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CASE REPORT

LACRIMO-AURICULO-DENTO-DIGITAL SYNDROME: A CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Background: Lacrimo-auriculo-dento-digital (LADD) syndrome is a rare autosomal dominant developmental disorder characterized by multisystem anomalies involving the lacrimal apparatus, salivary glands, dentition, auricular structures, and distal limbs. It is associated with pathogenic variants in fibroblast growth factor (FGF) signaling pathway genes, including *FGF10*, *FGFR3*, and *FGFR2*. Clinical expression is highly variable, and severe phenotypes remain uncommon.

Case Presentation: We report a 2-year-old male presenting with congenital xerostomia, feeding difficulties, hypodontia, and rapidly progressive early childhood caries. Clinical examination revealed craniofacial dysmorphism, auricular anomalies, and multiple digital malformations. Ultrasonographic evaluation demonstrated complete absence of the parotid, submandibular, and sublingual glands, consistent with total salivary gland agenesis. Genetic analysis identified a heterozygous de novo missense variant in *FGFR2* (NM_000141.5:c.1991G>A; p.Arg664Gln), classified as likely pathogenic and consistent with LADD syndrome. The patient underwent early preventive and restorative dental management.

Conclusion: This case expands the phenotypic spectrum of LADD syndrome by documenting a rare presentation with complete salivary gland agenesis and a de novo *FGFR2* variant. It highlights the critical role of early diagnosis through integrated clinical, radiological, and genetic assessment, as well as the importance of intensive preventive dental strategies in reducing long-term oral morbidity and improving quality of life.

Keywords: Autosomal dominant disorder, Congenital anomalies, Enamel hypoplasia, Hypodontia, Xerostomia

INTRODUCTION

Lacrimo-auriculo-dento-digital (LADD) syndrome, also known as Levy–Hollister syndrome (OMIM 149730), is a rare autosomal dominant developmental disorder characterized by congenital anomalies affecting the lacrimal system, salivary glands, dentition, ears, and distal limbs [1,2]. Since its initial description, fewer than 150 cases have been reported in the literature, reflecting both its rarity and significant clinical heterogeneity [4,5].

The phenotype of LADD syndrome is highly variable, ranging from isolated glandular hypoplasia to complex multisystem involvement. Core clinical features include lacrimal duct anomalies leading to epiphora, hearing impairment due to auricular malformations, salivary gland hypoplasia or aplasia resulting in xerostomia, dental abnormalities such as hypodontia and enamel defects, and digital malformations including brachydactyly and clinodactyly [3,5,13,18]. Additional systemic findings, including renal, craniofacial, and respiratory anomalies, have also been reported in selected cases [8,9,12].

At the molecular level, LADD syndrome is associated with pathogenic variants in genes involved in fibroblast growth factor (FGF) signaling, particularly *FGF10*, *FGFR3*, and *FGFR2* [16,17,31,32]. These genes play a critical role in epithelial–mesenchymal interactions during embryonic development and are essential for the formation of salivary glands, lacrimal structures, and distal limb tissues. Disruption of this pathway results in impaired organogenesis and the characteristic multisystem phenotype of LADD syndrome [17].

Among the clinical manifestations, salivary gland involvement is of particular importance due to its direct

impact on oral health. Salivary gland hypoplasia or aplasia has been reported in approximately two-thirds of affected individuals and leads to xerostomia, which significantly increases the risk of early-onset dental caries, mucosal disease, and feeding difficulties [19,21,28]. Dental anomalies, including hypodontia, microdontia, enamel hypoplasia, and delayed eruption, are among the most consistent findings, occurring in up to 90% of cases and often representing early diagnostic indicators [5,10,23].

Despite advances in molecular genetics and imaging techniques, reports combining early pediatric presentation, complete salivary gland agenesis, and confirmed molecular findings remain extremely limited. Furthermore, genotype–phenotype correlations in LADD syndrome remain incompletely understood, with significant variability even among patients carrying similar mutations [27,29].

This case report presents a rare and severe phenotype of LADD syndrome characterized by complete salivary gland agenesis, significant dental abnormalities, and a de novo *FGFR2* mutation. The aim is to highlight the diagnostic value of integrating clinical, radiological, and genetic findings, and to emphasize the importance of early recognition and preventive dental management in improving long-term outcomes in affected patients.

CASE REPORT

A 2-year-old male patient presented to our private Oral and Maxillofacial Medicine clinic in Erbil, Kurdistan Region of Iraq, with a chief complaint of persistent oral dryness since birth, accompanied by congenitally missing teeth and multiple dental caries. The patient had been diagnosed with LADD syndrome by a pediatrician within the first month of life.

