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Oral and perioral soft tissue lesions and oral functions in patients with dystrophic *epidermolysis bullosa*

Lezije oralnih i perioralnih mekih tkiva i oralne funkcije kod bolesnika sa distrofičnom buloznom epidermolizom

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Abstract

Background/Aim. Dystrophic epidermolysis bullosa (DEB) is characterized by distinct systemic and skin changes, as well as numerous oral manifestations. The aim of the study was to examine oral and perioral soft tissues and oral functions in DEB patients by monitoring changes over a period of one year. **Methods.** Twenty-four patients (1 month to 36 years old) were clinically examined initially (T0), after 6 months (T6), and after 12 months (T12). Appearance and localization of perioral and oral bullae and scars, maximum mouth opening, reduced vestibule depth, absence of lingual papillae and palatal rugae, and restricted tongue movement due to scarring were monitored. The values of maximum mouth opening at the initial examination were compared to those measured in the healthy control group of the same age. The age of patients and differences between the dominant and recessive subtypes of DEB were analyzed. **Results.** The average maximum mouth opening was significantly lower in DEB patients compared to healthy individuals. Oral and perioral bullae and scars, microstomia, and reduced vestibule depth were very common, with no statistically significant difference among T0, T6, and T12. The prevalence of restricted tongue movement due to scarring and the absence of lingual papillae and palatal rugae increased significantly over one year. Patients with microstomia, vestibule depth, and restricted tongue movement due to scarring were significantly older than patients without these characteristics. Lingual papillae and palatal rugae were more frequently absent in recessive than dominant DEB. **Conclusion.** DEB causes significant changes in oral and perioral soft tissues and oral functions impairment.

Key words:
blister; cicatrix; epidermolysis bullosa dystrophica; microstomia; mouth; preventive dentistry.

Apstrakt

Uvod/Cilj. Distrofijska bulozna epidermoliza (DBE) karakteriše se izrazitim kožnim i sistemskim promenama, kao i mnogobrojnim oralnim manifestacijama. Cilj rada bio je da se ispita stanje oralnih i perioralnih mekih tkiva i funkcionalnost usne duplje bolesnika sa DBE praćenjem promena u ovim tkivima u periodu od godinu dana. **Metode.** Klinički su pregledana 24 bolesnika sa DBE (uzrasta od 1 meseca do 36 godina), prvi put (T0), posle 6 meseci (T6) i posle 12 meseci (T12). Praćeni su pojava i lokalizacija perioralnih i oralnih bula i ožiljaka, maksimalno otvaranje usta, prisutnost smanjene dubine vestibuluma, odsustvo kvržica (papila) jezika i nabora (*rugae*) nepca i ograničena pokretljivost jezika usled formiranja ožiljka. Vrednosti maksimalnog otvaranja usta pri prvom pregledu upoređene su sa vrednostima izmerenim u zdravoj kontrolnoj grupi istog uzrasta. Analizirani su i uzrast bolesnika i razlike između dominantnog i recesivnog oblika DBE. **Rezultati.** Prosečna vrednost maksimalnog otvaranja usta je bila značajno niža u bolesnika sa DBE u poređenju sa zdravim osobama. Bule i ožiljci na oralnoj i perioralnoj regiji, mikrostomija i smanjen vestibulum bili su veoma često prisutni, bez statistički značajne razlike između T0, T6 i T12 pregleda. Učestalost ograničene pokretljivosti jezika i odsustvo papila jezika i nabora nepca su se u periodu od godinu dana statisitički značajno povećavali. Bolesnici sa mikrostomijom, smanjenim vestibulumom i ograničenom pokretljivošću jezika zbog formiranja ožiljka bili su značajno stariji u odnosu na bolesnike bez tih promena. Papile jezika i nabori nepca su bili značajno češće odsutni kod recesivnog u odnosu na dominantni oblik DBE. **Zaključak.** DBE dovodi do značajnih promena u oralnom i perioralnom mekom tkivu i poremećaja oralnih funkcija.

Ključne reči:
plik; ožiljci; epidermoliza, bulozna, distrofijska; mikrostomija; usta; stomatologija, preventivna.

