Global Pediatric Health
January-December 2015: 1–5

DOI: 10.1177/2333794X14567193
gph.sagepub.com
SAGE

Incidence and Interrelated Factors in Patients With Congenital Hypothyroidism as Detected by Newborn Screening in Guangxi, China

Xin Fan, MD[1], Shaoke Chen, MD[1], Jiale Qian, MD[1], Suren Sooranna, PhD[2,3], Jingi Luo, MD[1], Chuan Li, MD[1], Qin Tang, MD[1], and Caijuan Lin, MD[1]

Abstract

Background. A newborn screening program (NSP) for congenital hypothyroidism (CH) was carried out in Guangxi in order to understand the incidence of CH and the factors interrelated to major types of CH in this region of China. *Methods*. During 2009 to 2013, data from 930 612 newborns attending NSP in Guangxi were collected. Patients were classified with either permanent CH (PCH) or transient CH (TCH) after 2 years of progressive study. *Results*. A total of 1210 patients were confirmed with CH with an incidence of 1/769, including 68 PCH and 126 TCH cases with incidences of 1/6673 and 1/3385, respectively. The frequency of thyroid stimulating hormone values greater than 5 mIU/L was 7.2%, which, based on WHO guidelines, suggests that the population was mildly iodine deficient. *Conclusions*. The incidence of CH was high in Guangxi. Approximately two thirds of CH patients were TCH, which may be due to a deficiency in iodine within the population.

Keywords

congenital hypothyroidism, permanent CH, transient CH, iodine deficiency

Introduction

Congenital hyperthyroidism (CH) is a relatively common endocrine disease in children. CH is also one of the most classic diseases in newborn screening history, the incidence of which varied from 1:2000 to 1:4000 in different areas and different ethnicities.[1-4] CH is caused by a dysfunction of the hypothalamus–pituitary–thyroid axis, which leads to a reduction of thyroxin secretion, which, in turn, causes severe damage to the brain. According to the clinical course of the disease, CH can be classified as either permanent or transient CH (PCH/TCH). It was reported that the incidence of PCH was about 1:2000 to 1:3587 and that the incidence of TCH was about 1:1580 to 1:17 000.[5,6] The major etiology of PCH was linked to dysgenesis, including complications such as athyreosis, atrophy, and ectopic, but the etiology of TCH was not that clear. Many studies suggested that the etiology of TCH was multiplicity, prematurity, low birth weight, and iodine deficiency or excessive use of antithyroid drugs. In addition, an interaction between genes and the environment may also be related to the occurrence of TCH.[7-10]

Up to now, there have been very few reports regarding the incidence and etiology of PCH and TCH in China. Guangxi Province, which is located in the southwest of China, is the largest minority nationality area for the Han and Zhuang nations. Its geography and ethnic makeup means that it is different from other areas of China. A previous study reported the incidence of CH as detected by NSP to be about 1:835 in Guangxi,[11] which is much higher than the average for the whole country. But the incidence of confirmed cases of PCH and TCH among patients and the reasons of the high incidence of CH in this area are still unclear and is yet to be fully reported.

[1]Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi, China
[2]Imperial College London, London, UK
[3]Chelsea and Westminster Hospital, London, UK

Corresponding Author:
Shaoke Chen, Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, Nanning, 59 Xiangzhu Road, Nanning 530000, China.
Email: chenshaoke123@163.com

The objective of this study was to confirm the high incidence of CH as detected by NSP and look at the interrelated factors linked to the major types of CH in Guangxi.

Methods

A total of 930 612 newborns (511 555 females and 419 057 males) screened by the newborn screening program (NSP) at Newborn Screening Center of Guangxi, China, from January 2009 to December 2013, were included in this study, and the screening rate was about 93.1%.

