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Craniofacial manifestations of Loeys Dietz syndrome: A case report and a review of the literature

Case report

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Introduction

Loeys-Dietz syndrome（LDS）was first defined in 2006 by Loeys *et al.*[1)] and the follow-up report was published in 2014[2)]. LDS is an autosomal dominant disease characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate（OMIM, On-line Mendelian Inheritance in Man, # 609192）. The responsible genes of LDS are known for *TGFBR1*, *TGFBR2*, *SMAD3* and *TGFB2* [1), 3), 4)]. However, there were few reports described of the craniofacial and dental abnormalities of patients with LDS. In this report, we present the case of a 10-year-old female with LDS who exhibited severe micrognathia of the maxilla and mandible and dental crowding. The dento-skeletal features of the patient were evaluated using a cephalometric radiograph and computed tomography. The relevant literatures of LDS were also reviewed.

Case report

The case study involved a 10-year-old Japanese female who had referred to the Orthodontic Department of Osaka University Dental Hospital. The patient's chief complaint was dental crowding in both arches.

Previous Medical History

The patient was born at 40 weeks without intrapartum abnormalities. She was extremely tall at birth（75 cm; average height, 48.9 cm）. At the age of 3 years, she had an adenoidectomy to remove hypertrophied adenoid. At the age of 7 years, she had undergone a continuous positive airway pressure（CPAP）therapy during sleep to treat sleep apnea syndrome（SAS）and snore. In the same year, she had been referred to the department of pediatric dentistry in our hospital for treatment of dental caries, because she had suffered odontoid fracture by her struggle during dental treatment in private clinic. She had been treated with Halo vest system for three months to allow the bones to heal and an intravenous bisphosphonate therapy once every four months to increase bone density. At the age of 8 years, she had the Nuss Procedure to treat pectus excavatum. At the age of 9 years, she had a strabismus operation to treat

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exotropia. At the age of 10 years, she had a medial orbital decompression to treat bilateral exophthalmos.

General examination

Her height was within the normal range (154 cm, average height of 10 years-old female, 146.8 ± 6.6 cm) (Fig. 1). Arachnodactyly of the hands and toes and clinodactyly on the fifth finger of right hand was observed (Fig. 2 and 3).

Magnetic Resonance angiography (MRA) showed tortuosity of the basilar artery, known as one of the triad signs of LDS[1] (Fig. 4).

Extra-oral examination

Strabismus, exophthalmos, and hypertelorism were noteworthy (Fig. 5). She had a round face, and right side of her face was larger than the opposite side. As for her facial profile, she displayed a posterior divergent straight profile with midface hypoplasia.

Intra-oral examination

She had an Angle Class II malocclusion with severe crowding on both dental arches (Fig. 6). The score of Index of Orthodontic Treatment Need (IOTN)[5] was 4d on the dental health component and 8 on the aesthetic Component. High arched palate and bifid uvula was observed. Her upper arch exhibited narrow and V-shaped. The arch length discrepancies of upper and lower arches were -10.7 and -11.2 mm, respectively. Lateral crossbite existed only in the premolar regions on the right side. In this case, there was no suspicion of enamel hypoplasia, which was often observed in connection with osteogenesis imperfecta[6].

Radiological Examination

On the panoramic radiograph, congenital absence of maxillary and mandibular second premolars and the third molar germs were found (Fig. 7). Several primary teeth were remained because of ectopic erup-

Figure 1. General aspect of the patient.

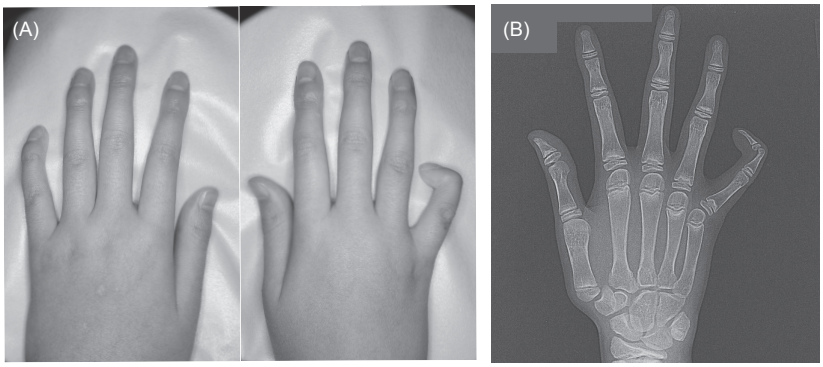

Figure 2. Photograph and X-ray photograph of the hands.

