Oral Care in Kindler Syndrome: 7-Year Follow-up of 2 Brothers

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Background: *Kindler poikiloderma is an inherited autosomal genodermatosis characterized by blistering of the epidermis and mucosae. Its prevalence is unknown.* ***Case*** *report: We monitored two brothers suffering from this pathology. Oral manifestations mainly take the form of periodontal lesions. In our patients we noted gingivitis progressing to periodontitis as follow-up care was not effective. We also diagnosed enamel hypoplasia, described more rarely in this pathology.* ***Conclusion:*** *Periodontitis in Kindler Syndrome responds to maintenance therapy, but the absence of surveillance is penalized by a deterioration in periodontal condition and complication of management. All restorative, endodontic, surgical, periodontal and orthodontic treatments should be performed with appropriate precautions.*

Keywords: *Kindler syndrome**,** epidermolysis bullosa,, enamel hypoplasia, periodontal disease.*

INTRODUCTION

Inherited epidermolysis bullosa (CIM-10 Q81.0, Q81.1, Q81.2, Q81.8, Q81.9; ORPHA:7936) is a group of rare genodermatoses. Four main subtypes are described: Epidermolysis Bullosa Simplex, Dystrophic Epidermolysis Bullosa, Junctional Epidermolysis Bullosa, and Kindler Syndrome (KS). In all these conditions, proteins involved in the junction between the epidermis and the dermis are abnormal, due to genetic mutation with consequences ranging from moderate discomfort to disorders that cause serious impairment according to the severity of the forms. Extreme fragility of the skin reduces resistance to shearing and frictional injury. A cleavage occurs between these two skin layers in the event of collision, friction or trauma and blisters can appear[1;2].

Kindler poikiloderma is an autosomal recessive pathology, characterized by blisters arising in multiple levels of cleavage within the epidermis and mucosae, and by specific clinical phenotypic features, such as photosensitivity. Its prevalence is unknown. Persons of any race can be affected and there is no gender predilection. Symptoms begin at birth, or during infancy[1]. Management of these patients requires a multidisciplinary team, in which a dentist is essential, because the hard and soft tissues of the oral cavity, and particularly the periodontium are very often involved in the clinical manifestations (Table 1). We introduce two brothers E., born in 2006 and S., born in 2002, treated in the Competence Center for Rare Odontological Diseases at Timone University Hospital (Assistance Publique-Hôpitaux de Marseille) since 2009 which specialises in KS.

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Table 1: Case reports describing the main oral manifestations and management of patients with Kindler Syndrome: review of literature published between 1997 and 2019.

Authors of Articles	Number of cases	Gender/Age	Oral manifestations	Oral care described
24 ➢ Anwar et al. ➢ Barbosa et al. ➢ Burch et al. ➢ De Almeida et al. ➢ Fischer et al. ➢ Ghosh et al. ➢ Gkaitatzi et al. Krishna et al. ➢ Kustner et al. Mansur et al. Mendes et al. ➢ Nofal et al. ➢ Penagos et al. Ricketts et al. Sharma et al. ➢ Suga et al. ➢ Suman et al. Torkzaban et al. Wada et al. ➢ Wiebe et al. (1) Wiebe et al. (2) ➢ Yazdanfar et al. ➢ Yildirim et al. ➢ Zhou et al.	*86*	38 F / 2-54y 48 M/4-49y	• Oral mucosa: Hyperkeratosis, Painful ulcers on soft palate, lips, floor of the mouth, labial commissure, hard palate • Gingivitis: Chronic, desquamative • Periodontitis: mild to severe with rapid progression • Tooth mobility, premature loss • Ankyloglossia • Difficulty in swallowing • Xerostomia • Microstomia • Synechiae between the lips and the gums • Poor hygiene • Carious lesions	• Instructions for tooth-brushing and use of chlorhexidine mouthwash • Dietary advice • Symptomatic treatments for oral dryness • Supragingival scaling • Gingivectomy • Tooth extraction • Implant treatment • Restorative dental treatment