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Introduction

Epidermolysis bullosa (EB) represents an inherited multisystemic, genetically and clinically heterogeneous group of diseases characterized by extreme fragility of the skin and mucous membranes leading to the development of bullae and erosions even after minor mechanical irritation [1, 2]. There are four basic types of this disease: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome. DEB is among the most serious forms of the disease, and it is divided into two main subtypes. Depending on whether it is inherited in an autosomal dominant or recessive manner, dominant DEB (DDEB) and recessive DEB (RDEB) could be distinguished [2, 3]. DDEB is characterized by generalized recurrent bullae formation, which can become localized with age. Atrophic nail changes or complete loss of the nail plate may be present on fingers or toes. Other systemic changes, in addition to esophageal changes, are generally absent and these patients may have a relatively good quality of life [4]. RDEB is characterized by highly pronounced skin and systemic changes. Bullous changes cover large areas of the skin with their scarring during healing leading to joint contractures and pseudosyndactyly [1, 5]. Dexterity, ability to walk and maintain balance in these patients are impaired. Gastrointestinal and urogenital tract changes, eye changes, and cardiovascular system diseases are also present [6, 7]. Chronic loss of blood, iron, and nutrients combined with inflammation and damage to the small intestinal mucosa leads to malnutrition, anemia, and retardation in the physical development of these patients [8]. Squamous cell carcinoma may develop as the most serious complication of the disease, which is highly aggressive and produces metastases early [9].

Changes in the oral cavity are also very pronounced in patients with DEB. Bullae occur frequently all over the oral mucosa. When bullae rupture eroded areas are left behind that tend to undergo fibrotic healing [10, 11]. Continuous bullae formation and repeated processes of reepithelialization lead to the formation of large and numerous scars and the development of microstomia [10, 12, 13]. In addition, the absence of lingual papillae and palatal rugae, restricted tongue movement due to scarring, loss of vestibule depth, and leukoplakia of the mucous membranes could be observed on the buccal mucosa. These pronounced oral changes can be potential signs of malignant disease, and thus the risk of oral squamous cell carcinoma in these patients is very high [14, 15]. In addition to interfering with speech, chewing, and ingestion of food, these oral conditions make it difficult to maintain oral hygiene and carry out dental procedures [16]. In these patients, early occurrence and high prevalence of caries in both dentitions are reported, as well as orthodontic anomalies, due to underdeveloped alveolar arches caused by generalized growth and development retardation [17, 18].

As numerous oral manifestations may occur within the underlying disease, the aim of the present study was to examine the condition of the oral and perioral soft tissues and the oral functions in patients with DEB.

Methods

The protocol for the clinical study is in compliance with the Helsinki Declaration and was approved by the Ethics Committee. The research was conducted at the University Clinic during the period from June 2016 to December 2017. The study included 24 patients with DEB: 8 (33.0%) female and 16 (67.0%) male patients, with their ages ranging between 1 month and 36 years [(average age ± standard deviation (SD) was 9.55 ± 8.01 years)] that were monitored for one year. Four (16.7%) patients had a dominant and 20 (83.3%) patients had a recessive form of the disease. Patients were recruited directly from the DEBRA (Dystrophic Epidermolysis Bullosa Research Association). All patients, i.e., their parents, were DEBRA members, and almost all DEB population from the country where the research was carried out was included. A healthy control group consisted of the same number of healthy, sex and age-matched subjects (8 females and 16 males, average age 9.52 ± 8.04 years). After obtaining the written informed consent from adult patients and parents or guardians of minor patients to participate in the study, three dental clinical examinations were conducted: the first examination (T0), followed by the second examination at 6 months (T6), and the third examination at 12 months (T12). All examinations were performed by one investigator with experience in working with patients affected with EB. A dental examination was performed using standard diagnostic tools (dental mirrors), under artificial light, and according to the World Health Organization (WHO) criteria [19]. The findings obtained were recorded in the specially designed investigation charts.

Clinical examinations evidenced the presence of bullae in the perioral region on the skin of the lips, chin, and cheeks in DEB patients. Maximum mouth opening (MMO) was measured at the first examination in both groups (healthy control and DEB group) as the distance between the upper and lower border of the upper and lower lip vermilions at the maximal mouth opening [20]. Reduction of the vestibule depth was recorded upon intraoral examination in cases where it was almost nonexistent due to the attachment of soft tissues directly below the vestibular tooth surfaces [14]. Inspecting the oral mucosa, the presence and localization of the bullae and scars, absence of lingual papillae and palatal rugae, and restricted tongue movement due to scarring were noted. The frequency of occurrence of the inspected changes was also analyzed with respect to the DEB subtype (DDEB and RDEB) at T0.

At all examinations, patients and parents were advised on proper and regular maintenance of oral hygiene (advice on the choice of oral hygiene products, techniques, frequency, length of tooth brushing), tips on correcting diet, the use of chemoprophylaxis, advice for relief of problems caused by the formation of bullae in the oral cavity. Exercises that patients could perform independently in order to increase the possibility of mouth opening and tongue mobility were demonstrated.

