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Risk Factors and Clinical Characteristics of Congenital Primary Hypothyroidism: A Case-control Study in Ulaanbaatar, Mongolia

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Objective: The study aimed to identify the risk factors and clinical features of congenital primary hypothyroidism (CPH). **Methods:** A matched case-control study recruited all children diagnosed with congenital primary hypothyroidism and children without disease as a control between 2012 and 2020. Controls were matched on their gender and age. We collected information on demographic, clinical, and laboratory characteristics from patient's medical records. **Results:** The birth weight (OR = 1.1; p = 0.001), gestational age (OR = 2.24; p < 0.001), maternal age (OR = 1.21; p < 0.001), additional congenital disabilities (OR = 1.1; p = 0.015) and maternal hyperthyroidism (OR = 1.21; p < 0.011) were significant factors for CPH. The baby's height (OR = 0.2; p = 0.012), maternal gestational diabetes (OR = 0.2; p = 0.002) and being a twin (OR = 0.91; p = 0.010) were significant protective factors for CPH. In terms of clinical symptoms of CPH, 70.2% had shown no clinical signs at births in our study. The most commonly identified clinical signs were: umbilical hernia, open posterior fontanel, feeding difficulty, hypothermia, abdominal stiffness, cold or mottled skin, prolonged jaundice, and low muscle tone. **Conclusion:** Children with CPH are often symptom-free at birth, and several risk factors contribute to CPH.

Keywords: Congenital Primary Hypothyroidism, Risk Factors, Clinical Signs, Thyroid Disease

Introduction

Congenital primary hypothyroidism (CPH) is defined as deficiency of thyroid hormones at birth, resulting in mental and growth retardation if not diagnosed and treated early [1]. The primary causes of CPH are incomplete development of thyroid glands (dysgenesis) or defects of thyroid hormone synthesis (dyshormonogenesis) [1]. CPH is classified as permanent and

transient CPH according to the etiology of CPH [2]. While transient CPH is a temporary deficiency of thyroid hormones at birth that can be treated during the first few months or years of life, permanent CPH requires lifelong treatment [2]. While thyroid dysgenesis accounts for 85-90% of all permanent CPH, the remaining 10-15% is due to thyroid dysmorphogenesis [3]. The most common forms of dysgenesis are the ectopic location of thyroid glands (ectopia) (60-65%), followed by incomplete development of thyroid glands (hypoplasia) and absence of thyroid glands (athyreosis) (35-40%) [1].

The incidence of CPH is approximately 1 in 3000 to 4000 live births [4]. Several studies have shown that the incidence of CPH [5, 6] and the reason for this may be ethnicity, environmental factors, or changes in testing strategies [6-9]. In terms of race, it has been reported by the U.S. screening program that the incidence of CPH is relatively higher in the Asian population than white and black populations [5]. Chen et al. have found the incidence of CPH in Taiwan 1 in 2000 live births between 1997 and 2008 [10], whereas a study from China has concluded the incidence of 1 in 2500 live births in 2015 [11]. Many studies have shown the female to male ratio for CPH as 2:1 [5, 12]. Since the initiation of the neonatal screening program in developed countries, the subsequent detrimental health outcomes of CPH have been prevented by early detection and treatment. However, a neonatal screening program cannot be fully implemented in developing countries, and data on CPH epidemiology and clinical forms among the Mongolian population has been studied insufficiently. The only study conducted in Mongolia has found the incidence of CHP of 1 in 1892 live births in 2002, which was relatively higher than average [13]. To our knowledge, there have been no other studies investigating CPH in Mongolia since then.

The clinical features of CPH are often subtle, and many newborn infants remain undiagnosed during the critical treatment-sensitive newborn period. The evolution of symptoms may also be prolonged. Hence, early detection is only possible through newborn screening. Common symptoms in infants are postmaturity, birth weight exceeding 90%, prolonged jaundice, feeding difficulties, abnormal cry, constipation, and lethargy. The examination may show macroglossia, cold or mottled skin, hypothermia, edema, wide fontanel, open sutures, flat nasal bridge, protuberant abdomen, umbilical hernia, delayed reflexes, and hypotonia. The presence of a goiter indicates CPH [14]. To date, several risk CPH factors have been studied, including genetic, environmental, parental, and perinatal [15-17]. In our previous study, we have found a high prevalence of intellectual disability (43%) and restricted growth development (mean delayed bone age: 12.74 ± 13.67 months) among children with CPH due to the absence of a nationwide neonatal screening program in Mongolia [18]. In our previous study, we evaluated the causes, mental retardation, and bone age of children with congenital hypothyroidism. This study examined the factors contributing to congenital hypothyroidism and its early clinical signs [18]. There is a significant knowledge gap identifying modifiable risk factors for CPH and the outcome of CPH in Mongolia. Therefore, we conducted this study to investigate the maternal and neonatal risk factors and clinical signs for CPH in Ulaanbaatar, the capital city of Mongolia.

