Dental caries risk in hereditary epidermolysis bullosa

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Abstract

Epidermolysis bullosa (EB) is a clinically diverse group of conditions characterized by skin fragility and, in certain types, marked dental involvement. The purpose of this study was to determine the prevalence of dental caries in EB and control populations. Healthy individuals and participants from the Southern Clinical Center of the National EB Registry were examined with artificial light and a #23 dental explorer. Caries levels were evaluated by chi-square analysis, regression analyses, and ANOVA (P < 0.05 being significant). The study included 252 individuals with EB, aged 2.3–71 years, and 57 similarly aged controls. The prevalence of dental caries, scored as DMFS (decayed, missing, filled surfaces), was significantly higher in the junctional (mean = 58.6) and recessive dystrophic (mean = 37.6) EB types than controls (mean = 23.2). The simplex (mean = 25.6) and dominant dystrophic (mean = 21.6) EB groups had DMFS levels similar to the control group. Individuals with recessive dystrophic EB had the most severe oral blistering and scarring and did not have generalized enamel hypoplasia. In contrast, junctional EB always was associated with generalized enamel hypoplasia yet the intraoral blistering rarely involved scarring. This study shows that dental caries is increased in recessive dystrophic and junctional EB compared with unaffected individuals or other EB types. While rampant caries appears related to the soft tissue and enamel involvement in these two EB types, other as yet unclear cofactors also must be involved. (Pediatr Dent: 16:427-32, 1994)

Introduction

Epidermolysis bullosa (EB) is a group of hereditary and acquired disorders characterized by mechanical fragility and blistering of the skin. Depending on the EB subtype, extracutaneous epithelial surfaces can be involved resulting in significant, if not incapacitating, scar formation and contractures. Distinct types of EB have been identified, each of which is classified into three major subgroups based on the level of tissue cleavage following mechanical trauma to the skin: epidermolytic (EB simplex), lamina lucidolytic (junctional EB), and dermolytic (dystrophic EB). Specific EB subtypes are further defined based on mode of inheritance, ultrastructural and phenotypic features, and the expression of specific basement membrane antigens. More recently, molecular genetics studies have shown a variety of defects in different EB types. The genetic defects in the Weber-Cockayne, Koebner, and Dowling Meara EB simplex subtypes are linked to defects of keratins 5 and 14. Dominant dystrophic EB shows linkage to the type VII collagen gene located on chromosome 3. Specific gene defects have not, however, as yet been identified for other major EB forms including recessive dystrophic and junctional EB.

Specific EB subtypes may have substantial involvement of extracutaneous structures including those of the oral cavity. For example, lesions can form on the cornea, in the esophagus, and in the intestinal tract. Furthermore, both the soft and hard tissues of the oral cavity may be affected, although precise characterization of the oral manifestations remains incomplete. Numerous reports describe abnormal dental development and dysplastic enamel in cases classified clinically as dystrophic and junctional EB. Despite these reports, the results of two large clinical investigations indicate that enamel hypoplasia is a common feature of junctional EB while other EB types tend not to be associated with abnormal enamel development. On the other hand, individuals with recessive dystrophic EB (EBDR) frequently are reported to suffer from rampant carious destruction of their dentition. Thus, the question remains: what factors are responsible for aggressive carious involvement in individuals with certain EB types?

Individuals with EB subtypes that predispose them to enamel hypoplasia, rapid attrition, and/or rampant dental caries can pose tremendous treatment difficulties. Rampant caries in EB has been attributed to defective enamel, prolonged food retention in the oral cavity, and changes in salivary consistency and quantity. Examination of salivary flow rates and salivary antibody titres in a large EB population indicates there is no diminution in salivary function that predisposes these individuals to dental caries. Furthermore, there have been no epidemiological studies of the dental caries prevalence in the different EB types. This leaves the clinician unable to accurately predict the degree of expected oral involvement, and therefore, unable to formulate a specific therapeutic approach based on risk factors associated with each EB subtype.

The purpose of this investigation was to evaluate the prevalence of dental caries in a well-defined population representing the various hereditary EB diseases. Additionally, this study examined the relationship
among potential etiologic factors — such as soft tissue involvement and enamel hypoplasia — that could contribute to the carious process.