Statistical analysis of the obtained data was performed using the software IBM SPSS version 21. Two independent

groups were compared using the *t*-test or Mann-Whitney *U* test depending on the type and distribution of numerical data. The arithmetic mean with SD was used for the description of continuous numerical data having a normal distribution, and for those that did not meet the criteria of the normality of the distribution, the median (med) and the range of values (min-max) were used. The frequencies of the studied changes are shown in absolute and relative numbers (n, %) and compared using the Fisher's exact probability test. Related samples of repeated measurements were analyzed using the Exact version of Cochran's Q and McNemar's tests. All statistical analytical methods were considered significant at the $p < 0.05$ level.

Results

The results of the average MMO at the first examination showed a statistically significant difference ($p = 0.005$, *t*-test) between DEB patients (35.92 ± 15.91 mm) and the healthy control group (52.90 ± 22.94 mm) at the first examination. The occurrence of the other investigated changes in DEB patients was compared among the examinations performed at six-month intervals. Upon all examinations, the majority of diseased children showed the presence of bullae on the perioral and oral soft tissues, as well as changes resulting in limited functions of the oral cavity, such as microstomia and restricted tongue movement due to scarring (Table 1). The appearance of a 5-year-old boy with DEB with noticeable microstomia and bullae on the lower lip and the tongue is presented in Figure 1. A statistically significant difference among the three examinations was found only for the presence of restricted tongue movement due to scarring ($p = 0.012$, Cochran Q test) and the absence of lingual papillae and palatal rugae ($p = 0.025$, Cochran Q test). The frequency of other changes observed in this study was not significantly different in the first, second, and third examinations (Table 2).

Table 1

The frequency of the studied characteristics at the first (T0), second (T6), and third (T12) clinical examination in patients with dystrophic epidermolysis bullosa (n = 24)

Characteristics	Patients exhibiting the disorders, n (%)		
	T0	T6	T12
Bullae in perioral region	16 (66.7)	17 (70.8)	15 (62.5)
Microstomia	17 (70.8)	17 (70.8)	17 (70.8)
Reduced vestibule depth	16 (66.7)	16 (66.7)	16 (66.7)
Bullae on oral mucosa	9 (37.5)	11 (45.8)	9 (37.5)
Scars on oral mucosa	6 (25.0)	6 (25.0)	6 (25.0)
Absence of lingual papillae and palatal rugae	14 (58.3)	18 (75)	19 (79.2)
Restricted tongue movement due to scarring	14 (58.3)	19 (79.2)	19 (79.2)

Table 2

The results of the statistical analyses of the frequency of the studied characteristics among the first (T0), second (T6), and third (T12) clinical examination and all in-between examination comparisons

Characteristics	*p*-value (McNemar's test)			*p*-value
	T0-T6	T6-T12	T0-T12	(Cochrane Q test)
Bullae in perioral region	0.500	0.250	0.500	0.667
Microstomia	1.000	1.000	1.000	1.000
Reduced vestibule depth	1.000	1.000	1.000	1.000
Bullae on oral mucosa	0.250	0.250	1.000	0.333
Scars on oral mucosa	1.000	1.000	1.000	1.000
Absence of lingual papillae and palatal rugae	0.063	0.500	0.031*	0.025*
Restricted tongue movement due to scarring	0.031*	1.000	0.031*	0.012*

*** – statistically significant values.**



Fig. 1 – Microstomia in a 5-year-old boy with dystrophic epidermolysis bullosa (bullae present on the lower lip and on the tongue).

The frequency of the studied perioral and oral soft tissue changes in patients with DDEB and RDEB subtype of the disease at T0 is shown in Table 3. Lingual papillae and palatal rugae were not present in patients with DDEB, while the same changes were present in 70% of patients with RDEB (p = 0.020, the Fisher's exact test). For all other changes, there was no statistically significant difference in frequency between the two subtypes of EB.

The age of patients with oral, perioral, and functional changes was compared with the age of patients not exhibiting those changes at T0. Statistically significant age-related difference (the Mann-Whitney *U* test) was determined in patients with microstomia (p = 0.001), reduced vestibule depth (p = 0.012) and restricted tongue movement due to scarring (p = 0.006). Specifically, patients with these pathologic characteristics were significantly older than patients without them (Table 4).

The localization of the bullae on the oral mucosa is shown in Table 5.