Materials and Methods

The case-control study was conducted between 2012 and 2020 based on the availability of data on medical records of children with CHP who were being monitored and treated at the Children's Hospital of National Center for Maternal and Child Health. The study participants were born during the study period with CHP, while the controls were healthy children matched on their gender, age, place of residence, season and month of birth. We have been studying the incidence, prevalence, causes, contributing factors, and clinical features of congenital hypothyroidism since 2012 and selected a control group from a database of more than 20000 healthy children born since 2012. More than 100 children with congenital hypothyroidism are being monitored by endocrinologists, and children born after 2012 are included in the study case group.

The diagnosis of CHP was confirmed with a laboratory test of thyroid hormones and the ultrasound of thyroid glands. Once we confirmed a diagnosis, patients underwent specialist examination of their physical and mental development every three months, and the ultrasound of thyroid glands was performed annually to assess morphology and development of thyroid glands. We collected data on clinical characteristics such as birth weight, height, gestational age, maternal age, clinical presentation of CPH, and laboratory test results from the participant's medical history.

Inclusion criteria

Children were included in a study if their legal guardians agreed for them to participate after obtaining informed consent.

Statistical analysis

All information was initially entered into a data collection form and then was analyzed using Stata version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) Descriptive statistics, including frequency, percentages, mean, and standard deviation (SD), were calculated to describe demographic and clinical data characteristics. The mean differences between groups were analyzed with an independent t-test or Mann-Whitney U test depending on assumptions of normal distribution and equality of variance of dependent variables. The chi-squared test was used to analyze differences between two categorical variables. Associations between risk factors and CPH were analysed using univariate conditional logistic analysis, and a multivariate model was conducted to adjust for confounding effects of multiple variables.

Ethical statement

The ethical approval for this study was obtained from the Medical Ethics Review Committee of the Ministry of Health (23 May 2012, No. 2), the Research Ethics Committee of Mongolian National University of Medical Sciences (17 January 2020, No. 2020/3-01), National Center for Maternal and Child Health (06. May 2015, No. 359), and Screening Diagnostic Reference Center, Mongolia, (19 January 2015, No. 01). Written consent was obtained from the parents or guardians of all children surveyed.

Results

Demographic and neonatal characteristics of congenital primary hypothyroidism

The case-control study was conducted on 201 children who were born between 2012 and 2020. A total of 67 children were included for the case group and 134 cases for the control group in this study. Of the total 201 participants, 70 were male, and 131 were female, making the female to male ratio approximately 2:1. The subjects' mean age was 4.2 ± 2.6 years both for the cases and controls.

The mean height at birth was slightly higher among those without CPH (50.6 ± 1.32 cm) than those with CPH (48.6 ± 0.33 cm), and the difference was statistically significant ($p < 0.001$). In addition, children with CPH had a slightly longer age of gestation (42.5 ± 1.1 vs. 38.9 ± 1.3 weeks. $p = 0.001$ and slightly higher weight than children without CPH (4236.6 ± 172.1 vs. 3581.1 ± 291.5 g. $p = 0.001$). In terms of the birth delivery method, the majority of children were vaginal deliveries among both the case group (55.7%) and the control group

Table 1. Clinical characteristics and laboratory findings of CPH between study groups and controls.

