

Hypophosphatemic Rickets as a Key Sign for the Diagnosis of Hereditary Tyrosinemia Type 1: Case Reports and Narrative Review of the Literature

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Raquitismo hipofosfatémico como un signo clave para el diagnóstico de la tirosinemia hereditaria tipo 1: Reporte de casos y revisión narrativa de la literatura

ABSTRACT

Hereditary tyrosinemia type 1 (HT-1) is an inborn error of metabolism caused by a defect in tyrosine (tyr) degradation. This defect results in the accumulation of succinylacetone (SA), causing liver failure with a high risk of hepatocarcinoma and kidney injury, leading in turn to Fanconi syndrome with urine loss of phosphate and secondary hypophosphatemic rickets (HR). HT-1 diagnosis is usually made in infants with acute or chronic liver failure or by neonatal screening programs. HR is rarely described in the literature as the main feature or chief complaint of patients with HT-1. **Clinical cases:** We present three children who presented signs of HR during infancy. Patient 1 had early liver dysfunction, leading to a quick diagnosis of HT-1. Patients 2 and 3 started conventional therapy for HR (calcitriol and oral phosphate) with partial clinical response. Later, both developed liver dysfunction, and patient 3 presented neurological symptoms (porphyria-like crises). An HT-1 diagnosis was made using tandem mass spectrometry, which confirmed high plasma levels of SA and tyr. After diagnosis, all started treatment with a specific diet and nitisinone with prompt recovery and a quick remission of clinical signs of HR, being able to discontinue their conventional rickets therapy successfully. **Conclusion:** We present three patients with HT-1 whose main complaint was HR. It is important to know the main features of this metabolic disorder and have a high index of suspicion when we follow-up children with HR, especially if they are not responding to conventional therapy or develop liver dysfunction. **Keywords:** Case Reports; Hypophosphatemia; Rickets; Tyrosinemias.

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Funding: This work received no financial support of any kind.

The authors declare no conflicts of interest.

Received: August 02, 2024.
Accepted: October 30, 2024.

RESUMEN

La tirosinemia hereditaria tipo 1 (HT-1) es un error innato del metabolismo causado por un defecto en la degradación de la tirosina (tyr), dando lugar a la acumulación de succinilacetona (SA) que provoca insuficiencia hepática con alto riesgo de carcinoma hepatocelular y daño renal, lo que puede conducir al síndrome de Fanconi con pérdida urinaria de fosfato y raquitismo hipofosfatémico (HR) secundario. El diagnóstico de HT-1 generalmente se realiza en bebés con insuficiencia hepática aguda o crónica o mediante programas de detección neonatal. El HR rara vez se describe como el signo principal de los pacientes con HT-1. **Casos clínicos:** Presentamos tres niños con signos de HR durante su periodo infantil. El primer paciente tuvo disfunción hepática temprana que llevó a un diagnóstico rápido de HT-1. Los otros 2 pacientes iniciaron terapia convencional para HR con respuesta clínica parcial. Posteriormente ambos desarrollaron disfunción hepática y el tercero presentó crisis tipo porfiria. El diagnóstico de HT-1 se realizó mediante espectrometría de masas que confirmó niveles plasmáticos elevados de SA y tyr. Tras el diagnóstico, todos iniciaron tratamiento con dieta específica y nitisinona con pronta recuperación y rápida remisión de los signos de HR, logrando suspender con éxito el tratamiento convencional. **Conclusión:** Presentamos tres pacientes con HTA-1 cuya principal queja fue el HR. Es importante conocer las principales características de este trastorno metabólico y tener un alto índice de sospecha en el seguimiento de niños con HR, especialmente si no responden a la terapia convencional o desarrollan disfunción hepática.

Palabras clave: Hipofosfatemia; Informes de Casos; Raquitismo; Tirosinemias.