Within 72 hours of birth, 3 drops of blood was taken from the heel of subjects and placed on a filter paper (S&S 903) for the measurement of thyroid stimulating hormone (TSH). TSH was measured by time-resolved fluorescence, Delfia method. The detection limit of the assay for TSH measurement was 8 mIU/mL. Patients with positive results at screening were recalled and a 90% recall rate was achieved. Venous blood samples were collected from the positive patients for a confirmation test by the chemiluminescence method. At this time serum blood TSH and free thyroxin (FT4) levels were also measured. After patients were confirmed to be positive for CH, it was still necessary to check the thyroid morphology by performing a thyroid ultrasound examination. For those patients where it was not possible to locate the thyroid by ultrasound, it was necessary to perform further scans using a radioisotope scanning technique.[12]

At the first diagnosis stage when recalled, patients were classified as CH, when their clinical profiles matched one of the following: (*a*) TSH ≥ 10 mIU/mL and FT4 < 12 pmol/L and (*b*) the thyroid imaging examination suggested athyreosis, atrophy, or ectopic. Other patients with elevated TSH continually, but normal FT4 values and normal thyroid morphology, were classified as hyperthyroxinemia (some studies also classified these patients as suffering from subclinical hypothyroidism).[13] At the second diagnosis stage, after being followed-up for more than 2 years, patients were classified as PCH, when their clinical profiles matched the following: patients who were unable to stop treatment and therefore needed constant hormone replacement therapy. Those patients whose clinical profiles matched both of the following were classified as TCH: (*a*) the thyroid imaging examination indicated the location and morphology of the thyroid to be normal and (*b*) the thyroid remained functional for more than 6 months after treatment was stopped and the thyroid function test would continue to be performed monthly.

Data were analyzed using SPSS 13.0, and the relationship between the multiplicity of factors and the results of the second diagnosis were analyzed with multiple logistic regression analysis.

Results

A total of 1210 patients (659 males and 551 females) were confirmed as potential CH cases among 930 612 newborns. Of these 559 were diagnosed with CH and 651 with hyperthyroxinemia. The incidence of CH and hyperthyroxinemia was 60.0/100 000 (1/1665) and 69.9/100 000 (1/1430), respectively, with the total being 120.0/100 000 (1/769). In the 1210 confirmed patients, 391 patients (32.2% of the total including 331 hyperthyroxinemia patients and 60 patients with congenital hypothyroidism) were lost to follow-up, and thus 819 patients took part in the study. From December 2009 to December 2013, 273 patients were followed-up for more than 2 years, and 68 patients were diagnosed with PCH, 126 patients were diagnosed with TCH, and 78 patients were still under review (Figure 1). Based on screening of the population at the present time, the incidence of PCH was 15/100 000 (1/6673), the incidence of TCH was 29.5/100 000 (1/3385), and the ratio of PCH to TCH is approximately 1:2.

In 194 patients (68 with PCH and 126 with TCH) with clear diagnosis of the disease, multiple logistic regression analysis was performed. The final diagnosis was considered as the dependent variable (PCH/TCH, 0/1), and the gender, gestational age, birth weight, and TSH and FT4 values at screening and diagnosis were considered as independent variables. The results indicate that TSH values at screening and diagnosis were correlated with TCH. However, gender, gestational age, and birth weight were not the independent risk factors for TCH (Table 1). The area under the ROC curve (AUC) of TSH values at screening and diagnosis were 0.78 and 0.73 and the *P* values were 1.16×10^{-6} and 1.08×10^{-7}, receptively.

To further analyze the reasons for the high incidence of CH, the TSH values of 930 612 newborns were classified following the guidelines for iodine deficiency as denoted by the World Health Organization. The results show that the TSH values of 7.2% newborns (67 208 out of 930 612 newborns) were above 5 mIU/mL (Table 2).

Discussion

The NSP has been developed in Guangxi since 1996, but in the early years of implementation the screening rate was lower than 10%. From 2009, when the government actively promoted the NSP in the whole province, the screening rate increased to 93.1%. The newborn screening laboratory of Guangxi accounts for around 50% of the newborns in Guangxi each year. Hence, data in this study are representative of the general population.