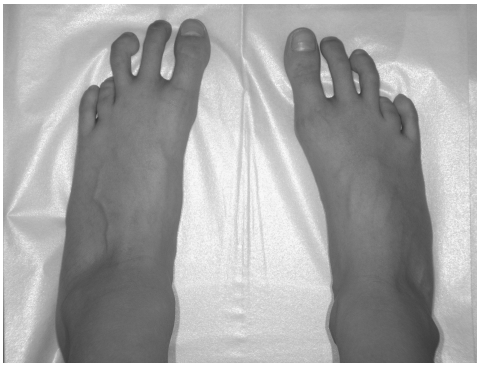

Figure 3. Photograph of the fingers of foot.

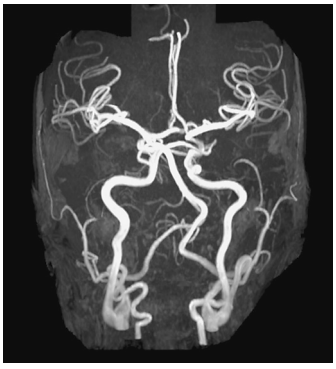

Figure 4. MRA image of the basilar artery.

tion or absence of permanent teeth. The panoramic radiograph also identified bilateral prominent antegonial notches indicating a small mandible[7]. Although there was periapical lesion under lower left second primary molar, she displayed no remarkable alveolar bone resorption.

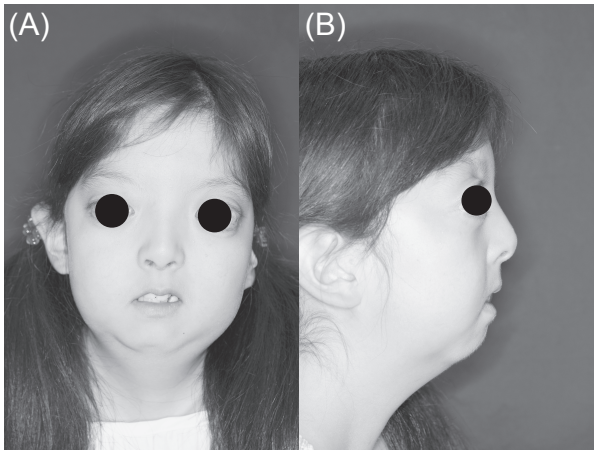

Figure 5. Facial photographs.
(A) Frontal view, (B) Lateral view.

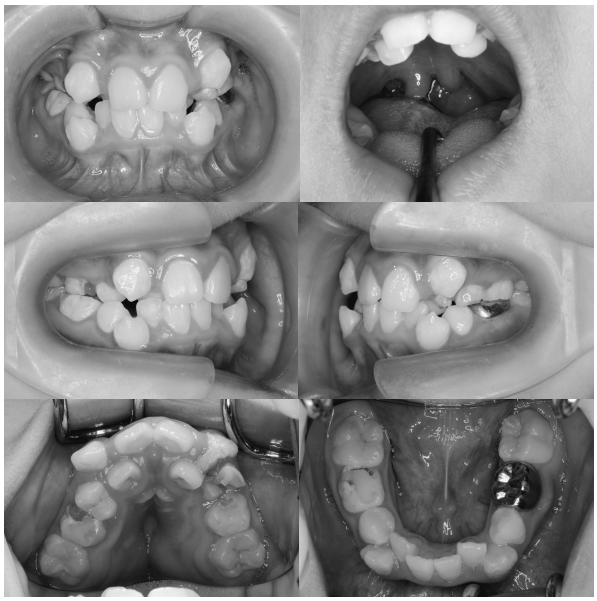

Figure 6. Intraoral photographs.

