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CASE BASED REVIEW
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Kohlschütter-Tönz Syndrome: A Rare Clinical Entity with Amelogenesis Imperfecta in Two Siblings, Dental Management and Scoping Review

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What is already known on this topic?

- *Kohlschütter-Tönz syndrome (KTS) is a rare autosomal recessive disorder characterized by epileptic encephalopathy, developmental delay, and amelogenesis imperfecta.*
- *Kohlschütter-Tönz syndrome is primarily associated with mutations in the ROGDI gene, affecting both neurological function and enamel development.*
- *Dental manifestations, particularly amelogenesis imperfecta, can serve as an early clinical marker for KTS, aiding in diagnosis.*

What this study adds on this topic?

- *This study presents 2 siblings with genetically confirmed KTS, highlighting the role of pediatric dentists in identifying the condition through enamel defects.*

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ABSTRACT

Kohlschütter-Tönz syndrome (KTS) (OMIM#226750) is a rare autosomal recessive disorder characterized by epileptic encephalopathy, developmental delay, and amelogenesis imperfecta. Early diagnosis and management are crucial, but the complexity of symptoms, particularly dental and neurological impairments, poses significant challenges. The aim of this report is to describe the clinical findings of 2 siblings and their dental management, whose dental examination led to genetic referral and subsequent diagnosis of KTS. Dental examinations revealed enamel defects consistent with amelogenesis imperfecta, including yellow-brown discoloration, soft enamel, and diastemas in both siblings. The younger sibling, a 9-year-old boy, exhibited early-onset seizures, intellectual disability, spasticity, and a history of kidney stones. The older sibling, a 13-year-old boy, presented with more severe neurodevelopmental delay, early-onset seizures, and drug-resistant epilepsy. Genetic testing confirmed homozygous deletions in the *ROGDI* gene, leading to the diagnosis of KTS in both siblings. The younger sibling received successful restorative treatment under general anesthesia, while the older sibling's oral care was managed conservatively due to contraindications for general anesthesia. These cases underscore the importance of pediatric dentists in the early identification of rare genetic disorders such as KTS, especially when dental anomalies like amelogenesis imperfecta are present. Timely referral for genetic evaluation can facilitate accurate diagnosis and appropriate care planning. Moreover, sharing clinical experiences and treatment outcomes contributes to a better understanding of this rare syndrome and helps guide future diagnostic and therapeutic strategies.

Keywords: Amelogenesis imperfecta, developmental delay, epilepsy, genetics, Kohlschütter-Tönz syndrome

INTRODUCTION

Kohlschütter-Tönz syndrome (KTS) is a rare autosomal recessive neurodevelopmental disorder first described in 1974 by Kohlschütter and Tönz and with only about 50 cases reported to date, highlighting its rarity.[1,2] The syndrome is primarily characterized by epileptic encephalopathy, amelogenesis imperfecta, and severe developmental delay.[3]

Kohlschütter-Tönz syndrome has been linked to pathogenic variants in the *ROGDI* gene, located on chromosome 16 (16p13.3).[4] The *ROGDI* gene encodes a protein that plays a crucial role in the regulation of exocytosis in ameloblasts and neurons, processes essential for both enamel formation and neurological function.[5] Disruption of this gene results in multisystemic manifestations affecting both the central nervous system and dental structures. Additionally,

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- *It provides detailed clinical and radiographic findings of KTS-related amelogenesis imperfecta and discusses the challenges in dental management.*
- *The study emphasizes the importance of a multidisciplinary approach in managing KTS patients, particularly regarding the risks and benefits of general anesthesia in those with drug-resistant epilepsy.*

although less commonly, pathogenic variants in the *SLC13A5* gene have also been associated with KTS.[6]

Clinically, patients with KTS exhibit a constellation of neurological symptoms that significantly impact their quality of life including infantile hypotonia, spasticity, ataxia, and nystagmus.[7] Neuroimaging often reveals cerebral anomalies such as cerebellar hypoplasia, lateral ventricle enlargement, cortical atrophy, and delayed myelination.[8] Behavioral problems and severe intellectual disability (ID) are frequent, with some patients being unable to develop speech or become bedridden early in life.[9] Epileptic seizures are a hallmark of KTS, often appearing in early childhood and proving refractory to treatment. These seizures contribute to the overall developmental delay and cognitive impairments seen in affected individuals, posing significant challenges for patient management.[10]