Hereditary tyrosinemia type 1 (HT-1) (OMIM: 276700) is a rare inborn error of metabolism caused by a defect in tyrosine (tyr) degradation due to deficiency of the enzyme fumarylacetoacetate hydroxylase (FAH)¹, leading to accumulation of fumarylacetoacetate (FAA), maleylacetoacetate (MAA) and succinylacetone (SA), which cause liver and kidney damage (Figure 1)². The presence of SA is pathognomonic in HT-1 and its presence in blood and/or urine confirms the diagnosis. It is also characterized by elevation of tyr, phenylalanine (phe) and methionine measured

by mass spectrometry (MS)^{1,2}. The incidence of the disease worldwide is around 1/100,000 live births³. In Quebec, Canada it is much higher, being 1/1,846 due to the presence of a founder mutation IVS12+5G>A⁴.

As mentioned above, the absence of FAH produces accumulation of FAA and MAA, which are reduced to succinylacetoacetate, and by decarboxylation produces the toxic metabolite SA, which damages liver cells, altering their function both acute and chronically, favoring the development of hepatocellular carcinoma^{5,6}.

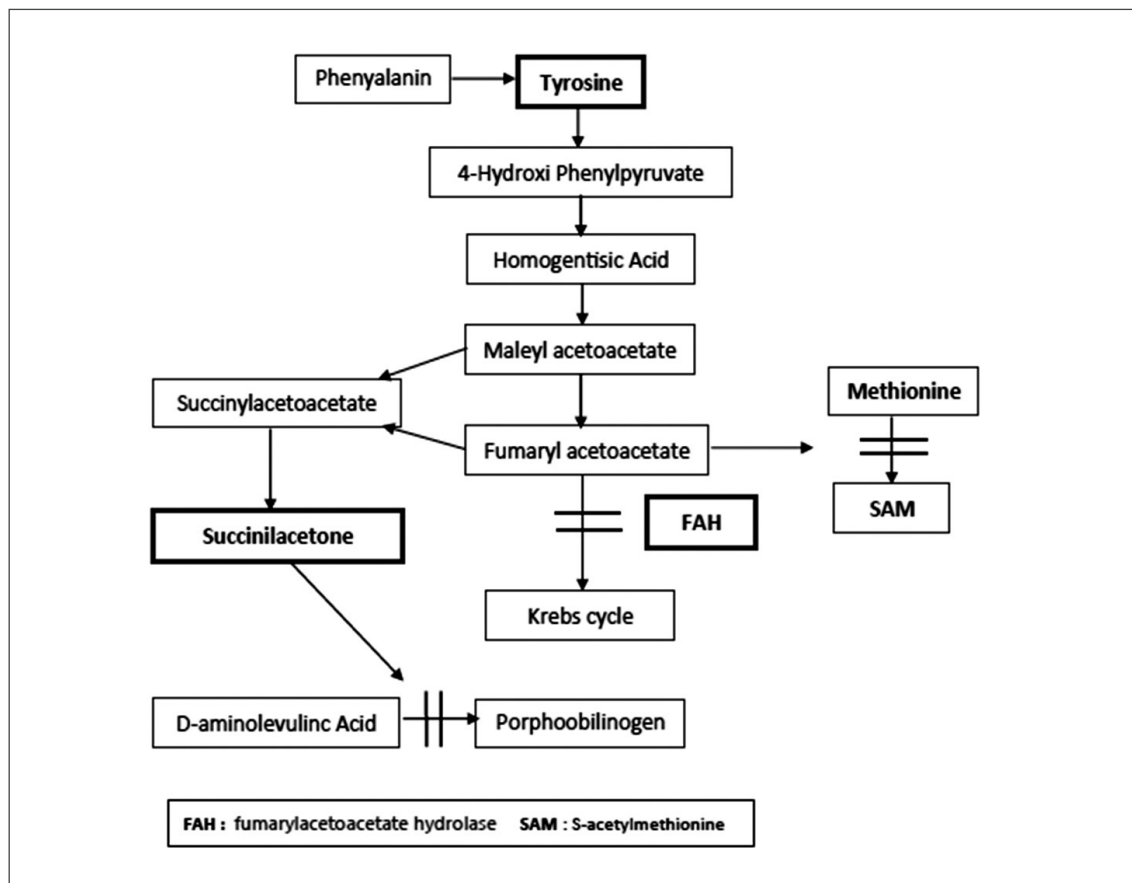


Figure 1: Metabolic pathway of tyrosine and pathogenesis in HT-1. Adapted from Chinsky, et al. 2017² and Larochelle, et al. 2012¹⁴.

It also induces apoptosis in kidney tissue, which generates fibrosis and glomerulosclerosis⁷. This causes tubular damage manifested by Fanconi syndrome; characterized by renal tubular acidosis, proteinuria, and phosphaturia, which leads to hypophosphatemic rickets^{2,8}. SA also produces elevation of 5-aminolevulinic acid (AA) by inhibiting porphobilinogen synthase, which is associated with porphyria-like neurological crises^{9,10}.

Three forms of presentation have been described. The acute form begins before 2 months of life and is characterized by severe acute liver failure associated with cirrhosis, hepatosplenomegaly, coagulopathy and hypoglycemia. This form pre-

sents with high mortality during the first months of life and there is an early and significant increase of alpha-fetoprotein (A-FP)¹¹, which can be more than 100 times higher than the reference range¹².

The subacute form is similar to the first, but symptoms develop between 2 and 6 months of life¹¹. In addition to liver damage, disorders caused by renal tubular losses become more evident, leading to hypophosphatemic rickets due to loss of urinary phosphate, which manifests more frequently in those patients who have been at least 12 months without treatment⁸. Acute porphyria-like neurological crises secondary to accumulation of AA may also occur in this form¹³.

