Special Issue: Rare Diseases: Advances in Diagnosis, Prevention, Treatment and Management

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(2) 1–7

DOI: 10.1177/0300060519863543
journals.sagepub.com/home/imr
SAGE

Hawkinsinuria clinical practice guidelines: a Mexican case report and literature review

Héctor Cruz-Camino[1,2], Diana Laura Vazquez-Cantu[1,3], Alexandra Vanessa Zea-Rey[1], Jaime López-Valdez[4], Jorge Jiménez-Lozano[5], René Gómez-Gutiérrez[1] and Consuelo Cantú-Reyna[1,3]

Abstract

Hawkinsinuria is an autosomal dominant disorder of tyrosine metabolism. Mutations in the 4-hydroxyphenylpyruvate dioxygenase gene (*HPD*) result in an altered HPD enzyme, causing hawkinsin and tyrosine accumulation. Persistent metabolic acidosis and failure to thrive are common features in patients with hawkinsinuria. We present the first known Latin American patient diagnosed with hawkinsinuria, and the tenth reported patient in the literature. We aim to establish clinical practice guidelines for patients with hawkinsinuria. The patient's plasma tyrosine level was 21.5 mg/dL, which is several times higher than the reference value. Mutation analysis indicated heterozygosity for V212M and A33T variants in *HPD*. In the case of altered tyrosine levels found during newborn screening, we propose exclusive breastmilk feeding supplemented with ascorbic acid. Amino acid quantification is useful for monitoring treatment response. If tyrosinemia persists, protein intake must be decreased via a low-tyrosine diet. Molecular studies can be used to confirm a patient's disease etiology. Further reports are required to elucidate new pathogenic and phenotypic variations to enable the development of an appropriate therapeutic approach.

[1]Genomi-k S.A.P.I. de C.V., Monterrey, Nuevo León, Mexico
[2]Tecnologico de Monterrey, Escuela de Ingeniería y Ciencias, Monterrey, Nuevo León, Mexico
[3]Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo León, Mexico
[4]Centenario Hospital Miguel Hidalgo, Aguascalientes, Aguascalientes, Mexico
[5]Centro Hospitalario MAC, Aguascalientes, Aguascalientes, Mexico

Corresponding author:
Consuelo Cantú-Reyna, Genetics Department, Genomi-k S.A.P.I. de C.V. Av. Cerro de las Mitras 2411-A. Col. Obispado, Monterrey, Nuevo León, Mexico. C.P. 64060.
Email: cocantu@genomi-k.com

Keywords
Neonatal screening, hawkinsinuria, Mexico, case report, tyrosinemias, 4-hydroxyphenylpyruvate dioxygenase

Date received: 4 April 2019; accepted: 24 June 2019

Introduction

Hawkinsinuria is an autosomal dominant metabolic disorder caused by specific mutations in the 4-hydroxyphenylpyruvate dioxygenase gene (*HPD*). This gene encodes the enzyme HPD, which catalyzes the reaction of 4-hydroxyphenylpyruvate to homogentisic acid in the tyrosine catabolism pathway. In the event of an alteration in its structure and/or activity, the metabolite (2-L-cysteine-S-yl, 4-di-hydroxycyclohex-5-en-1-yl) acetic acid is produced and accumulates in the body, which is known as hawkinsin.[1]

After weaning, the onset of symptoms is characterized by persistent metabolic acidosis, failure to thrive, as well as fine and sparse hair. Disease complications such as growth and developmental delays, and multiple organ failure may also be present.[2] Clinical manifestations may be ameliorated by a low-tyrosine diet in the first year of life without necessitating further therapeutic approaches. However, urine excretion in hawkinsinuria continues throughout the patient's life.

Newborn screening (NBS) is an essential tool for the early diagnosis and treatment of inborn errors of metabolism and other disorders. Because most hawkinsinuria patients remain asymptomatic during their first weeks of life, altered tyrosine levels are the only finding that can lead to an earlier diagnosis. However, further tests are needed to confirm this etiology.

