Chronic and Variable Manifestations of Ornithine Transcarbamylase Deficiency in Heterozygous Carriers: A Case Series of Three Colombian Patients

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Abstract

Ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle disorder with an estimated prevalence ranging from 1 in 56,500 to 1 in 113,000 live births. While hemizygous males typically present with early-onset hyperammonemic encephalopathy, females carrying pathogenic variants in OTC exhibit highly variable phenotypes due to random X-chromosome inactivation, ranging from asymptomatic states to severe metabolic and neuropsychiatric manifestations. In many cases, diagnosis in females is delayed, especially when symptoms are misinterpreted as behavioral or psychiatric disorders, increasing the risk of irreversible neurological sequelae. This case series describes three Colombian females with genetically confirmed OTCD: two pediatric patients and one adult. In pediatric cases, metabolic decompensations were triggered by febrile viral illnesses and infections. In the adult patient, initial symptoms occurred during pregnancy and were misattributed to a primary psychiatric disorder. In all three cases, diagnosis was established only after multiple episodes of illness. All patients presented early on with protein aversion, which we consider a significant red flag to suspect metabolic disorders. This series underscores the diagnostic challenges in females heterozygous for OTC, the importance of recognizing catabolic stressors as triggers for clinical deterioration, and the need for early biochemical and molecular evaluation to prevent complications and reduce diagnostic delays.

Keywords

Ornithine transcarbamylase deficiency, hyperammonemia, encephalopathy, Women.

Introduction

Ornithine transcarbamylase deficiency (OTCD) [MIM: 311250] is the most common urea cycle disorder (UCD) [1]. According to data from the National Institute of Health of Colombia (INS), reported through the national public health surveillance system (SIVIGILA), seven female cases of ornithine transcarbamylase deficiency (OTCD) were documented between 2020 and 2023. Specifically, in 2020, two cases were reported in females aged 17 and 11 years; in 2021, two cases in females aged 36 and 5 years; in 2022, one case in a 29-year-old woman; and in 2023, two cases in females aged 39 and 7 years [2]. The clinical presentation is highly heterogeneous, ranging from an asymptomatic carrier state to severe neonatal onset with hyperammonemic encephalopathy [3]. Neonatal-onset cases are typically diagnosed based on clinical features and biochemical findings, including elevated glutamine and orotic acid levels and low plasma citrulline concentrations. The main challenge lies in suspecting and timely diagnosing late-onset cases, particularly in heterozygous women, due to mosaicism caused by the Lyonization process [4].

OTC is a mitochondrial homotrimeric enzyme encoded by the *OTC* gene located at Xp11.4. It is expressed in hepatic and intestinal tissues, catalyzing the transfer of a carbamoyl group from carbamoyl phosphate to the amino group of L-ornithine,

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producing citrulline and phosphate in the ammonia elimination pathway [5)]. Signs and symptoms result from hyperammonemia and elevated glutamine levels in the central nervous system, leading to altered consciousness, seizures, cerebral edema, liver failure, and, in severe cases, coma and death [6].

Phenotypic heterogeneity is well-documented. Neonatal-onset phenotypes are usually observed in hemizygous males with null enzymatic activity. In contrast, late-onset phenotypes occur in males with residual enzymatic activity and in heterozygous women, who may be symptomatic in approximately 20 % of cases, with high variability in age of onset and clinical manifestations [7]. Symptoms include protein aversion, recurrent vomiting, learning difficulties, psychiatric disorders, and hepatic involvement [8].

Recent studies have expanded our understanding of the natural history of OTCD in heterozygous women, demonstrating that even those classified as "asymptomatic" may exhibit subtle cognitive, psychiatric, or radiological abnormalities and remain at risk for metabolic decompensation during catabolic stress [9]. Furthermore, the clinical diagnosis of OTCD in adult females is frequently delayed due to nonspecific symptoms and underrecognition by clinicians, especially during intercurrent illness, pregnancy, or postpartum periods [10,11]. These factors complicate management and increase the risk of adverse events.

