

Epidermolysis bullosa accompanied by amelogenesis imperfecta: A report of three cases and literature review

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Abstract

Introduction: Epidermolysis Bullosa (EB) is a group of genetic disorders characterized by skin and mucosal fragility. Similarly, Amelogenesis Imperfecta (AI) is a genetic condition that affects the development of dental enamel, leading to structural anomalies. Specific gene mutations, such as those affecting COL17A1, are known to cause both conditions, notably in patients with Junctional EB. This study explores the clinical presentations of three patients diagnosed with both AI and EB, with two cases confirmed to have COL17A1 mutations, linking the genetic mutation to both enamel defects and EBs.

Case Reports: The clinical findings from three patients are reported. Two of the cases were diagnosed with Junctional EB, with genetic testing confirming COL17A1 mutations, which correlated with the presentation of hypoplastic enamel and pitting. All patients exhibited gingivitis and oral mucosal fragility, which posed challenges in maintaining oral hygiene.

Discussion: Maintaining oral hygiene in patients with EB is particularly challenging due to the fragility of their oral mucosa. These challenges are exacerbated by the low socioeconomic status of the patients, limiting access to proper oral care tools. The study explores oral management strategies, including the use of soft toothbrushes, sucralfate for ulcer management, and the importance of a multidisciplinary approach. Regular dental check-ups and early intervention are emphasized as essential for improving patient outcomes and quality of life.

Conclusion: It is crucial for dental practitioners to identify signs of AI in EB patients and to ensure timely referrals and consultations. Furthermore, EB patients should be referred to dental professionals early to prevent oral complications. A multidisciplinary approach is vital for addressing the complex needs of these patients effectively.

Keywords: Amelogenesis imperfecta, epidermolysis bullosa, genetic disorders, COL17A1

1. Introduction

Epidermolysis Bullosa (EB) is a genetically heterogeneous group of rare disorders that affect the skin and mucous membranes. The primary characteristic of this group of diseases is the formation of blisters (bullae) and erosions (open wounds) on the skin and mucosal tissues with minimal trauma or pressure (1). The worldwide incidence of EB is approximately 1 in 50,000 live births. This disease affects both males and females equally and can be found in all ethnic groups (1).

The underlying cause of EB is mutations in the genes responsible for producing structural proteins that hold the skin layers together (2). These mutations weaken the connection between the epidermis, the outermost layer of the skin, and the underlying dermis. EB is usually inherited in an autosomal dominant or autosomal recessive manner (3).

The pathophysiology of EB is characterized by the separation of skin layers, resulting in the formation of blisters. This separation typically occurs in response to mechanical trauma but can also occur spontaneously in some types of EB (4). EB is divided into four main clinical subtypes: EB Simplex, Junctional EB, Dystrophic EB, and Kindler Syndrome. Each subtype is associated with the involvement of different structural proteins (2) (Table 1).

Some genes whose mutations cause Epidermolysis Bullosa also play a crucial role in the process of amelogenesis

(Table 2). Junctional EB (JEB) is caused by mutations in proteins such as laminin-332 and collagen XVII, which are found in the basal membrane of the skin. Laminin-332 plays a critical role in tooth development, and mutations in this protein can lead to enamel hypoplasia, as seen in amelogenesis imperfecta (5). In Kindler Syndrome, the mutated gene is FERMT1, which encodes for kindlin-1, a protein involved in cell adhesion. Mutations in this gene affect the amelogenesis process, leading to the development of amelogenesis imperfecta (6).

Amelogenesis imperfecta (AI) is an inherited condition characterized by abnormalities in the development of dental enamel. This condition can be inherited in an autosomal dominant, recessive, or X-linked manner and typically affects both primary and permanent teeth, showing significant variation in clinical phenotypes (16). The prevalence of AI is approximately 1 in 12,000 to 1 in 13,000 live births worldwide (17). The pathophysiology of AI is characterized by disruptions in the production or processing of enamel matrix proteins, leading to abnormal enamel structure (18).