Hawkinsinuria appears to be rare in the Latin American population because no patients in this group have yet been reported. In the present study, we present the first case of a Mexican newborn diagnosed with hawkinsinuria via NBS, and the tenth patient to be diagnosed with this condition worldwide (Table 1). We collected clinical and molecular findings from the patients described in the literature and compared them with those of our index patient. This study aimed to establish diagnosis and treatment guidelines for patients with hawkinsinuria.

Case report

We present a female newborn of Mexican descent (Figure 1) who is the only first child of a non-consanguineous 37-year-old woman and a 34-year-old man. The obstetric antecedents described an uncomplicated pregnancy with complete prenatal care. An emergency cesarean was performed at 35 weeks because of premature rupture of the membranes. The patient's weight at birth was 1940 g (p15), her length was 43 cm (p15), and she had an APGAR score of 8/8. She was admitted to the Neonatal Intensive Care Unit for 15 days because of respiratory distress secondary to transient neonatal tachypnea, as well as neonatal sepsis which was treated according to standard guidelines. There were no clinical signs associated with metabolic decompensation.

For NBS, blood samples were taken by venipuncture during the patient's first month of life and placed on filter paper. Dried blood spot (DBS) samples were

Table 1. Clinical history comparison between reported hawkinsinuria patients and our index patient.

Clinical history		Patient 1[1,4,7]	Patient 2[8]	Patient 3[9,10]	Patient 4[10]	Patient 5[2]	Patient 6[11]	Patient 7[3]	Patient 8[3]	Patient 9[12]	Index patient
Sex		Female	Male	Female	Female	Male	Male	Female	Female	Male	Female
Birth weight (g)		2780	3695	3580	SGA	N/A	N/A	2980	3280	1390	1940
Chief complaint		Failure to thrive	Failure to thrive	Failure to thrive	Failure to thrive	Failure to thrive	Multiple complaints	Elevated Tyr levels	Elevated Tyr levels	Direct hyperbilirubinemia	Elevated Tyr levels
Age at chief complaint (weeks)		20	7	24	20	12	24	0	0	5	4
Physical examination											
Nervous system		None	None	Hypotonia	Mild development delay	None	Mild development delay	N/A	N/A	None	None
Integumentary system		Pallor	Fair hair, pallor, swimming pool odor	Sparse hair, pallor	None	None	None			None	
Vascular system		Anemia	None	Pretibial edema	None	Clotting disturbances	Anemia, pedal edema			None	
Respiratory system		Tachypnea	Tachypnea and intermittent coughing	None	None	None	None			Hyaline membrane disease	
Gastrointestinal system		Abdominal distention	Regurgitation, hepatomegaly	None	None	Vomiting, inappetence, hepatomegaly, enteritis, diarrhea	Abdominal distension, hepatomegaly			None	
Urinary system		UTI, HE	HE	HE	Ketonuria, HE	UTI, RTA, HE	HE			UTI	
Biochemical and molecular testing											
Metabolic acidosis (pH)		+	+	+	+	+	+	−	−	−	−
[Tyr] (mg/dl)	Plasma	Mild 3.6	None	N/A	N/A	N/A	Mild 2.7	Mod 7.2	Mod 10.6	Mild 4.77	High 21.5
	DBS	N/A	N/A	N/A	N/A	N/A	N/A	Mod 7.6	Mod 12.3	N/A	Mod 15.96
HPD variants (configuration)		A33T/WT	N/A	A33T/WT	A33T/WT	N/A	N241S/I335M (*trans*)	A33T/WT	A33T-V212M/WT	A33T/WT	A33T-V212M/WT

DBS: dried blood spot, Mod: moderate, HE: hawkinsin excretion, N/A: not available, RTA: renal tubular acidosis, SGA: small for gestational age, Tyr: tyrosine, UTI: urinary tract infection, WT: wild type.

