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CASE REPORT

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Obiteljski hipoplastični jezični frenulum: prikaz slučaja i rasprava o diferencijalnoj dijagnozi

Familial Hypoplastic Lingual Frenum: Case Report and Discussion of Differential Diagnosis

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Sažetak
Jedna od najzanimljivijih, ali još nerazjašnjenih struktura usne šupljine jest oralni frenulum. Jezični frenulum (LF) važan je zato što spaja jezik i mandibulu te može biti izravno povezan s poremećajima u okluziji zuba. Morfološke ili brojčane promjene oralnih frenuluma u neposrednoj su vezi s mnogobrojnim genskim stanjima, posebice s Ehlers-Danlosovim sindromom. Neki autori smatraju da je odsutnost LF-a patognomonični znak za taj poremećaj. Svrha ovog opisa slučaja bila je izvijestiti o obiteljskoj hipoplaziji jezičnog frenuluma dijagnosticiranog rutinskim oralnim pregledom, te potaknuti raspravu o povezanosti abnormalnog LF-a s nesindromskim poremećajima i/ili genskim sindromima. Liječnici dentalne medicine i ostali specijalisti moraju biti oprezni tijekom kliničkih pregleda kako bi rano otkrili Ehlers-Danlosov sindrom jer može neposredno utjecati na ortodontsku terapiju.

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Uvod

Jedna od zanimljivih, ali i do kraja objašnjenih anatomskih struktura usne šupljine jest frenum ili frenulum (1, 2). Frenum, mukozno vezivno tkivo između tvrdih ili mekih dijelova usne šupljine histološki je sastavljeno od gustoga fibroznog tkiva i mjestimice umetnutih mišićnih vlakana. Obično se nalazi na trima mjestima (1,2), pa postoje gornji labijalni frenulum, donji labijalni frenulum i jezični frenulum (LF) (3). Lingvalni fenulum anatomski je važan jer povezuje jezik i mandibulu (4). U slučaju da je kratak može ograničavati pokrete jezika, pa se pojavljuje nekoliko problema – teškoće s dojenjem, poremećaji u govoru, frontalno otvoreni zagriz i mandibularni prognatizam (5-7). Morfološki ili brojčano promijenjeni oralni frenulum povezan je s mnogobroj-

Introduction

One of the most interesting and not yet understood anatomical structures of the oral cavity is the frenum or frenulum (1,2). The frenum, a mucous connective tissue inserted on hard- or soft-parts of the oral cavity, is histologically composed of fibrodense tissue and occasionally of striated muscle fibers (1,2). Three types are commonly identified in the oral cavity: superior labial frenum, inferior labial frenum, and lingual frenum (3). The lingual frenum (LF) is an important structure that anatomically relates to the tongue and mandible (4). A short LF can interfere with tongue mobility, which can lead to a few problems including breastfeeding difficulties, speech disorders, anterior open bite, and mandibular prognathism (5-7).

nim genskim poremećajima, poput Ehlers-Danlosova sindroma (EDS), infantilne hipertrofične piloričnе stenoze, holoprozencefalije, orofacijalnih digitalnih sindroma (OFD) te Rapp-Hodgkinova i Fraserova sindroma. Dodatno su opisani abnormalni razvojni poremećaji frenuluma kod Pallister-Hallova sindroma, Optizova trigonocefalijskog sindroma (Optizov C-sindrom), W-sindroma i Optizova sindroma (3, 8, 9).

EDS je nasljedni genski poremećaj kod kojega se događaju promjene u sklopu vezivnoga tkiva. Kako nastaje defekt u metabolizmu kolagena pucaju koža i krvne žile, te se pojavljuje hiperrastezljivost kože i hiperpokretljivost zglobova (3, 10 –17). Nekoliko istraživača tvrdi da je odsutnost LF-a potencijalni pokazatelj EDS-a (9). Obiteljski abnormalno kratak, ili čak nepostojeći LF, rijetko je stanje s kojim se susreću stomatolozi i ostali liječnici (18). Svrha ovog članka jest opisati slučajeve pacijenata s obiteljski naslijeđenim nedostatkom LF-a dijagnosticiranim tijekom oralnog pregleda te raspravljati o povezanosti s nesindromskim stanjima i/ili genskim sindromom povezanim s abnormalnim LF-om.

Prikaz slučaja

Pacijentica u dobi od 23 godine došla je na rutinski pregled u ordinaciju Stomatološkog fakulteta Sveučilišta Ceará Sobral u Brazilu. Tijekom kliničkog pregleda liječnik je uočio da nema LF, ali nije imala poremećaje u govoru i žvakanju ili druge funkcijske tegobe. Te su se promjene odmah počele provjeravati i istraživati jer se željelo doznati je li to izolirani slučaj. Zbog toga su pregledani i ostali članovi njezine peteročlane obitelji (slika 1.). Otac u dobi od 54 godine nije imao LF, a kod 49-godišnje majke bio je normalan. Najstarija kći (28 godina) imala je hipoplastični frenulum, a srednja (24 godine), u usporedbi sa starijom sestrom, jedva vidljivo kraći. Treća kći (23 godine), fenotipski slično ocu, nije imala LF. Svi članovi obitelji pregledani su zbog EDS-a jer neki istraživači smatraju da je nedostatak LF-a dijagnostički znak. Kako bi se dijagnosticirao EDS, u obzir su uzeti sljedeći klinički znakovi (tablica 1.):

1) hiperekstendibilnost kože,
2) hiperpokretljivost zglobova,
3) poremećaj u stvaranju ožiljaka,
4) česta subluksacija temporomandibularnog zgloba, parodontalna bolest,
6) Gorlinov znak (mogućnost da se vršak nosa dotakne jezikom),
7) labava oralna mukoza,
8) odsutnost LF-a.