One of the defining features of KTS is amelogenesis imperfecta, a dental condition that severely impacts the structure and appearance of dental enamel. In KTS, amelogenesis imperfecta often manifests as yellow or brown enamel that is prone to rapid wear and decay due to the malfunctioning of ameloblasts related to *ROGDI* deficiency.[8] In KTS cases associated with *ROGDI* pathogenic variants, seizures are rarely detected in the neonatal period and may occur as late as 3 years of age, with the enamel presenting in a hypocalcified form.[6] In contrast, cases with *SLC13A5* mutations typically exhibit seizures within the first few days of life, and the enamel is characteristically hypoplastic.[11,12] Amelogenesis imperfecta affects both the primary and permanent dentition and is considered a key clinical marker for KTS diagnosis.[13] The defective enamel impairs the mechanical properties of teeth, increasing susceptibility to caries, and functional difficulties such as tooth sensitivity and wear, necessitating comprehensive dental management.[14] Patients with amelogenesis imperfecta in the context of KTS often experience difficulties in maintaining oral hygiene and performing their masticatory functions due to enamel deficiency. Moreover, dental abnormalities contribute to aesthetic concerns and reduced quality of life in affected individuals.[15,16] Furthermore, amelogenesis imperfecta in KTS serves not only as a source of clinical complications but also as a diagnostic clue that, when combined with neurological symptoms, can guide genetic testing and confirm the diagnosis.

Despite the growing genetic understanding of KTS, its oral and dental implications remain underrepresented in the literature. Particularly, there is a lack of detailed information on how dental anomalies in these patients are managed clinically. Dental practitioners may face challenges in planning individualized treatment due to the scarcity of well-documented cases outlining effective dental management in KTS patients.

Given the rarity of KTS, documentation of new cases is crucial to enhance understanding and improve diagnosis and management strategies. The objective of this study is to present 2 Turkish siblings with genetically confirmed KTS, describe their clinical and dental findings, outline the dental management strategies employed, and review the relevant literature.

CASE PRESENTATIONS

This case report was prepared following the case report guidelines (CARE). Written informed consent for publication was obtained from the patients' parents.

Sibling 1

The first patient, a 9-year-old boy, presented to the clinic with parental complaints of yellow discoloration of his teeth and difficulties in chewing. He exhibited dysmorphic facial features, including deep-set eyes, horizontal eyebrows, a short nose with a concave nasal bridge, anteverted nares, and small ears. He also presented with severe global developmental delay, early-onset and refractory seizures, spasticity, and amelogenesis imperfecta in both primary and permanent dentition.

Medical history revealed that he was born to consanguineous parents (first cousins) at 33 weeks of gestation and required a 5-day neonatal intensive care unit (NICU) stay due to respiratory distress. He has been followed by pediatric neurology due to hypotonia since he was 9 months of age. His first febrile seizure occurred at 12 months, later progressing to afebrile seizures. Two years later, the frequency of seizures decreased. During follow-up, along with impulsive and autistic behaviors, the patient was diagnosed with ID and