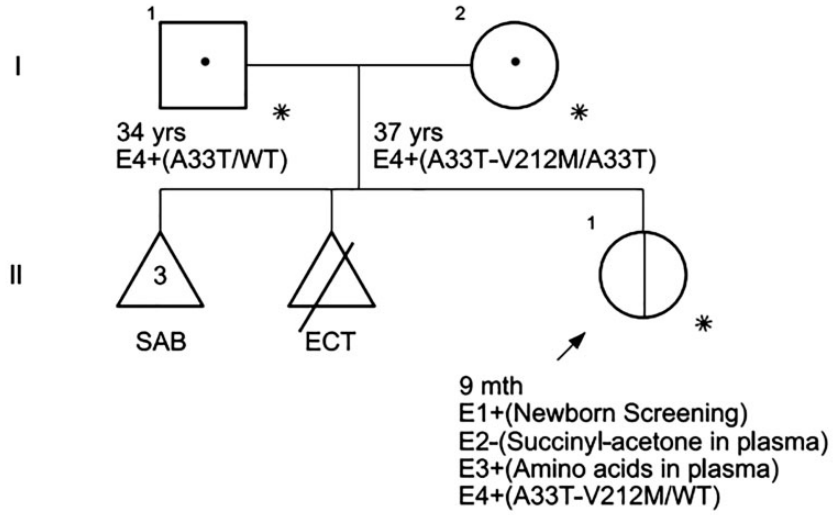

Figure 1. Pedigree of index patient's family. Abbreviations: yrs: years, WT: wild type, SAB: spontaneous abortion without further data, ECT: ectopic pregnancy, mth: months. Designed according to the Standardized Human Pedigree Nomenclature.

received by Genomi-k S.A.P.I. de C.V. and processed by PerkinElmer Genomics (Pittsburgh, PA, USA). Tandem mass spectrometry (MS/MS) revealed elevated tyrosine levels of 15.96 mg/dL without succinylacetone present.

Flow injection analysis MS/MS of DBS samples confirmed the absence of succinylacetone. Plasma amino acid quantification via liquid chromatography MS/MS identified tyrosine levels of 21.5 mg/dL, which were even higher than the NBS test 2 weeks earlier. These findings excluded tyrosinemia type I and neonatal transient tyrosinemia.

We began a therapeutic approach based on a low-tyrosine diet supplemented with ascorbic acid; we then requested a second plasma amino acid quantification 2 weeks later. At this time, the tyrosine concentration had decreased to 3.9 mg/dL, reflecting a high response to the special diet. We then re-adjusted the patient's protein intake to ensure it was maintained within an optimal range.

To identify the specific disease etiology, we performed molecular testing for tyrosinemias. We sequenced *FAH*, *TAT*, and *HPD* genes using a next-generation sequencing (NGS) Illumina MiSeq system (Illumina) with 2×150 bp of paired readings. The DNA sequence was mapped and compared to the reference hg19 sequence from the University of California, Santa Cruz. This detected two heterozygous *HPD* variants, V212M and A33T, which are associated with hawkinsinuria.[3]

To carry out genetic counseling, the patient's parents also underwent NGS for *HPD*. The mother's *HPD* gene showed a heterozygous V212M variant and a homozygous A33T variant, while the father carried a heterozygous A33T variant (Figure 1). These latter findings established the index patient's variant configuration in *cis*. She inherited the A33T-V212M allele from her mother and a wild-type allele from her father. Neither parent had associated findings in their clinical history.

At the time of writing, the patient is 9 months old. Her growth rate and psychomotor development seem adequate for her age. There are no findings on physical examination; the patient's weight is 7.5 kg (p25-50 corrected), her length is 66 cm (p10-25 corrected), and she has a cephalic perimeter of 44 cm (p75 corrected).

