The Incidence of Transient Neonatal Tyrosinemia Within a Mexican Population

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Abstract
Transient neonatal tyrosinemia (TNT) is a form of hypertyrosinemia produced by the immaturity of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), a high intake of phenylalanine and tyrosine, and a relative ascorbic acid deficiency. Our objectives are to determine the incidence of TNT in Mexican newborns and to correlate it based on their sex, gestational age, and weight for gestational age to determine whether these are risk factors that predict the development of TNT. A cross-sectional descriptive study was conducted from January 2006 to August 2017. We analyzed 175 976 of newborn screening reports and found that the overall incidence of TNT was 1 (0.29%) in 342 newborns. It is more prevalent in preterm infants and in small for gestational age newborns (0.35%). The TNT incidence was determined in this Mexican population, and it was established as the most frequently occurring amino acid defect. We propose that pediatricians intentionally search for this pathology to offer patients access to adequate and timely treatment.

Keywords
4-hydroxyphenylpyruvate dioxygenase deficiency, transient neonatal tyrosinemia, newborn, incidence, Latin America

Introduction
Transient neonatal tyrosinemia (TNT) is a form of hypertyrosinemia, which is the most common pathology of amino acid metabolism. It is produced by a combination of several factors including the immaturity of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), which results from alterations in its synthesis; TNT is also caused by an elevated intake of phenylalanine and tyrosine, and an ascorbic acid deficiency.

Scant information has been published on the etiology of TNT in the last 20 years; therefore, recent epidemiological figures, both nationally and internationally, remain unknown. Also, it has not been possible to establish the presence of long-term cognitive neurological complications, such as altered learning and neurolinguistic abilities. Most pathologies that affect tyrosine catabolism produce hypertyrosinemia, which has also been found in cases of severe hepatocellular dysfunction.¹

The pathologies associated with 4-HPPD include hereditary 4-HPPD dysfunction (OMIM 276710), also known as tyrosinemia type 1a or hepatorenal tyrosinemia, and tyrosine aminotransferase deficiency (OMIM 276600), which is also known as Richner Hanhart syndrome (or type II tyrosinemia).

The clinical manifestations of TNT are variable, since patients may be asymptomatic or present with lethargy, poor suction, prolonged jaundice, and hypotonia, which are all attributed to neonatal prematurity. Furthermore, hypertyrosinemia, as well as high urinary excretion of tyrosine and its metabolites, was the most common finding in the screening process.²

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metabolites (including hydroxyphenylpyruvic acid), are also present in TNT.²

There is no international consensus that currently defines the method of quantification and the limit values of detection for TNT; however, whereas normal serum tyrosine levels have reportedly ranged from 0.50 to 2.20 mg/dL, clinical significance is regarded as >3.60 mg/dL,³ although some authors consider it to be >5 mg/dL.⁴,⁵ These differing values were obtained using thin-layer chromatography, liquid chromatography, and gas chromatography tandem mass spectrometry (GC/MS/MS).⁶

The defect is more frequent in preterm infants (PI, <37 weeks of gestational age) than in full-term infants (FTI, 37 ≤ weeks of gestational age < 42), as the former have increased serum tyrosine levels between the second and third weeks of life; tyrosine levels return to normal values 2 to 3 weeks later.⁷⁻⁹ The incidence of TNT has ranged from 0.2% to 10%.¹⁰ Other sources reported that TNT affects as many as 0.5% to 5% FTI and up to 30% of PI.¹¹ In PI with high-protein milk intake, tyrosinemia may still be present, even when infants consume up to twice the recommended daily intake of ascorbic acid for infants and children (30 mg).¹²,¹³

Frequently, patients with TNT do not exhibit long-term complications, but some authors have reported the presence of cognitive dysfunction at 8-year follow-ups, especially in those with tyrosine levels >20 mg/dL.¹³⁻¹⁸ Menkes et al.,¹⁷ Partington et al.,¹⁹ and Light et al.²⁰ found no difference in neurological assessment scores among children aged 1 to 8 years with a history of prematurity; however, some authors reported the presence of lethargy and decreased muscle tone.²⁰

Transient neonatal tyrosinemia resolves without treatment in the first months of life.²¹ However, some substances, such as ascorbic acid, can increase the activity of the immature 4-HPPD enzyme.⁷ The administration of 200 to 400 mg/kg/d of vitamin C combined with a decreased protein intake of <2 g/kg/d has been described as a potential treatment for TNT.²

Table 1. Characteristics of the Studied Population by Sex, GA, and WGA.

