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Case Report

Lacrimo-auriculo-dento-digital syndrome with AIRE mutation: A case report

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ABSTRACT

Congenital absence or hypoplasia of the major salivary glands is rarely observed and easily overlooked in the clinic. Lacrimo-auriculo-dento-digital syndrome (LADD) is a congenital anomaly disorder that is characterized by aplasia, atresia, or hypoplasia of the lacrimal and salivary glands and caused by *FGFR2, FGFR3*, or *FGF10* gene mutation. Autoimmune polyendocrine syndrome type 1 (APS-I) caused by an *AIRE* gene mutation is a rare inherited autoimmune disease characterized by chronic mucocutaneous candidiasis, Addison disease, and hypoparathyroidism. However, simultaneous mutations in pathogenic genes of the two syndromes (LADD and APS-I) in one patient is rarely observed. Herein, we have presented a patient with main complaints of xerostomia and xerophthalmia that was diagnosed with LADD syndrome with *AIRE* mutation.

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1. Introduction

Salivary gland dysplasia is a rare and easily overlooked condition that is occasionally accompanied by developmental disorders, such as lacrimo-auriculo-dento-digital syndrome [LADD (MIM 149730)]. LADD is an autosomal dominant, multiple congenital anomaly disorder characterized by aplasia, atresia, or hypoplasia of the lacrimal and salivary systems, cup-shaped ears, hearing loss, and dental and digital anomalies [1]. LADD is a genetic disorder caused by mutations in at least one of three known genes, including fibroblast growth factor receptor 2 (*FGFR2*), fibroblast growth factor receptor 3 (*FGFR3*), and fibroblast growth factor 10 (*FGF10*), which are involved in the branching morphogenesis of organs, such as the lung, salivary and lacrimal glands [2]. Autoimmune polyendocrine syndrome type 1 (APS-I) caused by an *AIRE* gene mutation is a rare inherited autoimmune disease characterized by chronic mucocutaneous candidiasis (CMC), Addison disease, and hypoparathyroidism. Herein, we presented a patient who had symptoms of xerostomia and xerophthalmia, clinical signs of absence of bilateral parotid glands and hypoplasia of bilateral submandibular glands, and lacrimal glands, cup-shaped ears, symmetrical clinodactyly, and dental anomalies. In rare cases gene tests have indicated heterozygous mutations not only in *FGFR2* but also in *AIRE*. The patient was diagnosed with LADD and displayed an *AIRE* gene mutation.

2. Case report

The patient was a four-year-old Chinese girl with complaints of xerophthalmia and xerostomia since birth. The patient suffered from severe early childhood cavities and had undergone repeated dental treatment. Both eyes were barely moist, with no tears since birth, and artificial tears were used to relieve the gritty feeling in the patient's eyes. The patient suffered from cardiac hypertrophy, recurrent upper respiratory tract infections, and a recurrent body rash. No discomfort in the salivary or lacrimal glands was confirmed by the patient's parents. No symptoms related to connective tissue disorder nor family history was reported.

The patient presented with a normal appearance, except for the bilateral cup-shaped ears. No concomitant hearing loss was found. The patient's fifth fingers showed symmetrical clinodactyly. Her hair, nails, and sweat glands were normal and her eyes appeared dry with corneal redness. The oral mucosa was dry with a sign of mirror tongue. The saliva pool on the floor of the mouth was not present. The bilateral papillae of the Stensen's ducts were not detected. The patient was diagnosed with hypoplastic enamel and suffered from rampant cavities. Many decayed teeth or residual roots were observed in her mouth(Fig. 1). The whole saliva flow rate was 0 mL per 5 mins under both unstimulated and stimulated conditions. A Schirmer's test showed decreased tear secretion at 6.5 mm in the left eye and 8 mm in the right eye at 5 mins. A Schirmer test score of less than 10 mm after 5 mins was generally considered abnormal.