Characteristics	Case (n=67)	Control (n=134)	Total (n=201)	
	Mean ± S.D.	Mean ± S.D.	Mean ± SD	*p-value
Age (year)	4.2 ± 2.6	4.2 ± 2.6	4.2 ± 2.6	
Birthweight (g)	4236.6 ± 372.1	3581.1 ± 411.8	3608.5 ± 391.5	0.001
Height (cm)	48.6 ± 0.33	50.6 ± 1.32	49.8 ± 0.58	0.000
Age of gestation (week)	42.9 ± 1.1	38.9 ± 1.3	39.2 ± 1.3	0.001
Maternal age (year)	35.3 ± 5.6	24.8 ± 4.0	26.5 ± 3.2	0.000
TSH (mIU/L)	31.6 ± 5.2	3.9 ± 1.2	8.2 ± 2.3	0.000
Gender	N (%)	N (%)	N (%)	†p-value
Female	45 (64.2)	86 (64.2)	131 (65.2)	0.001
Male	22 (35.8)	48 (35.8)	70 (34.8)	
Birth delivery				
Caesarean section	27 (44.3)	23 (17.2)	50 (24.9)	0.158
Vaginal delivery	34 (55.7)	111 (82.8)	145 (72.1)	

*p-value calculated with the t-test; †p-value was calculated with the chi-square test

(82.8%). The maternal age and female gender were statistically higher among children with CPH than those without CPH ($p < 0.001$) (Table 1).

Risk factors of congenital primary hypothyroidism

Conditional univariate and multivariate logistic analyses were carried out to assess the effects of potential risk factors for CPH and to adjust for confounding effects. We analyzed the odds ratios with their 95% confidence interval for each effect and computed R^2 statistics for the goodness of fit in our model.

According to univariate logistic analysis, the gestational age (crude OR = 1.28; p = 0.005), maternal age (crude OR = 1.26; $p < 0.001$) and maternal hyperthyroidism (crude OR = 1.24; p = 0.015) were significant risk factors for CPH. The female gender (crude OR = 0.51; p = 0.001), birth weight (crude OR = 0.27; p = 0.003), height (crude OR = 0.52; $p < 0.001$), maternal gestational diabetes (crude OR = 0.54; p = 0.003), being a twin (crude OR = 0.54; p = 0.012) and additional congenital disabilities (crude OR = 0.63; p = 0.011) were significant protective factors for CPH. Maternal smoking (crude OR = 0.98;

Table 2. Multiple logistic regression model of CPH incidence with potential risk factors: Each predictor is adjusted for all the other predictors listed below (N = 195).

Variables	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Birth weight (g)	0.27	0.16-0.37	0.003	1.10	1.19-1.39	0.001
Age of gestation (week)	1.28	1.10-1.50	0.005	2.24	1.54-3.27	0.000
Maternal age (years)	1.26	1.17-1.36	0.000	1.21	1.10-1.35	0.000
Height (cm)	0.52	0.39-0.69	0.000	0.20	0.10-0.38	0.012
Gender						
Male	1.00	Reference		1.00	Reference	
Female	0.51	0.31-0.61	0.001	0.95	0.33-0.99	0.001
Gestational diabetes						
No	1.00	Reference		1.00	Reference	
Yes	0.54	0.38-0.68	0.003	0.20	0.10-0.39	0.002
Maternal smoking						
No	1.00	Reference		1.00	Reference	
Yes	0.98	0.98-1.00	0.573	1.00	0.32-2.72	0.913
Twin**s**						
No	1.00	Reference		1.00	Reference	
Yes	0.54	0.36-0.68	0.012	0.91	0.36-0.95	0.015
Additional congenital disabilities						
No	1.00	Reference		1.00	Reference	
Yes	0.63	0.38-0.72	0.011	1.10	1.01-1.23	0.015
Maternal hyperthyroidism						
No	1.00	Reference		1.00	Reference	
Yes	1.24	1.18-1.34	0.015	1.21	1.19-1.38	0.011
Maternal autoimmune disease						
No	1.00	Reference		1.00	Reference	
Yes	0.96	0.86-1.10	0.074	1.00	0.36-1.74	0.096

Note: The multiple logistic model was adjusted for birth weight, age of gestation, maternal age, gender, gestational diabetes, maternal smoking, being a twin, additional congenital disabilities, maternal hyperthyroidism, autoimmune disease; $R^2 = 0.67$; p-value < 0.05 were considered as statistically significant; Abbreviations: OR-odds ratio; CI - confidence interval; R^2 - pseudo R squared value.

p = 0.574) and autoimmune disease (OR = 0.96; p = 0.074) were not risk factors for CPH.

