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CASE REPORT

HEREDITARY TYROSINEMIA TYPE I DIAGNOSED AFTER LIVER TRANSPLANTATION FOR PROGRESSIVE HEPATIC FAILURE: DIAGNOSTIC CHALLENGES AND NUTRITIONAL MANAGEMENT

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Abstract

Introduction. Hereditary tyrosinemia type I (HT1) is a rare autosomal recessive metabolic disorder caused by fumarylacetoacetate hydrolase deficiency. Delayed diagnosis may result in progressive liver disease, cirrhosis, and liver failure requiring transplantation. We report a child with HT1 diagnosed only after liver transplantation.
Case presentation. A male infant, born at term without significant perinatal complications, presented at 4 months of age with abdominal distension and hepatosplenomegaly. Imaging studies revealed multiple intrahepatic cystic lesions and biliary abnormalities suggestive of Caroli disease and chronic cholangiopathy. Despite extensive investigations, the etiology remained unclear while progressive hepatic dysfunction, portal hypertension, and advanced cirrhosis developed.

Résumé

Tyrosinémie héréditaire de type I diagnostiquée après transplantation hépatique pour insuffisance hépatique évolutive: défis diagnostiques et enjeux de la prise en charge nutritionnelle

Introduction. La tyrosinémie héréditaire de type I (HT1) est une maladie métabolique autosomique récessive rare, due à un déficit en fumarylacétoacétate hydrolase. Un diagnostic tardif peut entraîner une atteinte hépatique progressive, une cirrhose et une insuffisance hépatique nécessitant une transplantation. Nous rapportons le cas d'un enfant atteint de HT1 diagnostiquée seulement après une transplantation hépatique.
Présentation du cas. Un nourrisson de sexe masculin, né à terme sans complications périnatales

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Metabolic evaluation performed during pre-transplant assessment demonstrated markedly elevated urinary succinylacetone, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylpyruvic acid levels, strongly suggestive of HT1. However, the diagnosis was established only after living-donor liver transplantation.
The absence of neonatal metabolic screening and limited access to specialized diagnostic testing contributed to significant diagnostic delay. Consequently, nitisinone therapy and dietary restriction of tyrosine and phenylalanine were not initiated before irreversible liver damage occurred. Following transplantation, disease-specific nutritional management and multidisciplinary follow-up became essential components of care.
Conclusions. HT1 should be considered in infants presenting with unexplained hepatosplenomegaly and progressive liver disease. Early metabolic screening, particularly urinary succinylacetone measurement, is essential for timely diagnosis and initiation of specific treatment, potentially preventing progression to end-stage liver disease and liver transplantation.

Keywords: hereditary tyrosinemia type I, liver failure, liver transplantation, succinylacetone, nutritional management.

List of abbreviations:
HT1 – hereditary tyrosinemia type I (FAH)
FAH – fumarylacetoacetate hydrolase

Les examens d'imagerie ont révélé de multiples lésions kystiques intrahépatiques et des anomalies biliaires évoquant une maladie de Caroli et une cholangiopathie chronique. Malgré des investigations approfondies, l'étiologie est restée indéterminée, tandis qu'une insuffisance hépatique progressive, une hypertension portale et une cirrhose avancée se sont développées. Le bilan métabolique réalisé en pré-transplantation a mis en évidence une élévation marquée des taux urinaires de succinylacétone, d'acide 4-hydroxyphénylactique et d'acide 4-hydroxyphénylpyruvique, fortement évocatrice d'une HT1. Cependant, le diagnostic n'a été établi qu'après une transplantation hépatique à partir d'un donneur vivant.
L'absence de dépistage métabolique néonatal et l'accès limité aux examens diagnostiques spécialisés ont contribué à un retard diagnostique important. Par conséquent, le traitement par nitisinone et la restriction alimentaire en tyrosine et phénylalanine n'ont pas été instaurés avant l'apparition de lésions hépatiques irréversibles. Après la transplantation, la prise en charge nutritionnelle spécifique à la maladie et un suivi multidisciplinaire sont devenus des éléments essentiels des soins.
Conclusions. La tyrosinémie héréditaire de type 1 (HT1) doit être envisagée chez les nourrissons présentant une hépatosplénomégalie inexpliquée et une maladie hépatique progressive. Un dépistage métabolique précoce, notamment le dosage de la succinylacétone urinaire, est essentiel pour un diagnostic rapide et la mise en place d'un traitement spécifique, pouvant potentiellement prévenir l'évolution vers une insuffisance hépatique terminale et la nécessité d'une transplantation hépatique.

Mots-clés: tyrosinémie héréditaire de type 1, insuffisance hépatique, transplantation hépatique, succinylacétone, prise en charge nutritionnelle.

Introduction

Hereditary tyrosinemia type I (HT1) is a rare autosomal recessive disorder caused by fumarylacetoacetate hydrolase deficiency, resulting in the accumulation of toxic metabolites that primarily affect the liver and kidneys. Early diagnosis is essential because treatment with nitisinone combined with dietary restriction of tyrosine and phenylalanine can prevent progressive liver disease and significantly reduce the need for liver transplantation. However, in countries without neonatal screening programs and limited access to specialized metabolic investigations, diagnosis may be delayed until advanced hepatic complications develop.