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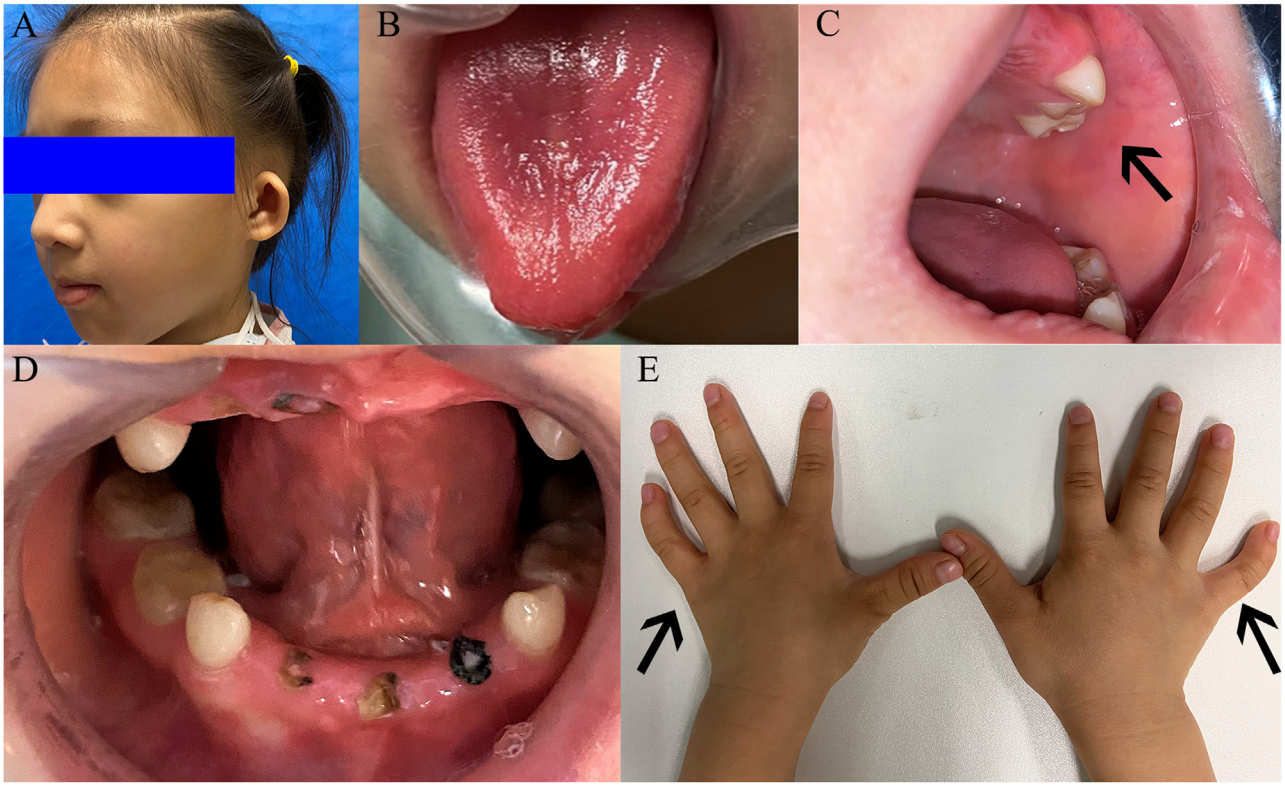

Fig. 1. Clinical manifestations observed in the patient. The patient showed low-set, cup-shaped ears (A); severe xerostomia, multiple cavities, enamel hypoplasia, residual roots, mirror-like tongue (B and D); absence of the orifices of Stensen's duct (C, arrow), and symmetrical clinodactyly of the fifth fingers (E, arrow).

Magnetic resonance imaging (MRI) showed an absence of bilateral parotid glands and small bilateral lacrimal glands and submandibular glands. Ultrasonography showed that the size of the left submandibular gland was 1.5 × 0.6 × 0.8 cm^3 and the right submandibular gland was 1.4 × 0.8 × 1.5 cm^3. Panoramic tomography showed the absence of bilateral second mandibular premolars and right mandibular incisor. X-ray showed symmetrical clinodactyly in the fifth fingers(Fig. 2).