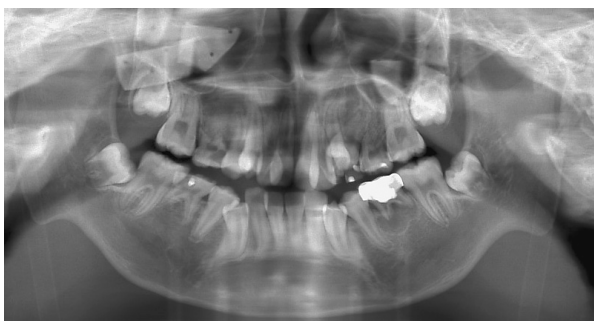

Figure 7. Panoramic radiograph.

Linear and angular measurements of lateral cephalometric radiograph are listed in Table 1. She had an average cranial base size compared with Japanese norms[8] (Fig. 8). The antero-posterior positions of the maxilla and mandible were both retrusive with reduced SNA angle (63.5°; Japanese female norm, 80.8 ± 3.2°) and SNB angle (59.9°; Japanese norm, 77.4 ± 2.6°). The ANB angle of 3.6° (Japanese norm, 3.3 ± 3.0°) indicated a skeletal Class I relationship. The size of maxilla and mandible were both extremely small. The angle between the SN line and mandibular plane line was significantly increased, suggesting the downward and backward growth rotation of the mandible. The upper incisors were significantly retroclined in relation to racial norms.

Finally, her maxillofacial deformity was characterized by significant maxillary and mandibular hypoplasia in connection with a high mandibular plane angle and bilateral prominent antegonial notches. According to the past report[1], the score of craniofacial severity index was 8.

From coronal CT image of the maxilla, the thickness of palatal bone near the mid palatal suture is remarkably thin. Meanwhile, overlying palatal mucosa is extremely thick. Abnormality of the nasal concha and nasal airway constriction were observed (Fig. 9).

In addition, craniosynostosis of all sutures was observed (Fig. 10). On the internal surface of calvaria, there were digital impressions indicating a rise in intracranial pressure.

Discussion

LDS was first reported as "Marfan syndrome (MFS) type 2" to describe patients with Marfan syndrome caused by mutations in *TGFBR2*[9]. MFS is an autosomal dominant disorder with a wide range of clinical variability caused by FBN1 mutations. The common physical findings in patients with MFS and LDS are tall stature, arachnodactyly, and pectus deformity and, as to the craniofacial manifestations, maxil-

TABLE 1. Cephalometric measurements.

Linear（mm）	Patient	Japanese Norm*（mean ± SD）	%SD	Angular（deg）	Patient	Japanese Norm*（mean ± SD）	%SD
Cranial base				Maxilla			
S-N	64.3	65.7 ± 2.7	−0.5	SNA	63.5	80.8 ± 3.2	−5.4
Maxilla				Mandible			
Ptm-A/PP	35.5	44.8 ± 2.6	−3.6	SNB	59.9	77.4 ± 2.6	−6.7
Ptm-ANS/PP	41.5	49.1 ± 2.4	−3.2	SNP	59.4	76.6 ± 2.7	−6.3
Mandible				Y-axis	76.6	64.6 ± 2.4	5.0
Ar-Go	35.7	40.4 ± 3.2	−1.5	Facial angle	72.8	94.1 ± 3.4	−3.4
Go-Me	50.0	65.3 ± 3.9	−3.9	Mandibular plane			
Ar-Me	78.6	96.7 ± 5.1	−3.6	SN-MP	53.6	38.3 ± 3.8	4.0
Anterior Facial Height				FH-MP	40.2	31.2 ± 3.6	2.5
N/PP	51.1	50.5 ± 2.4	0.2	Dental			
Me/PP	63.5	61.9 ± 3.7	0.4	U1-SN	88.0	106.8 ± 5.3	−3.5
Posterior Facial Height				U1-FH	101.4	113.8 ± 4.9	−2.5
S/PP	36.8	41.7 ± 2.9	−1.7	U1-PP	100.9	114.7 ± 5.2	−2.7
Go/PP	28.8	27.4 ± 3.6	0.4	L1-MP	87.3	91.8 ± 6.6	−0.7
				L1-FH	52.5	56.8 ± 5.4	−0.8
				L1-APo	15.9	22.2 ± 3.5	−1.8
				IIA	131.1	122.9 ± 4.9	1.7