After adjusting the explanatory variables with each other, the birth weight (OR = 1.1; p = 0.001), gestational age (OR = 2.24; p < 0.001), maternal age (OR = 1.21; p < 0.001), additional congenital disabilities (OR = 1.1; p = 0.015) and maternal hyperthyroidism (OR = 1.21; p < 0.011) were significant factors for CPH. The height (OR = 0.2; p = 0.012), maternal gestational diabetes (OR = 0.2; p = 0.002) and being a twin (OR = 0.91; p = 0.01) were significant protective factors for CHP. Maternal smoking (OR = 1.0; p = 0.913) and autoimmune disease (OR = 1.0; p = 0.096) were not risk factors for CPH.

Clinical signs of congenital primary hypothyroidism

Twenty children with congenital primary hypothyroidism showed clinical signs of CPH the first 28 days after birth. In this group, 29.9% of the newborns were assessed for CPH because they exhibited more than one of the disease's clinical signs. The most commonly identified clinical signs were: umbilical hernia (95%), open posterior fontanel (95%), feeding difficulty (50%), hypothermia (50%), abdominal stiffness (50%), cold or mottled skin (45%), prolonged Jaundice (35%), and low muscle tone (10%). After 28 days of life, the most commonly identified clinical signs were: hoarse voice (21.3%), cold or mottled skin (21.3%), lethargy (23.4%), feeding difficulty (63.9%), low muscle tone (34.1%), macroglossia (23.4%), edema (12.8%), prolonged jaundice (70%), constipation (68.1%), hypothermia (38.9%), abdominal stiffness (34.1%) and classic facies (23.4%) (Table 3).

Discussion

This study was the second phase of our research on congenital primary hypothyroidism in Ulaanbaatar, Mongolia. In this study, we investigated potential risk factors and clinical presentation of CPH and found prolonged gestational age, maternal age, birth weight, additional congenital disabilities and maternal hyperthyroidism were closely associated with the prevalence of CPH. We also identified the strong effect of female gender for developing this disease (2:1) in Ulaanbaatar.

Identifying risk factors and clinical symptoms for this disease is essential for public health practice in Mongolia, where the nationwide neonatal screening program has not been implemented yet, and the incidence of CPH and prevalence of its outcome are relatively high compared to developed countries. The results of our study were similar to other studies. Zhou et al. suggested that maternal age older than 35 (aOR = 2; p < 0.001), late-term birth (aOR = 3.8; p < 0.001), large birth

Table 3. Prevalence of signs and symptoms among children ≤ 28 days old vs. > 28 days old at the first consultation.

Signs and symptoms	Frequency (%)	
	≤ 28 days of age (n=20) N (%)	> 28 days of age (n=47) N (%)
Hoarse voice	-	10 (21.3)
Posterior fontanelle> 0.5mm^2	19 (95)	-
Cold or mottled skin	9 (45)	10 (21.3)
Lethargy	8 (40)	11 (23.4)
Feeding Difficulty	10 (50)	30 (63.9)
Low muscle tone	2 (10)	16 (34.1)
Macroglossia	-	11 (23.4)
Umbilical Hernia	19 (95)	-
Edema	-	6 (12.8)
Prolonged Jaundice	7 (35)	31 (70)
Constipation	8 (40)	32 (68.1)
Hypothermia	10 (50)	18 (38.9)
Abdominal stiffness	10 (50)	16 (34.1)
Classic facies	-	11 (23.4)

weight (aOR = 2.6; $p < 0.001$) were associated with incidence of CPH in China [16]. A study from the U.S. has concluded the incidence of CPH was higher in female offspring of mothers >39 years of age [5]. Medda et al. also found the age of gestation > 40 weeks ($p < 0.01$) was related to the increased risk of CPH in their case-control study among 863 children in Italy [19]. A study on 1313 infants from Iran found several significant risk factors for CPH, including > 35 maternal age ($p = 0.003$), and elective caesarean sections ($p = 0.001$) [20]. Clinical signs of CPH are usually rare at birth, which causes the high rate of undiagnosed CPH. Oliveri et al. also found similar findings on clinical features of CPH [21].

Another study concluded that clinical signs of CPH are rare at birth [22]. In our study, the most common signs of CPH were feeding difficulty, prolonged jaundice and constipation, occurring among 29.85% of confirmed cases. It has been argued that prolonged hyperbilirubinemia could result from a lack of expression of the liver's glucuronyl transferase [1]. Other studies have identified that females are more at risk of CPH than males [16, 19]. Undiagnosed CPH results in intellectual disability and restricted growth development. Our previous study suggested that age at diagnosis of CPH is important for preventing subsequent detrimental irreversible outcomes. The prevalence of intellectual disability (43%) and the mean of delayed bone age (12.74 ± 13.67 months) were notably high in Mongolia [18]. Therefore, it is important to recognize the burden of CPH and the benefits of implementing nationwide screening programs.