Laboratory evaluations showed negative reactions to RF, ANA, anti-SSA, and anti-SSB. The levels of IgG4 and IgG were within normal range, and the level of IgE was occasionally increased. No clinically significant abnormalities were detected by blood count assays and

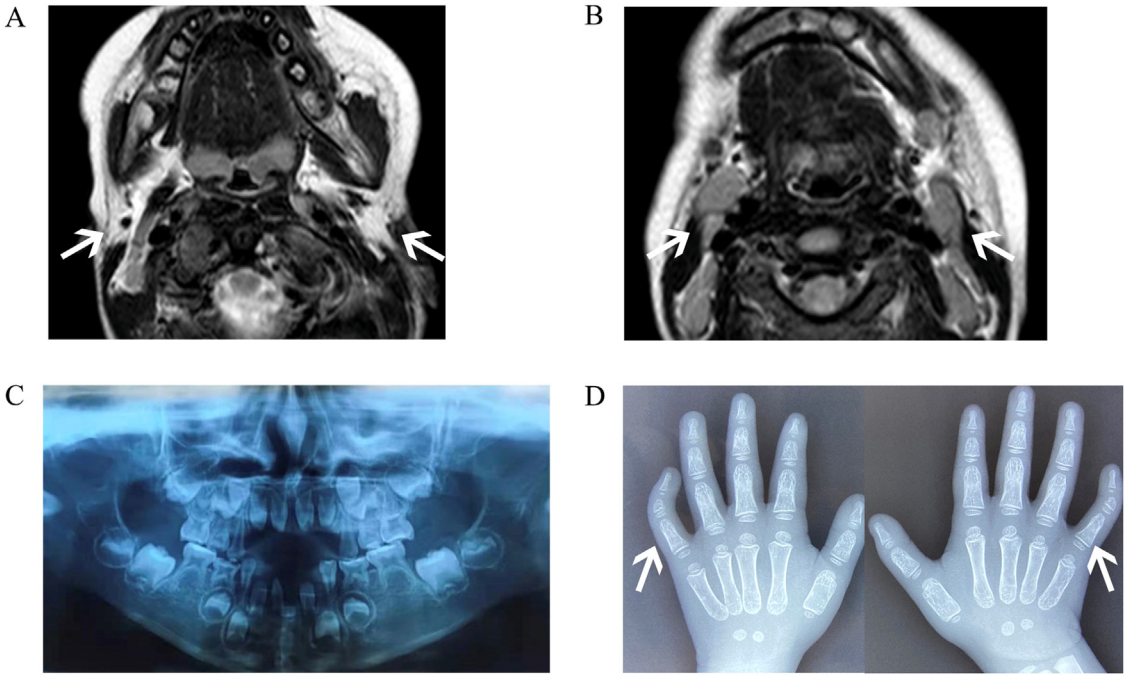

Fig. 2. Imaging findings of patients. MRI showed no visible parotid glands (A, arrow) and small bilateral submandibular glands (B, arrow). Panoramic tomography showed the absence of bilateral second mandibular premolars and right mandibular incisor (C). X-ray showed symmetrical clinodactyly in the fifth fingers (D, arrow).

bone marrow morphological assays. Genetic testing showed heterozygous mutations in the *FGFR2* (NM_000141; Exon14: c.1874G>A) and *AIRE* genes (NM_000383; Exon11: c.1310G>A). No abnormalities in the functions of endocrine glands, including the parathyroid, adrenal gland, gonads, or thyroid, were detected.

The patient was diagnosed with LADD and harbored an *AIRE* mutation based on results from physical examination, laboratory evaluations, and genetic tests.

The management of the patient was focused to maintain oral hygiene to prevent dental cavities and candidiasis, as well as protect the eyes from keratoconjunctivitis. Oral treatment included removing irreparable residual roots. Self-maintenance therapy, including chewing sugar-free gum, rinsing with artificial saliva, and keeping the mouth clean, was recommended to the patient's parents. The patient was advised to apply fluoride regularly to prevent cavities.