Samo 23-godišnja kći nije imala LF i pokazivala je lagane kliničke znakove nabrojene u točkama jedan i dva. Osim kod oca koji je također nije imao LF, ni kod koga u toj obitelji nisu pronađeni klinički znakovi.

Članovi te obitelji dodatno su bili na testu pokretljivosti zglobova prema Beightonu i suradnicima (19). To ispitivanje uključuje hiperekstenziju petog prsta, postavljanje palca na ventralnu stranu podlaktice, hiperekstenziju lakatnog zgloba veću od 10°, hiperekstenziju koljena veću od 10° i postavlja-

Oral frenulum altered in morphology or number has been associated with many genetic conditions, such as: Ehlers-Danlos syndrome (EDS), infantile hypertrophic pyloric stenosis, holoprosencephaly, orofacial digital syndrome (OFD), Rapp-Hodgkin syndrome and Fraser syndrome. Additionally, abnormal development defects have been described as characteristics of the Pallister-Hall syndrome, Optiz trigonocephaly syndrome (Optiz C syndrome), W syndrome, and Optiz syndrome (3,8,9).

EDS, a hereditary genetic disorder, consists of a group of alterations inherent of connective tissue that presents a defect in collagen metabolism, leading to fragility of the skin and blood vessels, hyperextensibility of the skin, and joint hypermobility (3,10-17). A few authors have described that the absence of LF is a potential indicator of EDS[9]. Familial abnormally short or even absent lingual frenulum is a rare condition to dentists and physicians (18). Thus, the aim of this study is to report a case of a patient with familial absent LF diagnosed during dental exam, and discuss the association of non-syndromic conditions and/or genetic syndromes associated with abnormal LF.

Case report

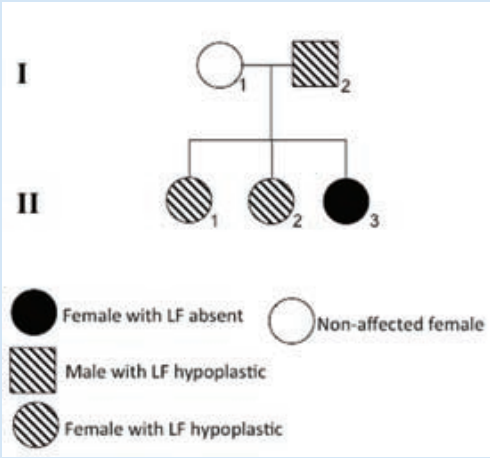
A 23-year-old woman, of normal systemic status, attended the Dental service of the Federal University of Ceará, Sobral Campus (Brazil) for dental evaluation. During the clinical examination, it was observed that the patient presented absence of LF without speech and chewing disorders, or any other functional impairment.

To evaluate if that alteration was an isolated case, other family members were investigated. The family in question is composed of five members (Figure 1). The 54-year-old father presents with absence of LF and the 49-year-old mother has a normal LF. It was observed that the oldest daughter (28 years old) presented with hypoplastic LF, whereas the second daughter (24 years old) had a shorter frenulum when compared to her older sister, almost imperceptible. The third daughter (23 years old) presented with absence of LF, phenotypically similar to her father. Posteriorly, all family members were investigated for EDS, since some authors consider the absence of LF as diagnostic sign. In order to diagnose EDS, the presence or absence of the following clinical signs were considered (Table 1): 1) hyperextensibility of the skin, 2) joint hypermobility, 3) cicatrization disorders, 4) recurrent subluxation of the temporomandibular joint, 5) periodontal disease, 6) Gorlin sign (the ability to touch the tip of the nose with the tongue), 7) friable oral mucosa, 8) absence of LF. Only the 23-year-old daughter, who presented with absence of LF, slightly exhibited the first and second clinical signs analyzed. With the exception of the father, who also presented with absence of LF, the other clinical signs were not observed in any other member of this family. In addition, the patient and her family members were asked to perform joint mobility tests proposed by Beighton et al., (19), hyperextension of the fifth finger; apposition of the thumb to the ventral aspect of the forearm; hyperextension of the elbow joint beyond 10º; hyperextension of the knee joint beyond 10°; placing