The classification of Amelogenesis Imperfecta (AI) by Witkop (1988) is based on four main types:

- Hypoplastic,
- Hypomaturation,
- Hypocalcification,
- Combined

Each main type is further divided into subtypes based on clinical and histological findings (16) (Table 3).

Table 1. Clinical subtypes of EB and associated genetic mutations.

EB Clinical Subtype	Clinical Features	Affected Layer of Epidermis	Associated Genes
Epidermolysis Bullosa Simplex (EBS)	- Usually appears shortly after birth or in early childhood. - Blisters form on the skin after minor trauma or friction. - Blisters are mostly seen on hands and feet. - Nail dystrophy, hyperkeratosis, and atrophy are common. - Generally, there are no severe systemic complications, and life expectancy is normal.	- Blisters form in the upper layer of the epidermis (intraepidermal).	KRT5, KRT14
Junctional Epidermolysis Bullosa (JEB)	- Appears at birth or shortly after. - Blisters are usually large and widespread, severely affecting the skin and mucous membranes. - In severe forms, patients may die within the first few years of life. - Chronic wounds, nail dystrophy, and dental anomalies can occur. - Respiratory and gastrointestinal complications are common.	- Blisters form in the basal membrane region between the epidermis and dermis (intra-lamina lucida).	LAMB3, COL17A1, ITGA6, ITGB4
Dystrophic Epidermolysis Bullosa (DEB)	- Begins at birth or early childhood. - Blisters form on the skin and mucosal surfaces and can leave deep scars. - Fusion of fingers (pseudosyndactyly) and other joint deformities are common. - In severe cases, patients may die in childhood or young adulthood. - Chronic wounds, nail dystrophy, and severe scarring are observed.	- Blisters form in the upper layer of the dermis (sub-lamina densa).	COL7A1
Kindler Syndrome	- Starts after birth or in early childhood. - Blisters form at various layers of the skin. - Photosensitivity, atrophic scars, and periodontal disease are observed. - Skin pigmentation changes and scleroderma-like skin hardening are common.	- Blisters form at different levels of the skin.	FERMT1

Table 2. Amelogenesis imperfecta (AI) clinical phenotypes and associated gene mutations.

Gene-Protein/EB Type	Amelogenesis Imperfecta Clinical Phenotype	Report
LAMA3 - 3333 amino acids / EB Junctional	Mild enamel pitting and susceptibility to caries	Yuen et al., 2012 (7)
	Focal, asymptomatic enamel pitting	Gostyńska et al., 2016 (8)
	Focal, asymptomatic enamel pitting	Gostyńska et al., 2016 (8)
LAMB3 - 1172 amino acids / EB Junctional	Hypoplastic	Prasad et al., 2016 (9)
	AI hypoplastic	Prasad et al., 2016 (9)
	Generalized irregular hypoplastic enamel in all primary teeth	Lee et al., 2015 (10)
	Irregular hypoplastic AI, frequent pain and aesthetic problems, multiple dental extractions, and restorative dental care	Poulter et al., 2014 (11)
	Generalized enamel hypoplasia, thermal hypersensitivity, deep grooves and pits, vertical linear grooves in incisors	Kim et al., 2013 (12)
	Enamel hypoplasia in all primary and permanent dentition, deep grooves and pitting defects, generalized enamel hypoplasia on radiographic examination. Taurodontism, vertical linear grooves in incisors, thermal hypersensitivity	Kim et al., 2013 (12)
	Enamel hypoplasia in all primary and permanent teeth, hypoplastic grooves, and pits	Lee et al., 2015 (10)
	Enamel hypoplasia in all primary and permanent teeth, hypoplastic grooves, and pits	Wang et al., 2013 (13)
COL17A1 - 1497 amino acids / EB Junctional	Extensive enamel pitting, horizontal ridging of incisors, and loss of enamel in molars	Murrell et al., 2007 (14)
	Hypoplastic enamel	Prasad et al., 2016 (9)
	Hypoplastic enamel	Prasad et al., 2016 (9)
	Hypoplastic, hypomature	Prasad et al., 2016 (9)
	Extensive enamel hypoplasia and pitting	McGrath et al., 1996 (15)
	Isolated AI. Hypoplastic enamel.	Prasad et al., 2016 (9)
FERMT1 / Kindler Syndrome	Hypoplastic pitted amelogenesis imperfecta	Krämer et al., 2024 (6)

Table 3. Classification of amelogenesis imperfecta (AI) by Witkop (1988).