Pregnancy poses a particular challenge for women with OTCD. Multiple retrospective cohort studies have shown that symptomatic heterozygotes have an increased risk of pregnancy-related complications, including hyperammonemic crises, hepatic dysfunction, and neurologic deterioration during the peripartum period [10–12]. Notably, some complications have been reported even in women previously considered asymptomatic, underscoring the importance of metabolic surveillance and preconception counseling. Clinical guidelines now recommend pre-pregnancy risk stratification and multidisciplinary care during gestation and delivery for all women with confirmed *OTC* variants, regardless of symptom history [12,13].

Our study aims to describe the phenotypic variability and genetic findings in Colombian female patients with OTCD, highlighting the clinical relevance of early identification, risk stratification, and family-based genetic testing.

Patients and Methods

We present three Colombian female probands from three unrelated families. All patients were referred to the inborn errors of metabolism (IEM) clinic for medical evaluation due to suspected IEM. Clinical histories were reviewed from medical records after obtaining informed consent from the patient and/or their legal guardian.

The Institutional Research and Ethics Committee of the Faculty of Medicine at Pontificia Universidad Javeriana and the San Ignacio University Hospital approved this study.

Case Descriptions

Case 1

A 7-year-old female, the first child of a 33-year-old mother, born at term without perinatal complications, normal weight and length, and no consanguinity, began at 6 months of age with aversion to animal protein, frequent vomiting, and selective feeding, preferring fruits, vegetables, and dairy products. Despite her restrictive intake, she did not experience weight loss; on the contrary, she showed progressive weight gain.

At 12 months, she had an episode of acute confusion during which she failed to recognize her parents, without an apparent trigger; No clinical or biochemical investigations were performed at that time. She remained stable until the age of 5, when she presented with two days of lethargy, dysarthria, and irritability, following a presumed viral infection. A clinical diagnosis of COVID-19 was made despite a negative PCR test.

She did not experience frank psychosis, but recurrent episodes of disorientation were reported. At 6 years of age, she was hospitalized due to (drowsiness). Hyperammonemia was documented, and a probable diagnosis of ornithine transcarbamylase deficiency (OTCD) was established.

Plasma amino acid analysis revealed elevated glutamine, and urinary organic acid testing showed increased orotic acid and uracil. Initial management included protein restriction, carbamoyl glutamic acid, and lactulose. Due to persistent symptoms and lack of biochemical improvement, she was referred to clinical genetics. Carbamoyl glutamic acid was discontinued, and oral sodium benzoate was initiated, with subsequent resolution of symptoms and normalization of ammonia levels. She has not required dialysis, likely due to adequate response to pharmacological treatment and dietary restriction.

Targeted next-generation sequencing and CNV analysis of urea cycle genes revealed no pathogenic variants in the *OTC* gene, but two heterozygous variants of uncertain significance were detected in *NAGS* and *OAT*. Genetic studies were completed using the MLPA technique (Multiplex Ligation Probe Amplification) for *OTC*, identifying a heterozygous deletion without defining breakpoints.

Due to the absence of precise breakpoint information, chromosomal microarray (array-CGH) was performed, revealing arr[Xp21.1p11.4(37005427_38688112)x1], a 1.6 Mb pathogenic deletion encompassing 15 genes, including *OTC*.

Parental genetic testing revealed the mother carries the same deletion but remains asymptomatic, with normal plasma ammonia and amino acid levels.

Neurodevelopmental evaluation revealed intellectual disability with an IQ of 53.

At the age of 8, a cognitive assessment (WISC-IV) reported an IQ of 66. Neurocognitive interventions were started.

Case 2

A 29-year-old woman was first evaluated at our institution at 19 weeks of gestation during her third pregnancy, with a long-standing history of neuropsychiatric symptoms since age 18. Initial manifestations included low mood, motor restlessness, aggressiveness, and dissociative episodes, such as failure to recognize close family members, including her son and father. At age 19, following the sudden death of her second child, she required psychiatric hospitalization and was diagnosed with a dissociative disorder. She was treated with pharmacotherapy, although details of specific agents used before referral were not available.