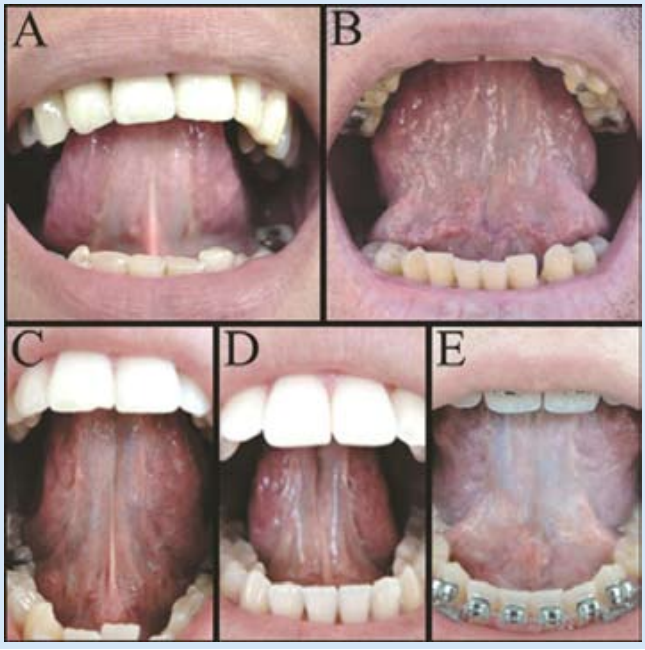
Tablica 1. Klinički nalazi članova obitelji prema karakteristikama EDS-a
Table 1 Clinical findings of the family members according to EDS characteristics.

Klinički nalazi • Clinical findings	I-1	I-2	II-1	II-2	II-3
Hiperelastičnost kože • Skin hyperelasticity	-	-	-	-	+
Hiperpokretljivost zglobova • Joints hypermobility	-	-	-	-	+
Poremećaj u stvaranju ožiljka • Disorders of cicatrization	-	-	-	-	-
Subluksacije TMZ-a • Subluxations of TMJ	-	-	-	-	-
Primljivost na parodontne bolesti • Susceptibility to periodontal disease	-	-	-	-	-
Gorlinov znak • Gorlin's sign	-	-	-	-	-
Nježna oralna sluznica • Friable oral mucosa	-	-	-	-	-
Hipoplastični lingvalni frenum • Hypoplastic lingual frenum	-	-	+	+	-
Nema lingvalnog frenuma • Absence of lingual frenum	-	+	-	-	+
#Pasivna dorzifleksija malog prsta veća od 90° • #Passive dorsiflexion of the little fingers beyond 90°	-	-	-	-	-
# Pasivno postavljanje palca na fleksornu stranu podlaktice • #Passive apposition of the thumbs to the flexor aspects of the forearms	-	-	-	-	-
#Hiperekstenzija lakta veća od 10° • #Hyperextension of the elbows beyond 10°	-	-	-	-	-
# Hiperekstenzija koljena veća od 10° • #Hyperextension of the knees beyond 10°	-	-	-	-	-
#Fleksija trupa naprijed, ravna koljena, dlanovi ruku plošno na pod • #Forward flexion of the trunk, with knees straight, so that the palms of the hands rested easily on the floor	-	-	-	-	-

Kratice • Abbreviations:
EDS – Ehlers-Danlosov sindrom • Ehlers-Danlos syndrome; TMZ • TMJ – temporomandibularni zglob • temporomandibular joint.
Odsutno • Absence (-); prisutno • presence (+); # Beightonov zbroj (procjena pokreta zglobova) • Beighton's score (assessment of joint mobility).



Slika 1. Shema rodoslovlja prikazane obitelji s čvrstim simbolom koji upućuje na individualnu pripadnost. Djelomično čvrsti simbol pokazuje osoba s hipoplazijom LF-a. Rimski brojevi identificirane generacije. Arapski brojevi predstavljaju pojedince u svakoj generaciji.
Figure 1 Family tree of the reported family. The solid symbol indicates affected individual. Partially solid symbol indicates individuals with hypoplastic LF. Roman numerals identify generations. Arabic numerals represent the individuals in each generation.



Slika 2. Klinička slika LF-a u svakoj obitelji A) I-1; B) I-2; C) II-1; D) II-2; E) II-3.
Figure 2 Clinical view of the LF in each family. A) I-1; B) I-2; C) II-1; D) II-2; E) II-3.

nje dlanova na podlogu uz ispružena koljena. Odgovorili su i na sljedeća pitanja u upitniku Hakima i Grahame:

1. Možete li (jeste li ikada mogli) staviti dlanove na podlogu, a da ne savijete koljena?
2. Možete li (jeste li ikada mogli) saviti palac i dodirnuti podlakticu?
3. Jeste li kao dijete zabavljali prijatelje postavljajući tijelo u neobične položaje i jeste li mogli napraviti špagu?
4. Jeste li kao dijete ili adolescent jedanput ili nekoliko puta iščašili rame ili patelu koljena? Smatrate li da su vam zglobovi gibljivi?

Svim tim ispitivanjima potvrdili smo da prikupljeni podatci ne zadovoljavaju kriterije za hiperpokretljivost zglobova. Poslije toga članovi obitelji poslani su na medicinsku procjenu o promjeni unutarnjih organa, kao što predlažu Castori i njegovi suradnici (2012.) (20). Ni nakon tih testova nisu detektirane promjene koje bi zadovoljile kriterije EDS-a kod bilo koga od njih. Zaključeno je da nitko od njih nema EDS. Budući da se dijagnoza EDS-a obično postavlja prema kliničkim nalazima (15), a ni kod jednog člana obitelji nije bilo karakterističnih znakova bolesti, te uzevši u obzir medicinske savjete, odlučeno je da se u dijagnostičke svrhe ne treba obaviti biopsija kože.

