ORIGINAL ARTICLE

Predictive Factors of Transient Congenital Hypothyroidism among Filipino Children: A Retrospective Study

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ABSTRACT

Background and Objective. Transient congenital hypothyroidism (TCH) refers to temporary deficiency of thyroid hormone identified after birth which later recovers to improved thyroxine production. Its prevalence in the Philippines has not been reported in a large-scale study. Its diagnosis remains difficult due to its numerous possible etiologies. Identifying the predictive factors of TCH may aid in earlier diagnosis and decreased risk of overtreatment. This study aimed to determine the predictive factors for TCH in children with congenital hypothyroidism (CH) detected by newborn screening (NBS) in the Philippines from January 2010 to December 2017.

Methods. In this multicenter retrospective cohort study involving 15 NBS continuity clinics in the Philippines, medical records were reviewed, and clinical and laboratory factors were compared between children with TCH and those with permanent congenital hypothyroidism (PCH). Of the 2,913 children diagnosed with CH in the Philippines from 2010 to 2017, 1,163 (39.92%) were excluded from the study due to an unrecalled or lost to follow-up status, or a concomitant diagnosis of Down Syndrome.

Results. Among the 1,750 patients included in analysis, 6.97% were diagnosed with TCH, 60.80% were female, mean gestational age at birth was 38 weeks, and mean birth weight was 2,841 grams. Confirmatory thyrotropin (TSH) was lower and confirmatory free thyroxine (FT4) was higher in the TCH group compared to those with PCH (TSH 32.80 vs 86.65 μIU/mL [p <0.0001]; FT4 9.90 vs 7.37 pmol/L [p 0.001]). The TCH group required lower L-thyroxine doses compared to the PCH group at treatment initiation and at 1, 2, and 3 years of age (initial 6.98 vs 12.08 μg/kg/day [p <0.0001]; at 1 year 1.89 vs 4.11 μg/kg/day [p <0.0001]; at 2 years 1.21 vs 3.72 μg/kg/day [p <0.0001]; at 3 years 0.83 vs 3.45 μg/kg/day [p <0.0001]). Among those with TCH, mean serum TSH decreased significantly after treatment with L-thyroxine (32.80 vs. 6.55 μIU/mL, p 0.0001). Other factors associated with TCH were results of thyroid ultrasonography (p 0.007), gestational age at birth (p 0.02), and maternal history of thyroid illness (p <0.0001).

Conclusion. Of all the patients with confirmed congenital hypothyroidism via the newborn screening, 6.97% were diagnosed with transient CH. Factors associated with TCH are confirmatory TSH and FT4, L-thyroxine dose requirements, thyroid ultrasound findings, gestational age at birth, and a maternal history of thyroid illness.

Keywords: congenital hypothyroidism, Philippines, neonatal screening, prevalence

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INTRODUCTION

Congenital hypothyroidism (CH) is the most common endocrine disorder detected by newborn screening in the Philippines. From 1996 to 2018, a total of 12,233,971 babies have been screened, of which 4,360 were confirmed to have CH, giving a prevalence of 1:2,805.[1] Included in this data are the cases of transient congenital hypothyroidism (TCH), a condition characterized by a temporary deficiency of thyroid hormone identified after birth, with low thyroxine (T4) and elevated thyrotropin (TSH), which recovers later to improved thyroxine production.[2]

The incidence of TCH from screened children from newborn screening (NBS) programs in different countries varies from approximately 17% to 40%.[3] Its recognition remains to be a challenge as there are no universally accepted endpoints for trials of thyroid hormone therapy withdrawal.[4]

Studies on the predictive factors of the permanence of hypothyroidism have been published. Congenital hypothyroidism is assumed permanent if the thyroid gland is absent or ectopic, if dyshormonogenesis has been demonstrated (except if due to the *DUOXA2* mutation), or if any time during the first year of life TSH level rises above 20 μIU/mL.[4] L-thyroxine doses at 2 years and 3 years were noted to have a predictive role on the permanence of hypothyroidism. Children receiving doses lower than 2.76 μg/kg/day of L-thyroxine were noted to have TCH.[5] In another study, permanence of hypothyroidism was noted in children with CH who needed some increments in L-thyroxine doses in the first year of treatment, and L-thyroxine requirement of >4.9 μg/kg/day at 1 year old or >4.27 μg/kg/day at 2 years, all irrespective of thyroid gland ultrasound results.[6]

The diagnosis of TCH is not easy. Due to its different etiologies, the duration of patients' therapy warranted to maintain normal thyroid function remains variable. One of the studied predictive factors for TCH was the dose requirement to maintain free thyroxine (FT4) and TSH within normal limits. The current approach when one strongly suspects TCH is to stop treatment when the child reaches the age of 3 years and to repeat thyroid function tests after four weeks. Normal laboratory results off medications is taken as confirmatory of TCH.[7] This, however, may not be the case for all patients. The study aimed to identify predictive factors for TCH which may translate to shortened duration of treatment.

Determining the predictive factors for transient congenital hypothyroidism may help shorten the treatment period which has economic implications for patients. This study aims to generate information which may help the local scientific community develop guidelines on this specific population of patients. Furthermore, unnecessary treatment may be avoided since thyroid hormone not only affects the pituitary-thyroid axis but other anterior pituitary hormones as well. Overtreatment with levothyroxine was reported to be associated with increased mortality and poorer cognitive outcome in later childhood and adolescence.[8,9]

This study aimed to determine the predictive factors for TCH in children detected by newborn screening (NBS) in the Philippines from January 2010 to December 2017. Specifically, it aimed to determine the prevalence of TCH in the NBS program of the Philippines from 2010 to 2017, and to investigate clinical and familial factors predictive of TCH, such as L-thyroxine dose requirement, confirmatory FT4 and TSH, duration of L-thyroxine treatment, radiographic findings, maternal age, number of children in the family, maternal education, and family history of thyroid disease among children with CH detected by NBS in the Philippines from 2010 to 2017. This study is limited to those who had medical consults at newborn screening continuity clinics.

