Dental Considerations in Patients with Loeys-Dietz Syndrome: A Review of the Literature and Case Report

Evelina Kratunova*/ Ivan L.Zhang**/ Marcio A da Fonseca ***

Loeys-Dietz Syndrome (LDS) is a rare connective tissue disorder with an autosomal dominant pattern of inheritance, linked to heterozygous mutations in six genes from the transforming growth factor beta receptor complex. The classical syndrome characteristics include aortic aneurisms with generalized arterial tortuosity, hypertelorism and cleft palate or bifid/ broad uvula. LDS is also associated with a wide range of skeletal, craniofacial, cutaneous and ocular abnormalities, as well as allergic, atopic and inflammatory diseases. Common oral findings include high arched and/or narrow palate, enamel defects and class II skeletal malocclusion. Dental management of patients with LDS is complex and includes approaches to prevent medical complications, as well as considerations for safe delivery of dental care. The purpose of this report, reviews the literature related to LDS oral manifestations as well as to describe the comprehensive dental management of an adolescent patient with LDS and discuss the challenges that dental practitioners may face when providing treatment for these patients.

***Keywords**: Loeys-Dietz Syndrome, Pediatric Dentistry, Oral Health, Hospital Dentistry*

LDS is a newly described syndrome and the literature reviewing its oral manifestations is limited.

Patients are reported to have lower oral health-related quality of life as a result of tooth sensitivity and malocclusions.

Dental management is compounded by the complexity of medical factors that should be taken into consideration for the safe delivery of care.

The presented case is an example of the challenges that dental practitioners may face when providing treatment for LDS patients.

INTRODUCTION

Loeys-Dietz Syndrome (LDS) is a rare connective tissue disorder with an unknown prevalence and no established race or sex predilection.[1-3] LDS is an autosomal dominant disorder, with approximately 75% of the cases being *de novo* mutations, whereas 25% are familial.[4] The diagnosis is established by molecular genetic testing and/ or characteristic clinical findings in the proband and/or family members.[4] In the late 1980's, the medical literature described a few cases of patients with marfanoid-like features and familial aortic dissecting aneurysms of unexplained etiology.[5,6] About 20 years later, the geneticists Bart Loeys and Harry Dietz discovered that mutations in genes from the transforming growth factor beta (TGFβ) receptor complex were responsible for a cluster of symptoms, including arterial tortuosity/ aneurysm, hypertelorism, and bifid uvula/cleft palate.[1,2] This classical phenotype triad is now referred to LDS,[2] whose medical management guidelines were established only in 2014.[3]

The TGFβ signaling pathway has an essential role in regulation of tissue homeostasis, cell proliferation, migration, and differentiation during embryonic development.[7] LDS is caused by pathological

*Evelina Kratunova, MDS, D.Ch.Dent, Clinical Associate Professor, Department of Pediatric Dentistry, College of Dentistry, University of Illinois at Chicago, Chicago, Ill., USA.

Ivan L. Zhang, DMD, MS, Pediatric Dentist in Private Practice, Washington, District of Columbia, USA.

Marcio A. da Fonseca, DDS, MS, Chicago Dental Society Foundation Professor and Head, Department of Pediatric Dentistry, College of Dentistry, University of Illinois at Chicago, Chicago, Ill., USA.

Corresponding Author:
Evelina Kratunova
Department of Pediatric Dentistry, College of Dentistry, University of Illinois at Chicago
801 South Paulina Street M/C 850, Room 269D
Chicago, IL 60612
Phone: (312) 996-1984
Fax: (312) 413-8006
E-mail: evekrat@uic.edu

alterations of the complex relationship between the TGF-β family of signaling mediators and the extracellular matrix in connective tissues.[8] Later it was discovered that gene mutations against decapentaplegic homolog 3 (SMAD3) gene and the TGFβ 2 ligand gene in the mothers were also associated with LDS phenotypes.[9]