We report the case of a young child with progressive liver failure and cirrhosis, initially investigated as a hepatobiliary malformation, who underwent liver transplantation before the diagnosis of HT1 was established. The case highlights the diagnostic challenges associated with atypical presentation and underscores the importance of metabolic evaluation in children with unexplained chronic liver disease.

Case presentation

A male child, born at term following an uncomplicated pregnancy and delivery, with no significant perinatal history and mixed feeding during infancy,

presented in June 2024 at approximately 4 months of age, when progressive abdominal enlargement was noted during a routine examination by the family physician. Abdominal ultrasonography revealed hepatosplenomegaly, prompting referral to the Institute of Mother and Child Chisinau, Republic of Moldova, for further evaluation.

At the initial hospitalization, the patient presented abdominal distension, pallor, mild scleral icterus, recurrent episodes of vomiting, profuse sweating, and marked hepatosplenomegaly. Imaging studies demonstrated multiple intrahepatic cystic lesions associated with hyperdense hepatic abnormalities, hepatosplenomegaly, and mesenteric and epicardial lymphadenopathy. The initial differential diagnosis included multiple biliary hamartomas, polycystic liver disease, and primary hepatic lymphoma.

During further investigations, magnetic resonance cholangiography revealed abnormalities of the intrahepatic biliary tree, including segmental bile duct dilatations suggestive of Caroli disease, primary sclerosing cholangitis, and possible liver cirrhosis. Over the following months, the clinical course was characterized by progressive deterioration of liver function, persistent hepatosplenomegaly, and the development of portal hypertension, without identification of a definitive underlying etiology.

Between October 2024 and February 2025, the patient required multiple hospital admissions for monitoring and evaluation of progressive chronic liver disease. Extensive investigations were performed to establish the indication for liver transplantation. A planned liver biopsy was repeatedly postponed because of recurrent respiratory infections and the patient's fragile clinical condition. In the setting of worsening hepatic insufficiency and suspected advanced cirrhosis, the child was ultimately enrolled in a liver transplantation program.

In March–April 2025, additional investigations revealed severe hepatomegaly, findings suggestive of congenital hepatic fibrosis, liver stiffness corresponding to stage F3 fibrosis (8.0 kPa), and markedly increased splenic stiffness (41 kPa). Given the absence of a clear etiological diagnosis, genetic and metabolic evaluations were requested. The differential diagnosis included Gaucher disease, glycogen storage disorders, alpha-1 antitrypsin deficiency, and HT1.

Metabolic screening and urinary organic acid analysis demonstrated markedly elevated concentrations of tyrosine degradation metabolites, including 4-hydroxyphenyllactic acid (2500 mmol/mol creatinine), 4-hydroxyphenylpyruvic acid (660 mmol/mol creatinine), and succinylacetone (63 mmol/mol creatinine), accompanied by increased glycine and galactitol levels. These findings were highly suggestive of hereditary tyrosinemia type I.

By the time the metabolic abnormalities were identified, the patient had already developed advanced liver cirrhosis and progressive hepatic failure and had been placed on the liver transplantation waiting list. Because of the delayed diagnosis, he had not received the internationally recommended first-line treatment for HT1, namely nitisinone therapy combined with dietary restriction of tyrosine and phenylalanine.

On May 26, 2025, the patient underwent living-donor liver transplantation, representing the first pediatric living-donor liver transplantation performed at such a young age in the Republic of Moldova. The diagnosis of HT1 was established retrospectively based on the characteristic metabolic profile. Molecular confirmation through *FAH* gene analysis was not available because disease-specific genetic testing could not be performed in the Republic of Moldova.

Following transplantation, management included close monitoring of liver function, immunosuppressive therapy with tacrolimus, and implementation of nutritional recommendations specific to HT1. The postoperative course was complicated by recurrent episodes of tacrolimus overdose, elevated liver enzymes, and suspected biliary and vascular graft complications, requiring repeated hospitalizations and multidisciplinary follow-up. In addition, poor adherence to the prescribed low-protein dietary regimen represented a significant challenge for the long-term management.

This case highlights the diagnostic difficulties of HT1 in a child presenting predominantly with progressive liver disease and demonstrates the consequences of delayed diagnosis, which was established only after the development of end-stage liver disease and liver transplantation. Furthermore, it underscores the importance of early metabolic investigations in infants and young children presenting with hepatosplenomegaly and progressive liver disease of unknown origin.

Discussion

HT1 is a rare autosomal recessive disorder caused by deficiency of fumarylacetoacetate hydrolase (FAH), the final enzyme in the tyrosine catabolic pathway. The resulting accumulation of toxic metabolites, particularly fumarylacetoacetate, maleylacetoacetate, and succinylacetone, leads to progressive hepatic and renal injury and significantly increases the risk of hepatocellular carcinoma. An early diagnosis is crucial because timely initiation of nitisinone therapy combined with dietary restriction of tyrosine and phenylalanine can substantially alter the natural history of the disease.