METHODS

The study utilized a retrospective study design. The study population included children in the Philippines who were diagnosed with congenital hypothyroidism from January 2010 to December 2017 through the newborn screening program. They presented with elevated TSH on newborn screening as per algorithm, which was subsequently confirmed by serum levels of TSH and FT4, and evaluation by a pediatric endocrinologist. These patients were regularly seen at the continuity clinics. All unrecalled and lost to follow-up patients, as well as those with known or identified syndromes like Down Syndrome, were excluded from the study.

Definition of Terms

Patients with an elevated TSH value (>15 μIU/mL) on newborn screening are recommended to undergo confirmatory testing of serum TSH and FT4 as soon as possible. Those identified as having congenital hypothyroidism are endorsed by the newborn screening center to a newborn screening continuity clinic near the patient's area of residence. If a patient failed to come in for consultation and had lost contact with their continuity clinic for at least six months, he or she was classified as an unrecalled patient. The continuity clinics are assisted by the Centers for Health Development of the Department of Health in a joint operation to locate the patient and determine the cause for missing consults. If, despite these efforts, the patient was still unrecalled, he or she was classified as lost to follow-up.

Data Collection

Data source was the NSRC database and chart records from all fifteen (15) newborn screening continuity clinics. Permission from the NSRC and NBS continuity clinics was obtained, and an online meeting was conducted with the continuity clinics to review the cases.

The following data were extracted from patients' medical record: sex, province and region of residence, birth weight, age of gestation and maternal age upon birth of the newborn, value of TSH on newborn screening, initial serum TSH and FT4 levels, results of thyroid ultrasound and/or thyroid scan, age of

treatment initiation, initial L-thyroxine dose, and L-thyroxine doses at 1, 2, and 3 years old. Other information such as a maternal history of thyroid disease, diabetes, or hypertension, highest educational attainment of the mother, number of children in the family, and presence of thyroid disease within 3 generations in family was also noted if available. For patients diagnosed with TCH who had undergone a trial off of L-thyroxine, serum TSH and FT4 levels at 3 to 12 months off medications was also recorded. In addition, TSH levels of 100 newborns born from January 2010 to December 2017 who had normal newborn screening results were requested from the NSRC to serve as the control group.

Analysis

The exact sample size formula from Levy and Lemeshow was used to determine the minimum sample size needed to achieve the primary objective.[10] As of December 2017, there were a total of 3,797 newborns diagnosed with CH by the newborn screening program. Thus, assuming a total of 507 babies (average per year of data from NSRC for the past 5 years) diagnosed with CH per year, the study was designed to enroll at least 388 participants to detect the proportion of TCH with 95% confidence and 5% precision.[1] Data were summarized in Microsoft Excel. Frequencies and corresponding percentages were obtained on demographic characteristics. Clinical and maternal factors of the TCH group were compared to those of the permanent congenital hypothyroidism group (PCH). The Chi-square test was used for categorical variables while t-test was used for continuous variables. Stata 17 was used in the data analysis.

This study was approved by the University of the Philippines Manila Research Ethics Board and the Single Joint Research Ethics Board.

RESULTS

Out of 2,913 children who were diagnosed with congenital hypothyroidism from 2010 to 2017, 837 (28.73%) were excluded because they were unrecalled; 314 (10.78%) were lost to follow-up, and 12 (0.41%) were excluded after having been identified to have Down Syndrome. A total of 1,163 patients were excluded from the study (39.92%). Eventually, 1,750 children with CH were included in the analysis (Figure 1).

Table 1. Demographic Characteristics of Study Participants (N = 1,750)

Demographic characteristics	Frequency	Percentage
Diagnosis		
Transient congenital hypothyroidism (TCH)	122	6.97%
Permanent congenital hypothyroidism (PCH)	1,628	93.93%
Age at enrollment in months		
Mean (SD)	7 (2)	-
Range (min, max)	4, 17	-
Sex		
Female	1,064	60.80%
Male	686	39.20%
Age of gestation in weeks		
Mean (SD)	38.48 (1.99)	-
Range (min, max)	26, 45	-
Birth weight in grams		
Mean (SD)	2,841 (568.26)	-
Range (min, max)	750, 5,200	-

Table 1 shows the demographic characteristics of study participants. The prevalence of transient congenital hypothyroidism in the sample population was 6.97%. Females comprised the majority of participants (60.80%), giving a female:male ratio of 1.6:1.

An equal number of females and males had TCH (F:M ratio 1:1), while there was a preponderance of females in the PCH group (F:M ratio 1.6:1, Figure 2). Region VI reported the highest number of CH (Figure 3).

The baseline clinical characteristics and maternal data of participants with TCH and those with PCH are seen in Table 2. While there were no significant differences in mean gestational age at birth, all post-term children had PCH (p-value 0.02). The mean birth weight was lower in those with TCH (p-value 0.05). Maternal history of thyroid disease

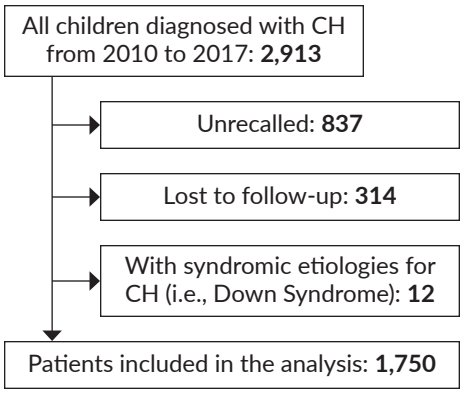

Figure 1. Flow of participant enrollment.

