Original Article

Hypothyroidism in First-Degree Relatives of Neonates with Congenital Hypothyroidism: Is there an Association?

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Abstract

Background: Recent studies have shown an increased incidence of congenital hypothyroidism (CH), especially in the middle-east region. The exact etiology is unknown; however, it has been related to several factors, the most noticeable being the high prevalence of transient CH (TCH), parental consanguinity, and the history of hypothyroidism in relatives. We sought to determine the impact of hypothyroidism in the relatives of patients with the observed trend. **Methods:** We included all patients with primary CH detected through the Newborn Screening (NBS) Program from 2007 to 2016. We analyzed the impact of consanguinity relationship, parental and siblings' thyroid function, second-degree relatives' thyroid function, parental educational level, age, and maternal gestational diabetes on the development of permanent CH (PCH) and TCH. **Results:** A total of 1447 consecutive eligible patients were recruited during the study period. Of this number, 1171 (81%) were diagnosed with CH: 623 (53.2%) had PCH and 548 (46.8%) had TCH. Six hundred thirty-three (54.1%) participants were men, and 814 (69.5%) had a history of relatives' hypothyroidism. Our data analysis revealed a significant difference regarding the male gender, having a history of relatives' hypothyroidism, and parental hypothyroidism compared to TCH ones ($P < 0.05$). Patients with a history of relatives' hypothyroidism had significantly higher PCH than TCH ($P < 0.0001$). However, consanguineous marriage was not comparable in patients regardless of their history of relatives' hypothyroidism (P-value >0.884). **Conclusions:** Our findings indicated the role of the history of hypothyroidism in neonates' relatives in the evolution of the PCH. Meanwhile, consanguineous marriage did not impress the development of PCH and TCH.

Keywords: *Congenital hypothyroidism, first-degree relatives, transient*

Introduction

Congenital hypothyroidism (CH) is a syndrome of thyroid hormone deficiency in newborns, with a high global incidence rate that differs from 1:2000 to 1:4000 in iodine sufficient regions. Also, CH is the most preventable cause of neurocognitive disorders.[1,2]

CH is divided into transient and permanent types, based on the duration of the disease. Permanent congenital hypothyroidism (PCH) is mainly caused by thyroid dysgenesis (TD) and thyroid dyshormonogenesis (TDH) accounts for 85% and 10-15% of CH cases, respectively.[3,4] However, recent studies revealed that TDH is the principal cause of CH in Iran.[5] TD is considered a sporadic disease, resulting mainly from nongenetic causes such as environmental factors and stochastic events during embryogenesis. However, TDH is a disease with a genetic origin.[6] Maternal thyrotropin receptor–blocking antibodies, anti-thyroid medications, iodine deficiency, and iodine excess are the leading causes of transient congenital hypothyroidism (TCH).[7,8]

Recent studies revealed an increasing trend in the incidence of CH worldwide, especially in the middle-east region.[9] However, there is doubt about the reality of the observed trend and the possible role of confounding factors, the most important being an increase in the TCH incidence rather than PCH.[10] However, the higher prevalence of CH among women, extrathyroidal congenital anomalies, gestational diabetes mellitus (GDM), maternal smoking, higher risk of CH in twins, high prevalence of consanguineous marriage among parents, and previous ultrasonographic studies reinforced the genetic involvement in the pathogenesis of CH. Meanwhile, autoimmune and environmental factors are considered to be involved in the development of

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the disease.[11-13] In this regard, previous studies, both conducted in our region and the rest of the world, declared the multifactorial basis of CH pathogenesis, including genetics, autoimmune, and environmental involvement.[11,14,15] Additionally, the previous study conducted in our region declared a higher prevalence of consanguineous marriage and a history of hypothyroidism due to TD among relatives of CH patients.[15]

Thus, considering that Iran is the country that documented a high incidence rate of CH and the possible role of consanguinity in the current observed trend, we aimed to evaluate the impact of the history of hypothyroidism in neonates' relatives and then the effect of consanguineous marriage as one of the risk factors with the observed trend.

Methods

Study design

This retrospective study included all patients with primary CH detected by the Newborn Screening (NBS) Program from March 2007 to March 2016 in Isfahan Province, Iran. We excluded patients who died before three years and those who migrated to other provinces. This study was approved by the local clinical research ethics committee, with an ethical code #IR.MUI.MED.REC.1399.089.

