Contemporary Pediatric Dentistry

Case Report
Contemp Pediatr Dent 2024:5(2):105-112
DOI: 10.51463/cpd.2024.20

Pediatric dentistry approach in a child with Aicardi-Goutières Syndrome type 2: A case report and literature review

Melis Arda Sözüöz[1] ✉, Ezgi Aydın Varol[2], Merve Aksoy[3]

Highlights

- Aicardi-Goutières Syndrome is a rare congenital disorder with limited documentation on dental management strategies for pediatric patients.
- This case report is the first to document delayed primary teeth eruption in Aicardi-Goutières Syndrome Type 2.
- Pediatric dentists should monitor patients with Aicardi-Goutières Syndrome for early caries and guide parents on oral hygiene to support healthy dental development.

[1] DDS PhD, Health Sciences University, Gulhane Faculty of Dentistry, Department of Pediatric Dentistry, Ankara, Türkiye
[2] DDS PhD, Health Sciences University, Gulhane Faculty of Dentistry, Department of Pediatric Dentistry, Ankara, Türkiye
[3] Assoc. Prof. Dr, Health Sciences University, Gulhane Faculty of Dentistry, Department of Pediatric Dentistry, Ankara, Türkiye

Correspondence:
Department of Pediatric Dentistry, Gulhane Faculty of Dentistry, University of Health Sciences, Türkiye
E-mail address: melisarda7@gmail.com

Abstract

Aicardi-Goutières Syndrome is a rare autosomal recessive disorder characterized by a triad of partial or complete agenesis of the corpus callosum, infantile spasms, and chorioretinal lacunae. The condition predominantly affects females, as males often do not survive the embryonic period. Intellectual disability associated with the syndrome ranges from mild to moderate. There is limited information in the literature regarding the oral manifestations of this syndrome. This case report aims to provide insights into the development of primary dentition in patients with Aicardi-Goutières Syndrome and to raise awareness about the oral and dental health needs of these rare pediatric patients, particularly during early childhood. In this case report, it was observed that the primary teeth of a 2-year-5-month-old patient had not yet erupted. Notably, even at 3 years and 1 month old, the patient's primary dentition remained incomplete despite continued monitoring during follow-up examinations. These patients often have limited ability to cooperate with dental treatments due to their intellectual disability, which complicates the process. Furthermore, due to the respiratory risks associated with the syndrome, dental treatments under general anesthesia are generally not preferred. In this context, maintaining the oral health of these patients and implementing preventive strategies, including topical fluoridation, along with appropriate oral hygiene instructions and dietary modifications, are crucial in managing patients with Aicardi-Goutières Syndrome. Pediatric dentists are responsible for educating families on these matters, and caregivers play a vital role in maintaining the oral health of these patients by collaborating closely with dental specialists.

Keywords: Aicardi Syndrome; Preventive Dentistry; Tooth Eruption

Received: 13 Jun 2024
Accepted: 18 Aug 2024
Online First: 21 Aug 2024

Copyright © 2024 Contemporary Pediatric Dentistry. This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license. (CC BY-NC-ND 4.0)

INTRODUCTION

Aicardi-Goutières Syndrome is an X-linked autosomal recessive neurodegenerative disease first described in 1984. Although the exact gene responsible for the disease remains unidentified, it is not inherited in a traditional manner, as almost all cases result from new gene mutations (de novo mutations).[1-4] This syndrome is encountered in approximately 1 in 100,000 to 150,000 live births and predominantly affects females, as the disease typically causes embryonic lethality in males.[5]

The diagnosis of Aicardi-Goutières Syndrome is based on clinical and radiological findings. The classical triad associated with the syndrome includes partial or total agenesis of the corpus callosum, infantile spasms, and chorioretinal lacunae.[2] In addition to this classical triad, diagnostic criteria for major and supporting findings have also been established (Table 1).[1] Infantile spasms, the most characteristic seizure type, usually begin around the third month of life and are often the first symptoms prompting clinicians to recommend further investigation.[2,6]

Although oral findings in Aicardi-Goutières Syndrome are limited, reported case studies indicate an increase in gingival inflammation and the prevalence of early childhood caries, likely due to patients' dietary habits, medications, and inadequate oral hygiene.[4,7]

Type I interferons play a significant role in the pathogenesis of Aicardi-Goutières Syndrome, with their expression upregulated, leading to increased production.[8] Consequently, one of the classic laboratory findings in these patients is elevated interferon alpha levels in the cerebrospinal fluid, pleocytosis, and similarly elevated levels of neopterin and biopterin.