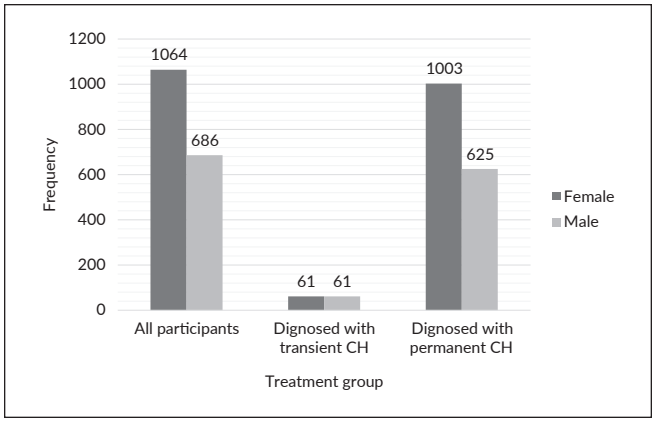

Figure 2. Sex distribution of study participants.

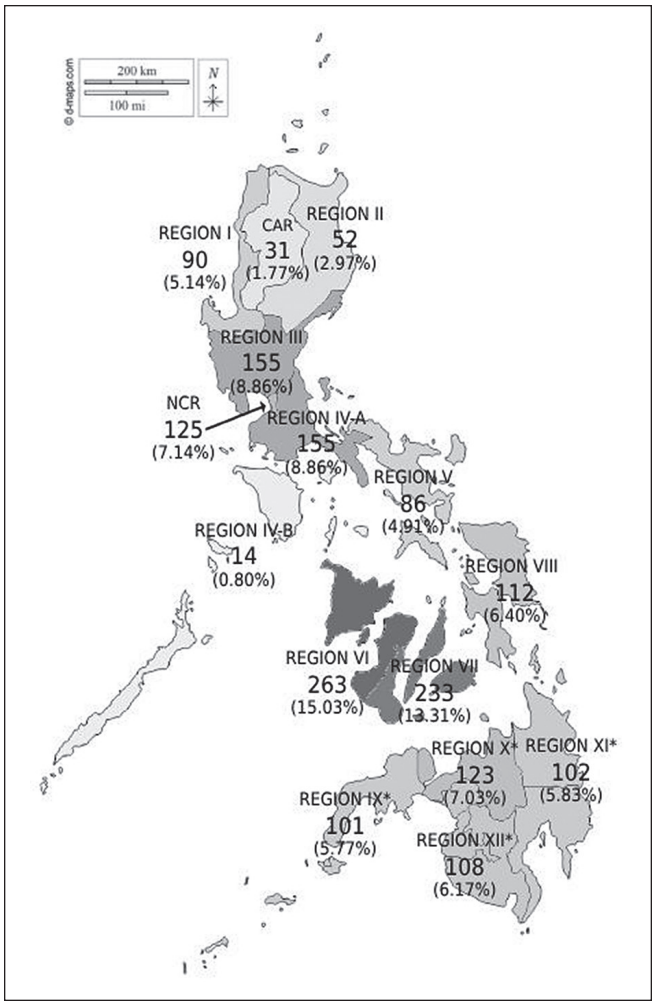

Figure 3. Regional distribution of children with congenital hypothyroidism (N = 1,750; CAR – Cordillera Administrative Region, NCR – National Capital Region).[11]

** Tallies of Regions IX, X, XI, and XII include localities that are currently classified under the separate regions of Caraga (Region XIII) and the Bangsamoro Autonomous Region in Muslim Mindanao (BARMM).*

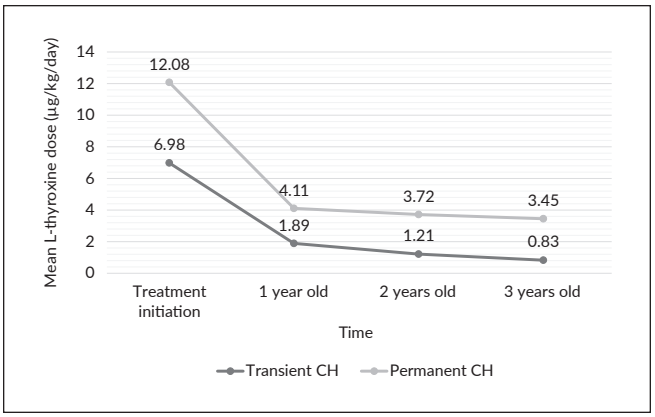

Figure 4. Mean L-thyroxine doses received by patients with transient or permanent congenital hypothyroidism upon treatment initiation and at 1, 2, and 3 years of age.

was significantly higher among those with TCH (p-value <0.0001). There were no differences between the two groups for the following maternal factors: age, diabetes mellitus, hypertension, number of children in the family, birth order, and family history of thyroid disease. Data on maternal age, parity, educational attainment, and socioeconomic status were not available in the database. Since electronic records were not yet in place, it was difficult to collect these data from the maternal records.

A one-way ANOVA was conducted to determine if newborn screening TSH levels were different for those with TCH, PCH, and the control group with normal expanded newborn screening results (Table 3). There was a statistically significant difference between at least two groups (F (2, 1,845) = 4.11, p-value 0.02). Tukey's test for multiple comparisons found that the difference in screening TSH was statistically significantly higher for PCH compared to TCH (94.55 ± 40.7 µIU/mL, p-value 0.05) and for TCH compared to controls (163.01 ± 58.5 µIU/mL, p-value 0.02). There was no statistically significant difference between PCH compared to controls (68.47 ± 44.69 µIU/mL, p-value 0.28) which could be due to the large disparity in sample size between the two groups. To further check whether a significant difference exists between the TCH and PCH groups, a t-test was done by comparing an equal number of samples (n = 179, β 0.2) resulting in a significant difference between TCH and PCH in mean screening TSH [SD] (695.75 [432.59] vs 601.20 [417.00] µIU/mL, p-value 0.02).