| WGA | Sex | PI | FTI | Postterm | NR | Total |
|-----|-----|----|-----|----------|----|-------|
| SGA | F   | 446| 1134| 16       |    | 1596  |
|     | M   | 368| 1078| 18       |    | 1464  |
| AGA | F   | 8390| 73 097| 189     |    | 81 676|
|     | M   | 9890| 75 660| 241     |    | 85 791|
| LGA | F   | 497 | 2233| 2        |    | 2732  |
|     | M   | 466 | 2248| 3        |    | 2717  |
| Total|     | 20 057| 155 450| 469   |    | 175 976|

Abbreviations: AGA, appropriate for gestational age; F, female; FTI, full-term infant; LGA, large for gestational age; M, male; NR, not registered (sex, GA, or WGA was not included in the NBS report); PI, preterm infant; SGA, small for gestational age; WGA, weight for gestational age.

Table 2. Characteristics of the TNT Population by Sex, GA, and WGA.

| WGA | Sex | PI | FTI | Postterm | Total |
|-----|-----|----|-----|----------|-------|
| SGA | F   | 1  | 7   | 0        | 8     |
|     | M   | 3  | 0   | 0        | 3     |
| AGA | F   | 79 | 150 | 0        | 229   |
|     | M   | 92 | 178 | 0        | 270   |
| LGA | F   | 1  | 2   | 0        | 3     |
|     | M   | 1  | 1   | 0        | 2     |
| Total|     | 177| 338 | 0        | 515   |

Abbreviations: AGA, appropriate for gestational age; F, female; FTI, full-term infant; LGA, large for gestational age; M, male; PI, preterm infant; SGA, small for gestational age; TNT, transient neonatal tyrosinemia; WGA, weight for gestational age.

Of the analyzed individuals, only 1 patient was excluded with the diagnosis of another type of tyrosinemia. Furthermore, 1028 reports were eliminated due to incomplete data (Table 1). A diagnosis of TNT was confirmed following a normal second NBS report. Descriptive statistics, Student t test, and logistic regression model were used to determine the relevance of the proposed variables.

Results

The 175 976 analyzed patients’ reports were classified into 1 of 3 groups by sex, GA, and WGA. According to GA, there were 20 132 PI, 155 990 FTI, and 471 postterm infants. When we classified cases by sex, there were 86 004 female and 89 972 male newborns. Once the population with TNT was identified, we classified those individuals into the same 3 groups (Table 2).

When examining the segmented sample among those with and without TNT, it was found that infants with TNT are, on average, 1.33 weeks younger than infants without TNT. Also, those with TNT tend to be classified as PI and SGA, with a WGA ratio smaller than that for the population without TNT (0.988 vs 1.014, respectively; Table 3).
We reported that 1 in 342 newborns had indications of TNT from their NBS results at an incidence of 0.29% without segmentation. Our obtained incidence rates corresponded with the TNT incidence range from 0.2% to 10% reported by Martin et al.\textsuperscript{11}

Our study showed that there is no correlation between sex and TNT, since 0.31% of males and 0.28% of females had TNT ($t_{513} = 1.032$; $P = .302$). The incidence rate increased to 0.36% in SGA and decreased to 0.09% in large for gestational age (LGA) newborns.

As shown in Figure 1 and Table 4, PI are 307% more likely than FTI to have TNT, whereas postterm newborns have a 75% lower probability of developing TNT. In the case of the WGA ratio, SGA infants have a greater probability for presenting with TNT than appropriate for gestational age (AGA) infants. Conversely, LGA infants are 34% less likely to develop TNT.

**Conclusion**

We reported that TNT is present in 1 out 342 Mexican newborns, making it the most common amino acid defect. In addition, the frequency of TNT was much higher in PI infants (1:113) than in FTI and postterm infants (1:461), and there is an increased risk of developing TNT among SGA newborns compared with AGA newborns.

Transient neonatal tyrosinemia has a higher incidence rate than the other metabolic defects currently detected by NBS, such as congenital hypothyroidism (1:2 000), phenylketonuria (1:15 000), and cystic fibrosis (1:5 900).\textsuperscript{2,23} Since neurological sequelae have been described, including alterations in learning and neurolinguistic abilities, we propose that clinicians should intentionally search for this pathology, so that timely treatments can be offered.

According to this study, the collaboration of a national-scale private company and a medical institution would strengthen NBS programs through follow-up strategies conducting new research to understand better the long-term neurological complications associated with this condition.

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