Case report

Two brothers (S. seven years old and E. three years old) diagnosed with a moderate form of KS, were treated in 2009 for dental care needs. The genetic analysis revealed a homozygous FERMT1 gene mutation g.80929_89169del. Their mother presented with the same mutation but was heterozygous for this gene. The father was not affected. With regard to general health status, S and E had urethral stenosis. S. also suffered from a hydrocele of moderate size on the right and a tendency to develop ingrown toenails due partly to poor nail trimming. He suffered from hyperhidrosis. E. was undergoing treatment with an angiotensin-converting enzyme inhibitor (enapril maleate) because of his proteinuria. They had no other health problems, in particular no anemia, no bone abnormalities, no gastrointestinal tract lesions and no eye impairments except moderate photosensitivity. No allergies were present, and no growth failure was noted. Mental development was not impaired.

With regard to their oral habits, food was served three times a day, with a varied diet and little snacking. Tooth sensitivity was exacerbated by cold. S. brushed his teeth every morning and evening, E. brushed only in the morning. Difficulties were reported in the anterior part of the mouth, caused by severe pain and bleeding gums, complicated by lesions on the skin of the hands (figure 1A) where there were severe erosive lesions with the presence of blisters and scars left by blisters. Despite the advice given by the medical dermatologist, no photoprotection or emollients were used.

The perioral examinations of the two brothers showed erosive lesions, blisters, and scars were detected on the neck, around the mouth, on the bridge of the nose, and at the labial commissures. There was noticeable pigmentation of the lips as well as erythematous zones around the corners of the mouth with angular cheilitis (Figure 1).

The key points of the dental, periodontal and mucosal approaches are summarized in Table 2.

Case one: Since the age of seven, S. has been seen regularly for dental management. Difficulties in maintaining good oral hygiene were observed in relation to the difficulty of using a toothbrush and oral pain due to blisters on the mucosae.

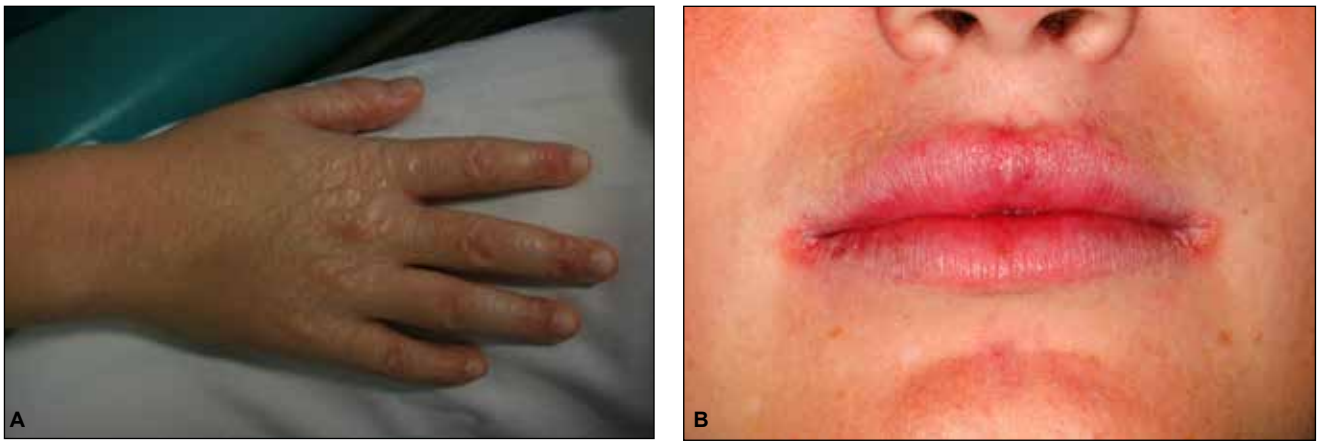
He presented with carious lesions on the primary molars. His lack of cooperation with dental care proved very difficult in the first appointment and we decided to avulse the primary teeth with local anesthesia in several sessions. We performed anesthesia with a topical xylocaine 2% gel followed by a prolonged, deep injection into the tissue to avoid blister formation using a periapical infiltration technique. Hemostasis was obtained by moderate compression with wet compresses. Post-operative advice emphasized the risk posed by biting the lips. No space-saving appliance was accepted.