Table 4 summarizes confirmatory TSH and FT4 in the TCH and PCH groups. Children with TCH had significantly lower mean confirmatory TSH (p-value <0.0001) and significantly higher mean confirmatory FT4 (p-value 0.001). For both groups, the majority of participants had confirmatory TSH >15 µIU/mL, and about half had confirmatory FT4 levels <15 pmol/L.

Data on thyroid imaging studies was absent in almost all children in the sample population. Of those with a thyroid ultrasound report (n = 144), a sonographically normal thyroid was seen in 9.84% of TCH and 5.10% of PCH (Table 5). The presence of a normal thyroid gland among those with PCH implies that dyshormonogenesis is a common cause. Among those with a thyroid scan report (n = 30), 1.64% of TCH had a eutopic thyroid gland with normal or increased uptake, compared to 0.43% in the PCH population. Among the PCH group with an available thyroid scan report, ectopic thyroid (0.74%) was the most common finding.

The mean age at treatment initiation in the TCH group was 29 days old compared to 40 days old in the PCH group (p-value 0.30, Table 6). Mean L-thyroxine dose requirements were consistently lower in the TCH group compared to the PCH group at treatment initiation and at 1, 2, and 3 years of age (p-values <0.0001, Figure 4).

For children with TCH, serum TSH and FT4 were re-evaluated one to six months after discontinuation of L-thyroxine treatment. These values were compared to their initial serum TSH and FT4 values from confirmatory testing, which was done prior to treatment initiation (Table 7). Serum TSH was statistically significantly higher prior to treatment initiation compared to post-discontinuation of L-thyroxine treatment in children who were eventually diagnosed with TCH (p-value 0.0001). There was no significant difference in serum FT4 before and after L-thyroxine treatment in these patients.

Table 2. Clinical and Maternal Parameters among Children with Transient or Permanent Congenital Hypothyroidism from 2010 to 2017

Participant characteristics	TCH (n = 122)	PCH (n = 1,628)	Test* *p*-value
Gestational age at birth in weeks			
Mean (SD)	38.32 (1.99)	38.63 (1.99)	0.11
Range (min, max)	30, 41	26, 45	
Preterm (<37), n (%)	9 (7.38)	122 (7.49)	0.02
Term (37–41), n (%)	108 (88.52)	1,393 (85.57)	
Post-term (>41), n (%)	0	42 (2.58)	
No data, n (%)	5 (4.10)	71 (4.36)	
Birth weight in grams			
Mean (SD)	2,786 (569.25)	2,896 (567.27)	0.05
Range (min, max)	930, 4,500	750, 5,200	
Maternal age in years			0.97
Mean (SD)	26.4 (4.56)	26.3 (6.06)	
Range (min, max)	21, 31	16, 42	
No data, n (%)	117 (95.90)	1,565 (96.13)	
Maternal history of thyroid illness, n (%)	3 (2.50)	4 (0.30)	<0.0001
No data	111 (91.00)	1,536 (94.35)	
Maternal history of diabetes mellitus, n (%)	0	1 (0.10)	0.18
No data	114 (93.44)	1,537 (94.41)	
Maternal history of hypertension, n (%)	0	3 (0.18)	0.81
No data	114 (93.44)	1,537 (94.41)	
Number of children in the family			0.22
Mean (SD)	1.43 (0.53)	1.93 (1.03)	
Range (min, max)	1, 2	1, 5	
No data, n (%)	115 (94.26)	1,561 (95.88)	
Birth order of participant in the family, n (%)			0.69
1	0	32 (1.97)	
2	1 (0.82)	18 (1.11)	
3	1 (0.82)	9 (0.55)	
4	1 (0.82)	8 (0.49)	
5	0	1 (0.06)	
No data	119 (97.54)	1,560 (95.82)	
Family history of thyroid disease, n (%)	1 (0.82)	17 (1.04)	0.26
No data	119 (97.54)	1,559 (95.76)	

** Chi-square test for categorical variables; t-test for continuous variables*

Table 3. Screening TSH Levels among Children with Transient Congenital Hypothyroidism, Permanent Congenital Hypothyroidism, and Control Group from 2010 to 2017

Screening TSH (μIU/mL)	Control (n = 100)	TCH (n = 122)	PCH (n = 1,628)
Mean (SD)	3.62 (1.89)	59.19 (65.15)	100.56 (104.53)
Range (min, max)	1, 7.3	7, 265	3.54, 1,378.02
<15, n (%)	22 (22)	2 (1.64)	17 (1.04)
≥15, n (%)	78 (78)	120 (98.36)	1,609 (98.83)
No data, n (%)	0	0	2 (0.12)

Table 4. Confirmatory TSH and FT4 of Children with Transient or Permanent Congenital Hypothyroidism from 2010 to 2017

Confirmatory test results	TCH (n = 122)	PCH (n = 1,628)	Test* *p*-value
Confirmatory TSH in µIU/mL			
Mean (SD)	32.80 (26.18)	86.65 (129.55)	≤0.0001
Range (min, max)	0.30, 140	0.02, 977.99	
<5, n (%)	3 (2.46)	16 (0.98)	
5–15, n (%)	21 (17.21)	95 (5.84)	≤0.0001
>15, n (%)	93 (76.23)	1,427 (87.65)	
No data, n (%)	5 (4.10)	90 (5.53)	
Confirmatory FT4 in pmol/L			
Mean (SD)	9.90 (7.54)	7.37 (6.58)	0.001
Range (min, max)	0.06, 48.4	0, 48.86	
<15, n (%)	66 (54.10)	916 (56.27)	
15–39, n (%)	13 (10.66)	111 (6.82)	≤0.0001
>39, n (%)	1 (0.82)	3 (0.18)	
No data	42 (34.43)	598 (36.73)	

