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CASE REPORT

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Case report: Maternal tyrosinemia type 1a under NTBC treatment with tyrosine- and phenylalanine restricted diet in Chile

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Abstract

We report the case of a 17-year-old girl with Tyrosinemia type 1a who carried a planned pregnancy to term while being under 2-(2-nitro-4-trifluoromethylbenzoyl)-1,-3-cyclohexanedione (NTBC, nitisinone) treatment and a tyrosine- and phenylalanine-restricted diet. She was on treatment since 2 months of age with poor metabolic control prior to her pregnancy (tyrosine 838 ± 106 umol/L). NTBC and a low tyrosine and phenylalanine diet were continued during her pregnancy. She unfortunately suffered from urinary tract infection and anemia during her pregnancy, with median plasma tyrosine and phenylalanine levels of 613 ± 106 umol/L (200–400 umol/L) and 40.2 ± 8 umol/L (35–90 umol/L), respectively. After 40 weeks of gestation, the patient gave birth to a healthy boy, with no adverse effects related to the use of NTBC. The newborn presented with a transitory elevation of plasma tyrosine levels and normal phenylalanine, methionine, and succinylacetone levels. By 12 months of age, the child was determined to have normal psychomotor development. At 20 months old, he was diagnosed with a mild developmental delay; however, global cognitive evaluation with the Wechsler Intelligence Scale for Children (WISC) test at 5 years old showed normal performance. Here, we discuss one of the few reported cases of nitisinone treatment during pregnancy and demonstrate a lack of teratogenicity and long-term cognitive disabilities.

KEYWORDS

NTBC, succinylacetone, tyrosine, tyrosinemia type 1

1 | INTRODUCTION

Tyrosinemia type 1a (HT1) is an autosomal recessive disorder caused by a defect in the fumarylacetoacetate hydroxylase enzyme that catalyzes the last step of the tyrosine (TYR) degradation pathway. Toxic metabolites like succinylacetone (SUAC), maleylacetoacetate, and fumarylacetoacetate are formed, producing the hepatic and renal manifestations of the disease (Lindstedt, Holme, Lock, Hjalmarson, & Strandvik, 1992). 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohex anedione, known as NTBC/nitisinone, was first instituted in 1992 to prevent the accumulation of these toxic metabolites in HT1 and was approved by the U.S Food and drug administration agency (FDA) in 2002. Implementation of nitisinone treatment has dramatically improved the survival rate of individuals with HT1 (Äärelä, Nevalainen, Kurppa, & Hiltunen, 2020).

Few cases of patients with HT1 on NTBC treatment while pregnant have been reported. To our knowledge, this is the fourth case

Abbreviations: HT1, tyrosinemia type 1a; NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione; PHE, phenylalanine; SUAC, succinylacetone; TYR, tyrosine.

reported worldwide and the first one in Latin America. In 2010, the case of a Belgian patient was reported with neither adverse effects to the fetus nor developmental delay up to 12 months of age (Lindstedt et al., 1992). In 2013, a report was published discussing a French patient whose newborn was diagnosed with HT1 and had normal social and physical development until 7 months of age (Vanclooster et al., 2011). In 2015, the first American case was published describing an uneventful 37-week pregnancy with a healthy newborn with normal development documented at 12 months of age (Kassel, Sprietsma, & Rudnick, 2015). No teratogenicity was observed in any of these reports (Garcia et al., 2012; Lindstedt et al., 1992; Vanclooster et al., 2011).

The aim of the present report is to describe the first Chilean case of a patient with HT1 treated with NTBC during pregnancy and to demonstrate the natural history of the exposed child's cognitive and physical development up until 5 years of age. This study was carried out as part of an HT1 follow-up program developed by the Institute of Nutrition and Food Technology (INTA) of the University of Chile and the Chilean Health Ministry, and it was approved by the ethics committee of the INTA.

2 | PERSONAL AND FAMILY HISTORY

The mother of the child in question was born in 1996. She was the fourth child to healthy, nonconsanguineous parents with the antecedent of a deceased brother at 10 months of age due to liver failure secondary to HT1. In spite of this, she did not undergo newborn screening given the lack of availability in Chile at the time of her birth.

