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CASE REPORT

Hercílio Martelli-Júnior[1,2]
Hélen Kaline Farias Bezerra[3]*
Anna Luiza Braga Albuquerque[4]
Rodrigo Rezende Arantes[5]
Marcelo Augusto de Oliveira Sales[6]
Felipe Paiva Fonseca[7]
Renato Assis Machado[3]
Ana Cristina Simões e Silva[4]

Dental anomalies in a patient with Tyrosinemia type I: first case report in the literature

Abstract:

This clinical report describes a 13-year-old female with a complex medical history and multisystemic symptoms, including lower-extremity deformities, hypercalciuria, low body mass, short stature, abdominal pain, seizures, and hypertension. Despite an initial clinical diagnosis of nonspecific renal tubular acidosis, further investigation revealed a likely pathogenic homozygous variant in the *FAH* gene, indicating the diagnosis of tyrosinemia type I (HT1). During the investigation, several dental anomalies were detected in this patient (tooth decay, delayed eruption, hypoplastic enamel, and changes in tooth shape). The patient has been receiving dietary adaptations and electrolyte and alkaline solutions supplementation and is under close medical and dental follow-up care. The aim of this report is to highlight the importance of a thorough investigation and genetic testing in patients with multisystemic symptoms and the possibility of oral manifestations and dental anomalies in association with renal tubular disorders, including Tyrosinemia type I.

Keywords: Tyrosinemia; Fanconi Syndrome; Hydrolases; Tooth Abnormalities.

INTRODUCTION

Hereditary Tyrosinemia type I (HT1; OMIM 276700) is the most severe inborn error of metabolism (IEM) involving the tyrosine catabolic pathway. HT1 is an autosomal recessive disease caused by loss-of-function mutations on the *FAH* gene, which is located on the long arm of chromosome 15 at position 25.1[1]. This gene encodes the enzyme fumarylacetoacetate hydrolase (FAH), which catalyzes the last step of tyrosine degradation. FAH converts 4-fumarylacetoacetate (FAA) into two substrates: fumarate, which proceeds towards the tricarboxylic acid cycle, and acetoacetate that is directed to cholesterol biosynthesis or ketogenesis.

Statement of Clinical Significance
This case underscores the importance of thorough investigation and genetic testing in patients with multisystemic symptoms, including oral manifestations, emphasizing the role of the dentist in the early detection of systemic conditions presenting oral manifestations such as tyrosinemia type I.

Although deficiencies in four out of the five enzymes involved in this pathway have been associated to IEMs due to accumulation of their respective upstream metabolites and tyrosine, HT1 has a particularly detrimental phenotype due to buildup of FAA, resulting in DNA repair impairment, oxidative damage,

[1]State University of Montes Claros, Oral Pathology and Oral Medicine, School of Dentistry – Montes Claros (MG), Brazil.
[2]Prof. Edson Antônio Velano University, Craniofacial Anomalies Rehabilitation Center (Pró-Sorriso Center) – Alfenas (MG), Brazil.
[3]University of Campinas, Piracicaba Dental School, Department of Oral Diagnosis – Piracicaba (SP), Brazil.
[4]Federal University of Minas Gerais, Faculty of Medicine, Pediatric Nephrology Unit – Belo Horizonte (MG), Brazil.
[5]Hospital of Clinics, Service of Pediatric Genetics – Belo Horizonte (MG), Brazil.
[6]Federal University of Paraíba, Department of Clinical and Social Dentistry – João Pessoa (PB), Brazil.
[7]Federal University of Minas Gerais, School of Dentistry, Departament of Oral Surgery and Pathology – Belo Horizonte (MG), Brazil.
***Corresponding author:** Email: helenkalinefb@gmail.com
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and increased mutagenic potential in cells[2]. There is a hypothesis that FAA might participate in liver damage and carcinogenesis[3]. Furthermore, excessive levels of FAA are shunted towards the production of succinylacetone (SA), a heme synthesis inhibitor that impairs mitochondrial function and disrupts renal tubular function, thus inducing a phenotype similar to the human Toni-Debré-Fanconi syndrome (FS) in murine models[4].

