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Evaluating Features of Congenital Primary Hypothyroidism and Its Outcomes in Mongolia

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Objectives: Our goal was to assess the outcomes of congenital primary hypothyroidism and evaluate forms of dysgenesis forms among children diagnosed with congenital primary hypothyroidism **Methods:** A cross-sectional study recruited all children diagnosed with congenital primary hypothyroidism between 2013 and 2020. All data, including demographic, clinical examination report, laboratory test results, and results of hand x-ray and ultrasound of thyroid glands, was collected from parents and medical records at hospitals. **Results:** Thyroid dysgenesis accounted for 76.3% of the causes of congenital primary hypothyroidism. Of all participants, 43% had an intellectual disability, and their average delayed bone age was 12.74 months. The most common abnormality of the thyroid gland was hypoplasia (76.3%). The age at diagnosis was the significant predictor for skeletal maturity delay ($k = 0.25$; 95% CI = 0.17 - 0.33; $p < 0.001$) and for intellectual disability (aOR = 1.04; $p < 0.004$). **Conclusions:** Dysgenesis of the thyroid gland was the main cause of congenital hypothyroidism. Age of diagnosis of congenital primary hypothyroidism was a significant determinant of irreversible adverse later outcomes among children in Mongolia.

Keywords: Hypothyroidism, Thyroid Gland, Bone Age

Introduction

Congenital hypothyroidism occurs in approximately 1 in 2000 newborns and can have devastating neurodevelopmental consequences if not detected and treated promptly [1]. Congenital hypothyroidism (CH) is the deficiency of thyroid hormone present at birth and is categorized into permanent and transient forms [2]. Infants with permanent CH have a persistent deficiency of thyroid hormone and need life-long supplementation [3]. Infants with transient CH have a temporary thyroid hormone deficiency, which increases to normal thyroid hormone levels, usually in a few months [4]. Transient hypothyroxinemia of prematurity is defined as deficiency of thyroid hormone accompanied by weak or absent TSH surge after birth in preterm infants [5]. Primary hypothyroidism is a deficiency in thyroxine due to functional or structural defects in the thyroid gland [6]. Secondary hypothyroidism is due to deficiency of the pituitary hormone, TSH, and is usually associated with other hormone deficiencies [7].

Primary hypothyroidism accounts for 85 - 90% of congenital hypothyroidism. Thyroid dysfunction accounts for 70 - 80% of the causes of primary hypothyroidism[8]. Over 1400 of the 3.4 million infants born in the United States of America (USA) are diagnosed with CH annually [4]. Before the universal implementation of neonatal screening, CH was a leading cause of intellectual disability [9]. The most frequent cause of primary CH is thyroid dysgenesis (85 - 90%), in most cases thyroid ectopia (60 - 65%), followed by thyroid agenesis or athyreosis (35%-40%) [10]. Different forms of thyroid dyshormonogenesis account for 10% of cases. Specific mutations in the transcription termination factor 2 gene (TTF2) and genes encoding other thyroid transcription factors have been identified in some patients with thyroid dysgenesis [11]. Several studies have reported the relationship between treatment initiation and intellectual function in patients with congenital hypothyroidism. Before establishing newborn screening, Klein et al. [12] Reported that patients treated before the age of 3 months showed better average IQ scores than patients treated after 3 months. An observational study in 2019 concluded that most studies concurred that treatment initiation in the first month of life was associated with more favorable outcomes, including intellectual development [13].

The first study of CPH we are aware of in Mongolia was conducted between 2000 and 2002 and found the prevalence was 1 in 1892 births [14]. We are not aware of subsequent research on its prevalence or its consequences. Since 2013, 93 children have been diagnosed with CH and are being monitored in Ulaanbaatar, Mongolia. In this study, we investigated characteristics of outcomes and clinical forms of congenital hypothyroidism among those children and examined associations between outcomes of hypothyroidism and potential risk factors.