The chronic form is initially less aggressive and insidious. This form appears after 6 months of life with kidney disorders and Fanconi syndrome, which may be its initial manifestation, with hepatic and neurological complications of later presentation¹¹.

Combined treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione or nitisinone (NTBC) plus a tyr and phe restricted diet has drastically changed the natural history of the disease, reporting a survival rate over 90%, especially if it's started early in life¹⁴. Patients evolve with normal growth, improvement of their liver function, prevention of cirrhosis and hepatocellular carcinoma, correction of renal tubular acidosis and reversal of secondary rickets^{14,15}.

We report three cases of patients with a late diagnosis of HT-1 in whom hypophosphatemic rickets was the chief complaint. Informed consent was obtained from all patients' parents or caregivers included in this study.

Case 1

One year old female infant born to non-consanguineous parents. She was evaluated at 9 months of age in the hematology department for recurrent epistaxis, finding a bleeding disorder characterized by aPTT of 38 seconds, INR 1.6, prothrombin time 52%, hematocrit 28% and hemoglobin 8.8 g/dl. Hemophilia was ruled out. She was later admitted because of an acute pyelonephritis. Her medical exam showed hepatosplenomegaly, thickened wrists, varus deformity and ricketic rosary. Laboratory showed hypophosphatemia, anemia and high levels of A-FP. Signs of rickets were found in costal and leg x-rays. Abdominal US showed signs of chronic liver damage and hepatic nodules. Studying her chronic liver failure, an expanded newborn screening by tandem MS was performed finding tyr levels of 207.5 $\mu\text{M}/\text{l}$ and SA acetone levels of 6.2 $\mu\text{M}/\text{l}$ (Table 1), confirming HT-1. Treatment with NTBC and restricted diet in tyr and phe was started, also phosphate 50 mg/kg/day 5 times daily was added. Her exams improved rapidly, and so did her anthropometry concomitantly with rickets improvement. Hepatic involvement showed portal

hypertension with grade 1 esophageal varices. Initially, after hospital discharge, she had regular adherence to medical controls, improving with time. An abdominal MRI was made showing a hepatic vascularized nodule measuring 2.6 mm which suggested malignancy. This was discarded with another MRI and decreasing levels of A-FP.