The most recent classification of LDS includes six types with respect to implicating gene.[3,9] LDS type 2 is the most common (55%–60% of the cases), while LDS type 1 is described as the most severe form.[3,9] While the different subtypes may vary in their prominent features, it is now recognized that LDS diagnosis is a continuum in which affected individuals may have a range of combinations of clinical signs (Table).[1,3] LDS is also associated with a wide range of skeletal, craniofacial, cutaneous and ocular abnormalities, as well as allergic, atopic and inflammatory diseases.[2,3] While the severity of systemic manifestations can be variable, most LDS patients are affected by considerable morbidity with the cardiovascular complications, posing the main risk of mortality.[3] Learning disability is most often associated with craniosynostosis and/ or hydrocephalus.[1,2]

Since this is a newly defined syndrome, there is a limited literature describing oral findings and dental treatment considerations in this patient population. Medical reports first indicated that LDS patients frequently complain of tooth sensitivity, allegedly a sign of dental hard tissue anomalies.[1,3] The craniofacial malformations associated with the syndrome has been implicated with the development of orthodontic malocclusions.[1] Presently, the dental literature comprises of only two research trials, both conducted at the at the National Institutes of Health, Clinical Center by the same group of investigators.[10,11] Jani et al.[10] evaluated the oral and dental anomalies in a cohort of 40 LDS patients (age range 2.4–57.4 years) recruited prospectively from August 2015 to January 2018. The authors found that the most common features were presence of a high arched and/or narrow palate, enamel defects and class II skeletal malocclusion, while less commonly patients presented with a bifid or broad uvula or submucous cleft, deep bite, dental crowding and abnormal eruption pattern with a delay in the eruption of the permanent teeth.[10] Additionally, the enamel defects were classified according to disease type and the it was determined that the most severe structural deterioration was seen in LDS type 2 with incomplete penetrance and variable expression.[10] The second study was completed by the same research group using the same patient cohort.[11] Nguyen et al.[11] assessed the influence of oral manifestations on the oral health-related quality of life (OHRQoL) in LDS patients. The authors reported that tooth hypersensitivity, temporomandibular joint abnormalities, and accretion of four-or-more oral manifestations had significant influence on worse OHRQoL.[11]

The purposes of this report are to describe the comprehensive dental management of an adolescent patient with LDS and discuss the challenges that dental practitioners may face when providing treatment for these patients.

Case report

A 14-year-old white male presented to the pediatric dental clinic at the College of Dentistry, University of Illinois for complete oral rehabilitation due to his medical and dental complexity. The chief complaint was a pronounced tooth sensitivity, permitting food and drink consumption only at room temperature. The patient perceived this symptom as markedly negative to his everyday quality of life. The dental history included routine regular oral exams and dental prophylaxis with a primary dental provider as well as a referral to a specialist orthodontist. However, the patient's mother desired a more comprehensive dental management for him and decided to seek care at our clinic.

The patient had a full-term birth without pre- or perinatal complications. His extensive medical background was concomitant with LDS type 2, which was established via genetic testing. His associated medical conditions were inherent of the syndrome and included aortic root dilation, arterial tortuosity, dysrhythmia, bifid uvula, hypertelorism, exotropia, joint hypermobility, osteoporosis/ osteopenia, clubbed feet, easy bruising, asthma, tension migraine, a soft cleft palate and low iron levels. He did not have craniovertebral instability nor any known drug allergies; however, allergies to shellfish, eggs, pollen, and animal dander were reported. The patient had multiple past surgeries, including aortic valve/root replacement, retinal neovascularization, and repairs of a hernia, exotropia, and soft cleft palate. His cardiovascular drug therapy comprised of a daily anticoagulant (warfarin 3 mg once a day) and angiotensin II receptor antagonist (irbesartan 150 mg twice a day). For asthma management, he was taking a steroid (beclomethasone diproprionate

Table: Clinical Manifestations of LDS.