**Methods and materials**

Individuals participating in the Southern Clinical Center for the National Epidermolysis Bullosa Registry, a federally funded project, were prospectively recruited for the present study. Unaffected, healthy individuals were recruited from the University of North Carolina School of Dentistry as the control population. Some individuals serving as controls were receiving treatment at the institution while others were parents or grandparents of child dental patients. Selection of the control population was not random — with specific age, gender, and racial characteristics being required to approximate the composition of the study population. Only individuals 2 years of age or older were accepted for inclusion in this report to ensure the presence of all primary teeth. Classification of individuals into specific EB subtypes was accomplished after gathering detailed family, medical, and dental histories, and was based on clinical findings, pedigree analysis, and the results of skin biopsy evaluations. Skin biopsies were analyzed using transmission electron microscopy, monoclonal antibody studies, and/or immunofluorescence mapping. Immunolocalization studies involved the use of a series of antibodies directed against skin basement membrane components or antigenic epitopes.

All oral evaluations were conducted by one dental examiner using artificial light, a dental mirror, and a #23 dental explorer. The teeth were not dried prior to examination due to the potential tissue trauma associated with soft tissue retraction and extensive use of compressed air. These techniques can cause bullae formation in the more severe EB types, precluding their use. Clinical photographs were taken to document the oral manifestations of each case. A caries score was established by clinical examination using the decayed, missing, filled surfaces (DMFS) and decayed, missing, filled teeth (DMFT) index. Both primary and permanent teeth were scored as DMFS/DMFT. Absent primary teeth only were scored as missing if the parents confirmed extraction or loss due to dental caries. Any teeth removed for orthodontic reasons or lost as a result of trauma were not counted as missing. Smooth surface and pit and fissure caries were defined and scored according to criteria established in the NIH caries epidemiology system.

During the clinical examination all well-demarcated areas of enamel with abnormal color and/or surface topography were noted and photographed. In each instance the teeth involved and a clinical description of the defect were recorded as to color, character, and location. Diffuse discolorations of enamel less than 2 mm were not recorded as enamel defects. All observable developmental topographic changes in the enamel were recorded excluding localized small white flecks. Areas of intact enamel that appeared chalky white, apparently due to decalcification, were excluded as a developmental defect. Disruptions in the enamel surface that were either actively carious (determined by retention of the explorer upon probing) or had decalcified borders indicating the possible presence of dental caries also were not scored as being developmental defects. Questionable areas of enamel integrity that could not be confirmed clinically or photographically were recorded as normal.

Soft tissue lesions were recorded as to location, size, and character. Individuals also were questioned as to history of oral blistering. The frequency of individuals with oral involvement was determined from the combined historical and examination data. Statistical analyses of age and DMFS scores included the use of regression analysis, Student's t-test, analysis of variance (ANOVA), and Fisher's protected least significant differences. Chi-square analyses were used to examine the relationship between enamel hypoplasia, oral blistering, and dental caries. All statistical analyses were performed accepting P < 0.05 as significant.

**Results**

Evaluated were 252 individuals with EB and 57 controls meeting the criteria for inclusion in this investigation. The study participants represented all the major EB types, as well as nearly all the known subtypes. The age, gender, and race distributions of the EB and control populations are presented in Table 1. Statistical analysis showed the EBDR group had a significantly lower mean age (P = 0.01) than the other EB or control groups. Age and gender distribution was similar for all other EB groups and the control population.

The various EB subtypes differed significantly in their phenotypic features and oral manifestations. While oral blistering was common in all of the EB groups, it was most prevalent and most severe in recessive dyst...
Fig 1. Percent of individuals with oral blistering by history or examination. Individuals in all EB groups show a significant risk for developing at least occasional oral blistering.

Fig 2. This 7-year-old child with EBDR shows severe microstomia, ankyloglossia, vestibular obliteration, and rampant cervical dental caries.

Fig 3. Severe enamel hypoplasia and extensive dental caries are seen in this 29-year-old with junctional EB.

trophic EB (EBDR, Fig 1). Lesions varied from small discrete vesicles to large intraoral bullae that ruptured, leaving denuded eroded areas. Lesions were distributed over the entire oral cavity, with all of the mucosal surfaces being potentially involved. No site-specific pattern of involvement, such as blistering limited to or absent from certain intraoral areas, was observed in any of the different EB categories or subtypes. Individuals with EBDR typically had extensive intraoral soft tissue involvement (Fig 2) including microstomia, ankyloglossia, and obliteration of the oral vestibule. Ankyloglossia and vestibular obliteration were not seen in any other EB type, although a significantly decreased oral opening as measured by the commissure to commissure width was observed in the Herlitz variant of junctional EB.¹⁰