The potential utility of assessing the expression levels of interferon-stimulated genes in peripheral blood as a diagnostic marker is currently under investigation, as there is evidence that these levels remain elevated beyond the encephalopathic phase, a phenomenon referred to as the "interferon signature."[8-10] Another key diagnostic feature is the detection of neuroimaging abnormalities, such as calcifications in the basal ganglia and changes in the white matter.

To date, mutations in seven genes have been identified that can lead to the upregulation of the interferon signaling pathway: *ADAR, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, TREX1,* and *IFIH1*. Heterozygous mutations have been identified in the *TREX1, ADAR,* and *IFIH1* genes, while all other reported mutations are homozygous.[11] Mutations in the *IFIH1* gene were identified in 2014[12] and are the least common pathogenic variants, whereas mutations in the *RNASEH2B* and *TREX1* genes account for the highest proportion of diagnosed Aicardi-Goutières Syndrome cases.

Homozygous mutations in the *RNASEH2B* gene, one of the most frequent variants associated with Aicardi-Goutières Syndrome, typically result in a phenotypic expression that closely aligns with the syndrome's classic presentation.[12]

While previous studies in the literature have outlined dental treatment strategies for patients with Aicardi-Goutières Syndrome, we found no reports specifically highlighting delayed tooth eruption in pediatric patients with this condition. Accordingly, the aims of this case report and literature review are (1) to provide general information about Aicardi-Goutières Syndrome to dental healthcare professionals and (2) to guide oral and dental health procedures for children with this syndrome.

Copyright © 2024 Contemporary Pediatric Dentistry

Table 1. Criteria for the Diagnosis of Aicardi Syndrome [1]

Classic Triad
Agenesis of the corpus callosum (may be partial)
Chorioretinal lacunae
Infantile spasms
Major Features
Cortical malformations (mostly microgyria)
Cysts around the 3d ventricle and/or choroid plexuses
Periventricular and subcortical heterotopia
Papillomas of choroid plexuses
Optic disc/nerve coloboma
Supporting Features
Vertebral and costal abnormalities
'Split-brain' EEG (dissociated suppression-burst tracing)
Microphthalmia and/or other eye abnormalities
Gross hemispheric asymmetry

CASE REPORT

Based on the medical history obtained from the family of a 2-year-old girl diagnosed with Aicardi-Goutières Syndrome Type 2 (OMIM #610181), it was determined that the mother conceived at an advanced age, underwent a monitored pregnancy, and delivered at 38 weeks gestation and the parents were seen to be related within the third degree of consanguinity. It is known that there is no inherited metabolic disease in the family. The patient has been exhibiting frequent fevers and failure to thrive since birth. During a previous physical examination, the patient's head circumference was measured at 37 cm, consistent with microcephaly. Deep tendon reflexes were noted to be more pronounced or increased compared to normal. The patient exhibited poor head control, hypotonia, lack of eye contact and object tracking, congenital glaucoma, facial dysmorphic features, spasticity throughout the body, and a simian crease on the hands (Figure 1).

Brain MRI revealed hypoplasia of the brainstem and inferior vermis, increased distance in the retrocerebellar cerebrospinal fluid space, decreased white matter at the level of the centrum semiovale, and increased signal intensity in the remaining portion. Other findings included corpus callosum atrophy and atrophy of the cortical sulci in the hemispheres. Genetic analysis conducted on the patient at 1 year of age at the Medical Genetics Clinic of Gülhane Training and Research Hospital, University of Health Sciences, confirmed a diagnosis of Aicardi-Goutières Syndrome Type 2 with a homozygous autosomal recessive c.511G>T variant (Table 2).