Case 2

Female infant aged 1 year 3 months, evaluated by her pediatrician for failure to thrive and bone deformities. Her laboratory findings showed hypophosphatemia, very high parathyroid hormone and alkaline phosphatase (ALP), normal calcium and vitamin D levels. Rickets was suspected and endocrinologic evaluation was requested.

Her physical exam showed short stature, malnutrition, mucosal cysts in superior teeth in addition to enamel deterioration. Prominent ribs, abdomen without visceromegaly, thin limbs, wrist enlargement and genu varus. She had bone pain and did not show autonomous gait.

Her exams showed normal urinary calcium levels and phosphate tubular reabsorption of 78% (RR 80-90%). Hypophosphatemic Rickets was suspected, starting calcitriol 0.5 $\mu\text{g}/\text{day}$, calcium carbonate, vitamin D and phosphate 30 mg/kg/day.

Six months later, being adherent to treatment, no amelioration was noticed in her biochemical exams. Moreover, incipient augmentation of aminotransferases was noted with normal bilirubin and INR. Hepatomegaly was noted in her physical exam. Abdominal US confirmed hepatomegaly showing heterogeneous parenchyma with multiple micronodular images. Very high A-FP levels were noted with mild proteinuria. HT-1 was suspected and MS showed high tyr and SA blood levels, confirming the diagnosis (Table 1).

NTBC 1 mg/kg/daily with a tyr and phe restricted diet was initiated and phosphorus progressively augmented, ALP diminished and so did her hepatomegaly. Transaminases and A-FP were normalized, while GGT persisted mildly elevated. After one month of treatment, she started walking alone and radiologic alterations improved (Figure 2).

Table 1. Clinical and laboratory characteristics of children with Tyrosinemia Type 1 and hypophosphatemic rickets at diagnosis.

Clinical and laboratory variable	Patient # 1	Patient # 2	Patient # 3
Age at diagnosis			
Rickets (months)	12	16	36
Tyrosinemia (months)	12	25	60
Clinical presentation			
Height / age z score	-3.20 z	-2.78 z	-0.76 z
Bone deformity	Yes	Yes	Yes
Visceromegaly	Hepatomegaly/ splenomegaly	Hepatomegaly	Hepatomegaly/ nephromegaly
Laboratory			
Calcium (mg/dL) (RR 8.9-10.2)	9.1	9.7	9.9
Phosphate (mg/dL) (RR 3.6-5.5)	1.6	2.7	3.4
ALP (UI/L) (RR 110-302)	715	1786	904
25-OH Vitamin D (ng/mL) (RR 30-100)	62	63.8	73
PTH (pg/mL) (RR 10-65)	98	62.7	41
TPR (%) (RR 78-91)	95	78	93
Glycosuria / proteinuria (+ or -)	- / -	- / +	- / -
TB/DB (mg/dL) (RR TB 0.2-1; DB<1)	N/A	0.8 /0.2	N/A
ALT/AST (UI/L) (RR ALT 7-40; AST 10-40)	11/66	69 /151	25/30
GGT (UI/L) (RR 6-50)	144	185	320
INR (RR 0.8-1.2)	1.6	1.3	1.2
Alpha-fetoprotein (ng/mL) (RR variable by age)	45,020	6,850	933
Metabolic laboratory			
Succinylacetone* (uM/L) (RR<1)	6.2	14.25	11.6
Tyrosine (uM/L) (RR 0-121)	207.5	495.45	190

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: aspartate aminotransferase, INR: international normalized ratio, GGT: Gamma glutamyl transpeptidase, N/A: not available, PTH: parathormone, RR: reference range, TB/DB: total/direct bilirubin, TPR: tubular phosphate reabsorption

*Succinylacetone determination in dried blood spots.