The characteristic findings of HT1 are involved in progressive liver damage with high incidence of hepatocellular carcinoma (HCC) and renal tubular dysfunction culminating into hypophosphatemic rickets[5,6]. Considering the three subtypes of the disease[7], the acute and subacute forms exhibit absent or nearly absent FAH activity before 2 and 6 months of age, respectively, and these forms are often lethal due to severe hypoglycemia, coagulopathy, and liver failure. In the chronic form, residual FAH activity results in an insidious onset and patients seldom present to medical care due to consequences of impaired renal tubular resorptive function. The kidney damage typically manifests as FS, a condition characterized by extensive loss of resorptive capacity in the proximal convoluted tubule, resulting in generalized aminoaciduria, hyperphosphaturia, glycosuria, renal tubular acidosis (RTA), among other electrolyte imbalances. The patients can also present severe growth retardation and vitamin D-resistant rickets due to phosphate wasting[8]. Children with the chronic form of HT1 have cirrhosis, neuropathic pain, muscle weakness, hypertension and frequently die from HCC or porphyria in the form of neurologic crises[9,10]. However, dental alterations were not previously reported in HT1.

The aim of this report is to highlight the importance of a thorough investigation and genetic testing in patients with multisystemic symptoms of HT1 and to report, for the first time, the occurrence of oral manifestations and dental anomalies in this disease. This report may help further studies to investigate these abnormalities and genetic mechanisms.

CASE REPORT

A 13 years-old female feoderm patient presented for diagnosis of unspecific symptoms. She is the biological daughter of a 3rd degree consanguineous couple, but was adopted at 5 months of age, and there is no known family medical history. Pathologic symptoms start at 2 years old, including lower-extremity deformities, hypercalciuria, low body mass, and short stature (Figure 1A). Later, she exhibited abdominal pain, seizures, and hypertension (with a systolic pressure of 200 mmHg). At first glance, she was diagnosed with nonspecific RTA on potassium replacement and hydrochlorothiazide therapy was started.

At the time of 11 years of age, she had another hypertensive crisis, marked by seizures, fever, and upper-extremity paresthesia. Her blood tests showed transient elevations in troponin I, amylase (518 U/L), and lipase (1963 U/L), as well as abnormal blood coagulation tests. Her renal ultrasound showed nephromegaly

Figure 1. (A) Patient at age 13 years presenting lower-extremity deformities, low body mass, and short stature. (B) Variant p.Gly170Val (ENST00000261755; hg38 chr15:80.168.105 G>T) in homozygosis (two copies) in *FAH* gene identified by the next generation sequencing.

with acute bilateral parenchymal damage, normal renal arteries, and signs of chronic fibrotic hepatopathy on her hepatic ultrasound. Cardiac and echocardiogram evaluation also showed abnormalities, including mild mitral and aortic insufficiency, ascending aortic and left coronary artery dilation, signs of septal and pericardial hypertrophy, and an overall hyperdynamic heart.

Laboratory tests for serologic markers of hepatitis B and C, HIV, Wilson´s disease, and rheumatologic disorders were negative. Urinalysis was performed and showed normal specific gravity, alkaline urine (pH=8), glycosuria despite normal blood glucose (+2/4), trace ketonuria, and non-nephrotic proteinuria (13 mg/Kg/24h). Blood-gas analysis confirmed metabolic acidosis with normal anion gap and her serum analysis showed persistent electrolyte abnormalities. She then underwent genetic testing to investigate IEM, which detected a likely pathogenic homozygous variant (c.509G>T) in the *FAH* gene (Fumarylacetoacetate Hydrolase, OMIM* 613871; Mendelics Genomic Analysis; https://www.mendelics.com.br), strongly associated with tyrosinemia type I, as shown in Figure 1B. The diagnosis of HT1 was confirmed by elevated urine Succinylacetone levels (238 umol/L, reference <20 umol/L).