Figure 1. Typical appearance of Aicardi-Goutières Syndrome

Copyright © 2024 Contemporary Pediatric Dentistry

Table 2. Genetic analysis result of the patient

Gene/ Transcript	Exon	Variant	Variant Type	Zygosity	Classification	Diseases	Inheritance
RNASEH2B NM_024570.4	Exon 7	c.511G>T (p.V171F)	Splicing	Homozygous	Likely Pathogenic	Aicardi-Goutières Syndrome Type 2	Autosomal Recessive

The patient, a 2-year-5-month-old female, was brought by her guardian to the University of Health Sciences, Gulhane Faculty of Dentistry, on 17 January 2022, with the chief complaint of delayed tooth eruption. According to the medical history provided by the guardian, the patient, diagnosed with Aicardi-Goutières Syndrome, was prescribed Baclofen (Lioresal, Novartis, Basel, Switzerland) and Levetiracetam (Keppra, London, England) for the management of infantile spasms. Clinical examination revealed developmental delay and severe mental retardation. The patient was unable to hold her head up independently and required support to sit (Figure 1). Intraoral examination showed that none of the primary teeth had erupted. Due to the patient's age and limited cooperation, periapical or panoramic radiographs could not be obtained. Oral hygiene and dietary recommendations were provided to the patient's parents, and a follow-up appointment was scheduled for 6 months later.

At the 6-month follow-up (2 years 11 months), the parents reported a white lesion on the underside of the patient's tongue. Intraoral examination revealed the eruption of teeth 51, 61, 71, and 81 according to the FDI World Dental Federation notation system.[13] Trauma from the lingually erupted tooth 71 had led to the development of Riga-Fede disease. Occlusal adjustment of tooth 71 was performed, and fluoride varnish (Polimo, Imicryl, Konya, Türkiye) was applied. A subsequent follow-up session was planned for 3 months later.

At the next follow-up appointment (3 years 2 months), intraoral examination revealed the eruption of teeth 54, 55, 64, 74, 84, and 85. The erupted teeth were noted to be covered with dental plaque, likely due to a lack of mastication and increased intake of sweetened liquids. Complete healing was observed on the underside of the tongue, which had previously been affected by Riga-Fede disease. Oral hygiene instructions were reiterated, emphasizing the need for improved oral hygiene practices. Intraoral photographs and periapical radiographs were obtained according to the patient's level of compliance (Figures 2 and 3).

Figure 2. Intraoral photographs of the patient during the last follow-up session (3 years 2 months)