** Chi-square test for categorical variables; t-test for continuous variables*

Table 5. Comparison of Thyroid Imaging Studies between Children with Transient or Permanent Congenital Hypothyroidism from 2010 to 2017

Thyroid imaging results	TCH (n = 122)	PCH (n = 1,628)	*p*-value
Thyroid ultrasound findings, n (%)			0.007
Normal thyroid	12 (9.84)	83 (5.10)	
Hypoplastic thyroid	0	36 (2.21)	
Non-visualized thyroid	0	10 (0.61)	
Enlarged thyroid	1 (0.82)	2 (0.12)	
No data	109 (89.34)	1,497 (91.95)	
Thyroid scan findings, n (%)			0.270
Eutopic with normal or increased uptake	2 (1.64)	7 (0.43)	
Eutopic with decreased or no uptake	1 (0.82)	2 (0.12)	
Ectopic thyroid	0	12 (0.74)	
Thyroid agenesis	0	6 (0.37)	
No data	119 (97.54)	1,601 (98.34)	

DISCUSSION

There is no single precise definition of transient congenital hypothyroidism up to this time. Some authors define TCH as normal thyroid function after a trial off-therapy, while permanent congenital hypothyroidism is defined after a failed trial off-therapy, or when the subject requires L-thyroxine therapy beyond three years of age. A transient thyroid function test (TFT) abnormality is defined when follow-up TFTs normalize without L-thyroxine therapy.[12] In the Philippine Newborn Screening Program, the ultimate decision lies on the expertise of the pediatric endocrinologists who collaborate with the newborn screening continuity clinics. Generally, the practice follows the stated definition in the absence of in-depth study looking into this phenomenon and no existing guidelines at the moment.

Prevalence

The prevalence of TCH among confirmed CH patients in the Philippines was 6.97%. This is lower compared to published data from other countries: 50% (India), 50% (Brazil), 35.2% (Korea), 34.5% (Italy), and 32.9% (France).[2,12-15] The higher prevalence rates in the cited studies could be due to the smaller sample sizes (ranging from 36 to 713 participants) and lower TSH cut-off levels (ranging from 5.2 to 90 µIU/mL) to confirm diagnosis. Another reason for the lower prevalence in this study is the significant number of patients who were lost to follow-up; if these patients are assumed to have TCH, the rate would be higher.

Sex Preponderance

TCH was predominant in males in Kang's study which is in contrast to this study's findings of equal sex distribution.[12] Reports from various center on sex predilection varies from 0.5:1 to 2:1 in favor of females. In a study in Egypt among 248 children, female:male ratio was 0.8 for PCH and 0.7 for TCH.[16] Among French children, female preponderance was likewise observed.[15] It is speculated that sex ratio among CH children vary significantly according to race or ethnicity.[17]

Table 6. Comparison of L-thyroxine Doses Received by Children with Transient or Permanent Congenital Hypothyroidism from 2010 to 2017 from Treatment Initiation to 3 Years of Age

Treatment and post-treatment results	TCH (n = 122)	PCH (n = 1,628)	Test* *p*-value
Age at treatment initiation in days			
Mean (SD)	28.80 (23.14)	39.83 (115.29)	0.30
Range (min, max)	3, 194	1, 2,463	
≤14, n (%)	4 (3.28)	48 (2.95)	≤0.0001
15–30, n (%)	7 (5.74)	170 (10.44)	
31–60, n (%)	21 (17.21)	190 (11.67)	
61–100, n (%)	6 (4.92)	99 (6.08)	
>100, n (%)	84 (68.85)	1,120 (68.80)	
No data, n (%)	3 (2.5)	26 (1.7)	
Initial L-thyroxine dose in µg/kg/day			≤0.0001
Mean (SD)	6.98 (4.74)	12.08 (3.86)	
Range (min, max)	0, 13.89	1.87, 25.88	
No data, n (%)	104 (85.25)	1,309 (80.41)	
L-thyroxine dose at 1 year old in µg/kg/day			≤0.0001
Mean (SD)	1.89 (2.15)	4.11 (2.27)	
Range (min, max)	0, 8.15	0, 24.69	
No data, n (%)	81 (66.39)	1176 (72.24)	
L-thyroxine dose at 2 years old in µg/kg/day			≤0.0001
Mean (SD)	1.21 (1.81)	3.72 (2.09)	
Range (min, max)	0, 6.55	0, 17.44	
No data, n (%)	75 (61.48)	1,171 (71.93)	
L-thyroxine dose at 3 years old in µg/kg/day			≤0.0001
Mean (SD)	0.83 (1.33)	3.45 (2.00)	
Range (min, max)	0, 5.58	0, 15	
No data, n (%)	77 (63.11)	1,221 (75.00)	

** Chi-square test for categorical variables; t-test for continuous variables*

Table 7. Comparison of TSH and FT4 Results in Participants with Transient Congenital Hypothyroidism upon Confirmatory Testing and at One to Six Months after Discontinuation of L-thyroxine Treatment

Thyroid function tests of TCH group (n = 122)	At confirmatory testing	After discontinuation of L-thyroxine	t-test *p*-value
Serum TSH in µIU/mL			0.0001
Mean (SD)	32.80 (26.18)	6.55 (7.45)	
Range (min, max)	0.30, 140	0.13, 25.31	
No data, n (%)	5 (4.10)	104 (86.7)	
Serum FT4 in pmol/L			0.14
Mean (SD)	9.90 (7.54)	12.96 (6.46)	
Range (min, max)	0.06, 48.4	1.01, 21.59	
No data, n (%)	42 (34.43)	105 (87.5)	