The prevalence of individuals with enamel defects differed among the various EB subtypes ranging from 18.1% in EBDR to 100% in junctional EB. Developmental enamel defects were seen clinically in 17.5% of the control population (Table 2). Junctional EB was the only group with significantly increased occurrence of enamel defects compared with the control group. Generalized enamel hypoplasia, presenting as either severe pitting or thin enamel, was seen in all individuals with junctional EB (Fig 3). One individual with EB simplex showed generalized motting of the enamel and occasional enamel pits. Generalized developmental defects of enamel were not seen in any other EB groups or the control population. Localized developmental defects of enamel occurred with similar frequency for all nonjunctional EB types and the control population.

The mean DMFS scores ranged from 21.6 in dominant dystrophic EB to 58.6 in junctional EB (Table 2). There was tremendous variability in the caries rate, even between individuals with the same EB type. There were individuals in all groups who remained caries free while others had extensive dental caries (Fig 4). The control group had a mean DMFS score of 23.3. Dominant dystrophic EB and EB simplex had DMFS scores (21.6, 25.6 respectively) that were similar to that of the control group. Both EBDR and junctional EB had significantly increased DMFS levels compared with the control population as determined by ANOVA and Fisher's protected least significant difference multiple mean comparison. Statistical analysis using the less sensitive measure of DMFT scores showed all groups being similar with the exception of junctional EB, which was associated with a significantly increased DMFT score.

The relationship between dental caries, developmental enamel defects, and oral blistering was examined for the entire EB population and by individual EB types. While the DMFS scores were significantly increased in

Table 2. Prevalence of enamel hypoplasia and dental caries in EB and control population

<table>
<thead>
<tr>
<th>Group</th>
<th>Enamel Hypoplasia*</th>
<th>Mean DMFS (± SD)</th>
<th>Mean DMFT (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recessive dystrophic EB</td>
<td>18.1</td>
<td>37.6± (43.4)</td>
<td>10.1 ± (6.8)</td>
</tr>
<tr>
<td>Dominant dystrophic EB</td>
<td>15.4</td>
<td>21.6 (25.6)</td>
<td>8.2 ± (6.8)</td>
</tr>
<tr>
<td>Junctional EB</td>
<td>100.0*</td>
<td>58.6± (51.9)</td>
<td>15.3± (10.5)</td>
</tr>
<tr>
<td>Simplex EB</td>
<td>21.9</td>
<td>25.6± (29.0)</td>
<td>8.8 ± (7.6)</td>
</tr>
<tr>
<td>Control</td>
<td>17.5</td>
<td>23.2± (25.2)</td>
<td>8.8 ± (7.1)</td>
</tr>
</tbody>
</table>

* Percent of individuals in group having at least one tooth with a developmental defect.
† Denotes groups significantly different from controls using chi-square analysis or ANOVA at P < 0.05.
EBDR and junctional EB, as compared with controls, there was no statistically significant relationship between dental caries and enamel hypoplasia or oral blistering in the EB population. Using chi-square analyses there was no significant relationship between a DMFS score >25 and the presence of either developmental enamel defects (P = 0.12) or oral blistering at examination (P = 0.47). Similarly, there was no relationship in EBDR between a DMFS score > 25 with ankyloglossia and vestibular obliteration (both of which are strong indicators of severe soft tissue involvement).

**Discussion**

Identifying populations at high risk for developing dental caries allows clinicians to apply specific preventive measures in a more cost effective and efficacious manner. This epidemiological investigation showed that while individuals with certain EB subtypes are at increased risk for developing extensive dental caries, others are not. Individuals with EBDR and junctional EB had significantly more dental caries when compared with other EB types or unaffected controls. These two former EB groups also typically exhibit the most severe cutaneous manifestations. Those EB types tending to have less severe cutaneous involvement (i.e., EB simplex and dominant dystrophic EB) had dental caries scores similar to unaffected individuals.

While the mean caries scores of EBDR and junctional EB were significantly increased, there was tremendous individual variation as indicated by the large standard deviations in DMFS scores. Even in the EBDR and junctional EB groups — both of which were at high risk for developing caries — a few people remained caries free while others had all of their dental surfaces involved. Although these EB groups showed an increased risk for dental caries, a certain subset of affected individuals clearly was resistant to developing dental decay. This finding indicates that while having either of these two EB types predisposes the individual to dental caries, there must be additional risk factors contributing to the disease process that result in the observed variability. These results are consistent with the accepted multifactorial etiology of dental caries and the reported difficulty in identifying specific factors useful in accurately predicting an individual's risk for developing dental caries.