Data collection

Demographic and clinical features of all patients were collected and registered in their files during the follow-up period. We analyzed the consanguinity relationship, thyroid function of parents and siblings, second-degree relativesfethyroid function, parental educational level, age, and maternal gestational diabetes status. Furthermore, we analyzed neonatal characteristics of patients, including the TSH profile, weight, height, head circumference, season at birth, way of delivery, and history of prematurity. Parents and siblings were considered first-degree relatives. Meanwhile, second-degree relatives were considered neonate' aunts, uncles, and grandparents. First and second cousin parental consanguinity was considered as first- and second-degree consanguineous marriage.[16]

NBS program

The primary TSH-based screening with T4 backup measurement was employed to detect CH. The whole blood heel prick samples were collected 3–7 days after birth. Neonates with a Guthrie TSH test mpleIU/L on the first TSH screening test were recalled to repeat the screening test; those with TSH 5–9.9 mIU/L were recalled for complimentary tests, and those with TSH 10 mIU/L were recalled for confirmatory venous sampling. TSH values <10 mIU/L and T4 values >6.5 µ6.5eson the second measurement were considered normal. However, those with abnormal results were referred to a pediatric endocrinologist to receive appropriate treatment and further follow-up. For confirmed patients, 10–15 µg/kg/day of levothyroxine was prescribed. Further follow-up was accomplished based on growth indices, T4, and TSH profile measurements. PCH was defined as the persistence of thyroid hormone deficiency even after withdrawal therapy. However, TCH referred to a temporary lack of thyroid hormone that recovered later in infancy. At the age of three, the TCH and PCH were determined by normal and abnormal TSH and T4 values (TSH <5 mIU/L and T4 >6.5 µg/dl) following the withdrawal of levothyroxine for a month, respectively.[17,18] The filter TSH value was measured by a TSH ELISA kit, and serum level of TSH and T4 was measured by immunoradiometric assay and radioimmunoassay, respectively, using Kavoshyar (Iran-Tehran) kits since the initiation of the CH screening in Iran. The sensitivity of the T4 and TSH tests was 0.38 mg/dl and 0.05 mIU/L, respectively; these were controlled with a Berthold LB 2111-12 gamma counter.[19]

Statistical analysis

Continuous variables were reported as mean n standard deviation. Distinct variables were presented as number and percentage. Shapiro–Wilk and Leven tests were performed to determine the normality and homogeneity of data. Based on data homogeneity, an independent *t*-test or ANOVA with post hoc test or Mann–Whitney *U* test and Chi-squared test were performed to compare continuous and distinct variables, respectively. IBM SPSS Statistics (SPSS Inc., version 22.0, Chicago, IL, USA) was used to perform all analyses.

Results

A total of 1447 consecutive eligible patients were recruited during the study period. Of this number, 1171 (81%) were diagnosed with CH: 623 (53.2%) with PCH and 548 (46.8%) with TCH. However, we were unable to determine the rest due to migration of patients to other provinces, mortality before the age of three, and other reasons. Table 1 shows the baseline characteristics of neonates based on their type of hypothyroidism. Six hundred thirty-three (54.1%) of the participants were male, and 814 (69.5%) had a history of relativesi hypothyroidism. Our data analysis revealed a significant difference regarding the male gender, having a history of relatives' hypothyroidism, parental hypothyroidism, and filter TSH in PCH patients compared to TCH ones ($P < 0.05$). PCH and TCH patients were not comparable in terms of their parental age during pregnancy, parental education degree, history of consanguineous marriage, type of delivery, and anthropometric indices at birth ($P > 0.05$). Though TCH patients were born primarily in spring and autumn compared to PCH patients, the observed difference was not significant ($P = 0.764$) [Table 1].

Table 2 shows the baseline characteristics of patients based on their first- and second-degree relatives' hypothyroidism history [Table 2]. Of the neonates, 53% were men, and 90%