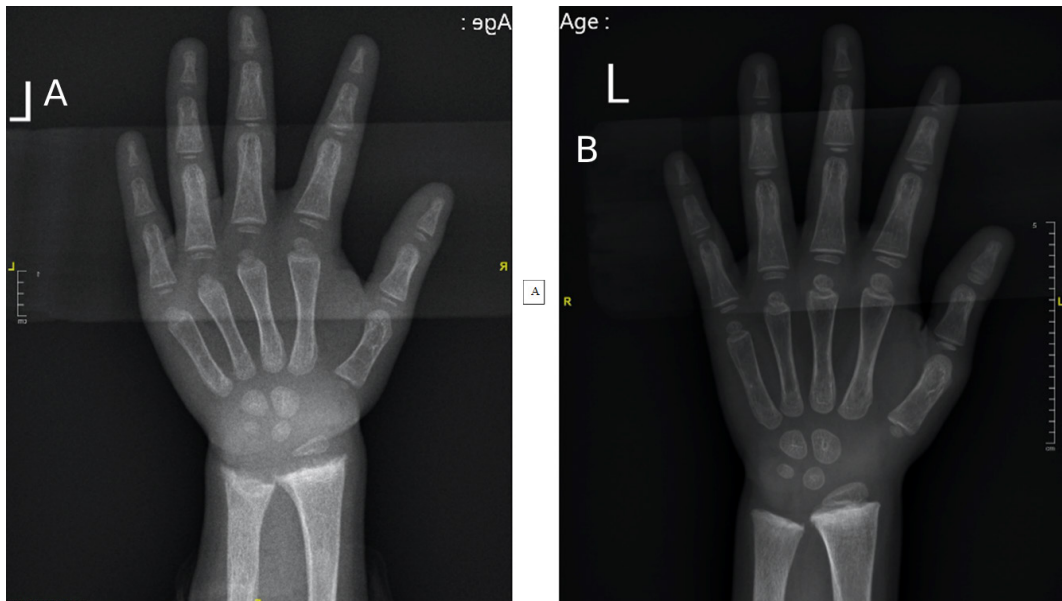


Figure 2: Wrist X-ray of patient #2 before treatment (A) and 1 month post NTBC treatment (B).

Case 3

Five-year-old girl without relevant familial pathological records. First evaluation was at 3 years of age by a pediatric orthopedist for asymmetric genu valgus, so an endocrinological consultation was suggested. Laboratory findings showed mild hypophosphatemia, phosphaturia and high ALP with normal calcium and vitamin D levels, so hypophosphatemic rickets was suspected. Treatment was initiated with calcitriol 0,25 ug/day and phosphate 40 mg/kg/day.

Three months later ALP levels were still high but were normal at 6 months. Calcitriol and phosphate doses were augmented reaching 0,75 ug and 60 mg/kg/day respectively. Even though laboratory exams normalized, genu valgum persisted. Moreover, anemia and a bleeding disorder were detected.

At 5 years of age she presented with fever, diarrhea and abdominal pain. Appendicitis was discarded. Pain persisted for 10 days and hepatomegaly was noted, requesting gastroenterological consultation. Physical exam showed hepatomegaly, rachitic rosary, limb deformities and digital clubbing. Laboratory showed abnormal liver

function. Abdominal US showed irregular and heterogeneous liver parenchyma, hypoechogenic pseudo nodular liver areas and bilateral renal enlargement. HT-1 was confirmed by MS with high SA and A-FP levels (Table 1).

The patient started with fluctuating weakness, pain in lower limbs and abdominal pain (porphyria like crisis), limiting normal autonomous gait for 2–3 days. She was evaluated in the emergency department and, after neurologic advice, NTBC (1m/kg/day) was started. Acute symptoms regressed with treatment and she progressively improved her liver function, recovered from her rickets and normalized her anthropometry.