Materials and Methods

The cross-sectional study was conducted in 2013 - 2020 at the Children's Hospital of the National Center for Maternal and Child Health. We collected data from 93 children with primary congenital hypothyroidism under the supervision of the National Center for Maternal and Child Health for whom a thyroid ultrasound and an x-ray of the left hand were taken. Of these 93 children with congenital primary hypothyroidism, eleven were detected by blood test screening within the first 24-72 hours of birth. A doctor's examination confirmed the diagnosis of CPH with laboratory results of thyroid hormones and thyroid ultrasound results. Once congenital primary hypothyroidism was diagnosed, the children were treated at the Pediatric Endocrinology Unit of the Outpatient Clinic of the National Center for Maternal and Child Health.

The children were examined by a doctor every three months, their physical and mental development monitored, and an annual thyroid ultrasound was performed to determine their thyroid morphology and development. Of these 93 children, 82 were diagnosed by clinical examination, and their thyroid-stimulating hormone and thyroid hormone levels were determined. An ultrasound of the thyroid gland was then performed to determine the cause. We included patients in our study if they were under 18 years of age, diagnosed with CHP, were not diagnosed with other disorders, and their parents agreed to participate in a study. Demographic data were collected from parents. Laboratory and clinical data were collected from patient's hospital medical records.

Inclusion criteria

Children 0 - 17 years of age with proven persistent hypothyroidism were included if their guardian agreed to include their child in the study and they had no other co-morbidities that could stunt the child's growth.

Statistical analysis

Descriptive statistics, including frequency, percentages, mean and standard deviation (SD), were calculated to evaluate demographic and clinical data characteristics. ANOVA tests with Tukey's multi-comparison test and chi-square tests were conducted to determine statistically significant differences. Multiple regression analysis and multiple logistic regression analysis were performed to evaluate the association between potential risk factors and later CHP outcomes and adjust the potential predictors. The initial diagnosis age was divided into four groups of 6 months based on the "Integrated Management of Childhood Illness" used to assess children's growth in Mongolia [15]. Age at initial diagnosis was studied as a categorical and continuous variable. For hypothesis testing, the critical p-value was set at 0.05. The statistical analysis was performed using Stata MP version 16.0.

Ethical statement

We obtained ethical approval for this study from the Medical Ethics Review Committee of the Ministry of Health (23.05.2012, No. 2), the Medical Ethics Review Subcommittee of the Mongolian National University of Medical Sciences (17.01.2020, No. 2020/3-01), National Center for Maternal and Child Health (06.05.2015, No. 359), and Screening Diagnostic Reference Center, Mongolia, (19.01.2015, No. 01). Written consent was obtained from the parents or guardians of all children surveyed.

Results

In terms of gender, there were 60 (65%) girls and 33 (35%) boys ($p \leq 0.001$). The average age of all participants was 6.8 ± 4.0 years. The average T3, T4, TSH were 2 ± 1.7 pmol/L, 21.16 ± 24.0 pmol/L, 151.04 ± 46.8 mU/L, respectively. All mean values were higher in males than females (Table 1).

Table 1. Descriptive analysis for T3, T4, and TSH by gender.

		N (%)	Mean ± SD
T3 (pmol/L)	Female	60 (65)	1.88 ±1.57
	Male	33 (35)	2.23±1.98
	Total	93 (100)	2.00±1.72
T4 (pmol/L)	Female	60 (65)	20.52±24.59
	Male	33 (35)	22.30±23.44
	Total	93 (100)	21.16±24.08
TSH (mIU/L)	Female	60 (64)	145.19±38.77
	Male	33 (36)	161.31±57.59
	Total	93 (100)	151.04±46.82

Of the 93 children who underwent thyroid ultrasound, 4 (4.3%) had a normal thyroid gland, 71 (76.3%) had thyroid hypoplasia, 4 (4.3%) aplasia, and 14 (15.1%) had echo-negative ultrasonography with cystic changes in the thyroid gland. Hypoplasia was the most common abnormality of the thyroid gland in both females and males (Table 2).