Type of AI	Subtypes of AI	Clinical Features
Hypoplastic	General Hypoplasia	Thin and flattened enamel, reduced enamel thickness.
	Local Hypoplasia	Insufficient enamel formation in specific areas.
	Pitting Type	Small pits and roughness on the tooth surface.
Hypomaturation	General Hypomaturation	Opaque and brittle enamel, often yellowish or brownish discolorations.
	X-linked Hypomaturation	Cracks and breakage in enamel, severe calcification deficiency.
Hypocalcification	General Hypocalcification	Insufficient calcification in enamel, rapid wear, and breakage of teeth.
Combined	Hypoplastic and Hypomaturation	Features of both hypoplastic and hypomaturation types, poor enamel quality.
	Hypoplastic and Hypocalcification	Features of both hypoplastic and hypocalcification types, teeth wear and break easily.

To date, more than 70 genes have been identified to cause mutations leading to amelogenesis imperfecta (AI). These genes encode a wide range of potential activities in amelogenesis, including enamel matrix proteins, intracellular vesicle trafficking, ameloblast attachment to the matrix or neighboring cells, ion

transport, mineralization, and matrix-protein degradation (19). While some cases reported in the literature highlight isolated AI, others reveal syndromic amelogenesis imperfecta, where AI occurs alongside a genetic syndrome such as EB Junctional and Kindler Syndrome (Table 4).

Table 4. Reported syndromes and their characteristics in syndromic amelogenesis imperfecta.

Disease Name	Characteristics	Mutations	Reported By
Enamel-Renal Syndrome (Amelogenesis Imperfecta type IG)	Hypoplastic enamel on primary and secondary dentition, pulp stones, delayed or failed eruption of secondary dentition, gingival overgrowth, nephrocalcinosis	FAM20A	Wang et al., 2013 (5)
Kohlschütter-Tönz Syndrome (KTZS)	Severe global developmental delay, early-onset intractable seizures, spasticity, amelogenesis imperfecta affecting both primary and secondary teeth, yellow or brown discoloration	ROGDI	Schossig et al., 2012 (20); Mory et al., 2012 (21)
Jalili Syndrome	Cone-rod dystrophy, significant visual impairment, abnormal enamel prone to rapid posteruptive failure	CNNM4	Parry et al., 2009 (22)
Trichodontoosseous Syndrome (TDO)	Abnormalities involving hair, teeth, and bones; thickened hair, hypomineralization in teeth, enamel hypoplasia	DLX3	Nguyen et al., 2013 (23)
Developmental and Epileptic Encephalopathy-25 with Amelogenesis Imperfecta (DEE25)	Refractory seizures in early infancy, global developmental delay, intellectual disability, dental anomalies including AI	SLC13A5	Thevenon et al., 2014 (24)
Dental Anomalies and Short Stature (DASS)	Significant short stature, hypoplastic amelogenesis imperfecta with almost absent enamel, sometimes valvular and/or vascular defects	FAM20A	Huckert et al., 2015 (25)

In this study, we discuss the clinical presentations of two different types of Amelogenesis Imperfecta (AI) observed in three distinct cases of Epidermolysis Bullosa (EB). We aim to contribute to the body of literature on the relationship between AI and EB, highlighting key considerations and challenges in managing patients with these dual diagnoses.

2. Case Reports

2.1. Case 1

Case 1 was an 11-year-old male patient diagnosed with Epidermolysis Bullosa. The patient was currently in the mixed dentition stage. His saliva flow rate was 3.5 ml/min, and he had a high buffering capacity. The family's socioeconomic status was low.