*Source of normal values[8)]

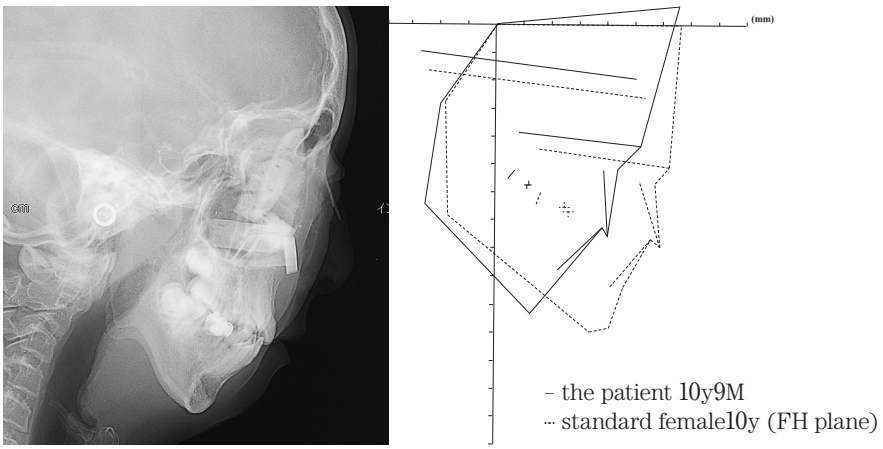

Figure 8. Lateral cephalometric radiograph and profilogram.

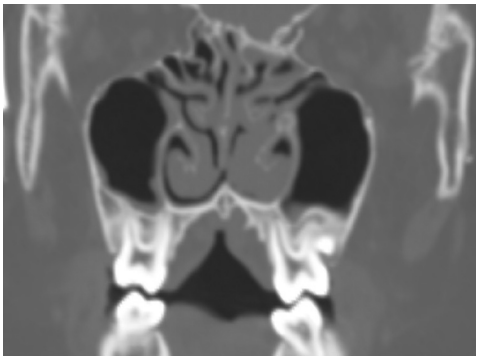

Figure 9. Coronal CT image of the maxilla.

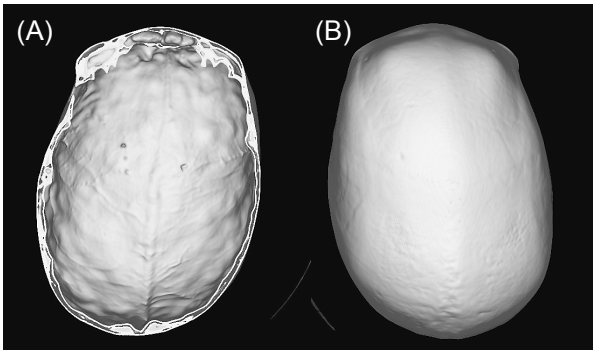

Figure 10. 3D reconstruction CT image of calvaria.
（A）Internal surface,（B）External surface.

lary and mandibular retrognathia, skeletal class II malocclusion with large positive overjet and posterior crossbite[1), 10) ~15)]. However, some characteristics of LDS, such as hypertelorism, craniosynostosis, and cleft palate/bifid uvula, are less common with MFS. In this case, she showed similar physical and craniofacial characteristics with MFS and LDS patients mentioned above. At the age of 10 years, she was finally diagnosed as LDS because the genetic test revealed that she had a de novo c.968 A>C variant in TGF-β receptor I. This mutation was included in exon 5 of *TGFBR1* caused amino acid mutation D323A in the serine-threonine kinase domain[1), 4)].

