Research Article

Evaluating the Incidence, Risk Factors, and Diagnostic Limitations of Transient Neonatal Tyrosinemia in Iranian Newborns

Saeideh Abdolahpour[1*], Maryam Nasri[1], Farzaneh Abbasi[1], Reihaneh Mohsenipour[1], Maryam Khazdouz[2], Farshad Sharifi[3], Sedigheh Shams[4]

[1] *Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Hazrat-e Ali Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran*
[3] *Elderly Health Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[4] *Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

Article info:
Received: 12 May 2025
Revised: 26 May 2025
Accepted: 02 June 2025

[*] **Corresponding Author:**
Saeideh Abdolahpour,
Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences
Email: abdolahpours@yahoo.com

ABSTRACT

Objectives: Transient Neonatal Tyrosinemia (TNT) is a benign, self-limiting disorder characterized by elevated blood tyrosine levels in neonates. It is often caused by immature hepatic enzymes, particularly 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), and may be influenced by factors such as prematurity, low birth weight, and high protein intake. Early detection via newborn screening is essential to differentiate TNT from more serious disorders such as tyrosinemia type I. The aim of this study is to determine the incidence of TNT and identify perinatal factors associated with its development in Iranian neonates.

Methods: This retrospective case-control study reviewed newborn screenings performed at the Growth and Development Research Center's metabolic laboratory between March 2019 and February 2023. The control group comprised newborns with normal metabolic screening results during the study period.

Results: Metabolic screenings were conducted on 73,349 infants. The incidence of TNT was found to be 0.47%, corresponding to a total of 345 diagnosed cases. TNT infants had a lower gestational age (37.7 ± 1.4 weeks), lower birth weight (2.94 ± 0.5 kg), and a higher rate of cesarean deliveries (83.9%) compared to the control group ($P < 0.05$). Logistic regression analysis showed significant associations between TNT and preterm birth (OR: 868.2, 95% CI: 168.9–4212.7, $P < 0.001$), cesarean delivery (OR: 3.5, 95% CI: 2.26–5.3, $P < 0.001$), and gestational age (OR: 0.17, 95% CI: 0.12–0.24, $P < 0.001$). No significant association was found with other parameters ($P \geq 0.05$).

Conclusion: TNT incidence in Iranian newborns is associated with prematurity and cesarean delivery. Optimizing screening protocols and encouraging vaginal delivery when possible may reduce TNT rates.

Keywords: Transient Neonatal Tyrosinemia, Neonatal Screening, Newborn, Cesarean Section, Premature Birth, Iran

Use your device to scan and read the article online

Citation: Abdolahpour S, Nasri M, Abbasi F, Mohsenipour R, Khazdouz M, Sharifi F, Shams S. Evaluating the Incidence, Risk Factors, and Diagnostic Limitations of Transient Neonatal Tyrosinemia in Iranian Newborns. Acta Biochimica Iranica. 2025;3(2):109-113.

https://doi.org/***

Introduction

Transient neonatal tyrosinemia (TNT) is a benign disorder of tyrosine metabolism (1). TNT is the most common type of hypertyrosinemia, often detected in newborn screening programs and associated with a high rate of false positives (2). The prevalence of TNT has been estimated by various studies, suggesting rates of approximately 1 in 342-372 neonates (3). Elevated blood tyrosine levels in newborn screening can arise from different etiologies, including acquired conditions such as extensive liver damage, high protein intake, and vitamin C deficiency (4). In contrast, hereditary tyrosinemia presents as an acute, progressive illness due to defects in various enzymes of the tyrosine metabolic pathway, manifesting as three distinct forms of tyrosinemia (5). Tyrosine serves as a nonspecific marker for both hereditary hypertyrosinemia and TNT, complicating the diagnosis of hereditary forms in newborn screening programs (6). A delay in the maturation of hepatic enzymes, particularly 4-hydroxyphenylpyruvate dioxygenase, is believed to underlie TNT (7, 8). Numerous studies have indicated the adverse effects of elevated blood tyrosine on growth, liver function, kidneys, and, importantly, mental development (9). Despite being a transient disorder, infants diagnosed with TNT typically do not exhibit long-term complications. Brief incidents of hypertyrosinemia may result in mild but comparable outcomes (10). Nevertheless, lethargy, decreased muscle tone, and cognitive disabilities have been reported in some infants with hypertyrosinemia (11, 12).