Table 3

The frequency of the studied characteristics in patients with dominant dystrophic epidermolysis bullosa (DDEB) and recessive DEB (RDEB) subtype of the disease at T0 examination

Characteristics	DEB subtype, n (%)		*p*-value
	DDEB (n = 4)	RDEB (n = 20)	(Fisher's Exact test)
Bullae in perioral region	2 (50.0)	14 (70.0)	0.578
Microstomia	1 (25)	16 (80)	0.059
Reduced vestibule depth	2 (50.0)	14 (70.0)	0.578
Bullae on oral mucosa	0 (0.0)	9 (45)	0.259
Absence of lingual papillae and palatal rugae	0 (0.0)	14 (70.0)	0.020*
Restricted tongue movement due to scarring	1 (25.0)	13 (65.0)	0.272

DEB – dystrophic epidermolysis bullosa.
*** – statistically significant value.**

Table 4

The average age of the patients with dystrophic epidermolysis bullosa and without studied characteristics

Characteristics	Age (years)		*p*-value
	med (min–max)	mean ± SD	(Mann–Whitney *U* test)
Bullae in perioral region			
yes	8 (1–21)	8.44 ± 5.26	0.690
no	10 (0.1–36)	11.79 ± 11.94	
Microstomia			
yes	12 (3–36)	12.35 ± 1.89	0.001*
no	3 (0.1–7)	2.76 ± 0.95	
Reduced vestibule depth			
yes	11 (3–36)	12.12 ± 8.27	0.012*
no	4 (0.1–13)	4.41 ± 4.33	
Bullae on oral mucosa			
yes	17 (16–18)	17 ± 1.41	0.060
no	7.5 (0.1–36)	8.88 ± 8.02	
Absence of lingual papillae and palatal rugae			
yes	8 (3–36)	9.86 ± 8.37	0.883
no	9.5 (0.1–21)	9.13 ± 7.88	
Restricted tongue movement due to scarring			
yes	12 (3–36)	12.93 ± 8.45	0.006*
No	4 (0.1–13)	4.83 ± 4.25	

SD – standard deviation; median – median; min – minimum; max – maximum.
*** – statistically significant values.**

Table 5

The localization of the bullae on the oral mucosa in patients with dystrophic epidermolysis bullosa

Localization	Patients exhibiting the disorders, n (%)		
	1st clinical examination (T0)	2nd clinical examination (T6)	3rd clinical examination (T12)
On one site only			
tongue	6/9 (66.7)	4/11 (36.4)	2/9 (22.2)
buccal mucosa	2/9 (22.2)	3/11 (27.3)	3/9 (33.3)
On two or more sites			
tongue and buccal mucosa	–	3/11 (27.3)	1/9 (11.1)
tongue and lips	1/9 (11.1)	–	1/9 (11.1)
tongue and palate	–	1/11 (9.1)	–
tongue, buccal mucosa, and palate	–	–	2/9 (22.2)

Discussion

Patients with DEB have major oral and perioral changes resulting from the underlying disease. A change that is highly characteristic of the most severe forms of the disease is microstomia, and it was present in more than 2/3 of the studied patients upon all three clinical examinations. In addition to significant disturbance of the oral cavity function, substantially smaller maximum mouth opening than in healthy individuals makes it difficult to maintain oral hygiene, especially if it is associated with syndactyly, which can compromise patients' oral health. This also poses a major problem and a challenge for the dentist when treating these patients [12, 20, 21]. Dental care is most commonly recommended to be performed under general anesthesia because the relaxation of the musculature allows wider mouth opening, better visibility of the working field, and greater space for instruments manipulation. However, intubation is highly perilous, and the introduction of these patients into general anesthesia requires special apparatus and additional education of anesthesiologists [22–24]. Microstomia was also a major difficulty in performing dental examinations during this study because it was often very difficult even to insert mirrors to examine the distal parts of the oral cavity. To maximize the mouth opening ability, manual exercises that are easy to perform at home were demonstrated to patients and their parents. This study, however, found that there was no statistically significant difference in mouth opening at the follow-up examinations despite the exercises performed, as microstomia was always present in 17 patients. Similar results have been reported in previous studies. Kramer et al. [13] achieved in their patients a greater mouth opening ability (from 19–23 mm to 30 mm) with ten-minute exercises, but soon after the cessation of exercises, the original microstomia values returned. Moreover, it was observed that only 7 patients in this study did not have microstomia and were very young (age around 3 years). Patients who had microstomia were significantly older (age around 12 years), indicating that with age the possibility of maximal mouth opening was significantly reduced. All this points to the importance of exercising as early as possible, from infancy and before the onset of microstomia, to improve the effect of exercises on facilitating and maximizing the mouth opening ability [13].