Discussion

HT-1 can be diagnosed from infancy to adulthood. The acute presentation is characterized by hepatomegaly and acute liver failure². Patients treated only with diet died before 2 years of age and just 10-30% survived¹⁶. These patients developed chronic liver failure, cirrhosis and hepatocellular carcinoma, requiring liver transplant, thus the importance of early diagnosis and treatment. NTBC has changed disease progression, 88% of children

treated before 2 years of age survive until the age of 4, unlike the untreated ones which only 28% survive till this age¹⁷.

All patients in this report had a subacute presentation, with hepatomegaly and altered liver function. Hypophosphatemic rickets was the first clinical presentation in two of them (cases 2 and 3), developing liver dysfunction afterwards. In case 1, instead, bone deformations were noticed while evaluating liver dysfunction.

Nonresponsive rickets to conventional medical treatment is described in the literature and should alert the clinician to perform further study¹⁸. Cases 2 and 3 started treatment with phosphate and calcitriol. While case 2 did not respond to therapy, case 3 showed a partial response, improving calcium, phosphate and ALP levels when using high doses of calcitriol and phosphate. Nevertheless, radiological and clinical deformities only responded to NTBC, reinforcing the importance of starting NTBC as soon as possible.

In cases 1 and 3 renal tubular reabsorption of phosphate (TRP) was within normal levels for a normal serum phosphate. Instead, in the pre-

sence of low serum phosphate, we should expect urinary phosphate to be minimal or close to zero, so its sole urinary presence reflects excessive phosphate loss.

In relation to tubular damage, it has been shown that NTBC treatment ameliorates phosphate absorption within the first days. Tubular phosphate loss is considerably diminished after 7 days of treatment and normalization of phosphate levels can be seen as early as 2 weeks after starting it, even without use of calcitriol and phosphate¹⁹. SA urine levels diminish from the first day of treatment in 28% of treated patients.

NTBC, which was initially used as an herbicide, is an inhibitor of the 4 HPPD enzyme. This results in an enzymatic block prior to the mutated enzyme, avoiding toxic metabolites accumulation and hence ameliorates hepatic and renal symptoms. The dose used is 1 mg/kg/day twice daily to maintain NTBC levels of 40-60 uM, undetectable SA levels, and normal liver and kidney functions². In our patients, both SA and A-FP levels decreased dramatically after the first month of NTBC treatment (Figures 3 and 4).