Table 2. Descriptive analysis for the ultrasound of thyroid glands by gender.

Ultrasound thyroid gland	Female	Male	Total
	N (%)	N (%)	N (%)
Aplasia	2 (3.3)	2 (6)	4 (4.3)
Hypoplasia and cysts	11 (18.3)	3 (9.1)	14 (15.1)
Hypoplasia	44 (73)	27 (82)	71 (76.3)
Normal	3 (5.1)	1 (3.0)	4 (4.3)
Total	60 (100)	33 (100)	93 (100)

Of our 93 study participants, 40 (43%) were diagnosed with intellectual disability, which is one of the later irreversible outcomes of untreated CPH. By gender, 31 girls (52%) and 9 boys (27%) had an intellectual disability (Table 3), and this difference was statistically significant. ($X2 = 5.17$; $p = 0.023$).

Table 3. Descriptive analysis for intellectual disability sorted by gender.

Intellectual disability	Female	Male	Total
	N (%)	N (%)	N (%)
Non intellectual disability	29 (48.3)	24 (72.7)	53 (57.0)
With intellectual disability	31 (51.7)	9 (27.3)	40 (43.0)
Total	60 (100)	33 (100)	93 (100)

Our multiple logistic regression model no association of gender with intellectual disability but found that age at diagnosis was a small although statistically significant predictor after adjusting for other potential factors (OR = 1.04; p = 0.004) (Table 4).

Table 4. Multiple logistic regression model of intellectual disability with potential predictors: Each predictor is adjusted for all other predictors listed below (N = 91).

Variables	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
T3 (pmol/L)	0.86	0.66-1.11	0.258	0.91	0.69-1.19	0.485
T4 (pmol/L)	0.99	0.97-1.01	0.314	0.99	0.98-1.02	0.734
TSH (mU/L)	0.99	0.98-1.00	0.425	0.99	0.98-1.0	0.780
Gender						
Female	1.00	Reference		1.00		
Male	0.35	0.14-0.87	0.025	0.47	0.17-1.29	0.146
Age at diagnosis (months)	1.04	1.02-1.07	0.001	1.04	1.01-1.06	0.004
						$R^2 = 0.1660$

Regarding delayed bone development, the average delay in bone age among participants was 12.74 ± 13.67 months. The children diagnosed with CPH within 6 months of birth had a mean of 5.19 ± 9.3 months delay in skeletal maturity. In contrast, children diagnosed at later than 18 months had an average of 23.3 ± 13.8 months delay (Table 5).

Table 5. Descriptive statistics for bone age delay (months), sorted by age at diagnosis.

Age at diagnosis (months)	N	Mean ± SD	Min	Max
0 - 6	46	5.19 ± 9.3	0	60
> 6 - 12	10	13.8 ± 9.4	0	50
> 12 - 18	8	16.5 ± 12.73	0	36
> 18	29	23.31 ± 13.87	0	60

Comparisons between chronological age (stratified into categories) and delay in bone age were identified by ANOVA ($F(3, 89) = 15.83$, $p < 0.001$). Tukey's multi-comparison tests found significant differences between the 0 - 6 months group and the 12 - 18 months group (5.19 ± 9.3 vs. 16.5 ± 12.7, p = 0.049) and the 0 - 6 months group and < 18 months group (5.19 ± 9.3 vs. 23.3 ± 13.8, p < 0.001) (Table 6).

Table 6. Multiple comparison tests (Tukey's method) comparing chronological age groups to determine the mean differences in bone age delay.