Over the following years, the patient developed progressive cognitive decline with impaired working memory, reduced job performance, insomnia, hyporexia, and self-injurious behavior. At age 29, during her third pregnancy, she was diagnosed with hyperemesis gravidarum at 8 weeks of gestation. Her psychiatric symptoms worsened, including depression and dissociation. Brain MRI revealed focal edema in the mammillary bodies and periaqueductal gray matter, consistent with Wernicke encephalopathy (Figure 1). She was treated with thiamine and cyanocobalamin, but her symptoms worsened, including disorientation. She was managed with haloperidol, metoclopramide, folic acid, thiamine, and quetiapine.

At 18 weeks of gestation, she developed sphincter incontinence and loss of awareness, related to consuming a hyperproteic food, prompting admission to the obstetric ICU at our institution. At admission, plasma ammonia was 228 µmol/L, rising to 293 µmol/L afterwards, so hemodialysis was urgently started for 72 hours due to the high risk of cerebral edema and neurological deterioration. Plasma and cerebrospinal fluid (CSF) amino acid profiles showed markedly elevated glutamine (2091 µmol/L; reference 363–785 µmol/L) and undetectable levels of citrulline, ornithine, and arginine. Plasma amino acid analysis revealed glutamine 1337 µmol/L (reference 364–781), low citrulline (5 µmol/L; reference 10–45), and low arginine (7 µmol/L; reference 15–49). Based on these findings, genetic testing for urea cycle disorders was requested. At the same time, Intravenous sodium benzoate was administered, followed by protein restriction However, the patient experienced a prolonged ICU stay with several complications, including chronic right jugular vein thrombosis, tracheal stenosis, upper gastrointestinal bleeding with secondary anemia, septic shock requiring broad-spectrum antibiotic therapy, prolonged intubation, and bilateral vocal cord paralysis that ultimately required tracheostomy.