On intraoral examination, mucosal and soft tissues appear normal. However, some tooth abnormalities were noted: tooth decay, delayed eruption of permanent teeth. At clinical examination, focal hypoplastic areas and a noted Hutchinson-like tooth shape change in #35 and #45 (Figure 2A-F) were observed. A panoramic radiography revealed an increased vascular-nervous caliber/widening of the mandibular canal on both sides, as well as sparse medullary bone trabeculae and thinning of the basilar mandibular cortex. Atypical stylohyoid calcification in relation to chronological age, taurodontism on maxillary and mandibular molars were also observed. Moreover, periapical radiographs suggested focal widening of the periodontal ligament space (Figure 3A-B).

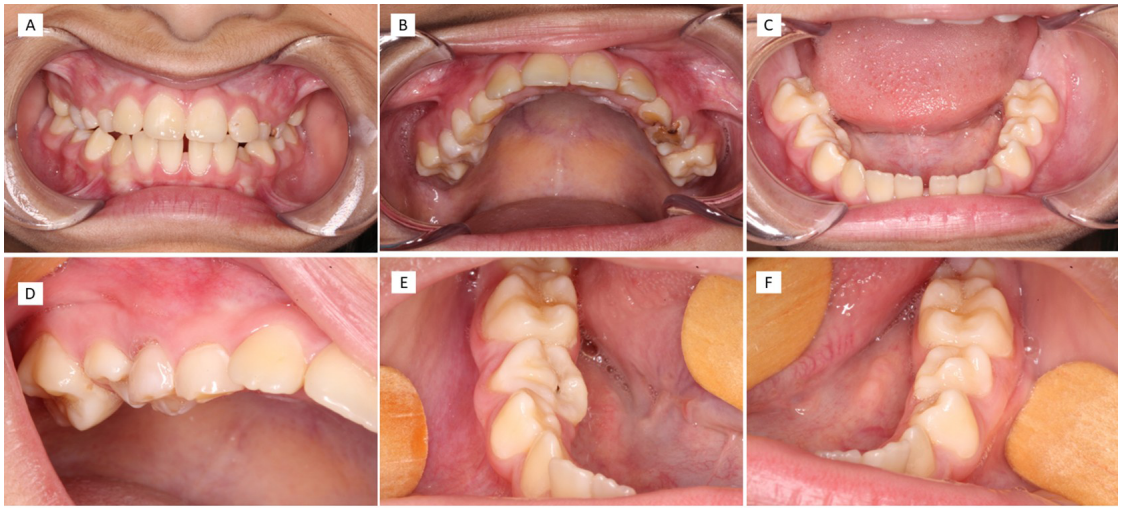

Figure 2. Intraoral examination showing tooth decay, focal hypoplastic areas, delayed eruption of permanent dentition, and Hutchinson-like shape of the #35 and #45.