Copyright © 2024 Contemporary Pediatric Dentistry

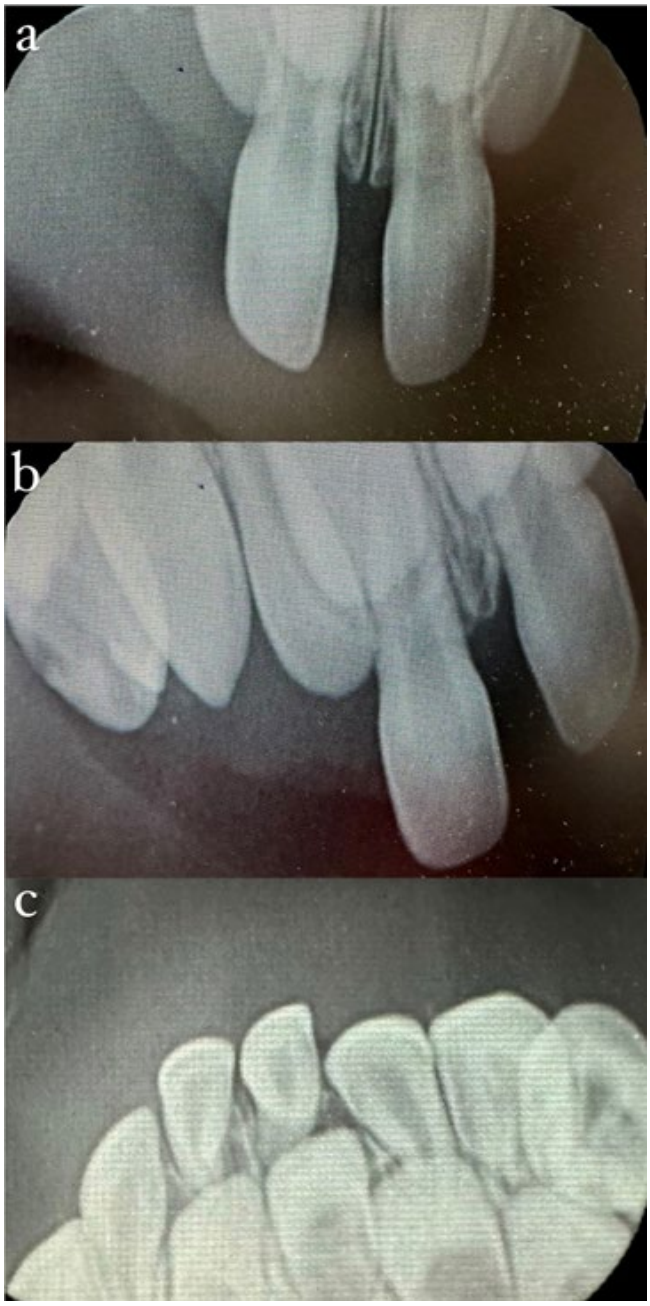

Figure 3. Periapical radiographs taken from the patient: a) Periapical radiograph of teeth 51-61; b) Periapical radiograph showing the presence of teeth 52-53; c) Periapical radiograph of the patient's anterior mandible

DISCUSSION

Aicardi-Goutières Syndrome is extremely rare, with an estimated prevalence of 1 to 5 cases per 10,000 live births.[14,15] Aicardi-Goutières Syndrome manifest in two forms: early-onsets: early-onset and late-onset. Diagnosis is based on typical clinical findings, characteristic abnormalities on cranial CT (calcifications of the basal ganglia and white matter), MRI (leukodystrophic changes), or the identification of mutations in one of seven genes (*ADAR, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, TREX1, IFIH1*).[16,17] In the present case, homozygous mutations in the *RNASEH2B* gene, one of the most frequent variants associated with Aicardi-Goutières Syndrome, closely aligned with the classic triad of the syndrome.[12] The c.511G>T variant detected in the *RNASEH2B* gene has not been previously reported in various databases containing information on the frequency and clinical significance of genetic variants, such as dbSNP, gnomAD, ExAC, 1000G, and CLINVAR, suggesting it is likely a rare and novel mutation. Furthermore, based on a review of the literature, this is the first case report detailing the oral manifestations associated with delayed tooth eruption in a child with Aicardi-Goutières Syndrome Type 2.

Aicardi-Goutières Syndrome is a rare genetic disorder characterized by varying degrees of developmental delay and mental retardation.[18,19] Behavioral management of these patients is challenging due to their lack of cooperation. Dental treatments under general anesthesia are not recommended, given the risks associated with respiratory management and the potential for epileptic seizures.[20] These patients are often fed with liquids for prolonged periods, and factors such as hypotonia of the masticatory muscles, poor oral hygiene, and the effects of medication further compromise oral and dental health. The primary goal in managing the dental care of these patients should be the prevention of oral and dental diseases through routine intraoral examinations during early childhood and by raising parental awareness about oral health through appropriate oral health instructions.