At ten years old, S. started orthodontic treatment for Dento-Maxillary Disharmony. Clinical examinations showed a short, U-shaped arch, a small space for the two permanent maxillary canines (14mm), mesial positioning of teeth in the maxillary area, a lack of space for the development of the two left mandibular premolars and the first right mandibular premolar, and crowding of 14mm. The radiological examination (Figure 2) confirmed that the maxillary canines were impacted, that the eruption of three mandibular premolars was blocked and that four wisdom teeth germs were present.

Table 2: Key points in the dental, periodontal, and mucosal approaches for Kindler syndrome

Management	Dental Approach	Periodontal Approach	Mucosal Approach
BEFORE COMMENCING	✓ Vaseline on lips and all instruments		
ANESTHESIA	✓ Topical anesthetic gel + local anesthesia ✓ Prolonged injection with deep placement		✓ Post-operative advice to reduce risk of self-inflicted lip trauma
RESTORATIVE SESSION	✓ All conventional restorative materials ✓ Restoration perfectly adapted and polished ✓ Avoid use of ✓ air-water syringe ✓ ⚠ Photopolymerization: Specific protective glasses ✓ Fluoride varnish		
PERIODONTAL MANAGEMENT		✓ Monthly monitoring ✓ Scaling polishing ok with abundant irrigation ✓ Prophylactic cleaning with polishing brushes and chlorhexidine mouthwash	
AVULSION			✓ Moderate compression with wet compresses for hemostasis
ORTHODONTIC TREATMENT	✓ As simple and short as possible ✓ Orthodontic wax on brackets ✓ Pansoral gel ®		
END OF SESSION	✓ No material residues in the sublingual region and the vestibule		✓ Blisters drained with a sterile anesthesia needle
GENERAL ADVICE	✓ Cheek retractors rather than mirrors ✓ Avoid lateral traction ✓ No strong suction ✓ Aspiration cannulas applied against a cotton roller		
INSTRUCTIONS REGARDING ORAL HEALTH	✓ Parents help with brushing ✓ Toothbrush with small head/soft and short bristles ✓ Soak toothbrush in hot water before brushing		

Figure 1: localization of lesions: the skin of the hand (A) perioral (B)



The orthodontic treatment consisted in avulsing the first four premolars and applying braces to *straighten the teeth* and to preserve space for the canines. Pain management required orthodontic wax and the prescription of an oral gel *(cetalkonium chloride 0.01 %, choline salicylate 8.7 %).* It was reported that many brackets had come loose. This could be explained by enamel dysplasia.

Three years later, the clinical examination carried out at the end of orthodontic treatment showed enamel hypoplasia of all teeth with partial lack of occlusal enamel on the first permanent molars (Figure 3C). We also noted intra-oral blisters on the attached gingiva of the maxillary central incisors, and on the mucous membrane of the palate which also white lesions. The gums were erythematous and edematous. Periodontal sounding was associated with gingival bleeding. There was an extensive band of dental plaque around the cervical zone of the teeth, but there was no calculus (Score of 2 on the Silness-Löe plaque index). It was difficult to perform a radiological survey because mouth opening was limited to 37mm due to microstomia. We were unable to finish despite the use of small X-ray sensors, and Vaseline (petroleum jelly). The pain induced was too great. An orthopantomogram was performed to complete the X-ray examination (Figure 3A).