Chronological age	Mean differences in bone age delay (months)	p-value
	Mean ± SD	
0 - 6 months vs. > 6 - 12 months	8.6 ± 3.27	0.132
0 - 6 months vs. > 12 - 18 months	11.3 ± 4.7	0.049
0 - 6 months vs. > 18 months	18.1 ± 2.92	0.001
> 6 - 12 months vs. > 12 - 18 months	2.7 ± 5.39	0.957
> 6 - 12 months vs. > 18 months	9.5 ± 3.93	0.103
> 12-18 months vs. > 18 months	6.8 ± 5.18	0.430
		ANOVA test result: $F(3, 89) = 15.83$, $p < 0.001$

As part of our multiple regression analysis, a correlation matrix was constructed to check for multicollinearity effects, and no significant correlation was found between predictor variables (Table 7).

Table 7. Correlation analysis between independent continuous variables (T3, T4, TSH, Age at diagnosis, delayed bone age).

Variables	T3 (pmol/L)	T4 (pmol/L)	TSH (mU/L)	Age at diagnosis (months)	Delayed bone age (months)
T3 (pmol/L)	1.0				
T4 (pmol/L)	0.12 (p = 0.231)	1.0			
TSH (mIU/L)	0.14 (p = 0.181)	-0.04 (p = 0.701)	1.0		
Age at diagnosis (months)	-0.07 (p = 0.481)	-0.15 (p = 0.131)	-0.06 (p = 0.571)	1.0	
Delayed bone age (months)	-0.04 (p = 0.691)	-0.06 (p = 0.591)	-0.1 (p = 0.331)	0.55 (p < 0.001)	1.0

Multicollinearity was also checked by examining the variance inflation factors, and all values were below the threshold of 5. After adjusting for other potential risk factors in our model, the effect of chronological age at diagnosis was a statistically significant risk factor for delayed skeletal maturity (Table 8).

Table 8. Multiple regression model of bone age delay with potential risk factors: Each estimate is adjusted for all other predictors listed below (N = 91).

	Unadjusted			Adjusted			
Variable	Effect	95% CI	p-value	Effect	95% CI	p-value	VIF
T3 (pmol/L)	-0.33	-1.98-1.32	0.691	0.04	-1.34-1.43	0.951	1.05
T4 (pmol/L)	-0.03	-0.15-0.08	0.591	0.008	-0.09-0.1	0.874	1.04
TSH (mU/L)	-0.03	-0.09-0.03	0.331	-0.018	0.07-0.03	0.478	1.05
Gender							
Female	1.00	Reference		1.00	Reference		
Male	-4.62	-10.46-1.21	0.119	0.85	-5.84-4.15	0.737	1.07
Age at diagnosis (months)	0.25	0.17-0.33	0.001	0.25	0.17-0.33	0.001	1.06
							$R^2 = 0.33$
							F (5, 85) = 8.38; p < 0.001

Each month's delay in diagnosis led to a 0.25 month delay in bone age (95% CI = 0.17 - 0.33; p < 0.001). However, our multiple regression model explained only 33% of the bone-age delay variability ($R^2 = 0.33$).

Discussion

The causes of congenital primary hypothyroidism include developmental disorders of the thyroid gland with loss of thyroid hormone production, hypothalamic-pituitary-thyroid axis signaling disorders, and connective tissue disorders [15]. Eighty-five percent of congenital primary hypothyroidism results from thyroid dysgenesis, of which 33% is thyroid dysfunction-aplasia, 66% is thyroid hypoplasia and ectopy, and the remaining 10 - 15% is thyroid dyshormonogenesis, thyroid hormone transport, metabolism, and dysfunction [11].

In 2002, Erdenechimeg conducted a pilot study of congenital hypothyroidism screening to assess the need for neonatal screening in Mongolia [14]. To our knowledge, our study is the first to investigate the incidence, features, and association of outcomes of this disease with potential predictors in Mongolia.