We identified an increased risk for permanent CPH in twins by multivariate analysis (odds ratio (OR) = 12.2, 95% confidence interval (CI): 2.4-62.3). We also found a statistically significant association of CPH with additional congenital disabilities, female gender and gestational age > 40 weeks. Although not significant, we observed a trend towards increased risk of CPH among infants with a family history of thyroid diseases among parents (OR = 1.9, 95% CI: 0.7-5.2). Maternal diabetes was also found to be slightly associated with permanent CPH (OR = 15.7, 95% CI: 0.9-523) in infants who were large for gestational age.

Concerning transient CPH, intrauterine growth retardation and preterm delivery were independent risk factors for this form of CPH [23]. In China, the conditional logistic regression analysis showed that older maternal age, family history of thyroid diseases, maternal exposure to formaldehyde during pregnancy, maternal exposure to radiation during pregnancy, and medication during pregnancy, were risk factors for CPH ($p < 0.05$). In contrast, low maternal age at delivery and progesterone intake during pregnancy were protective factors against CPH ($p < 0.05$) [24]. A study from Brazil in 2013 by Maria and Teruko found that 95% of children with congenital primary hypothyroidism had no signs of disease, and 5% had common signs including prolonged jaundice, feeding difficulty ($p < 0.001$), and less common sign including hypotonia, macroglossia, and umbilical hernia ($p < 0.01$) [25]. Our findings were similar. Another case-control study from Spain in 2019 found several risks of CPH, including being female, post-term birth (< 40 weeks), < 3500 gr birth weight, prolonged jaundice, feeding difficulties, and umbilical hernia ($p < 0.01$) [26]. Furthermore, our results were similar to a case-control study from Seoul, Korea, that found significant signs for permanent CPH, including umbilical hernia, large fontanel, and prolonged jaundice. For transient CHP, mottled skin and a large belly were important signs [27]. These results are similar to ours.

In twenty percent of pregnancies, gestation extends beyond forty-two weeks [1]. Once home, these babies may be quiet and sleep through the night, thereby not suggesting CPH. However, the symptoms of a hoarse cry and constipation prompted further investigation. Neonatal hyperbilirubinemia for more than three weeks was common [1]. The most common symptoms were prolonged jaundice, lethargy, feeding difficulty and constipation [1]. The most prevalent clinical signals were umbilical hernia (51%), enlarged anterior fontanel (50.3%), and open posterior fontanel (47.2%). Hypotonia, macroglossia and feeding difficulties were the clinical signs most frequently associated with the biochemical severity of the disease [28]. In our study of babies less than 28 days of age, 70.15% had shown no signs. Our research found the most commonly identified clinical signs were umbilical hernia (95%), open posterior fontanelle > $0.5mm^2$ (95%), feeding difficulty (50%), hypothermia (50%), abdominal stiffness (50%), cold or mottled skin (45%), prolonged Jaundice (35%), and low muscle tone (10%).

Our study has several limitations. In this study, the number of cases was small, the data collected were slightly limited, comparing fewer factors. Another weakness is that we could not take other risk factors such as genetic, environmental exposures, and pregnancy complications into consideration due to the retrospective process of data collection and availability of information. There were 67 cases in our study, which might be insufficient to be generalizable and draw conclusions. However,

our study was at a single site, which allowed the diagnosis and data collection to be relatively consistent. Future studies should involve more variables that could be potential factors for CPH with a sufficient number of participants. Also, participants should be recruited nationwide to make the study externally valid. Environmental exposures, health-damaging behaviors, exposure to radiation, and genetic factors need to be better studied to ensure a complete understanding of CPH in Mongolia.

Conclusions

The main contributing factor of risk to congenital primary hypothyroidism is maternal age, birth weight, and gestational age. Children with congenital primary hypothyroidism are often symptom-free at birth; therefore, implementing nationwide screening programs is crucial for detecting cases and preventing irreversible adverse outcomes.

Conflict of Interest

The authors state no conflict of interest.

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