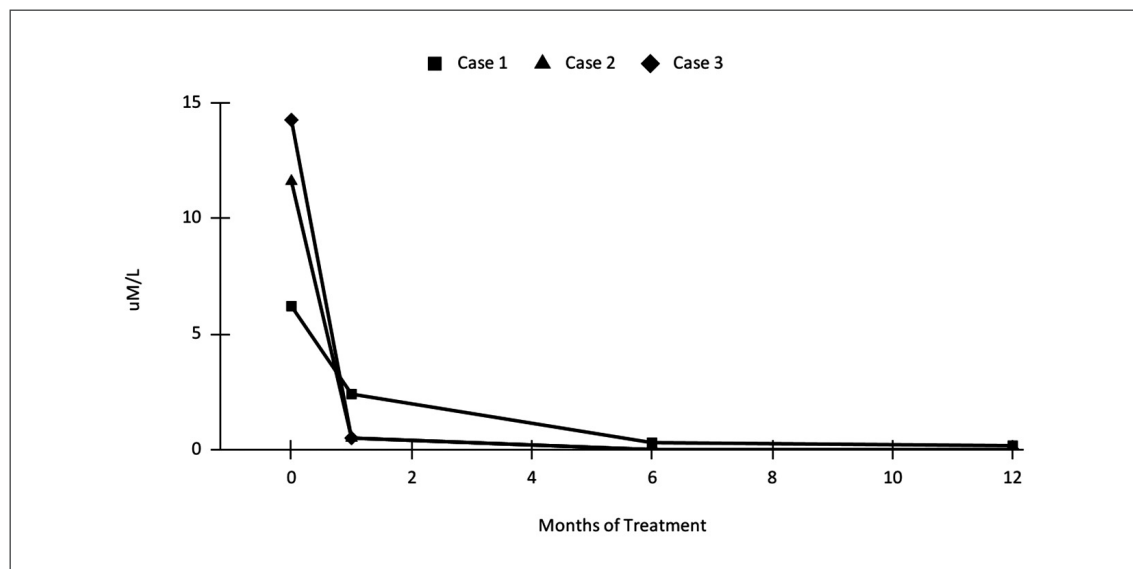


Figure 3: Initial succinylacetone levels and evolution post NTBC treatment.

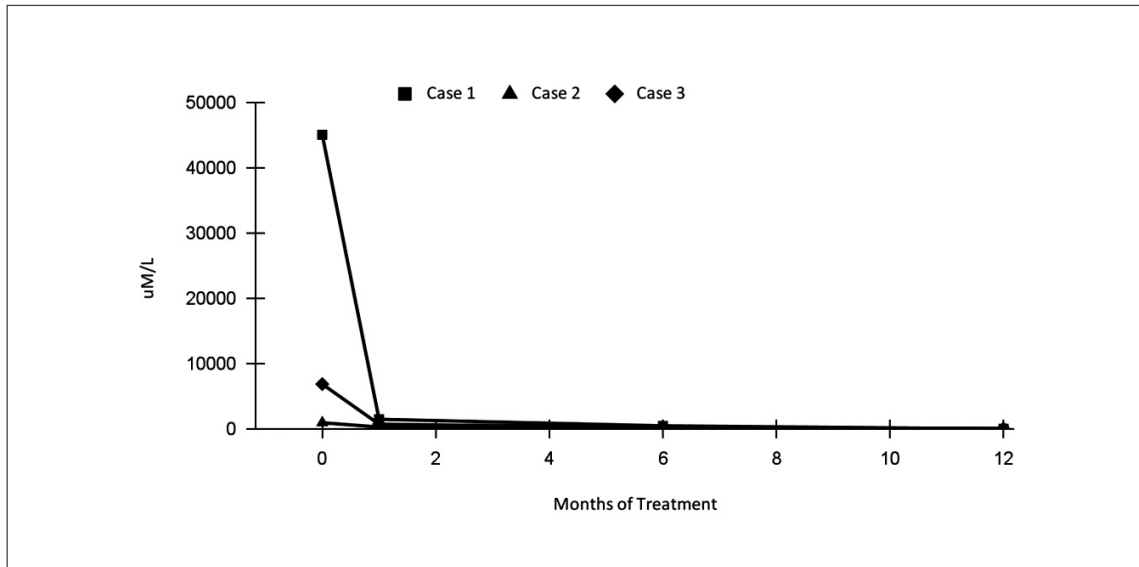


Figure 4: Initial alpha-fetoprotein levels (0) and evolution in months after NTBC treatment.

Suboptimal doses can produce new neurological crisis and disease progression. Optimal levels required should be determined in future studies^{19,20}. Liver function can improve one week after treatment initiation and even some hepatic lesions can regress²¹. Hepatic transplant in HT-1 is indicated when there are nodules with malignant signs. It has been reported that liver transplant has a better prognosis than in other diseases²². Patients requiring transplantation have been reduced since the introduction of NTBC. Before its use, 70-86% of patients required a transplant at a median age of 2 years. This reduction is seen regardless of whether treatment is started early or late^{23,24}.

In patients starting NTBC treatment before 2 months of age none have required transplant, 27% of those starting before 6 months and 44% above 6 months have required it. It is not clear whether treatment should be continued after transplantation^{19,20}. Our patients started treatment at 4 years on average (range 1 to 3,6 years) and though they started late, they have evolved favourably.