Systemic Involvement	Clinical Features
Vascular	Dilation or dissection of aorta and other arteries (cerebral, thoracic, abdominal), arterial aneurysms and tortuosity.
Skeletal	Pectus excavatum or pectus carinatum, scoliosis, joint laxity or contracture (typically involving fingers), arachnodactyly, talipes equinovarus, cervical spine malformation/instability, club feet, osteoarthritis, osteoporosis/-osteopenia.
Craniofacial	Hypertelorism, bifid uvula, cleft palate, craniosynostosis.
Cutaneous	Soft and velvety skin, translucent skin with easily visible underlying veins, easy bruising, dystrophic scars, milia (prominently on the face).
Allergic/ Inflammatory Disease	Food/seasonal allergies, asthma, chronic sinusitis, eczema, eosinophilic esophagitis/gastritis, inflammatory bowel disease.
Ocular	Blue or dusky sclerae.
Other	Spontaneous rupture of the spleen and bowel, and uterine rupture during pregnancy. Neuro-radiologic findings are dural ectasia and Arnold-Chiari type I malformation, which may be relatively rare.

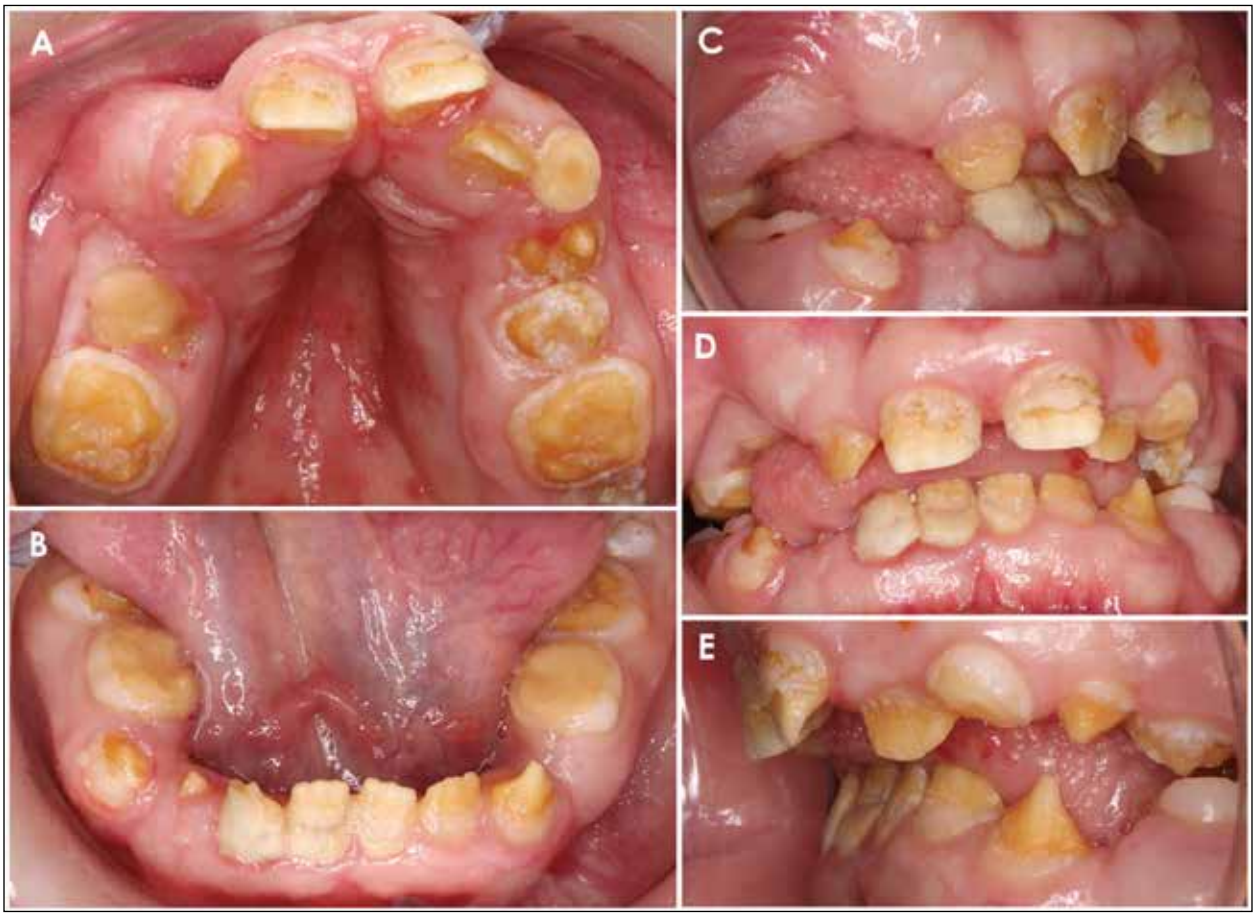
HFA 40 mcg two puffs twice a day) and two bronchodilators (levalbuterol tartrate 45 mcg one to two puffs every four to six hours and albuterol 90 mcg one to two puffs every four hours as needed). He also took iron, mineral and vitamin supplements daily. For osteoporosis treatment he received intravenous bisphosphonate (zoledronic acid) infusions every three months. A daily anti-convulsant (divalproex sodium 250 mg at nighttime) and a barbiturate (butalbital acetaminophen 162.5 mg as needed) were prescribed for migraine therapy. An interdisciplinary healthcare team closely followed the patient and regular imaging examination was required for ongoing screening of potential cardiac and skeletal complications.