Etiology of Transient Congenital Hypothyroidism

Causes of TCH include exposure to maternal thyrotropin receptor-blocking antibodies, exposure to anti-thyroid drugs, iodine deficiency, and iodine excess.[17,18] In the setting of this study, exposure to anti-thyroid medications is the only etiology that can be obtained from the history; no laboratory tests are done to document the other three mentioned causes. While maternal history of thyroid illness seemed to be a significant factor, the available information was limited to 3 and 4 children in the TCH and PCH groups, respectively, posing difficulty in deriving a robust conclusion. All patients included in the study with TCH who underwent imaging had either normal or enlarged thyroid glands on ultrasound. This suggests other possible causes which were not documented and may be recommended as part of prenatal care for expectant mothers.

In a study by Oron et al. of 142 children with CH who all underwent thyroid imaging, scintigraphy can predict permanency or transience of the condition.[19] Thyroid agenesis and ectopia imply PCH, but a eutopic thyroid gland is not predictive of the course and outcome as to the final category of hypothyroidism. With the availability of more laboratory facilities and possible financing through universal health care, there is a brighter outlook for CH patients to be able to undergo imaging studies.

The age at which thyroid imaging was done should also ideally be noted. The difficulty of performing an accurate thyroid ultrasound on infants and younger children who are more prone to fussing, combined with the subjective nature of ultrasound readings, makes alternative imaging studies an important decision-making tool in equivocal cases.

Clinical conditions that may cause TCH due to immature hypothalamic-pituitary axis and limited capacity to generate bioactive thyroid hormones are seen in preterm and low birth weight infants.[3] Children in the TCH group had significantly lower birth weights. In a study of French children with TCH who had eutopic thyroid glands, 14.2% were preterm and 13.8% had low birth weight.[13] This has a very significant implication in local newborn screening practices involving these special populations.

Initial Free Thyroxine (FT4) and Thyrotropin (TSH) Levels

This study showed no significant difference in the screening FT4 and TSH in the TCH and PCH groups. However, a significant difference was noted in the confirmatory TSH and FT4 values, where TSH was high and FT4 was low in those with PCH. Because of the wide variation in the reported reference values from the different laboratories where the thyroid function tests were done, it was decided to treat the data as categorical variable in the analysis. In the TCH group, 76% had TSH levels above 16 μIU/mL and 88% in those with PCH. This was also the observation noted in previously cited studies.[12-14,16] In a study done by Scavone et al., 58 Indian children showed a median (IQR) initial TSH level of 73.3 (276.5) μIU/mL among children with PCH and 24.2 (52.4) μIU/mL among those with TCH (p-value 0.013).[2] Tuli et al. showed that among Italian children with PCH, serum TSH above 60 μUI/mL had 72.4% sensitivity and 80.7% specificity and likelihood ratio of 2.8.[20]

A possible explanation for the comparable screening TSH levels in the TCH and PCH groups in this study is the physiologic rise in TSH seen during the first 72 hours of life. Newborn screening in the Philippines utilizes TSH and is performed immediately after the 24th hour of life to ensure that all babies are screened prior to discharge. At the time confirmatory TSH and FT4 are taken (usually after the 7th day of life), neonates with thyroid dysgenesis leading to PCH will have persistently high TSH but low FT4.

Thyroid Imaging

Thyroid imaging (either a neck ultrasound or scintigraphy) has an important role in establishing the etiology of congenital hypothyroidism. It may help in distinguishing TCH from PCH. The presence of a normal-sized gland in the normal anatomic location favors a transient state. Majority of study participants did not undergo imaging studies. Only 10.66% of TCH and 8.05% of PCH had documentation of a thyroid ultrasound. The presence of a normal gland in those with PCH implies that dyshormonogenesis could be a common cause. It might be worthwhile to do further tests in this group of patients. For thyroid scan, only 2.46% in the TCH group and 1.66% in the PCH group had the benefit of the procedure. Possible reasons for this low rate include: lack of accessibility to facilities offering such studies; financial constraints (cost is shouldered by the family); and the physician's decision to forego imaging in cases when delayed treatment will further compromise the patient's health. The presence of a normal gland in the TCH group supports the decision to stop treatment and confirm the diagnosis.

L-thyroxine Dose

The age at initiation of treatment was comparable between patients with TCH and PCH. A remarkable finding was the dose requirement to maintain normal thyroid function. Children with TCH required significantly lower doses throughout the first three years of life compared to those with PCH. The doses to maintain normal thyroid function tests was below the recommended doses for the specific groups: 10-15 μg/kg/day on the first year of life and 5-7 μg/kg/day from the second to third years of life.[21] The L-thyroxine requirements for the TCH group in this study were 1.89, 1.21, and 0.83 μg/kg/day at 1, 2, and 3 years of age, respectively. This result was similar to the findings of Ünüvar et al. among Turkish children, where among all parameters studied as possible predictors of TCH (age, TSH and FT4 levels at the time of diagnosis, sex, gestational age, birth weight, symptoms, ultrasonographic and scintigraphic findings), only T4 dose required to maintain a euthyroid state distinguished TCH from PCH.[22] The conclusion of Scavone et al. among Indian children stated that L-thyroxine dose requirement at the 24th month greater than 3.2 μg/kg/day is predictive of PCH while those requiring a 24-month dose of less than 0.94 μg/kg/day most probably have TCH.[2] A recent publication from Canada showed that L-thyroxine dose of less than 3 μg/kg/day at ages 1 and 2 years and less than 2.5 μg/kg/day at age 3 years can be predictive of TCH.[23] Another supporting study on the use of L-thyroxine as an indicator of TCH was done in Turkey where treatment was discontinued before the age of 3 years on the basis of dose requirement of 1.25 ± 0.27 μg/kg/day with normal thyroid function tests on follow-up.[24] A study on Japanese children with CH found that L-thyroxine doses above 4.7 μg/kg/day at one year old was predictive of PCH whereas a dose below 1.8 μg/kg/day was a predictor of TCH.[25] It is important to monitor the dose of L-thyroxine as both undertreatment and overtreatment have repercussions. In a study among Polish children, the risk of overtreatment is seen in children with eutopic thyroid glands.[9]