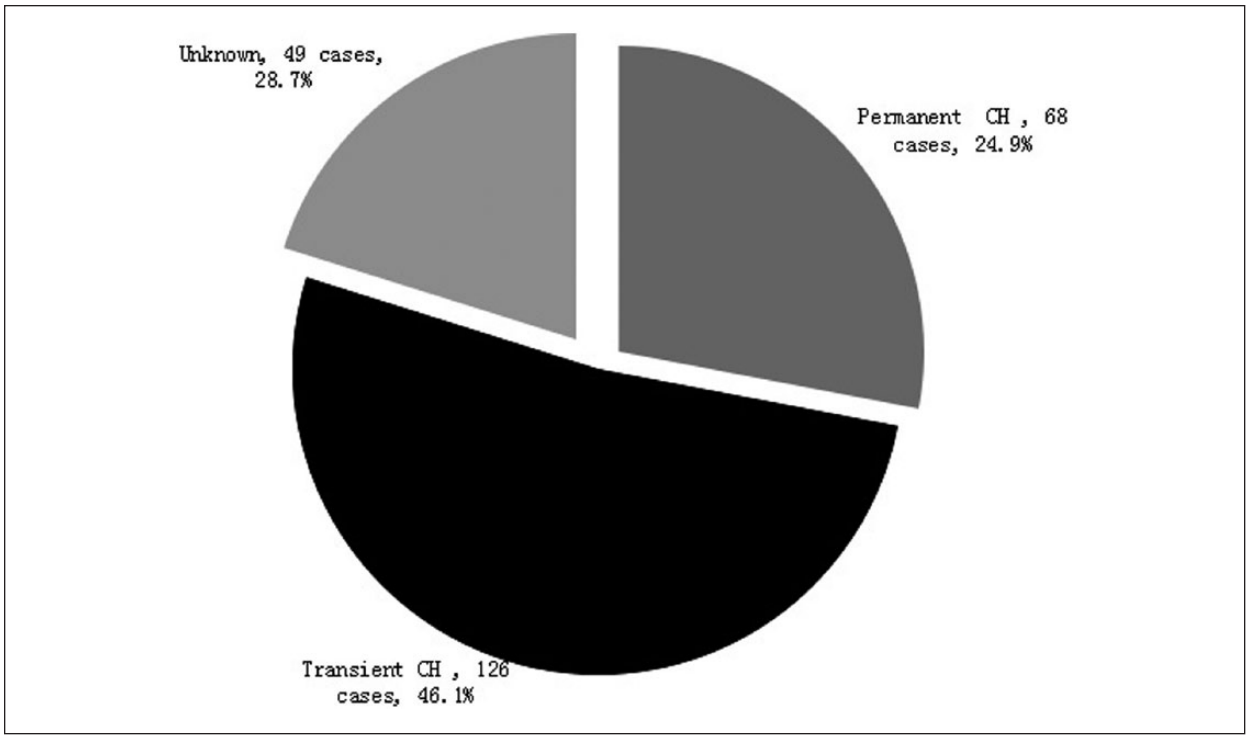

Figure 1. Distribution of permanent and transient CH in 273 patients followed-up for more than 2 years.

Table 1. Multiple Logistic Regression Analysis of Transient CH.

	Estimate	Wald χ^2	P^a	AUC
Diagnosis TSH	0.02	23.64	1.16×10^{-6}	0.73
Screening TSH(log)	1.02	28.23	1.08×10^{-7}	0.78

Abbreviations: CH, congenital hypothyroidism; AUC, area under the curve; TSH, thyroid stimulating hormone.
[a]$P < .05$ was considered statistical significant.

Table 2. The Frequency of TSH Values Greater Than 5 mIU/L in Newborns From 2009 to 2013.

Year	Population Screened (n)	Number of TSH > 5 mIU/mL (n)	Proportion of TSH > 5 mIU/mL (%)
2009	58 135	4716	8.11%
2010	154 072	10 241	6.65%
2011	214 839	12 749	5.93%
2012	241 565	20 938	8.67%
2013	262 001	18 564	7.08%
Total	930 612	67 208	7.22%

Abbreviation: TSH, thyroid stimulating hormone.