Table 1: Baseline characteristics of permanent and transient CH neonates

Variables		Total (*n*=1171)	Type of hypothyroidism		*P*
			Permanent (623)	Transient (548)	
Male (%)		633 (54.1)	315 (50.6)	318 (58)	0.011
History of relatives' hypothyroidism (%)	First-degree	403 (34.4)	270 (43.3)	133 (24.2)	<0.0001
	Second-Degree	411 (35.1)	264 (42.3)	147 (26.8)	<0.0001
	No history	357 (30.4)	89 (14.2)	268 (48.9)	<0.0001
Season of birth	Spring	306 (26.1)	160 (25.7)	146 (26.6)	0.764
	Summer	309 (26.4)	171 (27.4)	138 (25.2)	
	Autumn	302 (25.8)	155 (24.9)	147 (26.8)	
	Winter	254 (21.7)	137 (22)	117 (21.4)	
Mother's age (years)		27.79±5.66	27.87±5.73	28.00±5.54	0.829
Father's age (years)		32.43±6.04	32.48±5.93	32.59±6.21	0.612
Weight (kg)		3.33±0.95	3.31±0.97	3.36±0.97	0.634
Height (cm)		48.67±4.65	48.69±5.27	48.69±4.21	0.986
Head circumference (cm)		35.33±2.80	35.57±3.11	35.17±2.40	0.388
Mother's thyroid function	Hypothyroidism	284 (24.4)	185 (29.9)	99 (18.2)	<0.0001
	Normal	880 (75.6)	434 (70.1)	446 (81.8)	
Father's thyroid function	Hypothyroidism	97 (8.3)	73 (11.8)	24 (4.4)	<0.0001
	Normal	1067 (91.7)	546 (88.2)	521 (95.6)	
Filter TSH		46.73±102.37	61.42±131.53	32.47±75.81	<0.0001
Neonatal serum TSH		36.53±69.57	45.22±76.28	22.11±23.19	<0.0001
Consanguinity	First- degree	97 (8.4)	54 (8.8)	43 (8)	
	Second- degree	317 (27.6)	168 (27.5)	149 (27.7)	0.884
	No familial relationship	735 (64)	390 (63.7)	345 (64.2)	
Mother's education	No university education	540 (46.1)	294 (47.2)	246 (44.9)	0.431
	University education	631 (53.9)	329 (52.8)	302 (55.1)	
Father's education	No university education	589 (50.3)	323 (51.8)	266 (48.5)	0.259
	University education	582 (49.7)	300 (48.2)	282 (51.5)	
Delivery (NVD**)		412 (35.7)	210 (34.3)	202 (37.4)	0.265
Prematurity (yes)		82 (10)	44 (9.6)	38 (10.5)	0.656
Gestational diabetes mellitus (yes)		65 (10.6)	42 (12.3)	23 (8.4)	0.119

*Results from Mann–Whitney and Chi-squared tests. **NVD=normal vaginal delivery

were born at term. The parents of 35.9% of the participants had a consanguineous marriage with a second-degree relationship predominancy. Patients with a history of first-degree relatives' hypothyroidism had a higher birth weight and history of cesarian section delivery ($P < 0.05$). Meanwhile, patients with a history of relatives' hypothyroidism had significantly higher PCH than TCH ($P < 0.0001$). A lower parental educational degree was significantly higher in patients with a history of relatives' hypothyroidism $P < 0.0001$). Parental age during pregnancy, history of consanguineous marriage, and maternal gestational diabetes mellitus (GDM) were not comparable in patients regardless of their history of relatives' hypothyroidism ($P > 0.05$) [Table 2].

Discussion

The impact of first- and second-degree relatives' history of hypothyroidism and its contribution to the type of hypothyroidism were investigated. Our results are compatible with the genetic role of CH caused by TDH as a principal cause of CH in Iran with autosomal recessive inheritance.[5] The findings of our study demonstrate the higher prevalence of hypothyroidism among the relatives of patients. Prior ultrasound survey conducted in our region confirmed our result regarding the familial component of this entity.[15] Contrary to prior studies, our study revealed no significant consanguineous marriage difference among parents of patients with PCH and TCH.[20,21] This can be explained by genetic factors with inheritance other than autosomal recessive, autoimmune, and environmental factors. Our hypothesis is supported by the study conducted by Medda *et al*. declaring the multifactorial origin of CH.[4]

Fifty-four percent of whole neonates were of male gender, and more than half of the patients with PCH and TCH were of male gender, with a predominancy of males experiencing TCH. The male predominancy in patients with PCH in our study is contrary to numerous studies conducted in Europe, Canada, and Australia due to the reported 2:1 female-to-male ratio.[4,22-25] However, the reported ratio among cases with TCH was confirmed in our study.