Copyright © 2024 Contemporary Pediatric Dentistry

Iwamoto et al.[21] reported a syndromic infant patient with cleft lip and palate, providing information on dental treatment approaches in this context. Another case report[4] described a 4-year-old patient with Aicardi-Goutières Syndrome who presented with acute dental pain. Intraoral examination revealed that the primary dentition was complete, but early childhood caries were observed, likely due to poor nutrition and inadequate oral hygiene. It was also noted that children with this syndrome may experience gingival inflammation, possibly as a result of medications used to manage seizures. Pathak et al.[7] documented a 3-year-old patient with Aicardi-Goutières Syndrome Type 3 who had been suffering from painful oral ulcers for over two months. Intraoral examination revealed complete primary dentition but severe early childhood caries. Literature reviews indicate that oral findings in children with Aicardi-Goutières Syndrome are limited. In these patients, it is believed that the prevalence of gingival inflammation and dental caries is increased due to the consumption of soft and liquid foods, inadequate oral hygiene habits, and the effects of medications used for seizure control. However, the recent case report differs from previous studies by offering an opportunity to evaluate the development of primary dentition in early childhood.

The eruption of primary teeth typically starts between 4 to 10 months of age. This process progresses with the appearance of approximately one new tooth each month, culminating in the near completion of all 20 deciduous teeth by the time a child is around 30 months old.[22] However, in the present case, none of the primary teeth were detected in the oral cavity at the first examination of the patient, who was 2 years and 5 months old. Although this phenomenon has not been previously reported in the literature, the delay in primary tooth eruption may be related to the developmental deficiencies observed in these syndromic patients. This paper is the first to report delayed primary tooth eruption in patients with Aicardi-Goutières Syndrome, thereby highlighting an additional aspect of the oral findings associated with this syndrome.

CONCLUSIONS

Pediatric dentists frequently encounter children who require special healthcare. The most crucial step in managing these patients is educating their guardians on oral and dental health. Ensuring the continuity of oral and dental health necessitates early and regular dental check-ups, along with strict adherence by the guardian to the dentist's oral hygiene instructions. In the present case, due to the patient's early admission, our primary goal has been to maintain oral and dental health from the moment the primary teeth erupted. The guardian has been instructed on plaque removal, which is essential due to the patient's consistent consumption of soft foods, and routine fluoride applications are repeated at each check-up session. The patient continues to attend follow-up appointments every three months. In conclusion, it is essential to recognize that pediatric dentists play a significant role in maintaining overall health in patients who require special healthcare.

REFERENCES

1. Aicardi J. Aicardi syndrome: Old and new findings. Int Pediatr 1999;14:5-8

2. Aicardi J. Aicardi syndrome. Brain Dev 2005;27:164-171

3. Fischbach M. Rare genetic diseases - New opportunities and challenges through biotechnological progress and scientific knowledge. Eur J Paediatr Neurol 2002;6(Suppl A):71-75

4. Guadagni MG, Faggella A, Piana G. Aicardi syndrome : a case report. Eur J Paediatr Dent 2010:146-148

Copyright © 2024 Contemporary Pediatric Dentistry

5. Aicardi J, Lefebvre J, Lerique-Koechlin A. A new syndrome: spasm in flexion, callosal agenesis, ocular abnormalities. Electroencephalogr Clin Neurophysiol 1965;19: 609-610

6. Prats Viñas JM, Martinez Gonzalez MJ, Garcia Ribes A, Martinez Gonzalez S, Martinez Fernandez R. Callosal agenesis, chorioretinal lacunae, absence of infantile spasms, and normal development: Aicardi syndrome without epilepsy? Dev Med Child Neurol 2005;47:419-420

7. Pathak PD, Shah PP, Lkade LS, Shinde MU. Full Mouth Rehabilitation of a Child with Aicardia-Goutières: A Rare Syndrome. J Clin Diagn Res 2023;17: 19-21

8. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. Nat Rev Immunol 2015;15:429-440

9. Al Mutairi F, Alfadhel M, Nashabat M, El-Hattab AW, Ben-Omran T, Hertecant J et al. Phenotypic and Molecular Spectrum of Aicardi-Goutières Syndrome: A Study of 24 Patients. Pediatr Neurol 2018;78:35-40

10. Takeichi T, Katayama C, Tanaka T, Okuno Y, Murakami N, Kono M et al. A novel IFIH1 mutation in the pincer domain underlies the clinical features of both Aicardi-Goutières and Singleton-Merten syndromes in a single patient. Br J Dermatol 2018;178:111-113