Systemic physical examination revealed features consistent with LADD syndrome. Head and neck examination demonstrated craniofacial dysmorphism, including a prominent forehead and broad nasal bridge. Ophthalmic evaluation revealed epiblepharon.

External ear examination showed low-set, cup-shaped auricles (Figure 1). On palpation of the parotid and submandibular regions, no discrete glandular enlargement was detected; however, there was an absence of palpable salivary gland bulk and no identifiable submandibular gland outline.

Figure 1. Extraoral craniofacial features of the patient with LADD syndrome.
Lateral profile view showing low-set, cup-shaped auricles. These craniofacial features are consistent with previously reported phenotypic characteristics of LADD syndrome.

On palpation of the parotid and submandibular regions, no discrete glandular enlargement was detected; however, there was an absence of palpable salivary gland bulk and no identifiable submandibular gland outline.

Digital anomalies were observed on physical examination. The right hand showed brachydactyly and nail dysplasia, with mild periungual erythema around the thumb. Additional findings included clinodactyly of the middle finger and symbrachydactyly of the index finger (Figure 2a). Examination of the left hand revealed brachydactyly of the index finger, clinodactyly and symbrachydactyly of the middle finger, along with a hypoplastic thumb and a soft tissue appendage at its base, suggestive of a rudimentary digit or accessory limb remnant (Figure 2b).

Intraoral examination revealed poor oral hygiene, with missing mandibular central incisors and mandibular primary first molars (previously extracted). Stainless steel crowns were present on the bilateral mandibular second primary molars (Figure 3a). The maxillary anterior teeth showed enamel hypoplasia with cervical caries affecting all anterior teeth. Marked xerostomia was evident, with absence of salivary pooling. The tongue appeared dry, erythematous, and depapillated. The lips, particularly the upper lip, were dry and crusted (Figure 3b). The child was uncooperative during intraoral photography, which limited complete photographic documentation.

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Intraoral Findings

Intraoral examination revealed:

- Severe xerostomia with absence of salivary pooling
- Dry, erythematous mucosa and depapillated tongue
- Crusted lips
- Hypodontia and enamel hypoplasia
- Extensive dental caries

These findings are consistent with previous reports linking salivary gland dysfunction to increased caries risk [5,19,20].

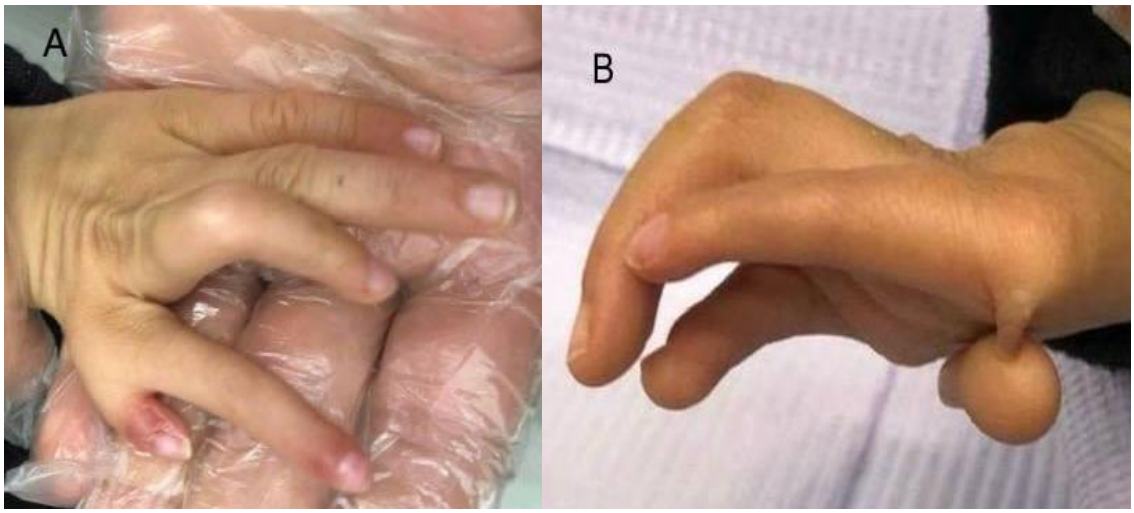

Figure2. (A) Photograph of the right hand showing brachydactyly and nail dysplasia, with mild periungual erythema observed around the thumb. Clinodactyly of the middle finger and symbrachydactyly of the index finger. (B) Photograph of the left hand showing brachydactyly of the index finger, symbrachydactyly and clinodactyly of the middle finger, along with a hypoplastic thumb and a soft tissue appendage at its base.