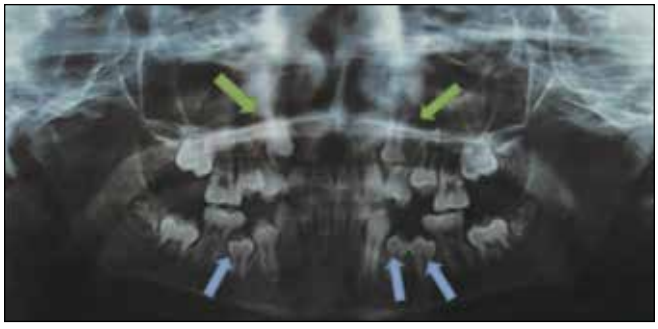
We advised S. of exercises to try to reduce his microstomia by gentle stretching of the mouth, repeated opening / closing movements, to beperformed every day and half an hour before his appointment with the dentist.

At 13 years old, S. underwent an operation to dilate the urethra. A regular dental follow-up was medically indicated. Due to the moderate nature of the oral effects, no modification of the treatment plan was considered, only precautionary measures were implemented. Follow-up is provided by a pediatric dentist.

Before each session we took care to lubricate the lips and all instruments with Vaseline to reduce adhesion. The aspiration cannulas were pressed against a cotton roll to keep them away from soft tissue. No strong suction was used. We avoided lateral traction as much as possible, preferring light pressure by compressive force. When it was necessary to pull on the mouth, we used cheek retractors rather than a mirror. After each session, we checked for blisters.

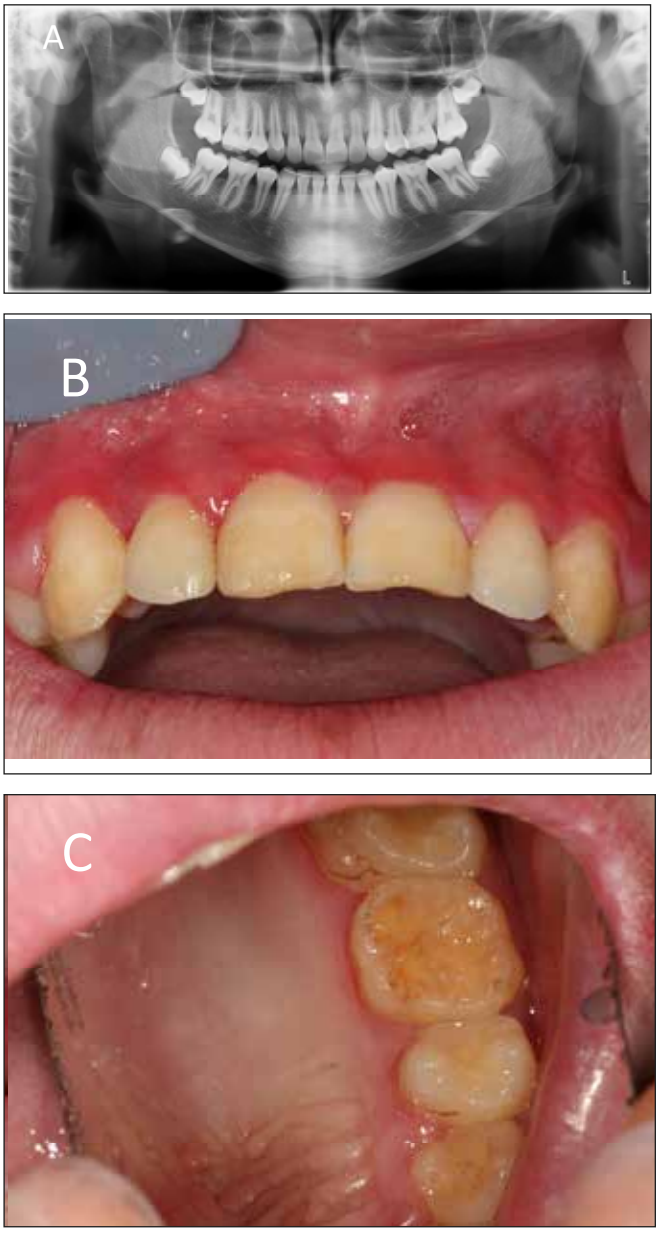
This always involved cautious prophylactic cleaning using polishing brushes and alcohol-free 0.12% chlorhexidine gluconate mouthwashes and the application of a fluoride varnish to reduce sensitivity during meals. Immediate relief was reported by the patient. Indication for partial or total covering of the teeth concerned will be re-assessed when the patient is fully grown. At the moment, areas of exposed dentin could not be covered without creating a permanent vertical over-bite of the molars.