11. Livingston JH, Crow YJ. Neurologic Phenotypes Associated with Mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, and IFIH1: Aicardi-Goutières Syndrome and Beyond. Neuropediatrics 2016;47:355-360

12. Florido-Rodriguez A, Eiris-Punal J, Barros-Angueira F, Toledo-Bravo de Laguna L, Santana-Artiles A, Sebastian-Garcia I et al. Sindrome de Aicardi-Goutieres por mutacion en el gen IFIH1 con afectacion pontina. A proposito de un caso [Aicardi-Goutieres syndrome due to mutation of the IFIH1 gene with pontine involvement. A case report]. Rev Neurol 2016;63:309-314

13. ISO 3950:2016 Dentistry: Designation system for teeth and areas of the oral cavity. [Internet] 2020 [cited 2024 Aug 1]. Available from: https://www.fdiworldental.org/

14. Piccoli C, Bronner N, Gavazzi F, Dubbs H, De Simone M, De Giorgis V et al. Late-Onset Aicardi-Goutières Syndrome: A Characterization of Presenting Clinical Features. Pediatr Neurol 2021;115:1-6

15. Viguera-Elías D, de la Iglesia-Nagore I, Toledo-Gotor C, Domínguez-Garrido E, Poch-Olivé ML. Síndrome de Aicardi-Goutières: un caso familiar por alteración del gen RNASEH2B [Aicardi-Goutieres syndrome: a family case due to alteration of the RNASEH2B gene]. Rev Neurol 2021;72:407-409

16. Rice GI, Forte GM, Szynkiewicz M, Chase DS, Aeby A, Abdel-Hamid MS et al. Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: A case-control study. Lancet Neurol 2013;12:1159-1169

17. Wu D, Fang L, Huang T, Ying S. Case Report: Aicardi-Goutières Syndrome Caused by Novel TREX1 Variants. Front Pediatr 2021;28;9:634281

18. Rosser TL, Acosta MT, Packer RJ. Aicardi syndrome: spectrum of disease and long- term prognosis in 77 females. Pediatr Neurol 2002;27:343–346

19. Grosso S, Lasorellab G, Russo A, Galluzzi P, Morgese G, Balestri P. Aicardi syndrome with favorable outcome: case report and review. Brain Dev 2007;29:443-446

20. Lacobucci T, Galeone M, de Francisci G. Anaesthesia management in a patient with Aicardi's Syndrome. Anaesthesia 2003;58:95-95

21. Iwamoto T, Fukumoto S, Yamada A. Presurgical treatment of cleft lip and palate in Aicardi syndrome : A case report. Pediatr Dent J 2008;18:204-209

22. Baykan Z, Sahin F, Beyazova U, Ozçakar B, Baykan A. Experience of Turkish parents about their infants'teething. Child Care Health Dev 2004;30:331-336

Copyright © 2024 Contemporary Pediatric Dentistry

How to cite this article:
Melis Arda Sözüöz, Ezgi Aydın Varol, Merve Aksoy. Pediatric dentistry approach in a child with Aicardi-Goutières Syndrome type 2: A case report and literature review. Contemp Pediatr Dent 2024:5(2):105-112.

Declarations

Acknowledgements: *Authors kindly thank to Res.Assist. Barış Sözüöz and Res.Assist. İrem Atay for their helps in the treatment sessions of this patient.*

Conflict of Interest Statement: A*uthors disclose no potential conflicts of interest.*

Ethics Statement: *This case report has been prepared in accordance with Helsinki Declaration with all amendments.*

Informed Consent: *Written informed consent was obtained from parents.*

Author contributions: *Conception and design: All Authors; Acquisition of data: MAS; Interpretation of data: MA; Drafting article: EAV; Revision artice: All Authors; Final approval: All Authors.*

Funding: *Not applicable.*

Data Availability: *The data used to support the findings of this study can be made available upon request to the corresponding author.*

Peer-review: *Externally double-blinded peer-reviewed.*

Copyright © 2024 Contemporary Pediatric Dentistry