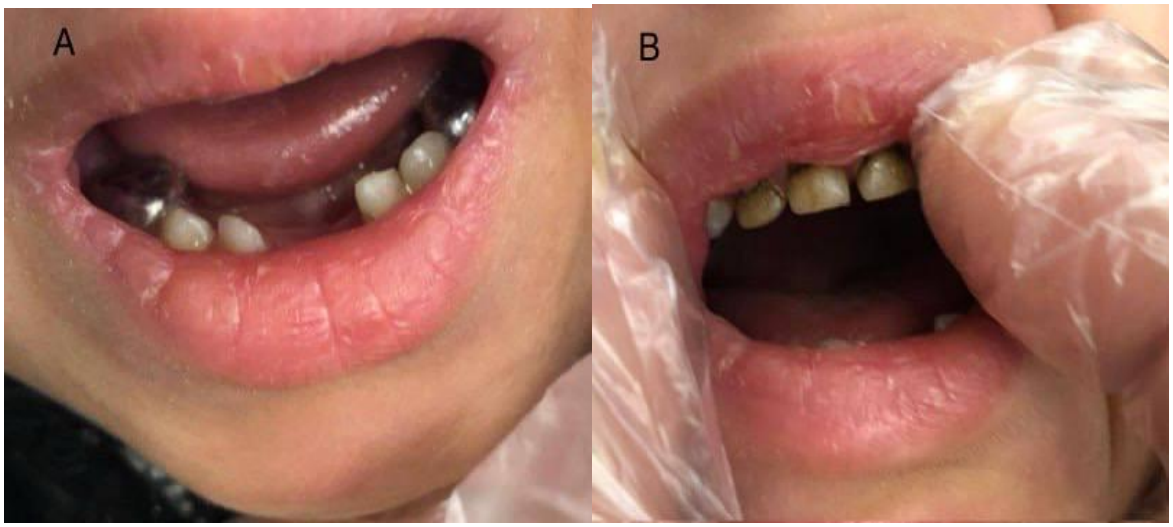

Figure3. Intraoral findings associated with salivary gland aplasia.
(A) Photograph showing missing of mandibular central incisors and primary first molars. Metal crown restorations on mandibular second primary molars bilaterally. (B) The maxillary anterior teeth exhibited enamel hypoplasia accompanied by cervical caries affecting all upper anterior teeth.

Prior to referral, the patient underwent a comprehensive medical evaluation. Investigations included complete blood count (CBC), abdominal and pelvic ultrasonography, neck and major salivary gland imaging, hip joint radiographic assessment, echocardiography, and molecular genetic analysis. All investigations were within normal limits except for neck ultrasonography and genetic testing, which revealed abnormalities consistent with the diagnosis.

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Neck Ultrasound + Doppler:

- Both parotid glands are absent, and no lobes or parotid tissue could be detected in the normal anatomical location. Ectopic parotid tissue can only be identified by isotope scanning.
- Both submandibular and sublingual glands are also absent, and no glandular tissue could be detected in their usual anatomical positions. Ectopic glandular tissue can only be identified by isotope scanning.
- Multiple enlarged cervical lymph nodes (L.N.) are observed on both sides of the lateral neck (anterior and posterior triangles), with the largest located on the right side measuring 15 × 12 mm and on the left side measuring 16 × 10 mm; the remaining nodes are smaller in size. All lymph nodes demonstrate an anechoic texture with normal shape and preserved hilum. These findings suggest post-infectious or inflammatory cervical lymphadenopathy.
- Both thyroid gland lobes and the isthmus are normal in size, with a regular surface and normal texture. No cystic or solid masses are detected. Doppler examination shows normal blood flow. No diffuse parenchymal or focal lesions are observed.

Genetic analysis

Genetic analysis identified a heterozygous mutation in *FGFR2*:
NM_000141.5:c.1991G>A(p.Arg664Gln).
This variant is classified as *likely pathogenic* according to ACMG guidelines and has been associated with LADD syndrome [16,27].
The mutation affects the tyrosine kinase domain, impairing FGF signaling pathways essential for organ development [17]. Parental testing was negative, indicating a de novo mutation, consistent with recent studies reporting sporadic cases [27].

The treatment plan focused on preventive and minimally invasive management. Caregivers were instructed in comprehensive oral hygiene measures, including toothbrushing with a soft-bristled toothbrush and non-foaming fluoride toothpaste. Restoration of carious maxillary anterior teeth was planned using glass ionomer cement or composite resin, depending on the child's cooperation. Monitoring and possible replacement of existing stainless steel crowns were advised as the child grows and occlusion develops. Regular application of topical fluoride varnish was recommended to arrest caries progression and prevent new lesions.

To manage xerostomia, salivary substitutes and oral moisturizing gels were prescribed. The parents were advised to increase the child's water intake and to avoid sugary and acidic foods. Finally, regular dental follow-up every 3 months was scheduled for reassessment, preventive care, and early management of new lesions.