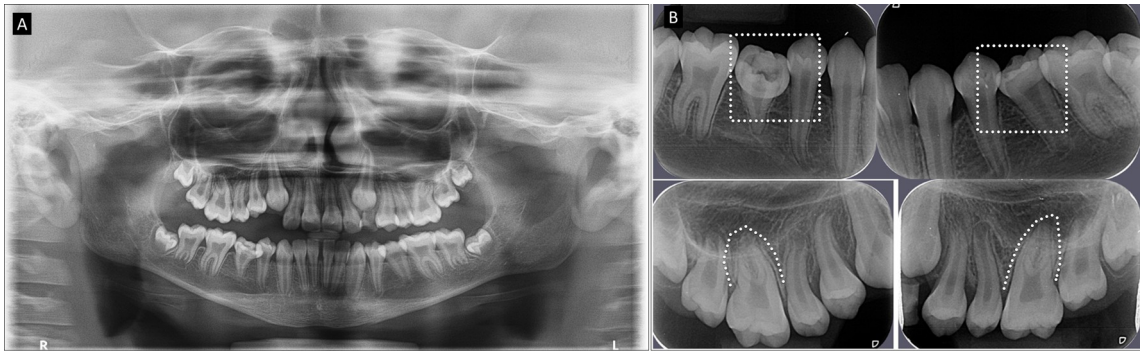

Figure 3. (A) Panoramic radiography. Atypical pattern of dental rhizolysis in deciduous teeth, delayed eruption and development of permanent teeth, crown alteration in #45 and #35, with anomalous morphology (Hutchinson-like) and taurodontics pulp chambers in molars; Increased vascular-nervous caliber in the mandibular canal; sparse medullary mandibular bone trabeculae and thinning of the basilar mandibular. (B) Periapical images highlighting anomalous morphology of #45 and #35 and focal widening of the periodontal ligament space.

Since her diagnosis, the patient has been receiving dietary adaptations and electrolyte and alkaline solutions supplementation and is under close follow-up care in the Genetics Service and Pediatric Nephrology Unity. She has not exhibited new episodes of hypertension or seizures, but she still has short stature, bone, and dental deformities. NTBC treatment has not yet been started because the medication is not available in the Brazilian Public Healthcare System. The patient was referred to dental treatment and received preventative care and interventions to reduce the impact of the dental abnormalities related to the underlying disease.

DISCUSSION

The presented case describes a 13-year-old female with HT1, a multisystemic disease characterized by RTA, hypercalciuria, hypertension, and abnormal liver and cardiac findings. This is an autosomal recessive disorder caused by a deficiency in FAH activity, leading to toxic accumulation of SA in the liver, kidney, and other organs[11]. This rare metabolic disorder affects 1 in 100,000 to 120,000 individuals worldwide, with higher prevalence in the Canadian and Scandinavian populations[12].

The clinical features of HT1 are highly variable, ranging from mild to severe and fatal if untreated, making early diagnosis essential for effective treatment and long-term outcomes[13]. The most common presenting signs and symptoms include liver dysfunction, renal tubular dysfunction, and neurological crises, such as seizures and encephalopathy, usually in the first year of life[14]. However, some patients may have a milder phenotype and present later in childhood with short stature, osteopenia, or FS[15].

Usually, the diagnosis of HT1 involves early SA detection in the urine, blood or amniotic fluid by tandem mass spectrometry. The presence of elevated levels of tyrosine and alpha-fetoprotein are also indicative of the disease and genetic diagnosis may be useful when other IEMs partake in the differential diagnosis. The gold standard for detection of HT1 is through newborn screening (NBS). Nonetheless, routine NBS panels in Brazil do not include tyrosinemia diagnosis.

Previously, the only available intervention for HT1 was dietary restriction of phenylalanine and tyrosine, which was poorly effective in preventing disease-progression. Hence, most patients eventually required orthotopic liver transplantation, which did not correct the renal and systemic manifestations nor prevented further damage. Nowadays 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) is the first-line agent for early treatment of patients with HT1[16]. This kind of medication acts by inhibiting the second enzyme of the tyrosine catabolic pathway, minimizing the downstream production of FAA and SA, which showed significant efficacy in order to prevent renal injury, hepatic damage, neurologic crises, and other secondary manifestations.

In the present case, the patient had unusual presentation, with lower-extremity deformities and short stature as the first symptoms started at 2 years of age, followed by hypercalciuria, non-nephrotic proteinuria, and RTA. The diagnosis of HT1 was delayed until 13 years of age when genetic testing revealed a homozygous variant in the FAH gene and elevated SA levels. This case highlights the challenges in diagnosing HT1, particularly in patients with atypical presentations, such as late-onset or non-specific symptoms.