Discussion

In the present study, we compared reported genotypes and phenotypes of patients diagnosed with hawkinsinuria. The A33T variant of *HPD* has been described as benign, but it may produce a partially effective enzyme that is not capable of undergoing the rearrangement phase.[4] The V212M variant has been referred to with uncertain clinical significance, although it was identified in one patient whose mutational analysis established it as disease-causing.[3]

Patients with hawkinsinuria were shown to have failure to thrive, persistent acidosis accompanied by vomiting and diarrhea, and growth rate anomalies. Less-reported clinical manifestations include developmental delays, anomalies related to hair growth, pretibial edema, and the presence of a swimming pool-like odor. These clinical manifestations typically start at approximately 18 weeks of age. With an NBS program, therapeutic approaches may be implemented as early as the first few weeks of life, while patients are still asymptomatic. Therefore, tyrosine restrictions are leveraged as measures to prevent the accumulation of byproducts that could otherwise lead to neurological complications.

Based on our experience and on the retrospective analysis of the approach we adopted for this patient, we propose a number of clinical practice guidelines, as outlined in Figure 2. Once an alteration

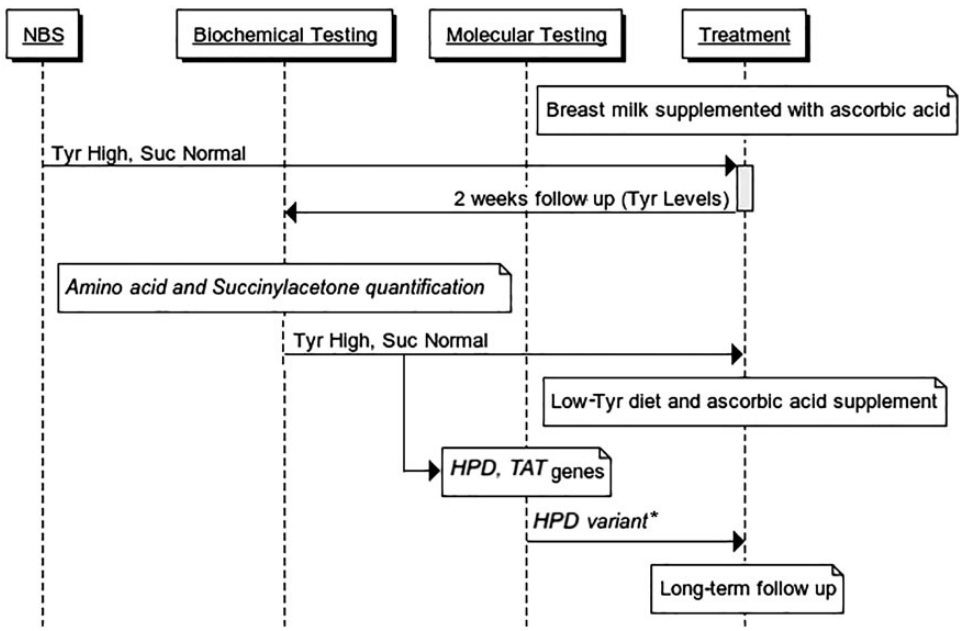

Figure 2. Hawkinsinuria's clinical practice guidelines. Abbreviations. NBS: Newborn screening, Tyr: tyrosine, Suc: succinylacetone.

in tyrosine levels is detected via NBS, it is essential to ensure exclusive breastmilk feeding and to supplement this with ascorbic acid because this can serve as a preventive measure against possible transient neonatal tyrosinemia. Additionally, biochemical testing is necessary to understand the disease etiology. This will allow for the continuous monitoring of nutrition intake and metabolism. If tyrosinemia persists, the natural protein intake should be re-adjusted, and the use of low-tyrosine products and an ascorbic acid supplement is recommended. Molecular testing can also be used to confirm the patient's disease etiology. If hawkinsinuria is diagnosed, long-term follow-up is needed for at least the first year of life.