At 1 month old, she was admitted to the hospital due to upper gastrointestinal bleeding. Initial laboratory testing showed hyperbilirubinemia and elevation of transaminases and total creatine kinase (CK) levels. Given her family history, acute liver failure, and hepatomegalia, HT1 was suspected. She was referred to INTA for further diagnostics because this was the national reference center for the diagnosis and treatment of inborn metabolic diseases in Chile.

A month later, the diagnosis of HT1 was confirmed given detected elevated urine SUAC at 140 (mmol/mol creatinine) (normal value: <0.5 mmol/mol/creatinine) and plasma SUAC at 32 μmol/L (< 0.5 μmol/L normal value:); tyrosine (TYR) was 455 μmol/L, phenylalanine (PHE) was 76 μmol/L, and methionine (MET) was 300 μmol/L, and alpha-fetoprotein (AFP) was markedly elevated (AFP) at 32,2000 ng/ml (NV <2,0–4,5 ng/ml). At 2 months old, she began follow-up treatment with NTBC and a TYR- and PHE-restricted diet including medical formula provided by the Metabolic Disease Laboratory of INTA.

After 1 month of NTBC treatment, different biochemical laboratory parameters were assessed showing levels of AFP of 14.600 μg/L, TYR of 142 μmol/L, PHE of 65 μmol/L, MET of 35 μmol/L, blood succinylacetone of 1.4 μmol/L, urine succinylacetone of <1 mmol/mol creatinine, and blood NTBC of 10.7 μmol/L. During her first year of life, the hepatomegaly fortunately reversed. Evaluation was uneventful until 4 years of age, when she developed photophobia and elevated plasma tyrosine concentrations due to poor treatment compliance. A year later, she abandoned NTBC treatment for a month and developed peripheral neuropathy (porphyria-like crisis), resulting in lifelong gait difficulty. She began menstruation at 13 years old and at the age of 17 became pregnant.

She was periodically studied with either abdominal ultrasound or magnetic resonance imaging (MRI), both showing signs of chronic liver disease with no evidence of portal hypertension and focal lesions.

In the 9 months prior to the pregnancy, she showed persistently elevated serum TYR and PHE levels as a result of dietary noncompliance. These parameters were observed in a range between 600 and 900 μmol/L (median of 780 ± 148 μmol/L) for TYR and 99–180 μmol/L for PHE (median of 100 ± 45.9 μmol/L) (Figure 1). NTBC levels also varied widely throughout this period, with values both above and under the target range of 30–60 μmol/L (Kassel et al., 2015). AFP plasma levels dropped promptly after initiating NTBC treatment, with complete reversal after a month of therapy. Unfortunately, AFP could not be monitored regularly because the patient could not attend the scheduled sampling sessions. In the 3 years prior to the pregnancy, she presented with a mean plasma AFP of 50.4 ± 51 ng/ml, with 34.9 ng/ml being the highest measurement directly before conception.

3 | PREGNANCY COURSE

The patient became pregnant at 17 years of age, with detection at 7 + 5 weeks estimated gestational age. The risks and benefits of NTBC treatment during pregnancy were discussed based on available evidence. The patient consented to continue NTBC treatment. Nitisinone was continued at a dose ranging 0.7–0.8 mg kg^{-1} day^{-1} during pregnancy.

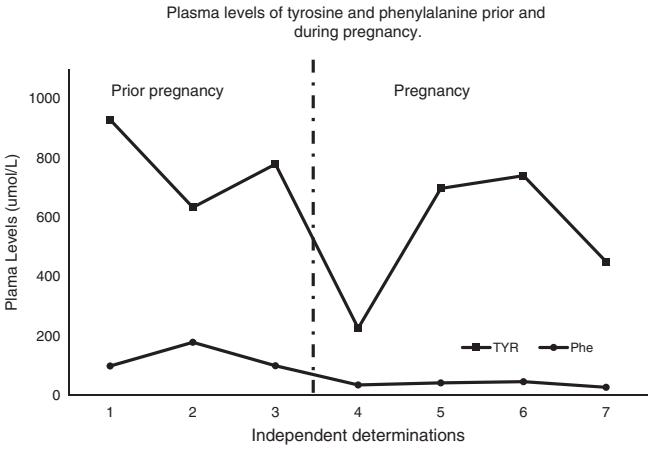

FIGURE 1 Tyrosine (TYR) and phenylalanine (PHE) levels in mother before and during pregnancy. Plasmatic levels of TYR and PHE were measured at the following weeks: points 1, 2, and 3 were determined at 33, 21, and 10 weeks prior to pregnancy, respectively. Points 4, 5, 6, and 7 were taken at 7.5, 13.6, 22, and 26 weeks of gestation, respectively

