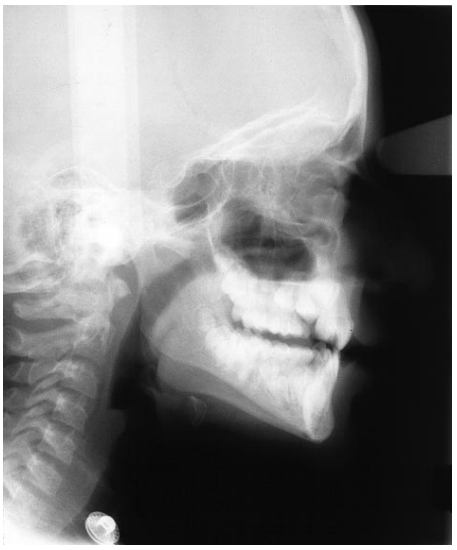

FIGURE 7. Lateral cephalometric view of a child with RDEB aged approximately 9 years.

and control data was so great that any ethnic differences would have only a minimal effect.

A further concern is the relatively small sample size. This is because RDEB is a rare condition and even tertiary referral centers such as Great Ormond Street Hospital for Children, which acts as a national referral center, have only relatively small numbers of suitable patients for study. Collection of further radiographs was not possible because patients with inadequate growth were managed by placement of a feeding gastrostomy. The numbers were further reduced because some of the radiographs were not of diagnostic quality.

This study supports numerically and statistically the clinical perception that RDEB patients have small jaws and faces. Although bone growth is significantly affected by malnutrition,[9,10] it is clear that even under conditions of severe growth inhibition from growth hormone deficiency and reduced caloric intake, the teeth are relatively unaffected.[11] The clinical impression is that RDEB children have teeth of normal size which, because of the reduced jaw size quickly leads to severe dento-alveolar disproportion manifest as severe anterior crowding[10] (Figure 2). In fact, dento-alveolar disproportion is so severe in these patients that removal of up to 8 teeth in the premolar-molar area has resulted in reasonably good spontaneous alignment of teeth.

The overall effect on facial aesthetics of this poor bony growth is clearly apparent with children often having a flat profile that, coupled with the microstomia and scarring, leads to poor facial appearance. The use of gastrostomy may have a sufficiently profound effect on growth to compensate for this severe skeletal retardation.[7]

It is difficult to know the relative contribution of the perioral scarring to the growth inhibition. Such growth inhibition is seen in cleft lip and palate cases following their surgical repair. Studies of unoperated clefts of lip, palate, or both have indicated that the maxilla was similar in size and relationships compared with a control sample.[12] Repair of a cleft lip or palate causes scarring of the soft tissues and affects the normal growth of the bones.[13] In children with RDEB it is probable that there is an association between the scar formation during the healing of intra-oral ulcerative lesions and the abnormal growth of the maxilla and mandible similar to the scarring deformities that occur in the hands (Figure 4).

CONCLUSIONS

The clinical significance of these findings is clear. The combined effects of malnutrition and scarring cause a marked inhibition of facial growth. This contributes significantly to the marked dento-alveolar disproportion and consequently to dental crowding. Combined with poor diet and poor oral hygiene there is an increased risk of dental caries, which is difficult to treat.[14] This is a significant burden for patients with RDEB and detracts further from the already reduced quality of life experienced by patients with this debilitating condition. In addition, there is an important aesthetic disfigurement associated with the malposed and malaligned anterior teeth.

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The institutional review boards for this study were the Research Ethics Committees of The Great Ormond Street Hospital for Children and The Eastman Dental Hospital, London, UK.

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