The results of our study were similar to those obtained by researchers in other countries. In a study of 384 children in China with CH, 58.5% had an underdeveloped thyroid, 17.1% had cystic changes, 5% had no thyroid, 7.9% had positional abnormalities, and 11.5% had normal thyroid [17]. In Latin America, 18% of 210 cases with CH had a normal thyroid gland, 17% had no

thyroid at all, and 75% had an underdeveloped or misaligned thyroid gland [18]. In the Republic of Korea, 78 infants with CH underwent thyroid ultrasound, and 56.4% had abnormal thyroid development, 5 agenesis, 7 hypoplasia, 10 ectopy, 20 dyshormonogenesis, and 2 were normal [19]. In our study, of the 93 children who underwent thyroid ultrasound, 4 had normal thyroid gland (4.3%), 71 (76.3%) had hypoplasia of the thyroid gland, 4 (4.3%) aplasia, and 14 (15.1%) had echo-negative ultrasonography with cystic changes in the thyroid gland.

The female to male ratio of children with CH in our study was 1.82:1, and this is lower than most reports in other countries, which report a female to male ratio nearer to 2:1. However, our results are comparable with Karamizadeh et al., who related their difference to different etiologies of CH in the Iranian population [20].

Grant et al.'s study in London found that by 3 - 4 years of age, the stature in children with CH treated early becomes normal [21]. Feizi et al. believed that CH patients had impaired growth that improved during follow-up, but the time required to catch-up was faster for head circumference than weight [22].

In their study, 760 infants with congenital hypothyroidism were followed up for five years to investigate the relationship between initial treatment onset and physical development found that age at initial treatment was a significant determinant of growth in height and weight ($p < 0.05$) [22]. In contrast, our results are different from a study from Korea, which found no association between the time of treatment initiation and children's height ($p = 0.713$) [16]. Our research differed from the study above by measuring participants' hand x-ray to estimate skeletal maturity to determine their skeletal maturity. Our analysis also allowed us to measure the impact of multiple factors and adjust for potential confounders. Unlike previous studies, our research considered the effect of gender on age at diagnosis and later outcomes.

A study from Cipto Mangunkusumo Hospital, Jakarta, found that late treatment initiation was correlated with a low IQ score ($r = -0.0325$, $p = 0.025$) [13]. A study from Isfahan also had similar findings that suggested a negative correlation between age of treatment initiation and IQ score ($r = -0.04$; $p < 0.05$) [23]. A study from Taiwan found the age of diagnosis more than 1 year had an increased risk of intellectual disability than the age of diagnosis less than 3 months (adjusted HR = 3.18, $p = 0.009$) [24]. Our study used intellectual disability classification instead of IQ tests and used age of diagnosis as a continuous variable. We found a significant association between age of diagnosis and intellectual disability (aOR = 1.04; $p < 0.004$).

Our study had several limitations. First, this study didn't consider some potential confounders, including mother's nutrition during pregnancy, socio-economic status, health-damaging behaviors, and family history of hypothyroidism, which could affect the association between the age of initial diagnosis and hypothyroidism-related outcomes. Second, for some causes of CH, there was an insufficient number of cases resulting in wide confidence intervals and an inability to perform meaningful statistical analyses for these groups. Lastly, our cross-sectional study could not track subsequent health outcomes among participants since they were not followed in this study.

Further research should be focused on the different effects of the various clinical forms of hypothyroidism with a sufficient number of cases. Also, potential confounders should be taken into consideration. More importantly, risk factors and etiology for congenital hypothyroidism in Mongolia should be studied critically to fill gaps in knowledge in this field. In the meantime, policymakers and clinicians could use our study to understand the prevalence of CH and make correct decisions regarding the allocation of research and treatment resources.

In our study, the prevalence of irreversible adverse mental and physical outcomes was less in children diagnosed early, suggesting early diagnosis and treatment are critical to prevent later problems.

Conclusions

The majority of cases (76.3%) of congenital primary hypothyroidism were hypoplasia of the thyroid gland among Mongolian children. The age at diagnosis of CPH is a significant determinant of subsequent adverse irreversible outcomes.

Conflict of Interest

The authors state no conflict of interest.

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