Rasprava

LF je mali pregib mukozne membrane koja spaja gingivu s donjom stranom jezika pokrivajući lingvalnu stranu prednjeg alveolarnog nastavka (1). Histološki se sastoji od fibroznog tkiva i pojedinačnih vlakana genioglosnog mišića. LF se klinički smatra normalnim ako insercija počinje u sredini donje strane jezika i završava u dnu usne šupljine. Smatra se da LF ima anteriornu inserciju ako počinje na donjoj strani jezika između njegove sredine i vrška, a kratak je ako je veličinom manji (1, 21) ili može čak nedostajati kod sindromskih ili nesindromskih stanja (9, 17, 18). Ankiloglosija (jezična kravata) relativno je uobičajeno nesindromsko stanje povezano s kratkim LF-om i s prevalencijom od oko četiri do pet posto. Premda može biti u sklopu posebno rijetkih sindroma (rascjep nepca vezan za X-kromosom i van der Woudeov sindrom), obično je izolirani slučaj u usnoj šupljini mladih pacijenata (18). Klinički LF može potpuno nedostajati, a katkad, doduše rijetko, pojavljuje se potpuna ankiloglosija (22). U ovom istraživanju je, među članovima analizirane obitelji, pronađena varijabilnost u stupnju skraćenja LF-a. Dijagnoza za ankiloglosiju nije postavljena. Prema tablici 2. mnoga su genska stanja povezana s promjenama LF-a, poput hipoplazije, hiperplazije, frenuluma bifida, multiplog LF-a ili odsutnog LF-a. Premda orofacijalno-digitalni sindrom može imati kliničke i molekularne nalaze slične EDS-u, nije u pitanju odsutnost/hipoplazija LF-a. Isto vrijedi za anencefaliju i holoprozencefaliju kod koje nedostaje gornji labijalni frenulum (tablica 2.). Među sindromima kod kojih nema LF-a su Rapp-Hodgkinov (9), Fraserov (8) i Ehlers-Danlosov (3, 10 – 17).

Rapp-Hodgkinov sindrom povezan je s ektodermalnom displazijom, promjenom kapilara s tendencijom alopecije i rascjepom usne ili nepca (9).

the palms of the hands flat on the floor while maintaining the knees in full extension. The questionnaire proposed by Hakim and Grahame was also performed, and the following questions were asked: 1. Can you now (or could you ever) place your hands flat on the floor without bending your knees? 2. Can you now (or could you ever) bend your thumb to touch your forearm? 3. As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits? 4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion? 5. Do you consider yourself double-jointed?. We verified that the data found in the clinical exam did not meet the criteria of hypermobility of joints. Subsequently, the patients were referred for medical evaluation to investigate changes in internal organs and nervous system as suggested by Castori et al., 2012 (20). After all evaluations, no alterations that met the criteria for EDS were found for any of the evaluated patients. Thus, the patients were not affected by EDS. Since the diagnosis of EDS is usually obtained through clinical findings[15], in the absence of the characteristic signs of the disease and considering medical suggestion, it was decided not to perform a skin biopsy for diagnostic purposes.

Discussion

The LF is a small fold of mucous membrane that connects the gum with the posteroanterior face of the tongue, covering the lingual face of the anterior alveolar crest[1]. It is histologically composed by fibrodense tissue and occasionally by the superior fibers of the ginioglossus muscle. Clinically, the LF is considered normal when its insertion starts in the middle of the inferior surface of the tongue and ends in the floor of the mouth. It is considered to be with anterior insertion when its insertion starts between the middle of the inferior surface of the tongue and the tip of the tongue. It is considered short when it presents a small size (1,21), and it may also be absent in syndromic or non-syndromic conditions (9,17,18).

Ankyloglossia (tongue-tie) is a relatively common non-syndromic condition related with short LF, presenting a prevalence of approximately 4-5%. Although it might be a part of specific rare syndromes (X-linked cleft palate and van der Woude syndrome) it usually represents an isolated condition in the oral cavity of young patients (18). Clinical appearance may range from complete absence of lingual frenulum to complete ankyloglossia (rare),(22). In the present study, a variability in the degree of shortening of the lingual frenulum among the analyzed family members was observed. However, the diagnosis of ankyloglossia was not established.

Furthermore, according to Table 2, many genetic conditions have been associated with alterations in the LF, such as hypoplasia, hyperplasia, bifid frenulum, multiple LF or absent LF. Although the orofacial-digital syndrome may present clinical and molecular findings similar to the EDS, it does not present absence/hypoplasia of the lingual frenulum. The same fact is true for anencephaly and holoprosencephaly that present absence of upper labial frenulum (Table 2).

Tablica 2. Morfologija LF-a ovisno o raznim genskim sindromima
Table 2 Morphology of LF according to different genetic syndromes.