The patient was born at term with a birth weight of 3000 g through normal vaginal delivery. There was no need for NICU admission. The mother reported experiencing a complication-free pregnancy with no notable issues. The patient was exclusively breastfed for 12 months. During infancy, the patient frequently suffered from throat infections, that required antibiotic treatment.

The patient's oral hygiene habits were insufficient. Intraoral examination revealed enamel defects, including brown discoloration and hypoplastic enamel

across all teeth, which is indicative of amelogenesis imperfecta. According to Witkop's classification, the AI clinical type is likely to be the hypoplastic pitting type (Fig. 1). Multiple carious lesions were also observed in the posterior teeth, specifically teeth numbers 16, 47, 26, and 36.



Figure 1. Intraoral view of Case 1 diagnosed with hypoplastic pitting type Amelogenesis Imperfecta.

A panoramic radiograph revealed mixed dentition with evident enamel defects and multiple carious lesions (Fig. 2). Developing permanent teeth exhibit irregular enamel formation, consistent with amelogenesis imperfecta. Additionally, primary teeth with only the crowns remaining due to root resorption were identified, specifically, teeth numbers 55, 53, and 65. No other pathological findings were observed.



Figure 2. Panoramic radiograph of Case 1, primary teeth numbers 55, 53, and 65, with only the crowns remaining owing to root resorption.

The permanent teeth numbered 16, 47, 26, and 36 were restored using posterior composite resin. The primary teeth, numbers 55, 53, and 65, were extracted under local anesthesia.

2.2. Case 2

Case 2 was a 9-year-old male patient diagnosed with Epidermolysis Bullosa. He is currently in the mixed dentition stage. His saliva flow rate was 1.5 ml/min, and he had a high buffering capacity. The family's socioeconomic status is low.

The patient was born at term with a birth weight of 4000 g through normal vaginal delivery and required a stay in the NICU. The mother reported experiencing a complication-free pregnancy with no notable issues. The patient had not been breastfed. In infancy, the patient did not experience any serious illnesses aside from Epidermolysis Bullosa. The patient demonstrated insufficient oral hygiene practices.

Intraoral examination revealed enamel defects, particularly yellow discoloration and hypomineralized enamel on all teeth, consistent with amelogenesis imperfecta (Fig. 3). Based on Witkop's classification, the AI clinical type is suspected to be the hypomineralized type. Deep dentin caries was detected in the primary molars (teeth numbers 65 and 84) and the permanent molars (teeth numbers 16, 26, 36, and 46). It was observed that primary molars negatively affected the occlusion.



Figure 3. Intraoral view of Case 2 diagnosed with hypomineralized type Amelogenesis Imperfecta.

A panoramic radiograph revealed mixed dentition with evident enamel defects and multiple carious lesions (Fig. 4). The developing permanent teeth exhibit irregular enamel formation, consistent with amelogenesis imperfecta. It was observed that the primary molars (65 and 84) had resorbed roots. No other pathological findings were noted.

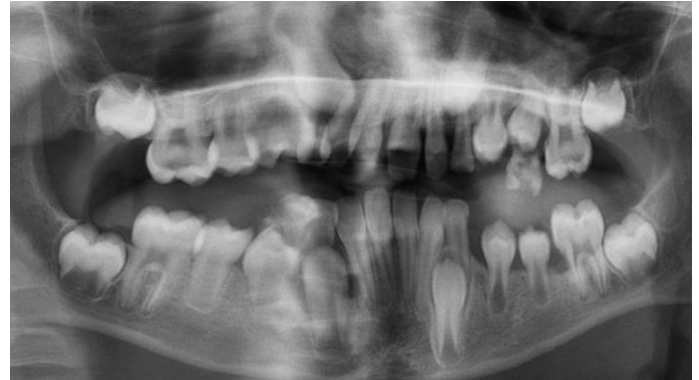


Figure 4. Panoramic radiograph of Case 2; primary teeth numbers 65 and 84 had resorbed roots.