Figure 2: Radiographic examination of S. at ten years



During monthly checks, we noted a regression of the gingivitis. Plaque removal was performed efficiently by the patient. The gums retained a slightly edematous, red appearance. Fifteen small blisters were present on the palate. At the age of 14, we noticed a break of six months in follow-up. When the patient returned, his gums were very inflamed and edematous. We noted spontaneous bleeding during the clinical examination and brushing (score of 3 on the Löe-Silness Gingival Index). There was gingival recession (Miller's Class III Classification) at the lower right central incisor, with plaque accumulation (Figure 4A) and a significant presence of calculus around the mandibular incisors. No sensitivity was reported. We were also able to notice mild bone loss here, and an X-ray revealed subgingival calculus (Figure 4B). We performed scaling and polishing under abundant gentle rinsing, and applied fluoride varnish with great caution. Despite our precautions a blister developed on the lip, which we

Figure 3: Clinical and radiographic (A) examination of S. at ten years: Enamel hypoplasia of the maxillary incisors (B) on the first permanent molar (C).



drained with a sterile anesthesia needle. We repeated our advice concerning oral hygiene, in particular regarding the need for regular periodontal monitoring in order to achieve good periodontal health. We prescribed a plaque disclosing solution, a very flexible surgical toothbrush (7 / 100th), and chlorhexidine gel (Elugel®) for gentle application to the area of recession at the lower right central incisor, for seven days.

One month later, oral hygiene had improved, and the plaque level and the gingival index were normalized. We suggested that the gingival recession be treated. The patient did not follow up and did not show up for his check-up appointments.

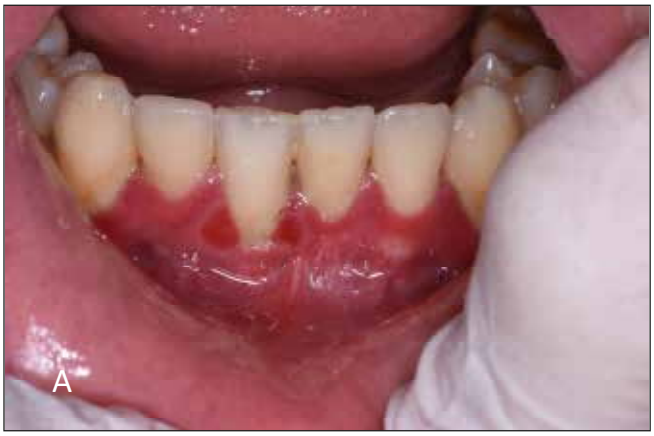
Case two: E.'s dental health has also been monitored since the age of three. Like his brother, due to the moderate nature of the oral effects, no modification of the treatment plan was considered, only precautionary measures were implemented. Follow-up is provided by a pediatric dentist. Before each session we took care to lubricate the lips and all instruments with Vaseline. The aspiration cannulas were pressed against a cotton roll to keep them away from soft tissue, no strong suction was used. We extracted his first lower right primary molar because of an overly deep carious lesion.