Stanje • Condition	Frenumsko stanje • Frenum's conditions				
	Hipoplastično • Hypoplastic	Hiperplastično / Hipertrofično • Hyperplastic / Hipertrofic	Odsutno • Absent	Bifid • Bifid	Multipli • Multiples
Ehlers-Danlosov sindrom • Ehlers-Danlos syndrome	lingvalni • lingual	-	lingvalni; donji labijalni • lingual; labial inferior	-	-
Holoprosencephaly	-	-	gornji labijalni • labial superior	-	-
Oral-facial-digital sindrom • Oral-facial-digital syndrome	-	lingvalni • lingual	-	-	-
Rapp-Hodgkinov sindrom • Rapp-Hodgkin syndrome	-	-	lingvalni • lingual	-	-
Fraserov sindrom • Fraser syndrome	lingvalni • lingual	-	lingvalni • lingual	-	-
Pallister-Hallov sindrom • Pallister-hall syndrome	-	-	-	-	gornji labijalni; donji labijalni • labial superior; labial inferior
Ellis-van Creveldov sindrom • Ellis - Van Creveld syndrome	-	gornji labijalni; donji labijalni • labial superior; labial inferior	-	-	-
Optizov trigonocefalijski sindrom • Optiz trigonocephaly syndrome	-	-	-	-	gornji labijalni; donji labijalni • labial superior; labial inferior
W-sindrom • W syndrome	-	-	-	gornji labijalni • labial superior	-
Optizov sindrom • Optiz syndrome	lingvalni • lingual	-	-	-	-

Fraserov sindrom manifestira se karakteristikama kriptoftalmusa (prirođeni djelomični ili potpuni nedostatak vjeđa), sindaktilije šaka i stopala te genitalnim anomalijama (8).

Ehlers-Danlosov sindrom povezan je s promjenama kolagena koje utječu na tkiva pa nastaje hiperrastezljivost i hiperpokretljivost (3).

U ovom radu EDS je bio glavni genski poremećaj na koji se posumnjalo jer može upućivati na to da nema labijalnog frenuluma, a ponekad i LF-a, što je patognomoničan znak. EDS je opisao danski dermatolog Edvard Ehlers još 1901. godine na temelju slučaja pacijenta s karakterističnim zglobovima, tendencijom krvarenja i rastezljivom kožom (*cutis laxa*). Francuski dermatolog Henri-Alexandre Danlos opisao je 1908. godine slučaj pacijenta s tankom i hiperelastičnom kožom te mekušastim pseudotumorima. Na temelju tih dvaju prikaza slučajeva iz sredine 1930-ih godina određeno je ime toga sindroma – Ehlers-Danlosov za pacijente sa simptomima koje su opisali Edvard Ehlers i Henri-Alexandre Danlos (10).

Potkraj 1960-ih istraživači su podijelili EDS u kategorije – 1967. svrstali su ga u tri kategorije, 1968. u pet i 1972. u sedam. Sredinom 1980-ih bilo je dovoljno dokumentiranih slučajeva toga poremećaja da se uspostavi formalna nesonimija. Istraživači su 1986. godine stvorili dijagram korištenjem rimskih brojeva i klasificirali sindrom u deset tipova, ovisno o kliničkim pokazateljima i genskom nasljeđu. Kako je ta podjela zbunjivala, revidirana je 1997. godine u Ville-

Among the syndromes that present absence of lingual frenulum, there are: the Rapp-Hodgkin syndrome[9], the Fraser syndrome[8] and the Ehlers-Danlos syndrome (3,10-17). The Rapp-Hodgkin syndrome is associated with ectodermic dysplasia, capillary alterations with tendency to alopecia and the presence of labial or palatine cleft (9). The Fraser syndrome presents as characteristics the cryptophthalmos (congenital partial or total absence of the eyelids), hand and foot syndactyly, and genital anomalies (8). The Ehlers-Danlos syndrome is more related with collagen alterations that may lead to tissue involvement, allowing hyperextensibility and hypermobility (3). Regarding the present familial study, EDS was the main genetic disorder considered because it might exhibit absence of the labial frenulum or, notoriously, absence of the LF, as potential pathognomonic findings.

EDS was previously described by the Danish dermatologist Edvard Ehlers in 1901, who reported a patient with characteristics of loose joints, tendency to bleed and *cutis laxa*. In 1908, the French dermatologist Henri-Alexandre Danlos described a patient who presented thin and hyperelastic skin, in addition to molluscoid pseudotumors. From these reports, in the middle of the 1930s, the name Ehlers-Danlos syndrome was designated to describe patients who presented the characteristics cited by Edvard Ehlers and Henri-Alexandre Danlos (10). At the end of the 1960s, the investigators divided the EDS into three categories in 1967, into five types in 1968, and into seven types in 1972. In the middle of the

franchu u Francuskoj, što je rezultiralo trenutačnim sustavom klasifikacije koja sindrom dijeli na šest tipova, ovisno o manjim i većim simptomima (10, 11), (tablica 3.).