We recommend that the daily intake for infants with hawkinsinuria younger than 12 months of age is similar to that of the Reference Daily Intake guidelines.[5,6] We suggest a total energy intake of 100 to 120 kcal/kg/day, a protein intake of 2.5 to 3.5 g/kg/day (25%–50% of low-tyrosine formula), and a fluid intake of 130 to 160 mL/kg/day. We also suggest supplements of ascorbic acid (0.5–2 g/day), vitamin D (400 U/day), and iron (2 mg/kg/day). The treatment target is to maintain tyrosine and phenylalanine levels between 200 and 400 μmol/L and 35 and 120 μmol/L, respectively.

Further reports are required to elucidate new pathogenic variants, as well as their phenotypic variations, to develop appropriate therapeutic treatments for hawkinsinuria. Genetic counseling is also needed to educate on possible lifestyle modifications required and to ensure adequate family planning.

Acknowledgments

English language editing of this manuscript was provided by Journal Prep.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. These results have not been fully or partially published in, or submitted to, any other printed or electronic publication in any language.

Ethical statement

Written informed consent for the publication of patient and family information was provided by the patient's legally authorized representative.

Funding

This research did not receive any specific grants from any funding agencies in the public, commercial, or not-for-profit sectors.

ORCID iD

Héctor Cruz-Camino https://orcid.org/0000-0002-2815-6619
Diana Laura Vazquez-Cantu https://orcid.org/0000-0003-0914-6981

References

1. Danks DM, Tippett P and Rogers J. A new form of prolonged transient tyrosinemia presenting with severe metabolic acidosis. *Acta Pædiatrica* 1975; 64: 209–214.
2. Lehnert W, Stögmann W, Engelke U, et al. Long-term follow up of a new case of hawkinsinuria. *Eur J Pediatr* 1999; 158: 578–582.
3. Thodi G, Schulpis KH, Dotsikas Y, et al. Hawkinsinuria in two unrelated Greek newborns: identification of a novel variant, biochemical findings and treatment. *J Pediatr Endocrinol Metab* 2015; 29: 15–20.
4. Brownlee JM, Heinz B, Bates J, et al. Product analysis and inhibition studies of a causative asn to ser variant of 4-hydroxyphenylpyruvate dioxygenase suggest a simple route to the treatment of Hawkinsinuria. *Biochemistry* 2010; 49: 7218–7226.
5. Medeiros DM. Dietary reference intakes: the essential guide to nutrient requirements. *Am J Clin Nutr* 2018; 85: 924–924.

6. Cornejo EV, Raimann BE, Pérez GB, et al. Errores innatos del metabolismo de los aminoácidos. In: Colombo M, Cornejo V and Raimann E (eds). *Errores Innatos en el Metabolismo del Niño*. 4th ed. Santiago de Chile: Editorial Universitaria, 2013, p.97–192.
7. Niederwieser A, Matasovic A, Patricia T, et al. A new sulfur amino acid, named hawkinsin, identified in a baby with transient tyrosinemia and her mother. *Clin Chim Acta* 1977; 76: 345–356.
8. Wilcken B, Hammond JW, Howard N, et al. Hawkinsinuria. *Med Intelligene* 1981; 305: 865–869.
9. Tomoeda K, Awata H, Matsuura T, et al. Mutations in the 4-hydroxyphenylpyruvic acid dioxygenase gene are responsible for tyrosinemia type III and hawkinsinuria. *Mol Genet Metab* 2000; 71: 506–510.
10. Borden M, Holm J, Leslie J, et al. Hawkinsinuria in two families. *Am J Med Genet* 1992; 44: 52–56.
11. Item CB, Mihalek I, Lichtarge O, et al. Manifestation of hawkinsinuria in a patient compound heterozygous for hawkinsinuria and tyrosinemia III. *Mol Genet Metab* 2007; 91: 379–383.
12. El Khatib H, Asaad B, Zaylaa A, et al. Hawkinsinuria with direct hyperbilirubinemia in Egyptian-Lebanese boy – a case report. *Front Pediatr* 2019; 7: 69.