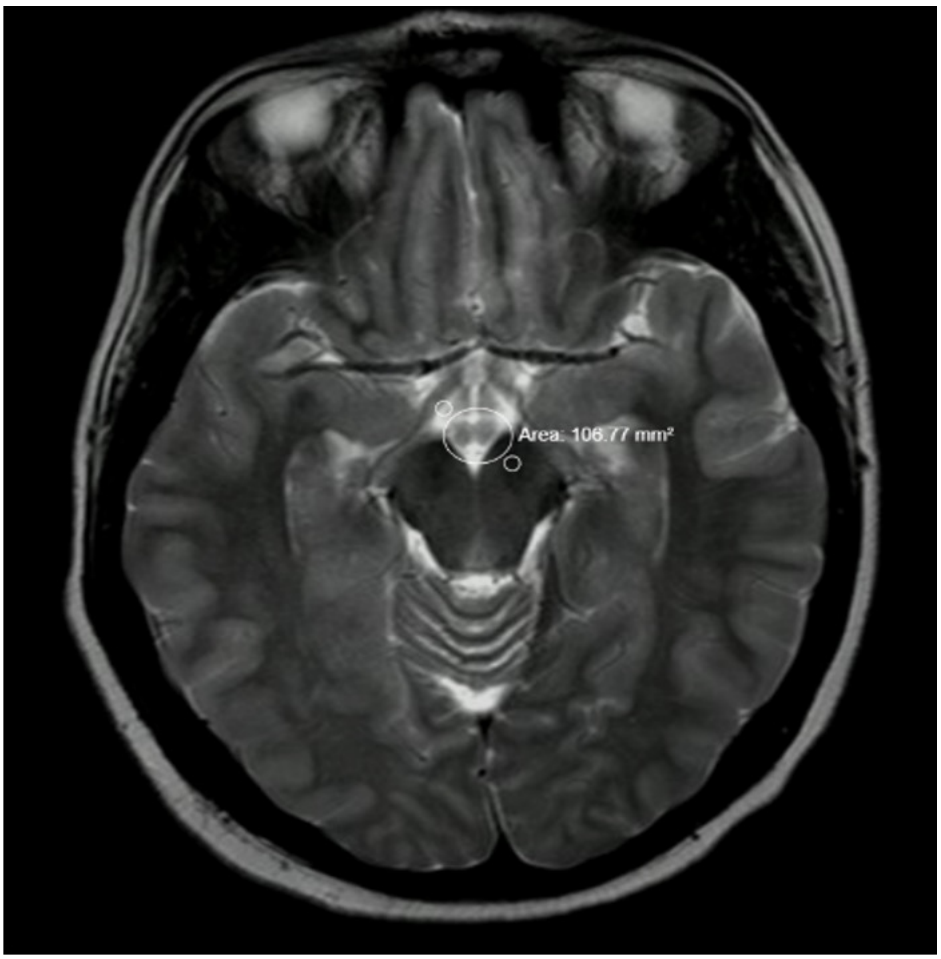

Figure 1. MRI Findings suggestive of the diagnosis of Wernicke encephalopathy with focal edema of the mammillary bodies and periaqueductal gray matter.

The NGS panel for hyperammonemia disorders confirmed a heterozygous variant in the *OTC* gene: c.77+5G>A, located in intron 1, classified as likely pathogenic. After two months, she was discharged on a strict low-protein diet based on plant-derived protein, citrulline 200 mg/kg/day in three divided doses, and oral lactulose, with close outpatient follow-up. No further metabolic decompensations were observed during the remainder of pregnancy. Delivery was planned and conducted via cesarean section at 36 weeks of gestation.

The patient remained stable postpartum, with ammonia levels not requiring sodium benzoate administration. The newborn presented with microcephaly and spastic quadriparesis, but no episodes of hyperammonemia were observed, and genetic testing for the familial *OTC* variant was negative. The child survived for one year and died of respiratory complications, not related to OTCD.

The patient remained clinically stable with dietary and pharmacologic treatment, with no further metabolic decompensations.

Unfortunately, the patient died at age 31 from causes unrelated to her metabolic disorder.

Case 3

A 13-year-old female patient with previously normal neurodevelopment presented with a relevant family history of four male stillbirths on the maternal side.

At age 4, she experienced an acute episode of loss of awareness, encephalopathy, hypotonia, and documented hyperammonemia. Treatment included protein restriction, oral sodium benzoate, carnitine, and lactulose. During follow-up, intermittent behavioral disturbances were noted, including episodes of hyporexia, recurrent abdominal pain, and stress-triggered decompensations. Due to persistence of symptoms, sodium phenylbutyrate (replacing benzoate) and citrulline supplementation were added.

She underwent genetic testing with a next-generation sequencing panel for urea cycle disorders, identifying a heterozygous pathogenic variant in the *OTC* gene (c.583G>A; p.Gly195Arg), findings consistent with partial ornithine transcarbamylase deficiency (OTCD).

The patient did not require dialysis at any time, likely due to prompt medical treatment and moderate levels of hyperammonemia that responded to pharmacotherapy. She has remained under follow-up with continued use of glycerol phenylbutyrate, citrulline, lactulose, and dietary restriction.

She currently attends school, though with learning difficulties. (WISC IV IQ 88). She received neurocognitive rehabilitation A recent abdominal ultrasound showed focal hepatic steatosis in liver segment VI, without evidence of fibrosis or nodular transformation. Her mother was confirmed as an asymptomatic carrier of the same *OTC* variant.

Discussion

Historically, there was a misbelief that OTC deficiency was an X-linked condition affecting only males and that heterozygous women, referred to as "carriers," did not require monitoring for disease manifestations. Over time, it has become clear that while women are less likely to present with early-onset lethal forms, they can experience variable and nonspecific chronic symptoms that are often misinterpreted or overlooked [14].

The pattern of X-chromosome inactivation in the liver determines the OTC enzyme activity in heterozygous women. If X-chromosome inactivation in hepatic cells is skewed toward the pathogenic *OTC* variant, heterozygous women are more likely to manifest symptoms of OTC deficiency [15].

OTC deficiency is now recognized as an X-linked condition without recessive or dominant inheritance patterns [14]. The terminology used to describe the clinical phenotypes includes neonatal-onset OTC deficiency (severe), postnatal onset, or late-onset (partial) forms [1]. Unfortunately, "partial" may mislead physicians and patients into believing the condition is not clinically severe or potentially life-threatening.