The dental examination revealed extraoral facial features consistent with those typical of the syndrome, including hypertelorism and mild facial asymmetry. Intraorally, the patient presented with generalized marginal gingivitis, thick and fibrous attached gingiva and scattered petechiae on the mucosa of the posterior hard and soft palate (Figure 1). He had heavy plaque accumulation on all teeth and substantial calculus deposits on the mandibular incisors. His dental development was delayed according to his age chronology. Four deciduous teeth were over-retained (maxillary left primary canine, mandibular right, mandibular left and maxillary right second primary molars, with the latter showing signs of ankylosis). While free from any carious lesions, the dental hard structures demonstrated a generalized developmental defect, affecting both dentitions in a similar manner. The tooth enamel was present only in the cervical third of the crowns of all erupted teeth, with clinical crowns mostly consisting of exposed dentin. Occlusion evaluation showed class II division 1 malocclusion, with moderate overcrowding in both arches, increased overjet of six mm and anterior open bite of two mm. He also had a high-vaulted palate.

The radiographic assessment showed congenitally missing maxillary left, mandibular right and mandibular left second premolars as well as potential impaction of the maxillary canines (Figure 2). The forming second and third permanent molars demonstrated enamel structure of appropriate radiopacity covering the entire crowns. In contrast, the developing maxillary right canine seemed to lack cuspal enamel. Superimposition of the images of the maxillary right canine and first premolar made it difficult to assess the presence and quality of their enamel structure.

In order to preserve the teeth from further loss of enamel and to alleviate the pronounced tooth sensitivity, the comprehensive dental management plan included direct full coronal coverage restorations for all erupted teeth. In view of the complex medical history, the extensive need of restorative care and the potential inability to fully anesthetize him for dental work, his mother consented for complete oral rehabilitation under general anesthesia (GA).

Figure 1. Intraoral photographs of the patient, including maxillary occlusal (A), mandibular occlusal (B), right lateral (C), frontal (D) and left lateral (E) views. Soft tissue findings include generalized marginal gingivitis, thick and fibrous attached gingiva and scattered petechiae on the mucosa of the posterior hard and soft palate. While free from any carious lesions, the dental hard structures demonstrate a generalized developmental defect (consistent with enamel hypomineralization and post eruptive enamel breakdown), affecting both dentitions in a similar manner. Heavy plaque accumulation on all teeth and substantial calculus deposits on the mandibular incisors are also evident.



Several consultations were obtained from the patient's medical team prior to GA. The cardiologist recommended antibiotic prophylaxis and a warfarin drug holiday beginning five days before the surgery date and restarting the day after. With respect to the bisphosphonate therapy, his endocrinologist did not advise for any regimen alteration as the risk of osteonecrosis of the jaw was perceived as minimal despite the planned extraction of all primary teeth requested by his orthodontist for malocclusion management.

The endocrinologist did not recommend a change in his steroid dosage prior to dental treatment.

The dental treatment under GA was uneventful and included provision of prefabricated stainless steel crowns for the molars, open face stainless steel crowns for the erupted premolars and direct resin composite crowns for the incisors. Partially erupted teeth were restored with direct composite resin veneer on the accessible surfaces (e.g., the mandibular right first premolar). The patient received 2 g ampicillin intravenously approximately 30 minutes prior to dental procedures started in the operating room.