Despite the lack of significant difference between the birth season of patients in our study, there were

Table 2: Baseline characteristics of CH neonates based on relatives' hypothyroidism history

Variables		Total (*n*=1447)	First-degree relatives' hypothyroidism history		*P*	Second-degree relatives' hypothyroidism history		*P*
			Hypothyroidism (469)	No (978)		Hypothyroidism (464)	No (937)	
Male (%)		767 (53)	261 (55.7)	506 (51.7)	0.163	260 (56)	481 (51.3)	0.097
Mother's age (years)		27.79±5.66	27.93±5.75	27.69±5.60	0.585	27.61±5.63	27.80±5.67	0.769
Father's age (years)		32.43±6.04	32.46±6.22	32.40±5.91	0.588	32.21±5.91	32.63±6.15	0.183
Weight (kg)		3.33±0.95	3.41±1.02	3.30±0.9	0.035	3.29±0.93	3.35±0.96	0.415
Height (cm)		48.67±4.65	48.66±5.75	48.67±4.04	0.410	48.36±5.43	48.81±4.22	0.317
Head circumference (cm)		35.33±2.80	35.72±2.75	35.09±2.80	0.055	35.23±3.36	35.45±2.31	0.165
Filter TSH		46.73±102.37	51.14±116.34	44.41±94.26	0.637	58.05±144.09	41.39±70.83	0.396
Neonatal serum TSH		36.53±69.57	35.67±82.21	36.99±61.78	0.233	36.73±77.91	37.14±66.45	0.103
Type of hypothyroidism	Permanent	623 (50)	270 (64.7)	353 (42.6)	<0.001	264 (62.3)	338 (43.6)	<0.001
	Transient	548 (44)	133 (31.9)	415 (50.1)		147 (34.7)	378 (48.7)	
Consanguinity	First degree	110 (7.8)	38 (8.4)	72 (7.6)		41 (9)	65 (7.2)	0.435
	Second degree	395 (28.1)	126 (27.7)	269 (28.3)	0.868	122 (26.9)	259 (28.5)	
	No familial relationship	902 (64.1)	291 (64)	611 (64.2)		291 (64.1)	585 (64.4)	
Mother's education	No university education	601 (41.5)	251 (53.5)	350 (35.8)	<0.0001	268 (57.8)	313 (33.4)	<0.0001
	University education	846 (58.5)	218 (46.5)	628 (64.2)		196 (42.2)	624 (66.6)	
Father's education	No university education	650 (44.9)	264 (56.3)	386 (39.5)	<0.0001	298 (64.2)	325 (34.7)	<0.0001
	University education	797 (55.1)	205 (43.7)	592 (60.5)		166 (35.8)	612 (65.3)	
Delivery (NVD**)		513 (36.1)	142 (30.7)	371 (38.7)	0.003	157 (34.2)	344 (37.5)	0.229
Prematurity (yes)		92 (9.9)	40 (10.4)	52 (9.6)	0.693	42 (9.7)	44 (9.7)	0.997
Gestational diabetes mellitus (yes)		71 (10.6)	35 (12.4)	36 (9.3)	0.199	47 (12.5)	22 (8.4)	0.104

*Results from Mann–Whitney and Chi-squared tests. **NVD=normal vaginal delivery

controversies about the role of seasonality in CH. A recent study conducted in New York revealed a higher TSH value in neonates born in cold seasons.[26] However, a study conducted in our region revealed a higher prevalence of CH in summer due to intrauterine viral infection exhibiting seasonal variations in incidence and exposure to chemical compounds, including phosphorylated insecticides.[27] Though we found no significant difference between the observed prevalence in seasons, a higher prevalence of PCH was seen in summer and winter.

We also found no significant difference between the parental educational level and parental age among patients with PCH and TCH. However, the study conducted in China revealed the association of older maternal age, lower maternal academic level, rural area residency, and family history of thyroid disorders with CH.[28]

The mean TSH level before initiating treatment was significantly higher in patients with PCH compared to those with TCH, which can be vindicated by the second most common cause of CH in our region, namely, thyroid dysgenesis.[6] Our findings are validated by studies conducted in other provinces of our country.[29,30]

Our study has several limitations. First, we could not determine the type of hypothyroidism in 5.9% of eligible patients. Second, we were unable to investigate the role of autoimmune and environmental factors. Third, our study methodology had a retrospective origin.

Conclusions

The current study represented the role of hypothyroidism in the development of CH. Meanwhile, this is the first study conducted in our region that emphasizes the lack of impact of consanguineous marriage in the development of PCH and TCH. Despite the lack of influence of consanguineous marriage in the development of PCH and TCH and the possible role of genetic, autoimmune, familial, and environmental factors in CH, we suggested conducting a prospective study with long-term follow-up to obtain the interaction of these factors and their roles in PCH.

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Conflicts of interest

There are no conflicts of interest.

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