Oral blistering was found to be common in all the EB subtypes but was most severe in EBDR. As reported previously and confirmed in this investigation, most individuals with EB develop oral blisters at least occasionally, with all areas of the oral mucosa showing increased fragility. Significant oral scarring with subsequent development of vestibular obliteration and ankyloglossia appeared to be limited to patients with EBDR. It has been hypothesized that the presence of oral lesions would influence dental caries development by altering the oral clearance time of foods, require consumption of softer diets, and would be deleterious to effective oral hygiene practices. In our study, no significant relationship was found to exist between increased dental caries and the presence of oral soft tissue lesions in the EB population as a whole or in the EBDR group, which showed the most severe oral blistering. While individuals with EBDR are at increased risk for developing dental caries and have extensive oral soft tissue involvement, it is not surprising that there is not a simple statistical relationship between caries and blistering given the multifactorial etiology of the carious process. Although it is likely that substantial oral blistering can alter a variety of caries risk factors related to diet, fluoride exposure, microbial flora, and oral hygiene, it is apparent that not all individuals with EBDR will develop dental caries despite the presence of significant oral lesions.

Developmental enamel defects in our study were seen in all junctional EB cases, with other EB types having a prevalence of enamel defects similar to unaffected individuals, thus corroborating the original findings of Gedde-Dahl. Enamel hypoplasia in junctional EB was highly variable. Some individuals had occasional pits of varying size while others had very thin to absent enamel. Although individuals with junctional EB had an elevated mean caries score, there was again no statistically significant relationship between dental caries and enamel defects. Even though enamel hypoplasia may place individuals with junctional EB at substantial risk for developing dental caries, other important cofactors appear to be involved.

This investigation has identified individuals with EBDR and junctional EB as being at increased risk for developing dental caries compared with unaffected
individuals. On the surface it seems that oral blistering and enamel hypoplasia are the principal etiologic factors predisposing these individuals to dental involvement and leading to an increased caries experience. However, further analysis indicates that there must be additional, as yet unclear, risk factors contributing to the presence of rampant carious destruction in these EB groups. Regardless, individuals with EBDR and junctional EB should be managed as patients at high risk for developing dental caries. Preventive intervention in this high risk population must consider traditional caries risk factors such as the frequency and amount of fermentable carbohydrate consumption, fluoride exposure, and oral hygiene.

It is possible that the unique soft tissue and enamel changes in EBDR and junctional EB are associated with substantial alterations of the oral microflora, further contributing to the caries process. While not tested specifically in this investigation, it seems probable that these traditional caries risk factors coupled with those inherent in these EB types (oral blistering and enamel hypoplasia) may be responsible for the observed increase in dental caries. Although diet is extremely difficult to manage in EBDR cases because of the presence of severe oral involvement and frequent esophageal strictures, a dietitian can recommend a less cariogenic diet that still meets patients’ caloric and nutritional needs. Increased fluid intake while eating may enhance oral clearance of food debris in EBDR patients with severe intraoral scarring and restricted tissue mobility. Heavily flavored or alcohol-based fluoride rinses and topical applications are often not well accepted in EB patients with substantial oral blistering because they may burn or irritate the mucosa. Neutral sodium fluoride topical applications and nonalcohol-based rinses may prove efficacious in these cases. Alternatively, topical application of a high-dose fluoride varnish may be preferable to more traditional, professionally applied topical fluorides in these patients. Chlorhexidine rinses could be beneficial in reducing the frequency of rampant carious destruction in these patients. Regardless, individuals with EBDR and junctional EB, results from soft tissue and enamel involvement, these features were not shown to be related statistically to dental caries in this investigation.

4. Alteration of the oral soft tissues and enamel defects may secondarily alter as-yet-undefined properties that participate in the multifactorial caries process in the EB populations at increased risk for caries development.

Conclusions

1. Individuals with EBDR and junctional EB are at increased risk for developing dental caries.

2. In contrast, EB simplex and dominant dystrophic EB do not have an elevated caries risk compared with unaffected individuals.

3. While it seems intuitive that the increased caries risk in individuals with EBDR and junctional EB results from soft tissue and enamel involvement, these features were not shown to be related statistically to dental caries in this investigation.

4. Alteration of the oral soft tissues and enamel

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