At the age of nine, he presented with hypomineralization and punctiform hypoplasia of the central maxillary incisors (Figure 5) and blisters on the attached gingivae of the left central and lateral maxillary incisors. We could see a blister on the lower lip. There was severe gingivitis (Score of 2 on the Löe-Silness Gingival Index) (Figure 5) around the anterior maxillary teeth, and moderate gingivitis (Score of 1 on the Löe-Silness gingival index) in other areas. Passage of the probe caused gingival bleeding. We noted a significant amount of dental plaque but no calculus.

Oral hygiene motivational sessions were repeated, but six months later we noticed the presence of cervical demineralization and an occlusal carious lesion of the enamel on the permanent maxillary molars. We treated this lesion by debridement after application of a topical xylocaine 2% anesthetic gel and periapical anesthesia (epinephrine 1:200,000 anesthetic carpule) and restoration with resin-modified glass-ionomer cement. The patient reported discomfort during photopolymerization of the restorative material, due to photosensitivity. We offered to reduce his discomfort by providing him with specific protective glasses. Particular attention was paid to polishing the restoration and we checked for the absence of material residues in the sublingual region and in the vestibule. There was profuse gingival bleeding. We performed prophylactic cleaning with an alcohol-free 0.12% chlorhexidine gluconate mouthwash and a toothbrush, descaling the maxillary and mandibular incisors and performing topical application of fluoride varnish. We repeated the encouragement to maintain oral hygiene.

At the age of ten, there was a break of 6 months in follow-up. On his return, E. had severe gingivitis related to dental plaque (Score of 2 on the Löe-Silness Gingival Index). His teeth were unbrushed, especially in the maxillary incisal block. We performed prophylactic cleaning with a brush and polishing paste, and a fluoride varnish (Fluor protector® 7100 ppm) was applied to all the teeth. We repeated the instructions regarding oral hygiene. Explanations were given to the patient regarding the need for regular periodontal monitoring in order to achieve good periodontal health. His mother must help him with toothbrushing.

Figure 4: A. Gingival recession at tooth 41 B. Retroalveolar X-ray anterior region of the mandible



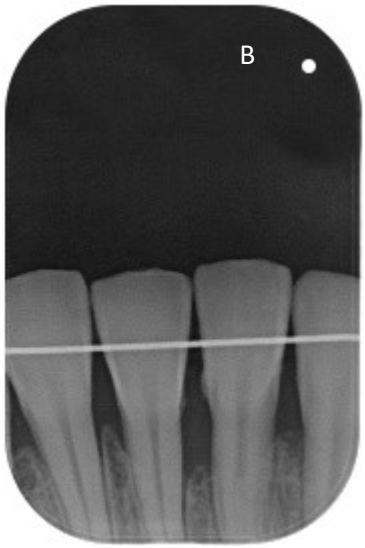
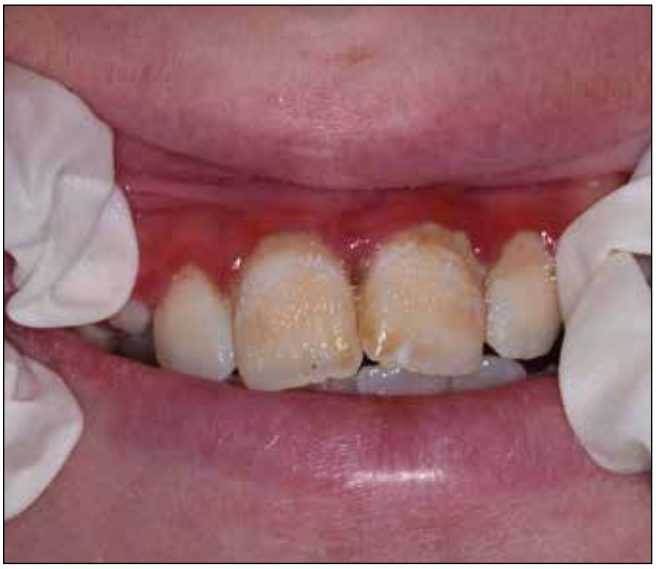