Research indicates that TNT is more prevalent in preterm infants and correlates with gestational age (13). Additionally, relationships may exist between the frequency of TNT and other risk factors, such as birth weight and newborn nutrition (14,15). Despite extensive research, TNT continues to be a prevalent false-positive result in newborn screening. Therefore, identifying risk factors to minimize false-positive screening outcomes is advantageous for both the healthcare system and families. Given the lack of data on TNT incidence in Iran, we conducted a retrospective case-control study to assess potential associations between various predisposing factors and the development of TNT. While previous studies have explored the correlation between preterm birth, birth weight, and TNT, no comprehensive analysis has been conducted in this specific population. Identification of key risk factors could potentially help reduce false-positive outcomes in newborn screening programs, benefiting both the healthcare system and families. This study aims to provide valuable insights into the epidemiology of TNT among Iranian newborns and to identify potential modifiable risk factors that could improve screening accuracy and reduce false positives.

Methods

Study Design

This retrospective case-control study was conducted on newborns screened for inborn errors of metabolism at the metabolic laboratory of the Growth and Development Research Center (GDRC), Tehran, Iran. The study period spanned from March 1, 2019, to February 28, 2023. Ethical approval for this study was obtained from the Ethical Council of Tehran University of Medical Sciences under approval code IR.TUMS.CHMC.REC.1400.308.

Study Population

Cases included newborns identified with elevated tyrosine levels during initial screening who were subsequently diagnosed with transient neonatal tyrosinemia (TNT) following confirmatory tests. Inclusion criteria required confirmation of TNT through normalization of tyrosine levels and normal succinyl acetone levels in urine. Newborns diagnosed with inherited tyrosinemia or those with incomplete data were excluded.

Controls included healthy newborns without metabolic disorders, randomly selected from the same screening population during the study period. Randomization was performed using a computer-generated list to minimize selection bias.

Data Collection

Data on infant demographics (such as birth weight, gestational age, and sex) as well as maternal information (e.g., age, delivery method, and contact details) were collected from related health centers. Additional information, including gestational age, feeding type, and delivery method, was obtained through parental interviews. Tyrosine measurement was used as the primary biomarker for TNT screening; however, relying solely on tyrosine may lead to false-positive results, particularly in newborns with enzyme deficiencies affecting tyrosine metabolism.

Laboratory Methods

Newborn screening was conducted using the MassChrom® Newborn Screening Kit (57000F, non-derivatized, Chromsystems Instrument and Chemicals, Germany) to analyze amino acid and acylcarnitine profiles. The analyses were performed using a triple quadrupole LC/MS system (Shimadzu-8045 LC/MS). The normal cutoff for tyrosine levels was established at less than 292.74 µmol/L. Levels exceeding 336.58 µmol/L were considered indicative of tyrosinemia.

Statistical Analysis

The Statistical Package for the Social Sciences version 20.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The Kolmogorov-Smirnov test assessed data normality. Categorical variables were

compared using Fisher's exact test and chi-square tests, and continuous variables were compared using the t-test. Univariate logistic regression was conducted before multivariate regression analysis. Variables with $p < 0.25$ in univariate analysis and those of clinical significance were included in the multivariate analysis (Backward LR method). A p-value < 0.05 was considered statistically significant. Data analysis conducted by using *SPSS* Statistics version 27.0.1.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means ± standard deviations for continuous variables and frequencies (percentages) for categorical variables. The Chi-square test was used to assess associations between categorical variables. Independent t-tests were applied to compare the means of continuous variables between two groups. Univariate analyses were initially conducted to identify variables significantly associated with the outcome of interest. A multivariate logistic regression model was used to control potential confounders. A P value of less than 0.05 was considered statistically significant.

Results

Of the 73,349 newborns screened at the Growth and Development Research Center (GDRC) during the study period, 351 were identified with elevated tyrosine levels. After excluding 21 cases with missing data and 6 cases diagnosed with hereditary tyrosinemia, 324 cases remained in the study. The control group included 372 newborns with normal metabolic screening results. The incidence of TNT was 0.47% (324 cases out of 73,349 births). There were no significant differences in sex, maternal age, neonatal feeding methods, or consanguineous marriages between the TNT and control groups.