The present case illustrates the diagnostic challenges associated with HT1 in countries where neonatal metabolic screening and advanced metabolic investigations are not routinely available. The patient initially presented with progressive hepatosplenomegaly and complex hepatobiliary abnormalities detected by imaging studies. The radiological findings, including segmental intrahepatic bile duct dilatations and suspected congenital biliary malformations, directed the diagnostic process toward structural hepatobiliary disorders such as Caroli disease, congenital hepatic fibrosis, and sclerosing cholangitis. Consequently, the underlying metabolic etiology remained unrecognized during the early stages of disease progression.

A notable feature of this case is the unusually long diagnostic delay. Hepatosplenomegaly was identified at approximately 4 months of age, whereas the metabolic diagnosis was established only after the child had already developed advanced cirrhosis, portal hypertension, and progressive liver failure requiring liver transplantation. This delay likely contributed to irreversible hepatic injury and eliminated the opportunity to initiate disease-specific treatment before the onset of end-stage liver disease.

The detection of markedly elevated urinary succinylacetone represented the key diagnostic finding. Succinylacetone is considered the most sensitive and specific biochemical marker for HT1 and forms the basis of newborn screening programs in many countries. In our case, metabolic investigations were performed only after extensive evaluations had failed to identify another cause of chronic liver disease. Earlier determination of succinylacetone might have facilitated a more rapid diagnosis and potentially altered the clinical course.

Current international guidelines recommend nitisinone (NTBC) combined with lifelong dietary restriction of tyrosine and phenylalanine as the standard first-line treatment for HT1. Since its introduction, nitisinone has dramatically reduced mortality, the incidence of hepatic failure, and the need for liver transplantation. Several studies have demonstrated that patients diagnosed early and treated before the development of cirrhosis achieve favorable long-term outcomes with preservation of liver function and significantly improved survival.

An important aspect of the present case is that the patient did not receive either nitisinone therapy or disease-specific nutritional treatment prior to transplantation because the diagnosis had not yet been established. Consequently, the natural progression of the disease was not interrupted, leading to irreversible hepatic damage. This observation highlights the critical role of early metabolic screening in children presenting with unexplained hepatomegaly, hepatosplenomegaly, chronic liver disease, or suspected congenital hepatobiliary abnormalities.

Although liver transplantation remains a life-saving therapeutic option for patients with acute liver failure, advanced cirrhosis, or hepatocellular carcinoma, it is currently reserved for selected cases in the era of nitisinone therapy. In HT1, transplantation corrects hepatic metabolic dysfunction but does not completely eliminate systemic metabolic abnormalities and exposes patients to lifelong immunosuppression and transplant-related complications. In our patient, the post-transplant course was complicated by recurrent elevations of tacrolimus levels, abnormal liver function tests, and suspicion of biliary and vascular complications, requiring repeated hospitalizations and multidisciplinary management.

Another important lesson from this case concerns the role of nutritional therapy. Restriction of tyrosine and phenylalanine intake constitutes an essential component of HT1 management and should be initiated immediately after diagnosis. In the present case, nutritional intervention was introduced only after transplantation, once the metabolic diagnosis had been established. Furthermore, limited adherence to the prescribed low-protein diet represented an additional challenge during follow-up. This emphasizes the importance of continuous nutritional counseling and long-term monitoring by specialized multidisciplinary teams.

To our knowledge, this represents the first reported pediatric case of HT1diagnosed in the Republic of Moldova and one of the few cases in whom the diagnosis was established only after liver transplantation. The case highlights existing limitations in access to metabolic diagnostics, molecular testing, orphan drugs, and specialized nutritional products. It also underscores the need to expand awareness of inherited metabolic liver diseases among pediatricians, gastroenterologists, hepatologists, surgeons, and geneticists to facilitate earlier recognition and intervention.

Overall, this case demonstrates that HT1 should be systematically considered in the differential diagnosis of infants and young children with unexplained hepatosplenomegaly, progressive liver dysfunction, or radiological findings suggestive of congenital hepatobiliary disease. Early metabolic evaluation may prevent diagnostic delay, allow timely initiation of specific therapy, and reduce the need for liver transplantation.

Conclusions

HT1 should be considered in infants and young children presenting with unexplained hepatosplenomegaly and progressive liver disease. Delayed diagnosis may lead to irreversible hepatic damage, advanced

cirrhosis, portal hypertension, and liver transplantation. Early determination of urinary succinylacetone is essential for establishing the diagnosis and initiating disease-specific treatment. Timely administration of nitisinone combined with dietary restriction of tyrosine and phenylalanine remains the cornerstone of HT1 management and may prevent progression to end-stage liver disease. This case highlights the importance of improving access to metabolic diagnostics and increasing awareness of inherited metabolic liver diseases to reduce diagnostic delays and improve clinical outcomes.

Author Contributions:

Conceptualization, methodology, software, validation, formal analysis, investigation, resources and data curation I.M., T.I., D.B., N.U., A.N., I.T., I.M.; writing–original draft preparation, writing–review and editing, visualization, supervision I.M., T.I., D.B., N.U., A.N., I.T., I.M.; project administration, I.M. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent for publication of the clinical data was obtained from the patient's legal guardians."

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