Post-operatively, the patient reported significant reduction of tooth sensitivity and considerable quality of life improvement, particularly with being able to eat ice cream and hot food for first time (Figure 3). Twelve months after the dental rehabilitation, all restorations remained intact, oral hygiene had improved substantially, the gingival tissues regained normal health and the patient has started successfully fixed orthodontic therapy (Figure 4). The composite resin veneers of the open-faced stainless-steel crowns provide facial surfaces for bonding of orthodontic brackets as well as improved esthetics. Any chipping or loss of structure of the composite resin crowns can be easily restored by directly adding more material. These restorations are inexpensive, easy to place and repair, and offer adequate esthetics. Both the patient and his mother were very pleased with the treatment outcome. Future considerations include regular recall visits, provision of full coronal coverage restorations for any newly erupted teeth, and a periodontal management of his gingival overgrowth.

Figure 2. Panoramic radiograph of the patient at the initial examination. The maxillary left, mandibular right and mandibular left second premolars are congenitally missing. The forming second and third permanent molars demonstrate enamel structure of appropriate radiopacity covering the entire crowns. In contrast, the developing maxillary right canine seem to lack cuspal enamel.

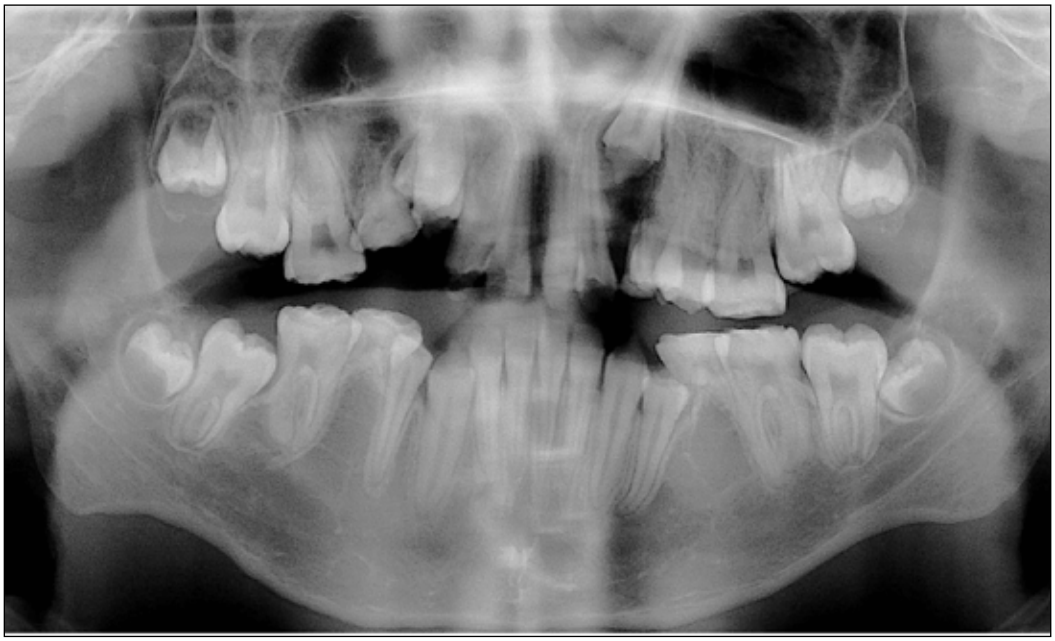


Figure 3. One-month postoperative intraoral photographs of the patient including frontal (A), maxillary occlusal (B), mandibular occlusal (C) views. The dental treatment included extraction of all remaining primary teeth, provision of prefabricated stainless steel crowns for the permanent molars, open face stainless steel crowns for the erupted premolars and direct resin composite crowns for the incisors. Partially erupted teeth were restored with direct composite resin veneer on the accessible surfaces (e.g., the mandibular right first premolar).