Significant differences were found in gestational age (37.7 ± 1.4 vs. 38.7 ± 1.0 weeks, $p < 0.002$), birth weight (2.94 ± 0.5 kg vs. 3.35 ± 1.6 kg, $p = 0.04$), and delivery type (cesarean section: 83.9% vs. 51.7%, $p < 0.001$). Moreover, the number of premature infants significantly differed between the two groups (26 vs. 14, $p = 0.02$). A history of hospitalization after delivery was reported in 12.3% of infants with TNT. Table 1 summarizes the demographic characteristics of the study newborns.

Based on logistic univariate regression analysis, a significant correlation was found between cesarean section (C/S) and TNT (OR: 4.8; 95% CI: 3.38–6.96; $p < 0.001$). Given the associations found between certain study variables and TNT, a multivariate logistic regression analysis was conducted. The odds ratios did not change significantly after controlling for variables, indicating a positive correlation (OR: 3.5; 95% CI: 2.26–5.3; $p < 0.001$). Thus, C/S was associated with a 3.5-fold increase in the likelihood of TNT occurrence. While univariate logistic regression did not identify preterm birth as a risk factor, multivariate regression analysis indicated a strong, significant association between prematurity and TNT (OR: 868.2; 95% CI: 168.9–4212.7; $p < 0.001$). The incidence of TNT was significantly influenced by smaller gestational age (OR: 0.17; 95% CI: 0.12–0.24; $p < 0.001$). However, no significant correlation was found between birth weight and TNT according to the multivariate analysis (OR: 0.91; 95% CI: 0.89–0.97; $p < 0.001$). No significant associations were observed with other assessed risk factors ($p \geq 0.05$). Table 2 presents the details of the factors influencing TNT, with column 1 displaying univariate analysis results and column 2 presenting odds ratios adjusted for the study variables identified as significant correlates of TNT in this study.

Table 1. Demographic and characteristic of the study participants

Variables	Transient neonatal tyrosinemia group n= 324	Control group n= 372	p value
Sex			
Male (n, %)	154 (47.5)	179 (48.1)	>0.05$^{\beta}$
Female (n, %)	170 (52.5)	193(51.9)	
Birth Weight (Kg)*	2.94 ± 0.5	3.26 ± 0.6	0.04$^{\alpha}$
Maternal age (years)*	29.5(6.4)	29.3(5.8)	>0.05$^{\alpha}$
Consanguineous marriages			
Yes (n, %)	106(32.7)	97(26.1)	>0.05$^{\beta}$
No (n, %)	218(67.3)	275(73.9)	
Gestational age (weeks)*	37.7 ± 1.4	38.7 ± 1.0	<0.002$^{\alpha}$
Term (n, %)	298(92.0)	354(95.2)	
Preterm (n, %)	26(8.0)	14(4.8)	0.031$^{\beta}$
Delivery type			
Vaginal (n, %)	52 (16.1)	180 (48.3)	< 0.001$^{\beta}$
Cesarean (n, %)	272 (83.9)	192 (51.7)	
Neonatal feeding			
Breast feeding (n, %)	222 (68.5)	260 (69.8)	>0.05$^{\beta}$
Commercial formula (n, %)	102 (31.5)	112 (30.2)	
Hospitalization (n, %)	40 (12.3)	11 (3.0)	>0.002$^{\beta}$

*Reported by mean (SD), $^{\alpha}$ according to Independent t-test, $^{\beta}$ according to Chi-square test

Table 2. Association between transit tyrosinemia incidence and study variables

Variables	Univariable model			Multivariable model*		
	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Preterm	0.53	0.28-1.02	0.059	868.2	168.9-4212.7	<0.00
Gestational age	0.39	0.31-0.48	<0.00	0.17	0.12-0.24	<0.00
Delivery type	4.8	3.38-6.96	<0.00	3.5	2.26-5.3	<0.00
Birth Weight	0.90	0.91-0.99	<0.00	0.99	0.99-1.00	0.546
Sex	1.03	0.76-1.41	0.818	1.06	0.69-1.64	0.756
Maternal age	1	(0.98-1.03)	0.714	0.98	0.95-1.02	0.426
Neonatal feeding	0.23	0.12-0.19	0.991	0.59	0.41-1.09	0.873
Consanguineous marriages	1.2	0.86-1.65	0.302	1.51	0.92-2.56	0.07

CI = confidence interval
*Odds ratio adjusted for the study variables identified as significant correlates of TNT in this study.