The procedure was performed under local anesthesia. The primary molars, numbers 65 and 84, exhibited deep dentin caries and were extracted as they affected occlusion, and their roots were resorbed. Deep dentin caries in the permanent molars (numbers 16, 26, 36, and 46) were also restored using a posterior composite resin with reinforced glass ionomer cement as the base material.

2.3. Case 3

Case 3 was an 11-year-old male patient diagnosed with Epidermolysis Bullosa. The patient was in the permanent dentition stage. His saliva flow rate was 3 ml/min, and he had a high buffering capacity. The family's socioeconomic status is low.

The patient was born at term through normal vaginal delivery without requiring a NICU stay. No birth weights were reported. His mother did not take any medications during her pregnancy. He was breastfed for 15 months of age. In infancy, he did not experience any serious illnesses aside from Epidermolysis Bullosa.

The patient's oral hygiene habits are insufficient. Intraoral examination revealed enamel defects, particularly brown discoloration and hypoplastic enamel on all teeth, consistent with amelogenesis imperfecta (Fig. 5). Based on Witkop's classification, the AI clinical type was suspected to be the hypoplastic pitting type. The patient exhibited a narrow maxilla, and the permanent lateral incisors were palatally positioned. Wear and deep dentin caries were observed in the molar, dentin caries in tooth number 35, and enamel caries were observed in the other premolar teeth.



Figure 5. Intraoral view of Case 3 diagnosed with hypoplastic pitting type Amelogenesis Imperfecta.

A panoramic radiograph revealed permanent dentition marked by pronounced enamel defects and widespread carious lesions across all molar teeth (tooth numbers 16, 17, 26, 27, 36, 37, 46, and 47) with significant wear (Fig. 6). A dentin caries lesion was detected in the 35th premolar, and enamel-level carious lesions were observed in the other premolar teeth. The developing permanent teeth exhibit irregular enamel formation, consistent with amelogenesis imperfecta. No other pathological findings were noted.

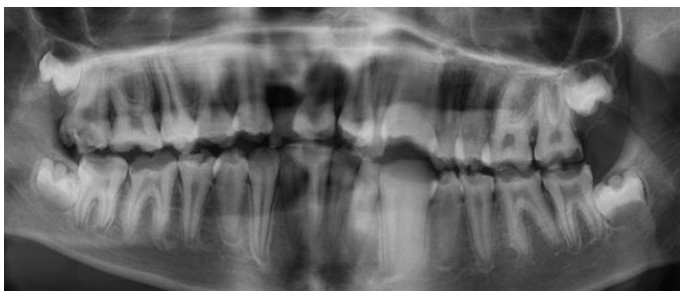


Figure 6. Panoramic radiograph of Case 3 showing carious lesions across all molar teeth (tooth numbers 16, 17, 26, 27, 36, 37, 46, and 47) with significant wear.

Deep dentin caries in the molar teeth were treated using reinforced glass ionomer cement as the base material, while enamel and dentin caries were restored solely with composite resin material. All procedures were performed under local anesthesia.

2.4. General treatment precautions

During the procedures, all possible precautions were taken to ensure atraumatic treatment. For the restorations, the rotary instruments were wrapped in gauze to minimize friction and contact. The patient's mouth opening was maintained as much as the patient could tolerate, with intermittent breaks to avoid fatigue.

Prior to the procedures, petroleum jelly was applied to prevent angular cheilitis and to soften the lips.

2.5. Overall management and future plans

Future treatment plans include full-coverage crowns to manage enamel defects and improve aesthetics and function. Medical management includes the care and monitoring of the skin lesions. Dental management involves the reinforcement of oral hygiene practices, fluoride treatments, and regular dental check-ups. These cases require regular follow-up to monitor dental development and manage any arising issues. Coordination with dermatological care is essential to ensure the comprehensive management of their condition.

2.6. Genetic Findings

Genetic testing for Case 1 and Case 3 identified mutations in the COL17A1 gene, confirming the diagnosis of Junctional Epidermolysis Bullosa (JEB). Unfortunately, genetic test results for Case 2 were not available, preventing further classification of the EB and AI subtypes in that patient.