After follow-up at 1.5 years, the patient failed to have candidiasis or additional cavities. However, there was no significant relief for dry mouth or dry eyes. Nevertheless, regular follow-up was required to take precautions against chronic mucocutaneous candidiasis (CMC) and cavities. Monitoring the endocrine glands' function was suggested, especially the parathyroid and adrenal glands.

3. Discussion

In the present case report, we described a 4-year-old girl with xerostomia and xerophthalmia due to the absence of bilateral parotid glands and aplasia of lacrimal and submandibular glands. Insufficiency of the major salivary glands could be divided into congenital and secondary according to the etiology. Hypofunction of the secondary salivary glands has been seen in Sjögren's syndrome, radiation-induced sialadenitis, and IgG4-related sialadenitis. Congenital absence or hypoplasia of the major salivary glands is rarely observed in the clinic. Aplasia of the salivary glands can occur both in isolation or in association with other developmental anomalies, such as hemifacial microsomia, first and second branchial arch syndrome, Velo-cardio-facial syndrome, oral-facial-digital syndrome, Klinefelter syndrome, Down syndrome, aplasia of lacrimal and salivary glands (ALSG), labyrinthine aplasia, microtia, microdontia (LAMM), and LADD syndrome.

Several signaling pathways participate in the development of salivary glands, including the epidermal growth factor (EGFs) family, FGFs, NOTCH signaling, WNT/β-catenin signaling, and EDA signaling [3]. Any loss- or gain-of-function mutations in the related genes have resulted in the alteration of the signaling pathways presented above, which have led to changes in ductal and ganglia morphogenesis and have resulted in aplasia of salivary glands and lacrimal glands [3]. Whole exon sequencing of the patient demonstrated there were heterozygous mutations in the *FGFR2* gene, which is the pathogenic gene associated with LADD [2]. A single nucleotide substitution (c.1874G→A) was found in exon 14 of the *FGFR2* gene and resulted in a non-conservative amino acid change from arginine to glutamine at position 625 (R625Q). Previous reports have identified pathogenic *FGFR2* variants in exon 11, exon 15, and exon 16 [2,4]. We revealed a novel variant in exon 14 in the *FGFR2* gene. Neither the patient's mother nor father had the *FGFR2* mutations or clinical features of LADD.

The gene analysis in the patient further revealed mutations in the *AIRE* gene, which plays a key role in the development of central immunological tolerance. *AIRE* is the pathogenic gene associated with APS-I, which is characterized by a classic triad, including CMC, Addison disease, and hypoparathyroidism [5]. APS-I can occur in patients from early infancy to old age, and new components of a given syndrome could appear throughout life. Accurate diagnosis of APS-I requires the presence of at least two of the three major components, or only one if a sibling has previously been diagnosed with the disease [6]. Interestingly, mutations in pathogenic genes of both LADD and APS-I simultaneously occurred in our patient, which is rarely seen.

The recurrent body rash and the upper respiratory tract infection that occurred in the patient may be due to autoimmune dysfunction. Even though the patient did not show classic triad symptoms of APS-I, long-term follow-up is necessary.

As a summary, severe xerostomia and xerophthalmia may be caused by congenital absence or aplasia of salivary and lacrimal glands due to LADD syndrome. Other gene abnormalities, such as *AIRE* mutation, might overlap in LADD.

Author contributions

Hui Zhu was involved in conceptualiazation,data curation, formal analysis, writing – original draft, and writing – review & editing. Guang-yan Yu was involved in conceptualization, formal analysis, supervision and writing – review & editing.

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Ethical approval

The Ethical Approval was given by Biomedical Ethics Committee, Peking University School and Hospital of Stomatology. (PKUSSIRB-202272002)

Patient consent

Consent was obtained.

Declaration of Competing Interest

The authors have declared that no conflicts of interest exist.

Acknowledgments

Not applicable.

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