Hospitalizations, acute liver failure and neu-

rological crisis also have been reduced since its introduction²¹. Patient 1 initially presented with epistaxis and alteration of coagulation tests. Haematologic causes were discarded and no follow up indicated. There is no data related to liver and tubular function in this evaluation. In this case, coagulation problems did not alert the physicians. It is of extreme importance that when evaluating a patient with bleeding disorders, liver function should be considered in the analysis. Severe haemorrhage, non-responsive to vitamin K, secondary to liver failure, has been described in HT-1²⁵.

Adverse reactions to NTBC are infrequent and transitory; thrombocytopenia and neutropenia have been described²⁶. Tyr levels elevate secondary to the metabolic block produced by NTBC. Some complications such as eye discomfort, ulcers and crystal deposits may present secondary to high tyr levels (>500 $\mu\text{mol/l}$)^{26,27,28}. This has also been associated with cognitive deterioration and executive dysfunction. It is not known how this central nervous system damage is produced. In a

Chilean series this relationship was not observed²⁹. Our patients have not developed cognitive or eye problems for the moment. Neurocognitive evaluations have shown normal results according to their age on Bayley-III scores and WISC-IV scales.

It is important to adhere to a low tyr diet using special formulas that diminish SA production, maintaining anabolism and growth. Combined treatment (NTBC and diet) has changed the disease's natural progression even when treatment has been started late, as in our cases²⁶.

Neonatal screening is done using MS. Dry blood drops in filter paper permit tyr and SA detection^{30,31}. Better prognosis and survival when using NTBC as early as possible justify the exclusion of TH-1 in neonatal screening programs³².

Countries like Canada (Quebec) where HT-1 has a higher prevalence due to a mutation with a founder genetic effect, have successfully incorporated the detection of tyr and SA by MS in neonatal screening program since 1970s. They established a prevalence of 1:19,819 newborns, even higher than phenylketonuria in this area³³.

The better prognosis and survival of patients with early use of NTBC, and the fact that those who start treatment before one month of life present with no mortality, no liver transplantation and have no hospitalizations due to acute neurological crises, are strong arguments for recommending its inclusion in neonatal screening programs. In contrast with patients without NTBC treatment who present a mortality of 29% at 2 years (with symptoms beginning before 2 months of age), a need for liver transplantation of 71% and spending about 71 months in a hospital because of neurological crises^{15,34}.

A Chilean study following 12 children with HT-1, reported that 66% of them presented with liver failure (being acute in 3 out of 8) and 41% with rickets. Just 1 presented with pseudo porphyria and 1 with peripheral neuropathy²⁹. These findings, and ours, reflect clinical characteristics in patients with late diagnosis. HT-1 in Chile is a disease included in Ley Ricarte Soto. This law guarantees diagnosis and treatment of high-cost diseases such as NTBC. Before this law, since 1996 patients received treatment thanks to an

international multicentric study³⁵. Special formula that assures a good metabolic control is also guaranteed by the state. Diagnosis and treatment are centralized in INTA. This helps concentrate patients and protocolize their follow up, being 20 patients currently in control up to this date.

Conclusion

HT-1 is a disease of very low incidence but with high morbimortality. Rickets presenting with liver failure, coagulation disorders and / or neurological crisis should alert the clinician to this diagnosis. It should be considered that all these symptoms may not be present at the same time, hence maintaining high levels of suspicion, especially when there is no response to conventional treatments, is essential.

Abbreviations

AA= 5-aminolevulinic acid
 A-FP= alpha-fetoprotein
 ALP= alkaline phosphatase
 aPTT= activated partial thromboplastin time
 FAA= fumarylacetoacetate
 FAH= fumarylacetoacetate hydroxylase
 HR= hypophosphatemic rickets
 HT-1= hereditary tyrosinemia type 1
 INR= international normalized ratio
 MAA= maleylacetoacetate
 MS= mass spectrometry
 NTBC= nitisinone
 phe= phenylalanine
 SA= succinylacetone
 tyr= tyrosine

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