CONCLUSION

The prevalence of transient congenital hypothyroidism in the study is 6.97%. Factors that are predictive of TCH are confirmatory TSH and FT4, doses of L-thyroxine at treatment initiation and at 1, 2, and 3 years of age, thyroid

ultrasonography, and gestational age at birth. Among the maternal risk factors, only thyroid illness was associated with TCH.

Recommendations

A prospective study is important to eliminate the limiting factors encountered in this retrospective study. In addition, logistic regression analysis may be considered in subsequent studies. The database should contain important maternal and neonatal information with possible impact on thyroid function. A stringent follow-up system should be devised and a clinical pathway applicable to the resources available should be designed. Standardized laboratory collection, analysis, and quality control should be implemented. Periodic assessment and re-orientation of the NBS continuity clinics staff should be conducted.

A standardized data input form may be developed for use by all newborn screening continuity clinics who oversee the long-term care of patients with congenital hypothyroidism. The development and enforcement of a standardized method may help avoid the omission of a variety of clinical information during patient hand-off.

Limitations

Due to nature of the study, several limitations were encountered. Several gaps in the medical record were discovered during chart review, resulting in cases with incomplete data (e.g., results of thyroid imaging studies, patient weight at the time of consult where L-thyroxine dose was adjusted, and history of maternal diseases during pregnancy), despite the collection of this information being a routine part of the newborn screening process and subsequent follow-up consults. This loss of information was primarily attributed to dissimilarities in record-keeping practices among the various institutions involved in handling patient data, leading to omission of parts of a patient's medical record during hand-off.

There was no standardized method for recording laboratory values among the various study sites. The frequent omission of the unit of measurement for FT4 values (which may be reported as pmol/L, nmol/L, ng/dL, or other variations) resulted in laboratory values that could not be standardized for data analysis. Furthermore, the detection limits for thyroid function tests used by different laboratories were highly varied and prevented reporting of laboratory values as continuous variables.

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Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

Author Disclosure

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REFERENCES

1. Newborn Screening Reference Center. NBS Statistics [Internet]. Newborn Screening Reference Center. [cited 2021 Jun 25]. Available from: https://newbornscreening.ph/index.php?option=com_content&view=article&id=83:nbs-statistics&catid=32:statistics&Itemid=57
2. Scavone M, Carboni E, Stefanelli E, Romano G, Vero A, Giancotti L, Miniero R, Talarico V. Prediction of Transient or Permanent Congenital Hypothyroidism from Initial Thyroid Stimulating Hormone Levels. Indian Pediatr. 2018 Dec 15;55(12):1059-1061. PMID: 30745478.
3. Kanike N, Davis A, Shekhawat PS. Transient hypothyroidism in the newborn: to treat or not to treat. Transl Pediatr. 2017 Oct;6(4): 349-358. doi: 10.21037/tp.2017.09.07. PMID: 29184815; PMCID: PMC5682382.
4. Mondal S, Mukhopadhyay P, Ghosh S. Clinical approach to congenital hypothyroidism. Thyroid Research and Practice. 2017 May-Aug;14(2):45–53. doi:10.4103/trp.trp_5_17
5. Park IS, Yoon JS, So CH, Lee HS, Hwang JS. Predictors of transient congenital hypothyroidism in children with eutopic thyroid gland. Ann Pediatr Endocrinol Metab. 2017 Jun;22(2):115-118. doi: 10.6065/apem.2017.22.2.115. Epub 2017 Jun 28. PMID: 28690990; PMCID: PMC5495977.
6. Messina MF, Aversa T, Salzano G, Zirilli G, Sferlazzas C, De Luca F, Lombardo F. Early Discrimination between Transient and Permanent Congenital Hypothyroidism in Children with Eutopic Gland. Horm Res Paediatr. 2015;84(3):159-64. doi: 10.1159/000435811. Epub 2015 Jul 8. PMID: 26160341.
7. American Academy of Pediatrics; Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association; Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society; Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006 Jun;117(6):2290-303. doi: 10.1542/peds.2006-0915. PMID: 16740880.
8. Ettleson MD, Papaleontiou M. Evaluating health outcomes in the treatment of hypothyroidism. Front Endocrinol (Lausanne). 2022 Oct 18;13:1026262. doi: 10.3389/fendo.2022.1026262. PMID: 36329885; PMCID: PMC9623066.
9. Lipska E, Lecka-Ambroziak A, Witkowski D, Szamotulska K, Mierzejewska E, Ołtarzewski M. Primary Congenital Hypothyroidism in Children Below 3 Years Old - Etiology and Treatment With Overtreatment and Undertreatment Risks, a 5-Year Single Centre Experience. Front Endocrinol (Lausanne). 2022 Jun 27;13:895507. doi: 10.3389/fendo.2022.895507. PMID: 35832434; PMCID: PMC9271568.
10. Levy PS, Lemeshow S. Sampling of Populations: Methods and Applications, 3rd ed. New York: Wiley; 1999.
11. d-maps.com [Internet]. France: d-maps; c2007-2023 [cited 2023 Aug 30]. Philippines free map, free blank map, free outline map, free base map boundaries, regions, white; [about 2 screens]. Available from: https://d-maps.com/carte.php?num_car=26029&lang=en
12. Kang MJ, Chung HR, Oh YJ, Shim YS, Yang S, Hwang IT. Three-year follow-up of children with abnormal newborn screening results for congenital hypothyroidism. Pediatr Neonatol. 2017 Oct;58(5): 442-448. doi: 10.1016/j.pedneo.2017.01.002. Epub 2017 Mar 27. PMID: 28412200.