Future discussions about nomenclature should emphasize that even patients with "partial" OTCD are at significant risk for decompensation under catabolic stressors.

OTC catalyzes the formation of citrulline from ornithine and carbamoyl phosphate in the liver and small intestine [16]. Citrulline synthesis occurs either as an intermediate of the urea cycle or as a precursor for arginine biosynthesis [17]. Enzymatic activity can be affected by various pathogenic variants, including frameshift mutations, missense variants that alter substrate binding, and nonsense variants that reduce enzyme stability [18]. Variants affecting mRNA splicing, as observed in one of the patients, or affecting regulatory regions, result in altered functional transcription [19].

OTCD exhibits a broad phenotypic spectrum, ranging from classic neonatal presentations often associated with long-term disability and even death to asymptomatic carrier states [8]. Literature suggests that some heterozygous women may present with symptoms ranging from altered neurological states to cognitive impairments, such as deficiencies in executive functioning, fine motor skills, and inhibitory capacity, particularly in response to cognitive challenges. This highlights the importance of evaluating and monitoring the neurocognitive function of carriers [20–22].

Symptomatic heterozygous women have also been described with a late onset of symptom presentation, emphasizing the need for early recognition and long-term follow-up.

In our series, all three patients experienced acute metabolic crises triggered by specific catabolic or stress-related events.

The first patient debuted during a viral illness, a recognized time of increased catabolism and metabolic instability.

The second patient began with psychiatric symptoms postpartum, but was not diagnosed until several years later, in her next pregnancy when she developed symptoms during

the first trimester in the setting of hyperemesis gravidarum, highlighting the susceptibility of early gestation to metabolic stress.

The third patient had her first decompensation during a febrile illness in early childhood, and she had a relevant family history related to it.

These cases reinforce the concept that infections, pregnancy-related conditions, and caloric deficits (e.g., vomiting, poor intake) are potent triggers of metabolic decompensation in heterozygous females.

At the time of diagnosis, none of the patients were under the care of metabolic specialists, and in all three cases, initial management was provided by general medical teams. Biochemical testing was not immediately directed toward inborn errors of metabolism. The second case required referral to a tertiary care hospital with access to genetic evaluation and molecular diagnostics. This delay underscores the diagnostic challenge in adult women with nonspecific neurological or psychiatric symptoms. Access to comprehensive metabolic testing, including plasma ammonia, amino acids, and molecular analysis, remains limited in many settings and often requires high clinical suspicion to be pursued.

In this series, we report three patients with manifestations from infancy to adolescence, reflecting the variability of presentation in OTCD. Given the X-linked inheritance of the disorder, constructing a pedigree and investigating family history is essential; two of our patients had no family history. However, it is noteworthy that the second patient had a male child who died neonatally of an unexplained cause, and she reported protein aversion since childhood.

Clinical manifestations varied among cases, presenting as acute or chronic symptoms including drowsiness, lethargy, encephalopathy, seizures, vomiting, behavioral alterations, irritability, developmental delay, and coma.

Intolerance to animal protein was a common feature in all cases, although it was not consistently recognized as a pathological sign before diagnosis.

Regarding disease progression, all three patients survived hyperammonemia episodes. Despite the severity of the second patient, who was diagnosed with hyperemesis gravidarum and encephalopathy, her pregnancy ended without complications during the puerperium or subsequent exacerbations. The male child from this pregnancy tested negative for OTC deficiency. However, he presented microcephaly and spastic paralysis and passed away secondary to a respiratory infection. Additionally, genetic tests were not possible.

The literature reports an 80–90 % survival rate in symptomatic heterozygotes and a generally favorable prognosis [23]. Pregnancy can be a high-risk condition as catabolic processes predominate, potentially leading to hyperammonemic encephalopathy and life-threatening coma [23]. Anorexia and nausea during the first trimester increase the risk of a hyperammonemic crisis, as observed in the pregnant patient before her diagnosis. Therefore, ensuring adequate energy intake and preventing dehydration is crucial. Given protein consumption restrictions, fetal growth and development must be closely monitored. While the reported cases showed no complications [23], our patient delivered a low birthweight infant with microcephaly. Vaginal delivery poses higher energy demands, so preventing prolonged labor and ensuring adequate hydration are recommended. These preventive measures contributed to this patient's normal course of labor and puerperium [24].