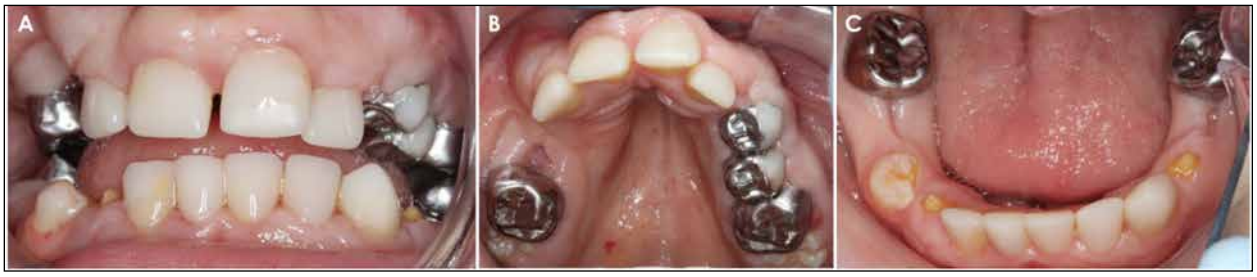
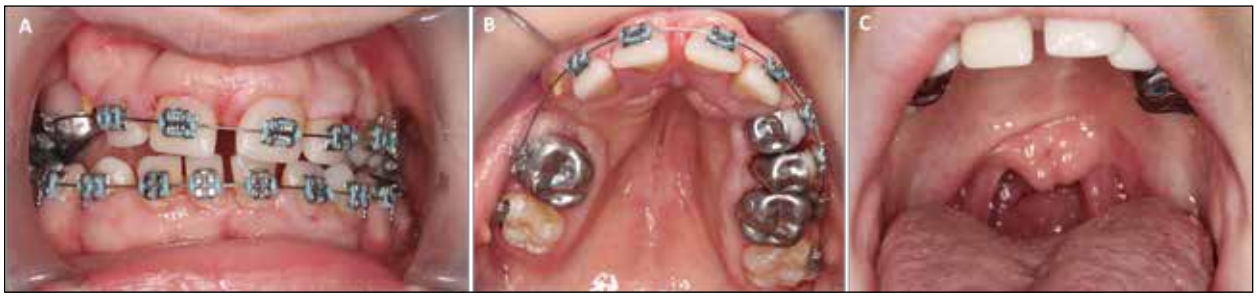


Figure 4. One-year postoperative intraoral photographs of frontal (A) and maxillary occlusal (B) views as well as a view of the repaired bifid uvula (D). All restorations remain intact, oral hygiene was improved, and a fixed orthodontic therapy was started successfully. The composite resin veneers of the open-faced stainless steel crowns provide facial surfaces for bonding of orthodontic brackets as well as improved esthetics.



DISCUSSION

The medical management of LDS comprises of pharmacological and surgical approaches that treat syndrome manifestations and prevent secondary complications.[1,4,3] Cardiovascular features, such as dilation, dissection, aneurysms and/ or tortuosity of the aorta and other arteries are treated with early and aggressive surgical interventions.[1,3] Angiotensin receptor blockers and beta-adrenergic receptor blockers are indicated to reduce hemodynamic stress and patients with cervical spine instability are managed with surgical fixation to prevent spinal cord damage.[1,3] Other skeletal features, such as bone overgrowth, clubfeet, ligamentous laxity, scoliosis and pectus excavatum may require orthopedic correction.[2] Bisphosphonate therapy is administered for osteoporosis management, with cleft palate and craniosynostosis being managed by a craniofacial team.[2] Standard medical treatment is typically instigated for allergic/ inflammatory diseases associated with LDS. Hernia repairs in this population have a high tendency for recurrence and a supporting mesh should be considered to minimize that risk.[4] Ocular refraction and visual correction are necessary in young patients at risk for amblyopia.[1,3]

The dental management of patients with LDS is complex in order to prevent medical complications. A thorough review of the medical history and consultation with patient's medical team are of paramount importance. The cardiovascular anomalies may require antibiotic prophylaxis prior to invasive dental procedures to prevent infective endocarditis, as our patient received. Patients using anticoagulant medications can present with increased risk of bleeding. Although the patient's cardiologist stopped his medication for a few days prior to the GA appointment, there is strong scientific evidence that dental surgery is safe for these patients and stopping the anticoagulant regimen, even for a short period of time, increases the risk of an embolic event that can be debilitating or even fatal.[12] Mandibular block injections are not contraindicated and post-operative bleeding can be easily contained with local hemostatic measures, even with an International Normalized Ration even higher than 3.5.[12] It is important for the dental practitioner to discuss this information with the medical team as they may not be up-to-date with contemporary standard of dental care. Our patient also presented easy bruising, which could have been due a side effect of medications he was taking, such as warfarin, divalproex and butalbital acetaminophen.