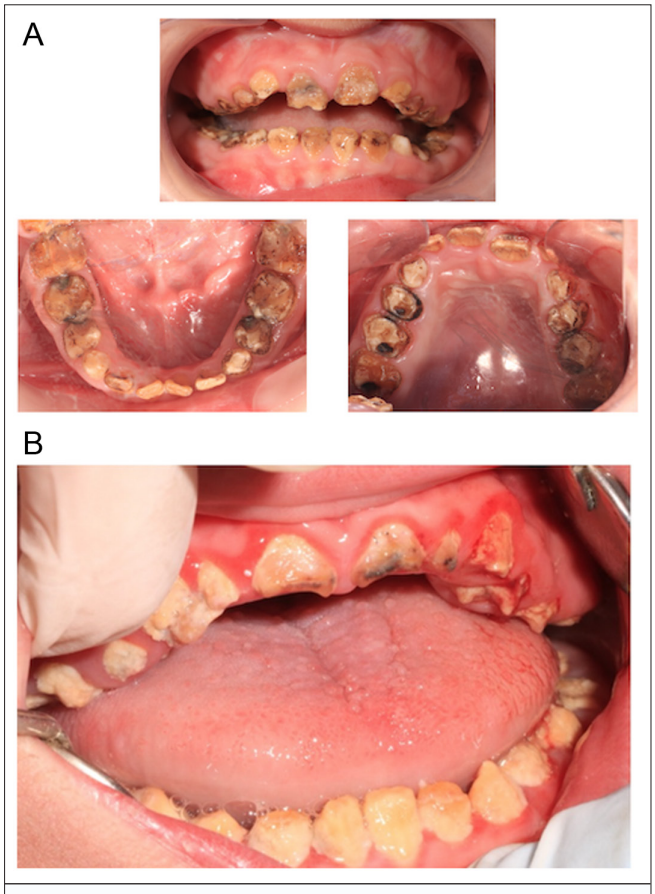


Figure 1. A. Preoperative intraoral clinical photographs of the younger sibling (9 years old) showing generalized yellow-brown discoloration, soft enamel with surface roughness, and multiple diastemas consistent with amelogenesis imperfecta (hypocalcified type, Type 3). B. Intraoral view of the older sibling (13 years old) revealing poor oral hygiene, severe enamel hypocalcification, extensive loss of tooth morphology, and generalized diastemas associated with amelogenesis imperfecta (hypocalcified type, Type 3).

attention deficit hyperactivity disorder. Motor development milestones were relatively preserved compared to cognitive and behavioral areas. The patient also has a documented history of nephrolithiasis (kidney stones). Currently, the patient is receiving special education and is under treatment with levetiracetam, phenobarbital, and risperidone. He has been seizure-free for the past year, and his electroencephalography (EEG) findings were normal. Additionally, no developmental regression has been observed during follow-up. He has no known allergies.

Intra-oral examination revealed that permanent teeth Dd 16, 26, 36, 46, 11, 12, 21, 22, 31, 32, 41, 42 were present in addition to primary teeth Dd 55, 54, 53, 63, 64, 65, 75, 74, 73, 83, 84, 85. Oral hygiene was severely compromised, with considerable plaque accumulation. The teeth exhibited a yellow-brown discoloration, generalized chipping, and soft enamel with a rough texture and substantial enamel loss. Diastemas were noted, particularly in the anterior region, contributing to the aesthetic and functional challenges. Based on clinical findings, amelogenesis imperfecta (hypocalcified type, Type 3) was diagnosed (Figure 1A).

Sibling 2

The second patient, a 13-year-old boy, and the older brother of the first patient, also presented to the clinic with his parents' complaints of severe caries, gingival bleeding, and yellow discoloration of the teeth. He was born preterm at 35 weeks and required a 20-day NICU stay. Like his sibling, he has been followed for drug-resistant epilepsy and motor-cognitive developmental delays, which are more severe in his case. He was diagnosed with autism spectrum disorder. Currently, the patient can sit unsupported but is unable to walk or communicate verbally. He does not respond to his name and avoids eye contact. His first seizure occurred at 7 months of age. Despite treatment with levetiracetam and phenobarbital, he continues to experience monthly seizures, especially during infection.

Due to the severe mental and motor impairment, comprehensive dental examination, and radiographic evaluation were not feasible. Intraoral examination revealed the presence of permanent teeth, including the following: 17, 16, 15, 14, 13, 12, 11, 27, 26, 25, 24, 23, 22, 21, 37, 36, 35, 34, 33, 32, 31, 47, 46, 45, 44, 43, and 42. Oral hygiene was markedly poor, with extensive plaque accumulation, severe gingival inflammation, and areas of spontaneous bleeding. The teeth exhibited severe yellow-brown discoloration, with enamel that was extremely soft and prone to chipping. Loss of tooth morphology was prominent, leading to masticatory dysfunction and aesthetic concern. Generalized diastemas were observed, particularly in the maxilla. Similarly, the intraoral findings of the elder sibling were consistent with amelogenesis imperfecta (hypocalcified type, Type 3) similar to his younger sibling (Figure 1B).