EDS čini skup poremećaja od ukupno šest tipova s heterogenim kliničkim i genskim karakteristikama zbog defekta u sintezi i strukturi vlakana kolagena te, do nekog stupnja, općom hiperpokretljivošću zglobova. Ta karakteristika, u većoj ili manjoj mjeri, nalazi se kod svih tipova sindroma (10). Etiologija sindroma tipa IV (vaskularni tip) rezultat je auto-

1980s, there were enough documented types of EDS to establish a formal disease. In the year 1986, the investigators organized a diagram using Roman numerals and classified the syndrome in ten types considering clinical manifestations and genetic inheritance. This classification system was very confusing, and was reassessed in 1997, in Villefranche – France, which originated the current classification system that divides the syndrome into six types according to minor and major criteria (10,11), (Table 3).

Tablica 3. Kliničke varijante EDS-a, ovisno o klasifikaciji defekata kolagena – modificirano prema Abelu i Carrascu (10).
Table 3 Clinical variants of EDS according to classifications and collagen defects. Adapted from: Abel and Carrasco[10].

klasifikacija EDS-a • EDS classification		Defekti kolagena • Collagen defects
Villefranche, 1997	Berlin, 1986	
Klinički • Classical	I (gravis) II (mitis)	tip V • Type V
Hiperpokretljivost • Hypermobility	III (hypermobile)	nepoznat Unknown
Krvožilno • Vascular	IV (arterial-ecchymotic)	tip III • Type III
Kyphoscoliosis • Kyphoscoliosis	VI (ocular-scoliotic)	Lysyl hydroxylase
Arthrochalasia • Arthrochalasia	VIIa (arthrochalasis multiplex congenita) VIIb (arthrochalasis multiplex congenita)	tip I • Type I
Dermatosparaxis • Dermatosparaxis	VIIc (human dermatosparaxis)	Procollagen N-peptidase

somno dominantne heterozigotne mutacije gena COL3A1 koja uzrokuje strukturne promjene u lancu kolagena Pro 1 (III) tip II. Pritom je karakteristično smanjenje termičke otpornosti, smanjena sekrecija i abnormalna proteolitička razgradnja (13). EDS tipa III (hiperpokretljivi tip) posljedica je nepoznate promjene gena, ali fenotipski se nasljeđuje autosomno dominantno. Primjerice, roditelji imaju neke blage sustavne manifestacije, što je najčešći oblik EDS-a, bez većih promjena na koži, pa se takvi slučajevi često ne dijagnosticiraju (10).

U prikazanom slučaju članovi obitelji bili su na testovima kako bi se isključio EDS tipa II, no ustanovljeno je da nitko od njih nema taj poremećaj.

Pacijenti s EDS-om klinički mogu imati sljedeća obilježja: hiperrastezljivost kože, hiperpokretljivost zglobova, povremenu luksaciju zglobova, Metenierov znak (rastezljivost vjeđa), krhkost krvnih žila i mekih tkiva, produženo cijeljenje tkiva, distrofične ožiljke (ožiljci poput cigaretnog papira), potkožne čvoriće pseudotumore i često spontano stvaranje hematoma.

Glavne opisane oralne manifestacije su sljedeće: Gorlinov znak (hiperpokretljivost jezika), gotsko nepce, odsutnost LF-a i donjega labijalnog frenuluma, rani parodontitis, nakupine fibrina u parodontu, krvarenje gingive, ulceracije sluznice, pokretljivost zuba, zubna hipoplazija, strukturalne nepravilnosti dentina, kratki nepravilni ili dilacerirani korijeni zuba, kalcifikacije pulpe, nedostatak zuba, prekobrojni zubi i promjene u temporomandibularnom zglobu (hiperpokretljivost, trismus, krepitacije, preskakanje i zapinjanje) (3, 10, 16). Analizom članova obitelji u prikazanom slučaju, samo je jedan član imao hiperpokretljive zglobove i hiperelastičnu kožu te nije imao LF. No kod njega ipak nije pronađena većina kliničkih obilježja EDS-a. Naime, pacijenti s promjenama poput hiperpokretljivosti zglobova, hiperrastezljivosti

EDS constitutes a group of disorders, comprising a total of six types, with clinical and genetic heterogeneous characteristics, resulting in defects in the synthesis and structure of fibrillar collagen, with some degree of generalized joint hypermobility. This characteristic is present in all types of the syndrome and expressed in greater or lesser degrees[10]. The etiology of type IV syndrome (vascular type) is the result of autosomal dominant heterozygous mutations in COL3A1 gen, causing structural defects in the Pro1 (III) chain of type III collagen, which are characterized by decrease in thermal stability, secretion decrease, and abnormal proteolytic processing (13). Type III EDS (hypermobile type) presents unknown genetic alterations, but the phenotype has autosomal dominant inheritance and the patients may have some subtle systemic manifestations. In addition, it represents the most common form of EDS and lacks major skin involvement, which frequently contributes to the occurrence of undiagnosed cases[10]. In the family described in the present case, to rule out type III EDS, adequate medical evaluation was performed, confirming that none of the evaluated individuals presented the disease.