Figure 5: E., nine years old: Intraoral view of the maxillary incisors with enamel hypoplasia and stage two gingivitis (score of 2 on the Gingival Index)



DISCUSSION

The prevalence of Kindler syndrome is unknown. This rare skin disease affects all populations with no racial or sexual differences. The known features of this disease are grounded in case reports published in the literature. Since 1997, 24 case report articles have appeared in the PubMed database, reporting on a total of 86 cases. The oral manifestations found most frequently are gingivitis, periodontitis, and oral ulcerations, and xerostomia and microstomia have sometimes been described. Kindler Syndrome is characterized by weakness of the periodontium[1]. The two brothers affected by KS presented with all the oral disorders described in the literature: lesions on the perioral tissues, the oral mucosa, the periodontium and carious lesions. They also presented with enamel defects.

Perioral sites around the mouth, on the labial commissures, on the lips, have been described in the literature. It is likely that the microstomia was caused by a constant process of blister formation and scarring. The modification of oral epithelium architecture induces scarring at the labial commissure and loss of vestibular space. Access to the oral cavity is complicated and this contributes to the difficulty in maintaining good oral hygiene, increases the risk of carious lesions and affects comfort during dental treatment. No study has demonstrated an optimal solution while techniques have been proposed to improve mouth opening: the occasional use of resin pads, daily exercises with wooden spatulas, combined with gentle stretching of the mouth, by repeated opening-closing movements and the intermittent use of resin pads 1.

The oral mucosa is one of the areas that is most frequently affected in children with KS3. All its surfaces can develop lesions such as blisters and erosions, ulcerations, erythema and atrophy1. All these forms were found in our patients. The palatal mucosa is the second most common site of lesion formation.

KS is particularly characterized by a greater predisposition to periodontal disease, which occurs early and progresses faster than in the general population2. The two brothers presented with the initial symptoms of periodontal disease: edematous and erythematous gums, with bleeding and dental plaque. Dental management needs to focus primarily on periodontal monitoring1. Initial periodontal therapy is essential, and it must be continued to be applied regularly. Indeed, we managed to stabilize a relatively good level of periodontal health during regular follow-up sessions. We observed a rapid, significant worsening of the periodontitis after a 6-month break in follow-up, with recession of the gingiva of the lower right central incisor for S. This deterioration complicates the management and maintenance of S's periodontal health. Gingival recession is caused by the lack of keratinized gingiva and is aggravated by the difficulties in maintaining oral hygiene. In these patients, complete and extensive destruction of the keratinized tissues can occur in a relatively short period of time, due to the constant cycle of mucosal lesion formation, with the development of blisters, then scars. Therefore, we think that it is essential to organize a monthly follow-up to maintain periodontal health in patients with Kindler Syndrome with the use of prophylactic cleaning and polishing techniques. Traditional non-surgical periodontal treatment has beneficial effects. Ultrasound should be used with care to avoid bleeding and blister formation. If blisters appear, they will need to be drained to avoid expansion of the lesion1. Extensive irrigation is necessary to avoid the heating of tissues, requiring the use of a suction cannula, which can increase the risk of mucosal trauma. However, it is difficult for patients to maintain sufficient motivation to carry out the diligent care procedures which are essential for their periodontal health. This demotivation is immediately penalised by a deterioration in the periodontal condition and complication of management. No treatment of choice for gingival recession using a surgical approach is indicated in the literature. One case report describes periodontal surgery in a patient with inherited epidermolysis bullosa, which was not Kindler Syndrome4. Therefore, there is no consensus in the literature. We think, however, that periodontal surgery techniques pose a real risk of causing blister formation in these patients. The periodontal type limits choice of technique. The risk of blistering during preparation of the operating site seems high to us. This should be done using a pad rather than by rubbing with a compress. There is also a risk when using aspiration cannulas which can cause desquamation of the mucosae, during suturing and even throughout surgery when the tissues are held under lateral traction. The palate is also at high risk of blister formation and is the second most common site in this respect. Moreover, Budunelli indicates in his case that it is better to choose a single surgical site, to avoid causing blister formation in two areas4.