Dental findings are rarely reported in cases of FS. Despite previous reports of dental deformities in patients with renal tubular diseases[17], this is the first report showing clinical and radiographic tooth alterations associated to HT1. These results suggest that renal tubular dysfunction could be involved in the abnormal development of oral mineralization, including teeth, periodontal tissues, and maxillofacial structures. The relationship between renal dysfunction and dental abnormalities has been documented in other conditions, such as Fanconi syndrome and chronic kidney disease, in which hypophosphatemia and metabolic imbalances lead to enamel defects, tooth hypoplasia and alterations in tooth eruption[17,18]. Thus, the oral manifestations observed in our patient may be related to hypophosphatemia secondary to proximal tubular dysfunction induced by type I tyrosinemia. Dental care for these patients requires close monitoring, with intensified preventive measures, including fluoride supplementation, the use of sealants and monitoring tooth eruption. In patients with hypophosphatemia, the use of minimally invasive restorative therapies and strict diet control are recommended to reduce the risk of dental caries. In this case, the patient was referred to a specialist dental care and received preventative care and interventions to reduce the impact of the dental abnormalities related to the underlying metabolic condition. In this case, the patient was referred to dental follow-up and received preventative care and interventions to reduce the impact of the dental abnormalities related to the underlying metabolic condition.

Compared with other cases reported in the literature, patients with renal tubular dysfunction may have dental features similar to those observed in our case, including enamel hypoplasia and delayed tooth eruption[17]. However, this is the first report to describe these manifestations in a patient with type I tyrosinemia, suggesting that further studies are needed to better understand this association. The lack of previous reports may be related to the rarity of the condition or the lack of detailed dental examinations in these patients. Early identification and appropriate management of dental abnormalities can improve the quality of life of these individuals and reduce oral health complications.

The management of HT1 involves a combination of dietary restriction of tyrosine and phenylalanine and NTBC therapy. Long-term treatment aims to prevent acute crises and minimize the risk of liver failure, liver cancer, and renal disease[19]. However, compliance with the restrictive diet and NTBC therapy can be challenging, and regular monitoring for metabolic control and potential complications is required. In the presented case, the patient is receiving supportive treatment, including dietary adaptations and electrolyte supplementation, while awaiting access to NTBC therapy, which is currently not available in the Brazilian public healthcare system.

This report reinforces the importance of genetic testing in patients with multisystemic symptoms of HT1, and the need for oral and dental investigation to diagnose oral and maxillofacial and dental anomalies. Early detection and treatment of these conditions may improve quality of life for patients with HT1.

CONCLUSION

In conclusion, the presented case illustrates the importance of considering HT1 in the differential diagnosis of multisystemic disorders, even in the absence of typical features or family history. Although not common, dental alterations should be evaluated in patients with primary and secondary renal tubular disorders. Early diagnosis and appropriate management of HT1 can improve the prognosis.

AUTHORS' CONTRIBUTIONS

HMJ: conceptualization, investigation, supervision, writing – review & editing. HKFB: data curation, investigation, visualization, writing – original draft. ALBA: data curation, investigation, writing – review & editing. RRA: formal analysis, investigation, writing – review & editing. MAOS: data curation, investigation, writing – review & editing. FPF: investigation, supervision, writing – review & editing. RAM: formal analysis, methodology, supervision, writing – original draft. ACSS: conceptualization, investigation, supervision, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Phaneuf D, Labelle Y, Bérubé D, Arden K, Cavenee W, Gagné R, et al. Cloning and expression of the cDNA encoding human fumarylacetoacetate hydrolase, the enzyme deficient in hereditary tyrosinemia: assignment of the gene to chromosome 15. Am J Hum Genet. 1991;48(3):525-35. PMID: 1998338.
2. Bartlett DC, Preece MA, Holme E, Lloyd C, Newsome PN, McKiernan PJ. Plasma succinylacetone is persistently raised after liver transplantation in tyrosinaemia type 1. J Inherit Metab Dis. 2013;36(1):15-20. https://doi.org/10.1007/s10545-012-9482-1
3. Kubo S, Sun M, Miyahara M, Umeyama K, Urakami K, Yamamoto T, et al. Hepatocyte injury in tyrosinemia type 1 is induced by fumarylacetoacetate and is inhibited by caspase inhibitors. Proc Natl Acad Sci U S A. 1998;95(16):9552-7. https://doi.org/10.1073/pnas.95.16.9552
4. Roth KS, Carter BE, Higgins ES. Succinylacetone effects on renal tubular phosphate metabolism: a model for experimental renal Fanconi syndrome. Proc Soc Exp Biol Med. 1991;196(4):428-31. https://doi.org/10.3181/00379727-196-43211
5. Jorquera R, Tanguay RM. Fumarylacetoacetate, the metabolite accumulating in hereditary tyrosinemia, activates the ERK pathway and induces mitotic abnormalities and genomic instability. Hum Mol Genet. 2001;10(17):1741-52. https://doi.org/10.1093/hmg/10.17.1741
6. Chinsky JM, Singh R, Ficicioglu C, van Karnebeek CDM, Grompe M, Mitchell G, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19(12). https://doi.org/10.1038/gim.2017.101
7. Morrow G, Tanguay RM. Biochemical and clinical aspects of hereditary tyrosinemia type 1. In: Tanguay RM, editor. Hereditary tyrosinemia: pathogenesis, screening and management. Advances in Experimental Medicine and Biology. Cham: Springer International Publishing; 2017. p. 9-21. https://doi.org/10.1007/978-3-319-55780-9_2