Regarding nutritional intake, the patient had a diet consisting of protein of 1.4 ± 0.1 g kg^{-1} day^{-1} (85% medical food) and a daily intake of 80 g/day (recommendation >60 g/day). Energy intake was 1.754 ± 410 kcal/ day (recommendation 1.400–2.500 kcal/day). Intake PHE + TYR was 627 ± 30 mg/day (recommendation 800–1,200 mg/day) (Table 1). In addition, she received calcium 1,000 mg/day, iron 20–60 mg/day, zinc 20 mg/day, and folic acid 5 mg/day.

During her pregnancy, metabolic control showed median plasma TYR levels at 613 ± 106 μmol/L (NV 200–400 μmol/L) and median plasma of PHE levels at 40.2 ± 8 μmol/L (35–90 μmol/L) (Figure 1). Due to poor medical compliance, it was not possible to maintain regular monitoring of all metabolic parameters during the pregnancy. Only one urine organic acid determination was made during pregnancy, showing SUAC 0.38 mmol/mol of creatinine (normal <0.5 mmol/mol creatinine). Two samples of AFP were obtained at weeks 5 and 21, resulting in 11.8 and 142 μg/L, respectively. AFP dropped to 26.8 μg/L a month after birth. NTBC blood levels were measured at three points during the pregnancy (5, 20, and 24 weeks), resulting in a mean of 8.3 μmol/L(±2.5), demonstrating adherence to NTBC treatment (doses in the range of 0.73–0.77 mg kg^{-1} day^{-1}) (Table 2). In addition, she had the following average lab values: hemoglobin at 11.02 ± 1.9 g/dL, hematocrit at 31 ± 5.8%, albumin at 3.5 ± g/dl, glycemia at 74 mg/dL, serum glutamic oxaloacetic transaminase (GOT) at 28 U/L (normal range 5–35 U/L), and serum glutamic pyruvic transaminase (GPT) at 30 U/L (normal range 5–30 U/L).

Ultrasound monitoring at weeks 9 + 2, 17 + 6, 23 + 2, and 29 + 2 showed normal fetal development and growth. Intrauterine growth restriction was detected at week 35 + 4, falling from the 50th percentile (P) to P30 and to P20 at week 38 + 3.

4 | NEONATAL COURSE

After 40 weeks of estimated gestation, the baby was born by an uncomplicated spontaneous vaginal delivery. Birth weight was 3.150 g (P50), length was 48 cm (P50), and head circumference was 32 cm (P50). APGAR scores were 9 after 1 min and 10 after 5 min. Neonatal plasma levels of PHE and TYR were documented at 12, 24, 48, and 72 hr of life, and NTBC and SUAC levels were documented at 24, 72 hr, and 15 days of life (Table 2 and Figure 2).

At 12 hr of life, TYR was high at 788 μmol/L (normal range 50–150 μmol/L), and PHE was low at 14 μmol/L (normal range 40–140 μmol/L). At 24 hr of life, TYR was still high at 565.7 μmol/L, and PHE had reached a low normal level at 46.1 μmol/L. By 48 hr of life, TYR was 514 μmol/L, and PHE was 38.7 μmol/L. Plasma NTBC was 3.48 μmol/L at 24 hr, 2.75 μmol/L at 72 hr, and undetectable at 15 days of life. The mother's NTBC level at 48 hr postpartum was 3.44 μmol/L (Table 2).

HT1 diagnosis was ruled out, and breastfeeding was initiated with good tolerance. The baby was discharged at 7 days of life.