Discussion

This study is the first to investigate the incidence of TNT among Iranian newborns, with a reported incidence rate of 0.47%. The findings underscore the significance of several risk factors contributing to the occurrence of TNT in this population. Consistent with previous studies, prematurity was identified as the most significant risk factor for TNT. The incidence of TNT in preterm infants in this study aligns with previous research, in which the prevalence of TNT among preterm newborns ranged from 0.2% to 30% (16,17). A study conducted in 2006 examined metabolic newborn screening outcomes in North Carolina and identified prematurity as the strongest risk factor for TNT (1). Moreover, in a study by Zea-Rey et al. conducted in the Mexican population, an overall incidence of 0.29% was observed, with 0.35% in preterm infants, similar to the results obtained in the present study. These findings reinforce the notion that prematurity is a key factor influencing the incidence of TNT (2).

Our observations showed that newborns with TNT had a shorter gestational age compared to the control group (37.7 vs. 38.7 weeks). Consistent with previous studies, low birth weight and small gestational age are recognized risk factors for TNT. However, we found a similar association in term neonates. Although the birth weight of neonates with TNT was, on average, 0.32 kg lower than that of neonates in the control group, this difference was not statistically significant. Based on these findings, we hypothesize that term neonates with a lower gestational age, similar to preterm infants, may experience delayed maturation of the enzyme 4-hydroxyphenylpyruvate dioxygenase, which could contribute to the incidence of TNT (18, 19).

Another significant finding of this study was the markedly higher rate of C/S births among newborns diagnosed with TNT. The incidence of TNT was 5.2 times higher in neonates born via C/S compared to those born vaginally. Despite ongoing efforts to reduce unnecessary C/S, its prevalence remains high in Iran. A recent survey in 2022 reported a C/S rate of 51.6% in Iran, exceeding global averages and WHO recommendations (20). In our study, approximately 84% of the neonates were delivered via C/S.

The high incidence of TNT raises concerns due to the need for repeat testing, which increases healthcare and laboratory costs and may cause psychological distress for families. Although previous studies suggest that transient elevations in serum tyrosine levels are unlikely to have long-term consequences (14, 21), a major limitation of current neonatal screening programs is the reliance on tyrosine measurement, which lacks specificity in distinguishing TNT from hereditary tyrosinemia type I. Given that HT1 is a severe metabolic disorder requiring early intervention, incorporating succinyl acetone measurement into newborn screening protocols would improve diagnostic accuracy and prevent delayed treatment (6). Considering the critical role of metabolic pathways in neurological development, preventive strategies to reduce TNT incidence should be considered.

This study provides novel insights into the incidence and risk factors of TNT in Iranian newborns, utilizing data from a leading newborn screening center in Tehran over a four-year period. However, as a single-center retrospective study, its findings may not be fully generalizable to broader populations. Additionally, reliance on existing medical records introduces potential biases that should be acknowledged.

Acknowledgements

We appreciate the support of the Metabolic Laboratory of the Growth and Development Research Center and Children's Medical Center.

Conf ict of Interest

The authors declared that they have no conflict of Funding: There is no funding in this study.

Funding

There is no funding in this study.