DISCUSSION

Lacrimo-auriculo-dento-digital (LADD) syndrome is a rare autosomal dominant developmental disorder caused by pathogenic variants affecting fibroblast growth factor (FGF) signaling pathways, most commonly involving *FGF10*, *FGFR3*, and less frequently *FGFR2* genes [16,17,31,32]. These genes are essential for epithelial–mesenchymal interactions during embryogenesis, particularly in the development of salivary glands, lacrimal apparatus, dentition, and distal limbs. Disruption of this signaling cascade results in the multisystem developmental abnormalities characteristic of LADD syndrome [17].

In the present case, a heterozygous missense variant in *FGFR2* (NM_000141.5:c.1991G>A; p.Arg664Gln) was identified. Although *FGFR2* is less commonly reported than *FGF10* in LADD syndrome, variants affecting FGFR signaling have been increasingly associated with overlapping phenotypes within FGFR-related developmental disorders [29,31]. The de novo origin of the mutation in this patient is consistent with recent literature reporting sporadic cases of LADD syndrome [16,27]. Taken together, the genetic finding supports the clinical diagnosis but should be interpreted as part of a broader genotype–phenotype correlation rather than a sole diagnostic determinant.

Clinically, the patient exhibited a severe multisystem phenotype involving craniofacial, auricular, digital, dental, and salivary structures. Digital anomalies, including brachydactyly, clinodactyly, and symbrachydactyly, are consistent with previously reported limb manifestations in LADD syndrome and reflect the wide phenotypic variability of FGFR-related disorders [13,18,23].

Although *FGF10* remains the most frequently implicated gene in LADD syndrome, emerging evidence suggests that *FGFR2* variants may also contribute to a broader FGFR-related developmental spectrum with overlapping phenotypes [29,31]. The identified p.Arg664Gln variant, located within the tyrosine kinase domain of *FGFR2*, is predicted to impair downstream FGF signaling, providing a plausible biological mechanism supporting its pathogenic role in the observed phenotype.

The most significant finding in this case was complete absence of all major salivary glands on ultrasonographic examination, resulting in profound congenital xerostomia. While salivary gland hypoplasia or aplasia has been reported in approximately two-

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thirds of LADD cases[19], complete agenesis of parotid, submandibular, and sublingual glands represents an exceptionally rare and severe phenotype [22,28]. Imaging-based evaluation is essential for confirming salivary gland abnormalities and contributes significantly to diagnostic accuracy [22].

Saliva plays a critical role in oral homeostasis, including lubrication, antimicrobial defense, buffering capacity, and enamel remineralization. Its absence leads to xerostomia, increased susceptibility to caries, mucosal irritation, and feeding difficulties [19–21,28]. In this patient, severe early childhood caries and mucosal dryness were direct consequences of complete salivary dysfunction. Dental anomalies such as hypodontia, enamel hypoplasia, and delayed eruption are among the most frequently reported features of LADD syndrome, occurring in up to 90% of cases [5,10,22–25.] These abnormalities may resemble other hereditary enamel defects, complicating early diagnosis [5,23]. However, in the present case, the severity and rapid progression of dental caries were significantly exacerbated by total salivary gland agenesis, demonstrating a synergistic effect between structural dental defects and functional salivary impairment.

Recent studies emphasize the importance of integrating clinical, radiological, and molecular data for accurate diagnosis of LADD syndrome due to its phenotypic overlap with other craniofacial developmental disorders [27–30]. Genetic analysis of FGFR-related pathways continues to expand the known mutation spectrum and highlights the variability of genotype–phenotype expression [29,31].

From a clinical management perspective, early recognition of severe salivary gland dysfunction is critical for preventing rapid oral deterioration. Patients with profound xerostomia require intensive preventive dental care, including frequent topical fluoride applications, strict dietary control, and use of saliva substitutes to improve oral comfort [28,30]. Remineralizing agents such as CPP-ACP may further support enamel stabilization in high-risk patients [28]. Due to the high caries risk, short recall intervals (every 2–3 months) are recommended for early detection and management of new lesions [28,30]. Minimally invasive restorative approaches should be prioritized, and advanced rehabilitation may require treatment under general anesthesia in young children with extensive disease burden [28].

This case highlights the importance of a multidisciplinary approach involving pediatric dentistry, genetics, pediatrics, and radiology in the management of LADD syndrome. Early diagnosis combined with preventive intervention is essential to reduce long-term oral morbidity and improve quality of life in affected patients.

In summary, this report expands the clinical spectrum of LADD syndrome by documenting a rare presentation with complete salivary gland agenesis and a de novo *FGFR2* variant, emphasizing both the phenotypic variability and the importance of early preventive dental management [4,5,27].

DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Conflict of Interest

The authors declare no conflict of interest.

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