Since LDS is associated with cervical spine instability,[2,3] a flexion/ extension radiograph of the neck may be advised prior to dental care intubation for dental patients requiring GA. However, the neck radiograph is controversial because it can be deemed inconclusive. Thus it is important to take precautions to avoid extremes of head position during dental treatment, including during GA intubation, for all patients who are at risk for atlanto-axial instability.[13,14] Use of protective stabilization or any type of physical restraint is discouraged for uncooperative patients due to the danger of spinal cord compression or other serious complications, including paralysis.

Asthmatic patients should achieve well-controlled disease level prior routine dentistry to prevent potential precipitation of asthmatic attack in a dental situation. Individuals affected with LDS are likely be on long-term oral or intravenous bisphosphonate therapy, as our patient was. There is a well-documented risk of osteonecrosis of the jaws (ONJ) in adult patients who have taken or are currently taking bisphosphonates after invasive dental procedures that may result in bone trauma, exposure or an open wound (e.g., extractions, implant placement and other surgical interventions, including periodontal therapy).[15] Dental care for these patients should be carried out according to medication-related ONJ (MRONJ) prevention and management protocols and in close collaboration with their physicians.[15] Fortunately, to date there are no reported cases MRONJ in children, possibly due to the relatively small wounds following extraction of primary teeth, the vascularity of young jaw bones and the lower doses given to children compared to adults.[16] Given that bisphosphonates decrease bone turnover, orthodontic treatment may become compromised.[17] As the drug may stay in the body for many years after discontinuing its use,[15-17] it is extremely important to remind patients (or parents, in case of pediatric patients) to inform their dental providers that they used bisphosphonates, which will put them at long-term risk for ONJ.

Craniofacial features of LDS include dolichocephaly, a tall broad forehead, frontal bossing, a high anterior hairline, hypoplastic supraorbital margins, prominent maxillary central incisors and tendency for open-mouth.[18] These extraoral characteristics were also observed in our patient and were consistent with the orthodontic diagnosis of class II division 1 malocclusion with increased overjet and open bite.

There is a limited knowledge of oral characteristics of the syndrome. Our literature review identified only one available study describing LDS oro-dental manifestations, which has shown results from a small sample of forty participants with a wide age variation.[10] Our patient had a generalized defect of the enamel structure, affecting both dentitions, consistent with the clinical presentation of enamel hypomineralization. It led to hypersensitivity and a decreased oral health-related quality of life, findings confirmed by

Nguyen et al.[11] The tooth sensitivity was also detrimental to effective oral hygiene practices, which resulted to substantial plaque and calculus accumulation. Furthermore, the tooth sensitivity was a barrier for the patient to undergo a comprehensive course of chairside dentistry as quadrant local anesthesia could not eliminate the discomfort to the rest of the teeth.

The patient's enamel structure appeared to be developmentally lacking or lost soon after tooth eruption, particularly in the incisal/cuspal third of the crowns. Generally, dental enamel development can be affected by long lasting adverse factors in the microenvironment of the teeth, by mutations in the genes responsible for normal enamel formation or by metabolic changes, characteristic for some inherited conditions.[17,18] While phenotypically the enamel defect appeared similar to amelogenesis imperfecta, the known genetic make-up of the latter differs from the genes implicated in LDS.[17,18] Since LDS is a multi-system connective tissue disorder, the etiology of the generalized tooth structure defect may be related to error in the formation of dentin or in the establishing the effective enamel dentin junction.

Future research is needed to confirm if developmental hard tissue anomalies are indeed a part of the syndrome and to catalogue any other oral and dental manifestations. Our literature search did not identify prior publications discussing dental management considerations of LDS patients and this case report is an illustration of the complex multidisciplinary approach required to prevent medical complications, as well as treatment decisions for safe delivery of dental care.