The prevalence of caries is significantly higher in patients with inherited epidermolysis bullosa than in the general population. The etiology is multifactorial, but the difficulty experienced by Kindler Syndrome patients in achieving good oral hygiene is particularly noted; it is difficult for their hands to hold the toothbrush properly, which leads to difficulty in brushing effectively, in the mechanical control of plaque, whilst blisters make brushing the teeth painful1. All conventional restorative materials can be used for restorative dental treatment. The choice is made according to the possibility of isolation, risk of caries, and socio-economic factors specific to each patient. Most of the recommended treatments use glass ionomer cement and preformed pedodontic caps, that are tried and tested methods of tooth restoration5. The restorations were perfectly adapted to the teeth and polished to prevent injuries, blisters and ulcerations 1. Photosensitivity is a specific feature of Kindler Syndrome. Treatment was performed under local anesthesia, which is the best technique for moderate forms of inherited epidermolysis bullosa1. Topical anesthetic gel was used. To prevent blister formation, the anesthetic solution was injected slowly into the tissues with deep placement. Postoperative advice was given to prevent biting or trauma to the lips that may occur under local anesthesia1.

The goal of therapy is the prevention of caries and mucosal damage. Maintaining a functional dentition reduces the risk of injury by more effective chewing1. Despite the pain, toothbrushing must be performed, using a toothbrush with a small head and soft, short bristles3, softened by soaking in hot water1. Mouthwashes can be administered for one minute, once a day, for a month. Chlorhexidine 0.12% does little to prevent decay, when there is insufficient brushing, its antiseptic action could be helpful. It could be used as mouthwash, as well as in the form of gels or swabs1.

Both brothers presented with minor enamel defects, which are reported in all subtypes of inherited epidermolysis bullosa 2, but E. presented with a rare form of enamel hypoplasia. These enamel defects take the form of a pit or groove on the crown and cause the retention of food fragments which leads to the development of caries. The prevalence of enamel defects in Kindler Syndrome

is similar to that in the general population (27%)3. The enamel hypoplasia present was therefore possibly independent of Kindler Syndrome. As recommended, topical fluoride was applied at each appointment in order to decrease tooth sensitivity.

S. received orthodontic treatment between the ages of 10 and 13 years. In these patients, the combined effects of malnutrition and mucocutaneous scarring leads to the inhibition of facial growth, and possibly dentoalveolar disharmony and dental malposition[1;6]. Because of possible gingival weaknesses, orthodontic treatment plans must be simplified and be of as short a duration as possible, with increased periodontal maintenance[6]. The difficulties encountered during orthodontic care are related to the use of orthodontic brackets and wires, which can cause ulceration of the mucous membranes. To avoid these injuries, orthodontic wax can be applied to the brackets[1,6].

Selective extractions of the first premolars can be programmed. These are not contraindicated but a benefit-risk analysis must be carried out. These procedures should ideally be performed under local anesthesia. Blood tests for anemia should be performed if possible. An atraumatic technique should be used, and mucosal incisions should be clean to prevent the formation of blisters[1]. Hemostasis should be performed using moderate compression with wet compresses to avoid tissue adhesion[1;5]. Stitches may be inserted, but they must be placed so as not to irritate the mucous membranes[20].

CONCLUSION

Thus, the follow-up of these two children diagnosed with a moderate form of KS shows that, in their case, dental care is tricky and requires monthly monitoring. Periodontal maintenance therapy is essential, so the absence of surveillance leads quickly to the recurrence of gingivitis. This demotivation is immediately penalized by deterioration in the periodontal condition and complication of management. Therefore, it is essential for the dentist to be part of the care team. However, all restorative, endodontic, surgical, periodontal and orthodontic treatments should be performed with appropriate precautions for hemostasis and should aim to avoid as much mucosal damage as possible.

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