Clinically, patients with EDS can present the following characteristics: hyperextensibility of the skin, joint hypermobility, recurrent luxation of the joints, Metenier sign (eyelid extensibility), fragility of blood vessels and soft tissues, delay of tissue repair, dystrophic scars (cigarette paper scars), subcutaneous nodules, pseudotumors and easy spontaneous formation of hematomas. The main oral manifestations described are: Gorlin sign (hypermobility of the tongue), high arched palate, absence of LF and of the inferior labial frenulum, early onset of periodontitis, deposits of fibrin in the periodontium, gingival bleeding, ulcerations of the mucosa, tooth mobility, dental hypoplasia, structural irregularities in dentin, short malformed or dilacerated teeth roots, calci-

tkiva i/ili drugim tkivnim promjenama imaju karakterističnu kliničku sliku zbog greške u enzimima pri stvaranju kolagena ili dominantno negativnog učinka zbog mutacije u lancima kolagena. Kolagen je fibrozni protein koji izlučuju uglavnom stanice vezivnog tkiva i važna je strukturna komponenta u ljudskom tijelu (10). Zato se pretpostavlja da promjene u njegovu nastanku mogu uzrokovati strukturne promjene u tkivima koja su većinom sastavljena od tih molekula poput, primjerice, lingvalnog frenuluma.

Smatra se da se rana dijagnoza EDS-a može postaviti pregledom oralnih nalaza, poput nedostatka LF-a koji se može uočiti tijekom kliničkog pregleda liječnika ili stomatologa (12, 15). Postavljanje rane dijagnoze EDS-a vrlo je važno za određivanje kliničkog stanja pacijenta i omogućuje pravodobnu primjenu odgovarajućih terapijskih postupaka. U vezi s tim, kako ističu Ong i suradnici, prve promjene uočavaju se kod 20-godišnjaka, a u oko 90 posto slučajeva nastaju prije dobi od 40 godina, uz srednju dob preživljavanja od 40 do 50 godina (13). Medicinska terapija uključuje antireumatike (protiv bolova u zglobovima), antibiotsku profilaksu (prevencija bakterijskog endokarditisa) te DDAVP (dezmopresin je koristan predoperativno zbog kontrole krvarenja). Drugi lijekovi koji se propisuju jesu askorbinska kiselina i cinkove masti kao dodatak fizikalnoj terapiji važnoj kod djece s hipodoncijom i zakašnjelim motoričkim razvojem jer stimulira razvoj mišića i koordinaciju (10). Istaknimo da se u prevenciji kliničkih posljedica do danas ni jedna terapija nije pokazala učinkovitom. Među novim terapijskim mogućnostima su Celiprolol, kardioselektivni β-blokator s vazodilatorom β2 agonistom koji se ordinira pacijentima s EDS-om kako bi se smanjio mehanički stres na kolagena vlakna u endotelu krvnih žila. Naime kod njih Celiprolol može smanjiti vaskularne komplikacije (poput ruptura ili disekcije) te sprječava vaskularne komplikacije i osigurava stabilnije hemodinamske uvjete stvarajući manje krhke stijenke arterija (13).

Pretpostavlja se da se EDS može rano dijagnosticirati s pomoću specifičnih oralnih nalaza, poput odsutnosti LF-a (15), što se lako može uočiti tijekom kliničkog pregleda liječnika ili stomatologa (12). Znanstvena literatura nije jedinstvena kad je riječ o povezanosti odsutnosti LF-a i EDS-a (11, 15, 16, 23). Povezanost EDS-a s odsutnošću LF-a ili labijalnog frenuluma, potaknula je kliničku sumnju i prvi su je put opisali Felice i njegovi suradnici. Oni su nakon usporedbe dvanaest pacijenata s EDS-om i 154 nesindromska pacijenta zaključili da su donji labijalni frenulum i/ili LF povezani s EDS-om. Istaknuli su da odsutnost donjega labijalnog frenuluma odgovara 100 posto osjetljivosti i 99,4 posto specifičnosti. Za odsutnost LF-a odgovara 71,4 posto osjetljivosti i 100 posto specifičnosti (15). Shankar i suradnici zaključili su nakon procjene istraživanja Bohma i njegovih kolega, da De Felice nije imao dovoljno velik uzorak i da se nije slagao sa statističkim podatcima. Autori su predložili daljnja istraživanja na većim uzorcima kako bi se dobila povezanost između odsutnosti LF-a i EDS-a (16). Perrinaud i suradnici (11) izvijestili su, nakon analize razlika u istraživanjima De Felicea (15) i Shankara (16) te proučavanja tih dvaju slučajeva, da je sustavni i oralni pregled vrlo važan ako se sumnja na EDS. U vezi s tim povezanost EDS-a s odsutnošću linfications of the pulp, absence of teeth, supernumerary teeth, and alterations related to the temporomandibular joint (hypermobility, trismus, crepitation, clicking and closed lock), (3,10,16). Analyzing the family member in the present study, only one presented joint hypermobility and hyperelasticity of the skin, in addition to absence of LF. However, the great majority of the other clinical findings of the EDS were not identified in this patient. In this context, patients who present alterations as hypermobility of joints, tissue hyperextension and/or other tissue alterations have this characteristic clinical aspect due to deficiency of collagen processing enzymes or dominant negative effect on the mutant collagen chains. The collagen is a fibrous protein secreted mainly by connective tissue cells, and is an important structural component of the human body (10). Therefore, we believe that alterations in its production can result in structural alterations in tissues composed by this substance, as the lingual frenulum, for example.