3. Discussion

The relationship between COL17A1 mutations and dental anomalies, particularly Amelogenesis Imperfecta (AI), has been well-documented in the literature. Early reports by McGrath et al. (1996) highlighted the presence of extensive enamel hypoplasia and pitting in patients with Junctional Epidermolysis Bullosa (JEB) (15). These findings were later corroborated by Murrell et al. (2007), who described extensive enamel pitting, horizontal ridging of incisors, and loss of enamel in molars (14). More recently, Prasad et al. (2016) further emphasized the link between hypoplastic enamel and JEB in patients with COL17A1 mutations (9).

In the present study, genetic testing revealed COL17A1 mutations in two patients, both of whom exhibited dental findings consistent with AI, particularly hypoplastic enamel and pitting. These clinical observations align with those reported in the aforementioned studies, reinforcing the connection between JEB, COL17A1 mutations, and AI phenotypes. When comparing the clinical findings observed in this study with those reported in the literature, notable similarities and differences emerge. Krämer et al. (2020) report that gingivitis is prevalent in Junctional and Recessive Dystrophic EB, which aligns with the findings in all patients of this study (26). While oral ulcerations are common across all EB types, patients with EB exhibit restricted mouth opening due to dryness of the perioral

tissues. Additionally, Case 3, diagnosed with Junctional EB, exhibited a small upper jaw and severe dental crowding, features reported in the literature for Recessive Dystrophic EB.

The oral hygiene status of patients with Epidermolysis Bullosa (EB), as observed in the three cases published here, is generally poor because it is difficult to maintain oral care without damaging the fragile oral mucosa. The risk of oral mucosal injury during tooth brushing can lead to severe discomfort and potential infections, making gentle oral hygiene practices crucial for preventing trauma and maintaining oral health. Additionally, the severity of EB should be considered when planning their oral care routines; more severe forms of the disease require even gentler care (26).

The literature outlines various requirements for optimizing oral hygiene in patients with EB. Early referral to the dentist, ideally between 3 to 6 months of age, is crucial before oral problems arise. Although oral bullae, ulcers, and erosions are common features of EB, therapeutic approaches for these lesions are limited. Marini and Vecchiet (2001) reported that sucralfate suspension reduces the development and duration of oral mucosal blisters and ulcers, alleviates oral pain, and improves plaque and gingival inflammation indices (27). Mouthwashes and oral gels are commonly prescribed for managing mucositis and oral lesions (28). The smallest toothbrush available, such as a baby-sized toothbrush, should be used. Patients with Recessive Dystrophic EB (RDEB) and Kindler EB are at an increased risk of developing intraoral squamous cell carcinoma (SCC), necessitating early screening (29,30). The frequency of dental reviews should be individualized based on plaque presence and caries risk, with intervals ranging from 3 to 6 months, and monthly for some patients (31).

According to the results of a study by Angelis (2016) on 204 patients with EB from various European countries, individuals living with EB have a significantly lower health-related quality of life than the general population. Additionally, their caregivers also experience decreased health-related quality of life (32). Similar to those in the literature, the patients included in the current study also had a low socioeconomic status. This low socioeconomic status may negatively impact their ability to maintain proper oral hygiene. Limited access to dental care and appropriate oral hygiene products exacerbates the challenges faced by these patients.

Improving the quality of life for patients with EB and AI requires dental professionals to be well-versed in oral hygiene recommendations and to offer practical advice that patients can easily follow. Regular follow-up and close coordination with dermatologists and geneticists are essential for holistic patient management. Dental professionals need to be aware of these genetic aspects to provide comprehensive care. Knowledge of the specific genetic mutations involved in AI and EB can guide clinicians in anticipating and managing the dental anomalies associated with these conditions (2).

4. Conclusion

In conclusion, dental practitioners should be vigilant in identifying signs of AI in patients with EB and ensure that appropriate consultations are sought when necessary. It is also essential for patients diagnosed with EB to be referred to dental professionals. Adopting a multidisciplinary approach is critical for effectively addressing the complex needs of these patients.

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