Genetic Analysis

Both siblings were referred for genetic consultations. The genomic DNA of both siblings was extracted from proband blood samples using the QiaAmp system (Qiagen, Hilden, Germany). Whole exome sequencing (WES) was performed with the Illumina Exome panel v1.2 (CEX) kit (Illumina, San Diego, CA, USA). All procedures for library preparation were carried out in accordance with the manufacturer's protocol, which is publicly available through Illumina's user documentation.[17] Following library preparation, sequencing was conducted using the Illumina NovaSeq 6000 platform, which enables high-throughput, high-fidelity WES.[18] Bioinformatic analysis of raw data was performed with Varsome Clinical Software (Saphetor SA, Lausanne, Switzerland) as described for Family 1 in a previous study.[19] The fraction of targets with a sequencing coverage of at least 20X was 95.3%, with an average on-target sequencing depth of 153X. Variants were filtered according to ClinVar[20] (pathogenic/likely pathogenic/conflicting interpretations of pathogenicity). Pathogenic/likely pathogenic variant classification was determined by Varsome Clinical Software,[21] Human Phenotype Ontology terms[22] associated with the clinical findings of the patients, and Genomics England Panels (Hereditary spastic paraplegia, version 1.311).[23] The variants were categorized based on the guidelines provided by the Association for Clinical Genomic Science (ACGS)[24] and Clinical Genome Resource (ClinGen).[25] Deletion/duplication analysis was performed using the Varsome Clinical software copy number variation (CNV) caller tool. Copy number variation interpretation was based on guidelines published by

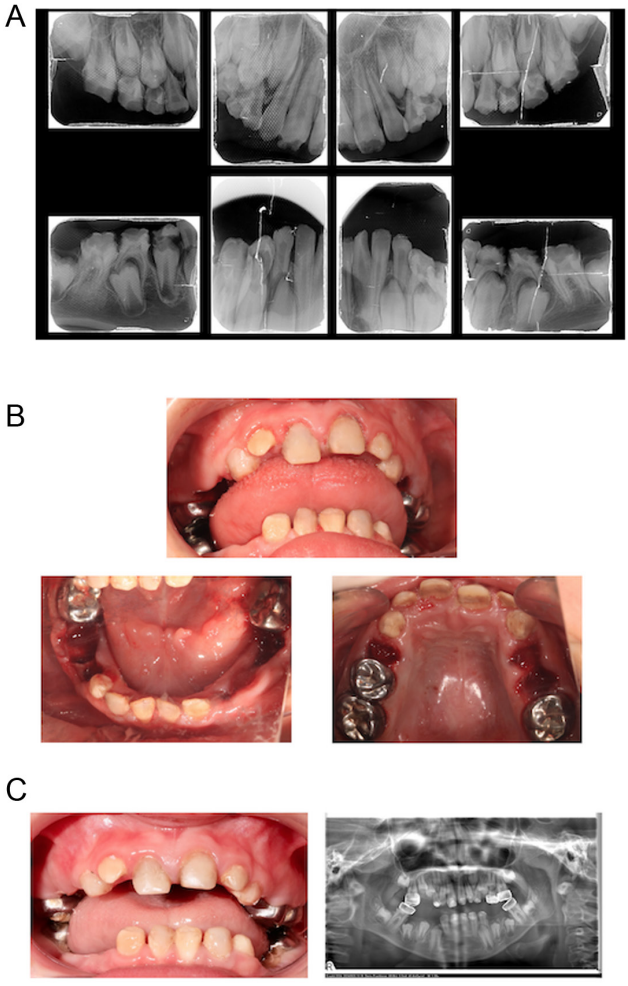


Figure 2. A. Full-mouth intraoral radiographic series obtained under general anesthesia from the younger sibling (9 years old). The radiographs demonstrate thin enamel layers, reduced radiopacity between enamel and dentin, and enlarged pulp chambers, all consistent with amelogenesis imperfecta. B. Immediate postoperative intraoral photographs of the younger sibling (9 years old) following restorative treatment under general anesthesia, including stainless steel crowns on molars and composite restorations on anterior teeth to restore function and improve esthetics. C. Follow-up intraoral photographs and panoramic radiograph obtained 1 month postoperatively in the younger sibling (9 years old), showing stable restorations and improved oral hygiene.