References

1. North Carolina metabolic newborn screening: abnormal screen follow-up, physician knowledge & risk for transient neonatal tyrosinemia [Dissertation]2010.
2. Zea-Rey AV, Cruz-Camino H, Vazquez-Cantu DL, Gutiérrez-García VM, Santos-Guzmán J, Cantú-Reyna C. The Incidence of Transient Neonatal Tyrosinemia Within a Mexican Population. J Inborn Errors Metab Screen. 2017;5:2326409817744230. https://doi.org/10.1177/2326409817744230
3. Camargo Neto EC, Schulte J, Anele EV, Rubim R, Lewis E, De Mari J, et al. Transient neonatal tyrosinemia: a frequent abnormality. J Pediatr 1998;74(6):447-50. https://doi.org/10.2223/jped.461
4. Zaleski WA, Hill A. Tyrosinosis: a new variant. Can Med Assoc J. 1973;108(4):477 passim.
5. Nakamura K, Matsumoto S, Mitsubuchi H, Endo F. Diagnosis and treatment of hereditary tyrosinemia in Japan. Pediatr Int. 2015;57(1):37-40. https://doi.org/10.1111/ped.12550
6. Varughese B, Madrewar D, Polipalli SK, Kapoor S. Development of Flow Injection Analysis Method for the Second-Tier Estimation of Succinylacetone in Dried Blood Spot of Newborn Screening. Indian J Clin Biochem. 2022;37(1):40-50. https://doi.org/10.1007/s12291-020-00944-z
7. Screening for inborn errors of metabolism. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1968;401:1-57.
8. Ohisalo JJ, Laskowska-Klita T, Andersson SM. Development of tyrosine aminotransferase and para-hydroxyphenylpyruvate dioxygenase activities in fetal and neonatal human liver. J Clin Invest. 1982;70(1):198-200. https://doi.org/10.1172/jci110593
9. Menkes JH, Welcher DW, Levi HS, Dallas J, Gretsky NE. Relationship of elevated blood tyrosine to the ultimate intellectual performance of premature infants. Pediatrics. 1972;49(2):218-24. https://doi.org/10.1542/peds.49.2.218
10. Komrower GM, Robins AJ. Plasma amino acid disturbance in infancy. I: Hypermethioninaemia and transient tyrosinaemia. Arch Dis Child. 1969;44(235):418-21. https://doi.org/10.1136/adc.44.235.418
11. Light IJ, Sutherland JM, Berry HK. Clinical Significance of Tyrosinemia of Prematurity. Am J Dis Child. 1973;125(2):243-7. https://doi.org/10.1001/archpedi.1973.04160020067013
12. Mamunes P, Prince PE, Thornton NH, Hunt PA, Hitchcock ES. Intellectual deficits after transient tyrosinemia in the term neonate. Pediatrics. 1976;57(5):675-80. https://doi.org/10.1542/peds.57.5.675
13. Fernbach SA, Summons RE, Pereira WE, Duffield AM. Metabolic studies of transient tyrosinemia in premature infants. Pediatr Res. 1975;9(4):172-6. https://doi.org/10.1203/00006450-197504000-00006
14. Martin HP, Fischer HL, Martin DS, Chase HP. The development of children with transient neonatal tyrosinemia. J Pediatr. 1974;84(2):212-6. https://doi.org/10.1016/S0022-3476(74)80604-9
15. Techakittiroj C, Cunningham A, Hooper PF, Andersson HC, Thoene J. High protein diet mimics hypertyrosinemia in newborn infants. J Pediatr. 2005;146(2):281-2. https://doi.org/10.1016/j.jpeds.2004.10.013
16. Roura JC JE, Viera IC, Cuervo OH, De la Peña D, Nogueras L. Transitory neonatal tyrosinemia: biochemical diagnosis of one case. Revista Cubana de Genética Comunitaria. 2012;6(1):57-60.
17. Martin HP, Fischer HL, Martin DS, Chase HP. The development of children with transient neonatal tyrosinemia. J Pediatr. 1974;84(2):212-6. https://doi.org/10.1016/s0022-3476(74)80604-9
18. Avery ME, Clow CL, Menkes JH, Ramos A, Scriver CR, Stern L, et al. Transient tyrosinemia of the newborn: dietary and clinical aspects. Pediatrics. 1967;39(3):378-84.
19. Russo PA, Mitchell GA, Tanguay RM. Tyrosinemia: a review. Pediatr Dev Pathol. 2001;4(3):212-21. https://doi.org/10.1007/s100240010146
20. Pourshirazi M, Heidarzadeh M, Taheri M, Esmaily H, Babaey F, Talkhi N, et al. Cesarean delivery in Iran: a population-based analysis using the Robson classification system. BMC Pregnancy Childbirth. 2022;22(1):185. https://doi.org/10.1186/s12884-022-04517-1
21. Menkes JH, Chernick V, Ringel B. Effect of elevated blood tyrosine on subsequent intellectual development of premature infants. J Pediatr. 1966;69(4):583-8. https://doi.org/https://doi.org/10.1016/S0022-3476(66)80044-6