8. Tanguay RM, Valet JP, Lescault A, Duband JL, Laberge C, Lettre F, et al. Different molecular basis for fumarylacetoacetate hydrolase deficiency in the two clinical forms of hereditary tyrosinemia (type I). Am J Hum Genet. 1990;47(2):308-16. PMID: 2378356.
9. Demers SI, Russo P, Lettre F, Tanguay RM. Frequent mutation reversion inversely correlates with clinical severity in a genetic liver disease, hereditary tyrosinemia. Hum Pathol. 2003;34(12):1313-20. https://doi.org/10.1016/s0046-8177(03)00406-4
10. van Spronsen FJ, Thomasse Y, Smit GP, Leonard JV, Clayton PT, Fidler V, et al. Hereditary tyrosinemia type I: a new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994;20(5):1187-91. PMID: 7927251.
11. Lindblad B, Lindstedt S, Steen G. On the enzymic defects in hereditary tyrosinemia. Proc Natl Acad Sci U S A. 1977;74(10):4641-5. https://doi.org/10.1073/pnas.74.10.4641
12. Chinsky JM, Singh R, Ficicioglu C, van Karnebeek CDM, Grompe M, Mitchell G, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19(12). https://doi.org/10.1038/gim.2017.101
13. Daou KN, Barhoumi A, Bassyouni A, Karam PE. Diagnostic and therapeutic challenges of hereditary tyrosinemia type 1 in Lebanon: a 12-year retrospective review. Front Pediatr. 2021;9:698577. https://doi.org/10.3389/fped.2021.698577
14. Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinemia. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews®. Seattle: University of Washington; 1993-2025.
15. Sniderman King L, Trahms C, Scott CR. Tyrosinemia type I. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews®. Seattle: University of Washington, Seattle; 1993-2025.
16. Lindstedt S, Holme E, Lock EA, Hjalmarson O, Strandvik B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. Lancet. 1992;340(8823):813-7. https://doi.org/10.1016/0140-6736(92)92685-9
17. Ferreira SBP, Aquino SN, Pereira PCB, Silva ACS, Martelli-Júnior H. Dental findings in Brazilian patients with Fanconi syndrome. Int J Paediatr Dent. 2016;26(1):77-80. https://doi.org/10.1111/ipd.12183
18. Martelli-Júnior H, Ferreira SP, Pereira PCB, Coletta RD, Aquino SN, Miranda DM, et al. Typical features of amelogenesis imperfecta in two patients with Bartter's Syndrome. Nephron Extra. 2012;2(1):319-25. https://doi.org/10.1159/000345801
19. Holme E, Lindstedt S. Tyrosinemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). J Inherit Metab Dis. 1998;21(5):507-17. https://doi.org/10.1023/a:1005410820201