13. Nair PS, Sobhakumar S, Kailas L. Diagnostic re-evaluation of children with congenital hypothyroidism. Indian Pediatr. 2010 Sep;47(9): 757-60. doi: 10.1007/s13312-010-0115-1. Epub 2010 Jan 15. PMID: 20308767.
14. Matos DM, Ramalho RJ, Carvalho BM, Almeida MA, Passos LF, Vasconcelos TT, Melo EV, Oliveira CR, Santos EG, Resende KF, Aguiar-Oliveira MH. Evolution to permanent or transient conditions in children with positive neonatal TSH screening tests in Sergipe, Brazil. Arch Endocrinol Metab. 2016 Oct;60(5):450-456. doi: 10.1590/2359-3997000000189. Epub 2016 Aug 25. PMID: 27812608; PMCID: PMC10118637.
15. Barry Y, Mandereau-Bruno L, Bonaldi C, Cheillan D, Coutant R, Léger J, Regnault N. Prevalence and Determinants of Transient Congenital Hypothyroidism in Children With Eutopic Gland in France: A Retrospective Cohort Study. J Clin Endocrinol Metab. 2022 Mar 24;107(4):e1501-e1509. doi: 10.1210/clinem/dgab854. PMID: 34850038.
16. Bekhit OE, Yousef RM. Permanent and transient congenital hypothyroidism in Fayoum, Egypt: a descriptive retrospective study. PLoS One. 2013 Jun 28;8(6):e68048. doi: 10.1371/journal.pone.0068048. PMID: 23840807; PMCID: PMC3695950.
17. Parks JS, Lin M, Grosse SD, Hinton CF, Drummond-Borg M, Borgfeld L, Sullivan KM. The impact of transient hypothyroidism on the increasing rate of congenital hypothyroidism in the United States. Pediatrics. 2010 May;125 Suppl 2:S54-63. doi: 10.1542/peds.2009-1975F. PMID: 20435718.
18. Stoupa A, Kariyawasam D, Nguyen Quoc A, Polak M, Carré A. Approach to the Patient With Congenital Hypothyroidism. J Clin Endocrinol Metab. 2022 Nov 25;107(12):3418-3427. doi: 10.1210/clinem/dgac534. PMID: 36107810.
19. Oron T, Lazar L, Ben-Yishai S, Tenenbaum A, Yackobovitch-Gavan M, Meyerovitch J, Phillip M, Lebenthal Y. Permanent vs Transient Congenital Hypothyroidism: Assessment of Predictive Variables. J Clin Endocrinol Metab. 2018 Dec 1;103(12):4428-4436. doi: 10.1210/jc.2018-00362. PMID: 30272179.
20. Tuli G, Munarin J, De Sanctis L. Diagnostic Re-Evaluation and Potential Predictor Factors of Transient and Permanent Congenital Hypothyroidism in Eutopic Thyroid Gland. J Clin Med. 2021 Nov 27;10(23):5583. doi: 10.3390/jcm10235583. PMID: 34884283; PMCID: PMC8658106.
21. van Trotsenburg P, Stoupa A, Léger J, Rohrer T, Peters C, Fugazzola L, Cassio A, Heinrichs C, Beauloye V, Pohlenz J, Rodien P, Coutant R, Szinnai G, Murray P, Bartés B, Luton D, Salerno M, de Sanctis L, Vigone M, Krude H, Persani L, Polak M. Congenital Hypothyroidism: A 2020-2021 Consensus Guidelines Update-An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. Thyroid. 2021 Mar;31(3):387-419. doi: 10.1089/thy.2020.0333. PMID: 33272083; PMCID: PMC8001676.
22. Unüvar T, Demir K, Abacı A, Büyükgebiz A, Böber E. The role of initial clinical and laboratory findings in infants with hyperthyrotropinemia to predict transient or permanent hypothyroidism. J Clin Res Pediatr Endocrinol. 2013 Sep 10;5(3):170-3. doi: 10.4274/Jcrpe.931. PMID: 24072085; PMCID: PMC3814532.
23. Marr A, Yokubynas N, Tang K, Saleh D, Wherrett DK, Stein R, Bassilious E, Chakraborty P, Lawrence SE. Transient vs Permanent Congenital Hypothyroidism in Ontario, Canada: Predictive Factors and Scoring System. J Clin Endocrinol Metab. 2022 Feb 17; 107(3):638-648. doi: 10.1210/clinem/dgab798. PMID: 34726229; PMCID: PMC8851917.
24. Kara C, Günindi F, Can Yılmaz G, Aydın M. Transient Congenital Hypothyroidism in Turkey: An Analysis on Frequency and Natural Course. J Clin Res Pediatr Endocrinol. 2016 Jun 5;8(2):170-9. doi: 10.4274/jcrpe.2345. Epub 2016 Apr 18. PMID: 27086592; PMCID: PMC5096472.
25. Itonaga T, Higuchi S, Shimura K, Nagasaki K, Satoh M, Takubo N, Takahashi I, Sawada H, Hasegawa Y. Levothyroxine Dosage as Predictor of Permanent and Transient Congenital Hypothyroidism: A Multicenter Retrospective Study in Japan. Horm Res Paediatr. 2019; 92(1):45-51. doi: 10.1159/000502418. Epub 2019 Sep 25. PMID: 31553976.