It is believed that the diagnosis of EDS can be obtained early through the investigation of oral findings, such as the absence of the lingual frenulum, which can be easily observed during clinical examination performed by physicians or dentists (12,15). Making an early diagnosis of EDS is very important to the evolution of the clinical aspects of the patients, and also to enable the implementation of an appropriate therapy for each case. In this context, according to Ong et al., the first alterations are observed at around 20 years of age, approximately 90% of the patients present an alteration before 40 years of age and the average survival rate is 40-50 years of age (13). The medical therapy can include antirheumatic drugs (for the treatment of joint pain), antibiotic prophylaxis (for the prevention of bacterial endocarditis) and DDAVP (desmopressin may be useful preoperatively for hemorrhage control). Other commonly used drugs are ascorbic acid and zinc therapies, in addition to a program of physical therapy, important for children with hypotonia, delayed motor development, and also important to promote the development of muscles and coordination (10). Until now, no treatment has proven efficient to prevent clinical events. Among new therapeutic options proposed, the Celiprolol, a cardioselective β-blocker with vasodilator β2 agonist, has been used in patients with EDS in order to reduce the mechanical stress on the fibers of the vascular endothelium collagen. Therefore, the Celiprolol can reduce these vascular complications (such as rupture or dissection), showing efficacy in preventing vascular complications in patients with EDS by providing more stable hemodynamic conditions and promoting a less fragile arterial wall (13).

It is believed that EDS can be diagnosed early considering specific oral findings, such as the absence of LF (15), which can be easily observed during clinical exams by dentists and physicians (12). However the scientific literature shows that there is no agreement about the association of EDS with the absence of LF (11,15,16,23). The association of EDS with absent lingual or labial frenulum was suspected clinically but was first demonstrated by de Felice et al., who, after comparing 12 EDS patients and 154 non-syndromic patients, argued that the absence of the inferior labial frenulum and/or LF is

gvalnog frenuluma potvrđena je u mnogobrojnim prikazima slučajeva Macheta i suradnika (12) – opisani su slučajevi 43 pacijenta s dijagnosticiranim EDS-om od ukupno 129 proučavanih. U tom istraživanju potvrđeno je da je odsutnost lingvalnog frenuluma specifični klinički nalaz pacijenata s EDS-om (12).

Zaključak

U ovom istraživanju složili smo se s ostalim autorima da je odsutnost LF-a manji znak EDS-a, za razliku od odlučujućeg čimbenika za postavljanje dijagnoze toga poremećaja. Premda u obrađenim slučajevima klinički nalazi nisu doveli do dijagnoze EDS-a, liječnici i stomatolozi moraju biti oprezni tijekom kliničkog pregleda kako bi uočili rane znakove EDS-a i uklonili sumnju na to genetsko stanje.

associated with EDS. They concluded that the absence of the inferior labial frenulum corresponded to 100% of sensibility and 99.4% of specificity. As for the absence of LF, it corresponded to 71.4% of sensibility and 100% of specificity (15). Shankar et al., after evaluating the study performed by Böhm et al., concluded that the study of De Felice did not consider a significant study sample, and that the sample was not in agreement with the statistical data reported. The authors suggested, therefore, that more studies with larger samples are necessary to establish an association between the absence of LF and EDS (16). Perrinaud et al., (11) after analyzing the differences between the studies of De Felice (15), and Shankar (16), and after observing two clinical cases, reported that systematic oral exam is important when there is a suspicion of EDS. In this context, the association of EDS with the absence of the lingual frenulum was confirmed by a broad case-control study performed by Machet et al., (12). comprising 43 patients diagnosed with EDS from a total of 129 studied patients, in which the absence of the lingual frenulum was a specific clinical finding of patients with EDS (12).

Conclusion

Considering the present study, we agree with other authors that the absence of LF represents a minor sign of EDS, as opposed to a determinant factor for the diagnosis of the disease. Although clinical findings did not lead to EDS diagnosis in the present case, physicians and dentists must be alert during clinical examinations, with an aim to recognize early signs that may lead to a suspicion and diagnosis of this genetic condition.

Abstract
One of the most interesting and not yet understood anatomical structures of the oral cavity is the frenum or frenulum. The lingual frenum (LF) is an important structure that anatomically relates to the tongue and mandible, and, therefore, might be directly related to dental malocclusions. Oral frenula altered in morphology or in number have been directly associated with a number of genetic conditions, specially the Ehlers-Danlos syndrome. Some authors describe that the absence of the LF is a pathognomonic finding for this disorder. The aim of this study was to report a case of familial hypoplastic lingual frenum diagnosed during routine dental exam, and also discuss the association of non-syndromic conditions and/or genetic syndromes with the occurrence of abnormal LF. Dentists and physicians must be alert during clinical exam, with the objective to recognize early the signs that might indicate the diagnosis of the Ehlers-Danlos syndrome, since this condition interferes directly with the orthodontic treatment.

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Lingual Frenum; Ehlers-Danlos Syndrome

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