Other intraoral lesions, as well as functional limitations, also became more pronounced with age. Patients who did not have restricted tongue movement due to scarring and reduced vestibule depth were about 4 years of age, whereas statistically significantly older patients were those with restricted tongue movement due to scarring and those who did not have reduced vestibule depth (about 12 years of age). In most patients, restricted tongue movement due to scarring was so pronounced that, in fact, the tip of the tongue was more mobile than the entire tongue. In the most severe forms of DEB, restricted tongue movement due to scarring is manifested at birth and prevents or impairs breastfeeding [25]. Later on, it compromises the child's speech and maintenance of oral hygiene [26, 27]. No significant differences in patients' age were observed for the other changes examined in this study.

When it comes to the two EB subtypes, although they differ widely in systemic characteristics [1, 21], the results of this study showed that they did not differ as much in changes in the perioral and oral soft tissue characteristics and the functionality of the oral cavity. The only statistically significant difference existed in the absence of lingual papillae and palatal rugae. Gradual atrophy of the lingual papillae and mucous membranes of the hard palate arised as a consequence of the continuous formation of bullae and frequent reepithelization of eroded surfaces [28]. This characteristic was significantly more frequently present in patients with RDEB in comparison to DDEB. The recessive form of the disease is otherwise considered to be a more severe form than the dominant one [1]. However, it should be emphasized that in this study, in the group of affected children, only 4 had DDEB type, while RDEB type was evidenced in 20 cases, which could affected the results of statistical analysis. Studies on a larger number of patients with both EB subtypes could provide different data. Moreover, in this study classification into two subgroups according to the subtype of the disease (DDEB and RDEB) was made based on standard diagnostic tests and skin biopsy, as well as according to their rather different clinical features based on which these two forms of EB can be distinguished with high certainty [1–7, 21]. It is important to note that patients with EB in the country where this research was performed are rarely subjected to genetic testing in order to determine what type of inheritance is involved, primarily because of the very high cost of such analyzes and because it is often necessary to conduct such tests abroad.

Furthermore, the number of patients who had restricted tongue movement due to scarring and the absence of the lingual papillae and the palatal rugae tended to change significantly during our performed clinical examination. That is, a significantly greater prevalence of restricted tongue movement due to scarring was evidenced at T6 and T12 examinations compared to T0 one. When lingual papillae and palatal rugae are in question, they were significantly more frequently absent at the T12 compared to the T0 examination. These results suggest that during the one-year follow-up period, significant mucous membranes of the tongue and palate changes occurred, as well as changes in the mobility of the tongue. Bullae and scars were present on the oral mucosa and in the perioral region at all examinations with no significant difference. This result indicates that bullae occur constantly, sporadically, and spontaneously, and are caused under the influence of minor local irritating factors. It was observed that intraoral bullae were most commonly localized on the tongue. In patients where they were localized on two or more sites, it was observed that the tongue was always involved in combination with bullae on the buccal mucosa, lips, or palate. In accordance with these findings, Serrano-Martinez et al. [11] and Wright [21] reported the mucosal membrane of the tongue as the most common site of onset of bullae. Furthermore, it was found that the occurrence of bullae was less frequent in DDEB and that repeated episodes of bullae did not lead to significant scar changes [20]. Conversely, the pronounced sensitivity of oral mucosa in RDEB was reported, where continuous bullae formation and repeated reepithelialization processes led to the formation of large and

numerous scars, which significantly impaired the function of the oral cavity, maintenance of oral hygiene, and dental treatment [11, 21, 29, 30]. Scar changes in the oral cavity, which additionally exacerbate microstomia and restricted tongue movement and compromise already shallow vestibule, are in the present study evidenced in 6 out of 24 examined patients (25%) upon all three examinations. However, their frequency was not increased over the one-year period.

Conclusion

Based on the results obtained in this study, it can be concluded that bullae and scars frequently appear on the mucous membranes of the oral cavity and the skin of the perioral region. Maximal mouth opening ability in persons with DEB is statistically significantly lower than in healthy patients. Specific changes, such as microstomia, restricted tongue movement due to scarring, and decreased vestibular depth, worsen significantly with patients' age. In the RDEB, the absence of lingual papillae and palatal rugae is very common. Therefore, the dental prevention program should be included as a mandatory part of the protocol for the complex treatment of these patients. Thus, the impact of oral diseases on the underlying disease and *vice versa* could be reduced, and the quality of life of these patients would be greatly improved.

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