5 | CHILD DEVELOPMENT

The child presented with normal anthropometric parameters and age-appropriate psychometric development up until 12 months of age. Later, he presented with mild developmental delay with a mental development index (MDI) of 73 and a psychomotor development index (PDI) of 80 points, corresponding to the expected results for a 17-month-old infant (2-month delay). The most recent cognitive evaluation using the Wechsler intelligence Scale for Children (WISC) was performed at 5 years and 2 months of age. The child presented with a normal-high total intellectual quotient (TIQ 111), average performance in verbal comprehension (VIQ 95), and a superior performance in visual-perceptive tasks (manual IQ 126).

TABLE 2 NTBC blood levels in mother and newborn during pregnancy and postpartum

		Mother's NTBC dose (mg kg^{-1} day^{-1})	Mother's NTBC blood levels (umol/L)
Time prior to pregnancy (weeks before pregnancy)	21	0.8	14.39
	17	0.8	5.8
	13	0.78	8.42
	10	0.78	11.69
Pregnancy (weeks)	5	0.77	11.75
	20	0.75	6.85
	24	0.73	8.5
Postpartum	12 hr	0.73	–
	48 hr	0.73	3.4
	72 hr	0.73	–
	15 days	0.73	–
	4 months	0.71	10.7
	11 months	0.67	37.9

TABLE 1 Nutritional intake during pregnancy

Pregnancy time (weeks)	Energy (kcal/day)	Protein (g/day) (g kg^{-1} day^{-1})	Protein formula (g kg^{-1} day^{-1})	Phe/TYR (mg/day)
7.5	1,231	70.2/1.4	1.2	584
13.6	1,702	71.2/1.4	1.2	642
22.0	1,864	88.0/1.5	1.3	654
26.0	2,219	82.0/1.5	1.3	627

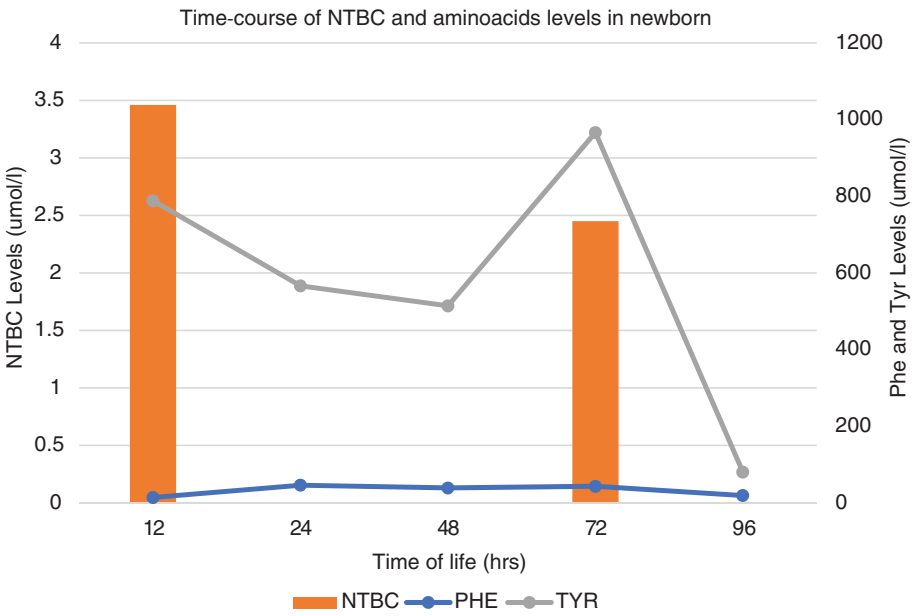

FIGURE 2 Time course of tyrosine and phenylalanine levels in cord blood and blood 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) levels

6 | DISCUSSION

Here, we present the case of a female patient diagnosed with HT1 at an early age who carried her pregnancy to term while on NTBC treatment. The assessment of risks and benefits of continuing this treatment was discussed by parties involved based on available evidence in animal models and human-reported cases. Given the risk of renal and hepatic failure related to NTBC suspension, the decision to continue treatment was made. Nutritional intake was adjusted to provide sufficient protein to allow fetal growth, and the importance of treatment compliance was discussed with the patient.