As of February 2025, at least 523 pathogenic or probably pathogenic variants have been identified in public databases (ClinVar and LOVD). Only 80 % of variants are detectable by sequencing [1], as rearrangements and mutations in non-coding regions (e.g., regulatory and deep intronic regions) are often missed. Large deletions involving all or most of the *OTC* gene account for nearly 5–10 % of all OTC deficiency cases [1].

In 2009, a study conducted at the Medical Genetics Laboratories at Baylor College of Medicine (Houston, Texas) analyzed 70 OTCD patients for mutations using sequencing (excluding promoter and deep intronic regions). Samples negative by sequencing were analyzed with array CGH, demonstrating that approximately 15 % of all OTC deficiencies referred to their laboratory were caused by deletions, which were more frequently observed in female patients. aCGH should be considered in patients with negative *OTC* sequencing and high suspicion of the disease [24]. This pattern aligns with the 1.6 Mb deletion identified in our first patient. It affects 15 genes, including *OTC* and *CYBB*. Although not previously reported, it was classified as pathogenic.

The second patient had an intronic variant c.77+5G>A. This intronic +5 variant likely affects the donor splice site in exon 1 and has previously been reported once in a newborn with OTC deficiency and in a female heterozygous with adult presentation [25]. The third patient harbored a c.583G>A variant, classified as pathogenic and previously reported in the literature. Martin-Hernandez et al. reported three female heterozygous for this variant: two asymptomatic cases detected by family history, and the third case was a late symptomatic presentation [26].

Conclusions

Early and accurate identification of ornithine transcarbamylase deficiency (OTCD) through genetic testing is essential to establish timely diagnosis, reduce diagnostic delays, and implement individualized treatment strategies that prevent irreversible neurological injury or death due to hyperammonemic crises.

Carrier testing in at-risk individuals enables risk stratification and informed reproductive decision-making through genetic counseling.

The management of OTCD must be comprehensive and multidisciplinary, including personalized protein restriction, pharmacological ammonia scavenging, and nutritional support. During pregnancy, particularly in the first trimester and postpartum period, close clinical surveillance is critical to prevent catabolic stress that may precipitate life-threatening

metabolic decompensation. Emergency protocols and family education are indispensable for early recognition and rapid intervention during acute episodes.

The underlying genetic heterogeneity of OTCD – including missense mutations, splicing alterations, and large deletions – requires the use of advanced molecular tools. Next-generation sequencing (NGS), MLPA, and array CGH are complementary technologies that increase diagnostic yield by identifying both single-nucleotide variants and structural rearrangements, including those in non-coding regions that standard sequencing may overlook.

Patients with OTCD require lifelong follow-up at centers with expertise in metabolic diseases, with regular assessments of neurocognitive function, psychiatric comorbidities, and developmental trajectories. Follow-up care should also incorporate psychosocial support and educational strategies for patients and their caregivers.

Expanding neonatal screening programs to include urea cycle disorders, could facilitate earlier diagnosis and improve clinical outcomes. Future research should prioritize the evaluation of long-term outcomes, refinement of treatment protocols, and development of targeted therapies, especially in heterozygous women and asymptomatic carriers who remain at risk for metabolic crises.

Supplementary Material

The following online material is available for this article:

Table S1 – Detailed Case Descriptions.

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Declaration of Conflicting Interest

The authors declare no conflicts of interest regarding the publication of this paper. No financial support, honoraria, or incentives were received in connection with this work.

Data Availability

The dataset generated and analysed during the current study contains personal health information that cannot be made publicly available to protect patient privacy. De-identified data may be obtained from the corresponding author upon reasonable request and with prior approval of the Ethics Committee of Hospital Universitario San Ignacio.

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