the American College of Medical Genetics and Genomics and ClinGen.[26]

Genetic analysis of both siblings revealed a homozygous pathogenic deletion of approximately 5.1 kb in the 16p13.3 region, encompassing the *ROGDI* gene on chromosome 16.

Dental Management

Sibling 1

Dental treatments for the child were attempted in the pediatric dentistry clinic across multiple appointments by an experienced pediatric dentist without the use of general anesthesia or sedation; however, adequate cooperation could not be established. The behavioral assessment was noted as Frankl score 1. After several unsuccessful attempts, comprehensive oral rehabilitation under general anesthesia was recommended. Consultations were obtained from both the patient's developmental pediatrician and pediatric neurologist. Their evaluations advised implementing all standard precautions necessary for treating a patient with comorbid epilepsy. General anesthesia was scheduled on 3 separate occasions but had to be postponed due to recurrent infections.

A full-mouth radiographic series, obtained during the oral rehabilitation appointment under general anesthesia, revealed no congenitally missing teeth and demonstrated a thin enamel layer with radiopacity lower than that of dentin (Figure 2A). The patient exhibited severe Class 2 malocclusion, an anterior open bite exceeding 6 mm, and an overjet of 3 mm. The restorative and surgical treatment plan included: composite restorations of permanent teeth Dd 11, 21, 22, 31, 32, 41, 42, and primary teeth Dd 53, 63, 73; stainless steel crown placement on permanent teeth Dd 16, 26, 36, 46 and primary tooth 65; and extractions of primary teeth Dd 55, 54, 64, 65, 75, 74, 73, 83, 84, and 85 (Figure 2B). The patient responded well to the treatment administered under general anesthesia. Postoperative analgesia was provided with paracetamol (acetaminophen) at 10 mg/kg. The anesthesia procedure was uneventful, and following spontaneous ventilation, smooth extubation was achieved. No complications related to anesthesia were observed, and there were no seizures in the postoperative period. The patient was discharged home after 6 hours.

The patient was followed both clinically and radiographically at 1 week and 1 month (Figure 2C). No functional or esthetic complications were observed, and the treatment outcome was deemed successful. The parents reported high satisfaction with the treatment and noted improvements in the child's nutrition and appetite.

Sibling 2

In light of the patient's persistent and pharmacoresistant epileptic seizures, the anesthesiology specialist and pediatric neurologist recommended that any surgical procedures be conducted at a medical facility equipped with an intensive care unit. He experienced seizures 2 to 3 times a month.

The patient's teeth were gently cleaned and polished under clinical conditions. Additionally, minimal abrasion was performed to blunt the sharp incisal and occlusal edges, thereby preventing injury to soft tissues such as the tongue and lips. Nutritional counseling and individualized oral hygiene instructions were provided to the parents, taking into account the patient's specific medical and developmental needs.

DISCUSSION

Since its first description in 1974, KTS presents a complex clinical status that requires a multidisciplinary approach for effective management.[8] Epileptic seizures are a hallmark of KTS, often appearing in early childhood and frequently resistant to treatment.[3] In this study, both siblings experienced early-onset seizures, consistent with the neurological profile of the syndrome. Sibling 1 also presented with a history of kidney stones. Although nephrocalcinosis has been associated with certain

enamel-renal syndromes (OMIM #204690), this finding is rare in KTS.[27] To the best of the authors' knowledge, only 1 previous case of nephrocalcinosis in a patient with KTS has been documented.[8] To investigate the etiology of nephrolithiasis in both siblings, WES was performed. However, no pathogenic variants were detected in known nephrolithiasis-related genes, suggesting that renal involvement in KTS may occur independently of known monogenic pathways and warrants further investigation.