There were few reports[1), 16)~20)] of the craniofacial and intra-oral features in LDS patients (Table 2). The present patient exhibited a bifid uvula, micrognathia of the maxilla and mandible and malar hypoplasia, which were reported with high prevalence in LDS patients[1), 17)]. The evidence from genetic ablation of *Tgfbr1* from embryonic epithelium or cranial neural crest cells in mice also showed soft cleft palate or cleft palate accordingly. It has also been shown that *Tgfbr1* works with *Tgfbr2* to activate the signaling pathway[21)]. Interestingly, epithelial elimination of TGFBR2 in mice also results in soft cleft palate with defects in mesenchymal proliferation and muscle differentiation[22)]. These results strongly suggest that retarded TGF-β signaling in LDS patient is strongly associated with the phenotypes of cleft palate and bifid uvula. Ades reported that patients with LDS often had prominent upper incisors[17)]. In this case, patient exhibited palatally inclined upper incisors. Additionally, the congenital absence of the permanent second premolars was observed in the present case. In general, the prevalence of congenital missing of the second premolar was approximately 3%[23)]. The relationship between the congenital missing tooth and LDS are unrevealed and the prevalence of congenital missing in LDS has not been previously reported. We also realized that some of the craniofacial abnormality in this patient such as craniosynostosis, high arch palate, aneurysms and hypertelorism resembled to the ones in Crouzon or Apert syndrome which are the diseases well known to result from disturbing FGF signaling[24), 25)]. Recent research revealed molecular interaction of TGF-β and FGF signaling during craniofacial development[26)] which could possibly explain the reason for sharing these phenotype between LDS and Crouzon/Apert syndrome patients.

According to the previous reports[27), 28)], most patients with MFS exhibited severe periodontitis caused by connective tissue disorder. Meanwhile, there have been no reports which described the relationship between the onset of periodontitis and LDS. In this patient, the sign of severe periodontal disease was not

TABLE 2 List of studies of LDS and their defining characteristics

Study or Case Report	*Sample Size*	*Features (prevalence)*
Loeys *et al*., 2005	16	Bifid uvula (91%), Cleft palate (19%), Retrognathia (57%), Malar hypoplasia (85%), Craniosynostosis (36%)
Loeys *et al*., 2006	30	Bifid uvula or Cleft palate (90%), Retrognathia (50%), Malar hypoplasia (57%), Craniosynostosis (50%), Hyperterolism (75%)
Ades, 2008	7	Bifid uvula (43%), Facial asymmetry (86%), Retrognatiha (29%) Malar hypoplasia (29%), High narrow palate (43%) Prominent upper central incisors (86%)
Drera *et al*., 2009	1	Bifid uvula, High-arched palate, Retrognathia
Breckpot *et al*., 2010	1	Bifid uvula, Malar hypoplasia, Small mouth and chin, Smooth philtrum, Thin upper lip
Lloyd BM *et al*., 2011	4	Bifid uvula (75%), High-arched palate (100%), Retrognathia (50%), Malar hypoplasia (25%)

observed.

After completion of growth, a surgical approach, including LeFort III osteotomy for the maxilla and bilateral sagittal split osteotomy for the mandible, should be considered due to her severe retrognathia of the maxilla and mandible. Additionally, an extraction of her retained primary teeth will be required to provide space for alignment of severely crowded teeth. However, she has been treated with an intravenous bisphosphonate therapy once every four months to increase bone density. It may lead to surgical complication in the form of impaired wound healing following maxillofacial surgery[29].

Additionally, Loeys *et al*. reported that the first cardiovascular event in LDS patients occurred at around the age of 25 on average[1]. The prognosis of LDS was considered unfavorable because an aortic dissection occurs earlier than MFS. Therefore, careful medical management of cardiovascular conditions is essential during orthodontic treatment in patients with LDS. *Tgfbr1* has been shown to play critical roles of vasculogenesis in animal model which could also help to understand the molecular mechanism of this phenomenon in LDS patients[30]. An antibiotic prophylaxis against Subacute Bacterial Endocarditis (SBE) is recommended before orthodontic treatment, especially during placing orthodontic bands[31].

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