CONCLUSIONS

LDS is a newly described syndrome and the literature reviewing its oral manifestations is limited. Patients are reported to have lower oral health-related quality of life as a result of tooth sensitivity and malocclusions. Dental management is compounded by the complexity of medical factors that should be taken into consideration for the safe delivery of care. The presented case is an example of the challenges that dental practitioners may face when providing treatment for LDS patients.

Data Accessibility

Data is available on request from the corresponding author.

Funding

This was an unfunded manuscript.

Conflict of Interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1133/
2. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet;37:275-81. 2005.
3. MacCarrick G, Black JH 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA Guerrerio AL, Sponseller PD, Loeys B, Dietz HC 3rd. Loeys-Dietz syndrome: a primer for diagnosis and management. Genet Med;16:576-87. 2014.
4. Van Laer L, Dietz H, Loeys B. Loeys-Dietz syndrome. Adv Exp Med Biol 2014;802:95-105.
5. Furlong J, Kurczynski TW, Hennessy JR. New Marfanoid syndrome with craniosynostosis. Am J Med Genet;26:599-604. 1987.
6. Nicod P, Bloor C, Godfrey M, Hollister D, Pyeritz RE, Dittrich H, Polikar R, Peterson KL. Familial aortic dissecting aneurysm. J Am Coll Cardiol;13:811-9. 1989.
7. Wu MY, Hill CS. Tgf-beta superfamily signaling in embryonic development and homeostasis. Dev Cell;16:329-43. 2009.
8. MacFarlane EG, Haupt J, Dietz HC, Shore EM. TGF-β family signaling in connective tissue and skeletal diseases. Cold Spring Harb Perspect Biol;9(11). 2017.
9. Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann Cardiothorac PSurg;6:582-94. 2017.
10. Jani P, Nguyen QC, Almpani K, Keyvanfar C, Mishra R, Liberton D, Orzechowski P, Frischmeyer-Guerrerio PA, Duverger O, Lee JS. Severity of oro-dental anomalies in Loeys-Dietz syndrome segregates by gene mutation. J Med Genet. Mar 8. 2020.
11. Nguyen QC, Duverger O, Mishra R, Mitnik GL, Jani P, Frischmeyer-Guerrerio PA, Lee JS. Oral health-related quality of life in Loeys-Dietz syndrome, a rare connective tissue disorder: an observational cohort study. Orphanet J Rare Dis. Dec 16;14(1):291. 2019.
12. Wahl MJ, Miller CS, Rhodus NL, Kammerer P, Dinkova A, Lalla RV. Bajkin BV. Anticoagulants are dental friendly. Oral Surg Oral Med Oral Pathol Oral Radiol; 125(2):103-6. 2018.
13. Cohen WI. Current dilemmas in Down syndrome clinical care: celiac disease, thyroid disorders, and atlanto-axial instability. Am J Med Genet C Semin Med Genet;142C(3):141-8. 2006.
14. Hankinson TC, Anderson RCE. Craniovertebral junction abnormalities in Down Syndrome. Neurosurg;66:A32-A38. 2010.
15. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaws – 2014 Update. J Oral Maxillof Surg 2014;72:1938-56.
16. da Fonseca MA. Osteoporosis: an increasing concern in pediatric dentistry. Pediatr Dent;33:241-5. 2011.
17. Iglesias-Linares A, Yanez-Vico RM, Solano-Reina E, Torres-Lagares D, Moles MAG. Influence of bisphosphonates in orthodontic therapy: systematic review. J Dent;38:603-11. 2010.
18. Adès LC. Evolution of the face in Loeys-Dietz syndrome type II: longitudinal observations from infancy in seven cases. Clin Dysmorphol;17:243-8. 2008.
19. Wright JT, Hart TC, Hart PS, Simmons D, Suggs C, Daley B, Simmer J, Hu J, Bartlett JD, Li Y, Yuan ZA, Seow WK, Gibson CW. Human and mouse enamel phenotypes resulting from mutation or altered expression of AMEL, ENAM, MMP20 and KLK4. Cells Tissues Organs;189:224-9. 2009.
20. Crawford PJ, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. Orphanet J Rare Dis;2:17. 2007.