Diagnostic challenges remain significant in KTS. While mutations in the ROGDI gene have recently been identified as causative in some families, molecular confirmation is still lacking in many reported cases. Additionally, there are no known biochemical or radiological markers that facilitate early or differential diagnosis, as emphasized by Schossig et al[9] in 2012. This highlights the need for increased clinical awareness, especially among dental professionals, as dental anomalies such as amelogenesis imperfecta may be the first identifiable sign prompting further genetic evaluation.

Currently, no standardized protocols exist for the dental management of pediatric patients with KTS or similar neurodevelopmental disabilities.[13,28] Individuals with KTS face numerous barriers in accessing dental care, including limited cooperation due to ID, the complexity of medical comorbidities, and a general lack of provider familiarity with rare syndromes.[29,30] This case underlines these challenges, especially in the management of Sibling 2, for whom outpatient treatment attempts failed due to insufficient cooperation. Ultimately, a conservative approach involving nutritional counseling and caregiver-delivered oral hygiene support was opted for after general anesthesia was deemed too risky due to the patient's active seizure status and lack of intensive care availability.

For Sibling 1, the use of stainless steel crowns was justified by both the patient's poor oral hygiene and the structural weakness of hypomineralized enamel. This treatment approach is consistent with that of Kulkarni et al,[13] who reported comprehensive dental rehabilitation under general anesthesia in a child with KTS. Although more than 50 individuals with KTS have been described in the literature,[31] detailed accounts of dental management are exceedingly rare. Apart from the current case, only the report by Kulkarni et al[13] provides full-mouth rehabilitation with documented outcomes. Other publications[32,33] describe amelogenesis imperfecta as a diagnostic clue but offer little to no information on treatment beyond extractions or procedures under sedation. The decision to use stainless steel crowns for Sibling 1 was based on the compromised state of oral hygiene and the structurally weak dentition. This aggressive restorative approach was necessary given the challenges in maintaining oral hygiene in KTS patients. Additionally, composite restorations for anterior teeth were selected because the patient was unable to verbally express pain or sensitivity due to enamel defects. These restorative measures aim to protect the remaining dentition and enhance oral function while considering the patient's medical limitations. Although many studies[34,35] have reported that stainless steel crowns are a good option in the dental management of patients with amelogenesis imperfecta, to the best of the authors' knowledge, there is only 1 case report in the literature detailing dental rehabilitation in a child with KTS. Similar to this case, stainless steel crowns were used to rehabilitate the molars and premolars in a KTS patient.[13]

These observations emphasize a significant gap in the current literature regarding evidence-based dental management strategies for KTS. Given the variability in neurological severity and patient cooperation levels among individuals with KTS (as highlighted by Haberlandt et al[32]), the development of personalized treatment plans is essential. While general anesthesia may be a feasible option in certain cases, others may require more conservative, home-based care coordinated by caregivers and supported by dental teams experienced in treating patients with special healthcare needs.

Ethical considerations are also central to treatment planning, especially in patients with poor long-term prognosis and limited ability to communicate pain or discomfort. This experience shows that collaboration among pediatric dentists, neurologists, anesthesiologists, and caregivers is indispensable for safe and effective treatment planning. In Sibling 1, general anesthesia was safely used following multidisciplinary consultation, while in Sibling 2, the same strategy was deemed contraindicated, requiring an alternative care plan.

In conclusion, KTS presents unique challenges in dental management due to the interplay of neurological impairments and amelogenesis imperfecta. This report underscores the critical role pediatric dentists play in recognizing rare genetic syndromes, where dental findings such as amelogenesis imperfecta may guide diagnosis and multidisciplinary referral. Future reports should aim to document detailed treatment protocols and long-term dental outcomes, as current data are scarce. More comprehensive reporting will enhance clinical decision-making, strengthen interdisciplinary care, and ultimately improve the quality of life for individuals living with this rare syndrome.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patients' parents who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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