Poor adherence to her prescribed diet and therapies, as well as participation in lab draws during pregnancy and postpartum, were complicated by her socioeconomic and geographic status. Despite these challenges, there were some lab values collected for the trending of PHE, TYR, NTBC, and SUAC levels, and she did undergo detection of NTBC in the blood during her pregnancy, suggesting some adherence to the drug treatment. Her blood NTBC levels were in the low range, with an average of 8.3 μmol/L (recommended level in plasma is 30–60 μmol/L); however, inactivation of the neurotoxic pathway seems to be effective as shown by registering urine SUAC levels under 0.5 mmol/mol creatinine. Recent reports show that 99% of patients with plasma NTBC level over 40 μmol/L present with SUAC levels in a range less than 0.25 mmol/mol creatinine (Davit-Spraul, Rhomdame, & Poggi-Bach, 2012). The recommended amount for HT1 patients is <1.0 mmol/mol creatinine (Jack & Scott, 2019). As reported in a recent study, our case also had a high AFP value at 21 weeks of pregnancy, a value that decreased postpartum, and the patient has no liver abnormalities detected thus far (Couce et al., 2010). Our NTBC determinations were collected via whole blood; however, conversion factors estimated in paired plasma and dried blood spot (DBS) samples of our group of patients demonstrated a conversion factor of 2.6 (Äärelä et al., 2020; Davit-Spraul et al., 2012). Given this conversion factor, the mean NTBC amount calculated in plasma increases by 20.5 μmol/L, and it has been reported in a considerable percentage of patients who handle a range of NTBC between 20 and 30 μmol/L, and it has also been reported that they can still present with a SUAC excretion below 0.5 mmol/mol creatinine (Davit-Spraul et al., 2012). Transference of NTBC from mother to fetus through the placenta has been previously reported (Garcia et al., 2012). Here, we show a newborn who presented with an NTBC level similar to the mother's levels at 48 hr of life, with decreasing levels over time until they were undetectable at 15 days of life despite an exclusive breastfeeding regimen (Table 2) (Garcia et al., 2012; Lindstedt et al., 1992; Vanclooster et al., 2011).

We were unable to compare the ratio between maternal and fetal PHE and TYR plasma levels at birth. It is known that fetal plasma PHE is, on average, 1.5 times higher than maternal levels (Laeremans et al., 2020) and that fetal TYR levels tends to be 2.2 ± 0.5-fold higher when compared to maternal TYR (Schoonheyt, Clarke, Hanley, Johnson, & Lehotay, 1994). If we compare the latest known maternal PHE and TYR levels to the highest newborn determinations, we can observe a ratio of 1.7 for fetus/mother PHE and 2.1 fetus/mother for TYR. The transitory raise in TYR levels could be explained by the active transplacental transport this amino acid presents (Cornejo, Raimann, Pérez, Desviat, & Arias, 2017).

Previous studies in animal models have shown teratogenic effects of NTBC, such as omphalocele, gastroschisis, and growth restriction, when administered at doses 2.5–125-fold higher than the maximum human dose (Vanclooster et al., 2011). So far, no human reports have suggested an association between the use of NTBC and negative effects in fetal development (Garcia et al., 2012; Lindstedt et al., 1992; Vanclooster et al., 2011). In this case, fetal development was normal until the third trimester when intrauterine growth restriction was detected. Even though reduced mean pup weight has been described in murine models under NTBC, in this particular case, this

could be secondary to hypertyrosinemia related to poor dietary compliance rather than a direct effect induced by nitisinone as reported previously (Jack & Scott, 2019).

At birth, the newborn presented with normal physical examination, including appropriate weight, length, and head circumference. This supports the preliminary evidence that treatment with nitisinone during pregnancy has no teratogenic effects on fetal development or subsequent child development. Nevertheless, further research is needed to establish a conclusion regarding the potential risks and benefits of NTBC therapy on the developing fetus.

CONFLICT OF INTEREST

None of the authors present financial, personal, institutional, or academic conflicts of interest that could have interfered with the confection of this document. All authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Maria F Medina: Drafting, design, data analysis and interpretation. Carolina Arias: Drafting, data acquisition, and revision. Juan F Cabello: critically revised the article. Alicia De la Parra: Data acquisition, analysis, and interpretation. Alf Valiente: Data acquisition, analysis, and interpretation. Gabriela Castro: Drafting, design, data acquisition, and analysis. Karen Fuenzalida: Data acquisition, analysis, and interpretation. Veronica Cornejo: critically revised the article

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs

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