The overall incidence of the disease was 1/769, with the incidence for CH and hyperthyroxinemia being 1/1665 and 1/1430, respectively. The overall incidence of the disease was much higher than previous reports. In the cities of Beijing, Shanghai, and Zhejiang, the incidence of CH was reported as 1/2034,[14] 1/2050,[1] and 1/1618,[15] respectively, and the incidence of the whole country was found to be approximately 1/2000.[1] In this study, for patients with a final diagnosis made at the second diagnosis stage, the ratio of PCH to TCH was about 1:2, with TCH being in the majority, and this was also different from other reports,[16,17] and indicated that the

higher incidence of CH in Guangxi is mainly due to increased TCH.

The etiology of TCH is complex, with several factors correlating to the disease including prematurity, low birth weight, intake of iodine, as well as genetic factors.[18,19] Based on the available data of gender, gestational age, birth weight, and TSH and FT4 values, the cause of the high incidence of CH was investigated by multivariate logistic regression analysis. The results indicate that TSH values were related to TCH, and gender, gestational age, and birth weight were not independent risk factors for TCH.

For further analyses, the guidelines for determination of iodine deficiency as laid down by the World Health Organization were considered. The World Health Organization guidelines are based on neonatal TSH values of above 5 mIU/L of whole blood and a frequency of less than 3% of the population is considered iodine deficient. Frequencies of 3% to 19.9% indicate mild iodine deficiency disorders, frequencies of 20% to 39.9% and above 40% indicate moderate and severe iodine deficiency disorders, respectively. In 930 612 newborns, the frequency of neonatal TSH above 5 mIU/L was about 7.2% and this indicated there was mild iodine deficiency in the population in Guangxi.[20] Iodine is distributed all over the natural world, especially in the soil and water, but unfortunately it is not evenly distributed. The content of iodine in the soil of mountain areas tends to be the lowest with the highest levels found on the plains. The landscape of Guangxi is made up of karst landforms, with the surface of the earth being rough and with a poor soil quality. Both these conditions discourage the storage of iodine in the soil and therefore the water and crops inevitably possess low iodine content in comparison with other regions. People living in this type of environment are bound to suffer from iodine deficiency. Our data would strongly suggest that the iodine deficiency may well be related to the high prevalence of TCH in Guangxi.

Conclusions

The overall incidence of CH in Guangxi was relatively high in comparison to other areas of China. Among those patients, the majority had TCH and this may be related to iodine deficiency in the population. Future work should focus on determination of urinary iodine in the local population in order to clarify these findings. It would also be useful to explore whether the geographic and ethnic makeup of the Guangxi region of China contribute to presence of TCH in population by determining whether gene mutations are contributing factors. It is important to determine the etiology of the disease so that preventative strategies can be implemented to improve health care within these communities.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the National Natural Science Fund (81260126) and the National Key Technology R&D Program (2012BAI09B04) and the National Natural Science of Guangxi (2012GXNSFAA053174), the Key Program from the Health Department of Guangxi (2012025), and project from Health Department of Guangxi (Z2011085).

References

1. Gu X, Wang Z, Ye J, Han L, Qiu W. Newborn screening in China: phenylketonuria, congenital hypothyroidism and expanded screening. *Ann Acad Med Singapore*. 2008;37:107-114.
2. Harris KB, Pass KA. Increase in congenital hypothyroidism in New York State and in the United States. *Mol Genet Metab*. 2007;91:268-277.
3. Deladoey J, Ruel J, Giguere Y, Van Vliet G. Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Quebec. *J Clin Endocrinol Metab*. 2011;96:2422-2429.
4. Skordis N, Toumba M, Savva SC, et al. High prevalence of congenital hypothyroidism in the Greek Cypriot population: results of the neonatal screening program 1990-2000. *J Pediatr Endocrinol Metab*. 2005;18:453-461.
5. Unuvar T, Demir K, Abaci A, Buyukgebiz A, Bober 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;5:170-173.
6. Zung A, Tenenbaum-Rakover Y, Barkan S, et al. Neonatal hyperthyrotropinemia: population characteristics, diagnosis, management and outcome after cessation of therapy. *Clin Endocrinol*. 2010;72:264-271.
7. Bhavani N. Transient congenital hypothyroidism. *Indian J Endocrinol Metab*. 2011;15:S117-S120.
8. Srinivasan R, Harigopal S, Turner S, Cheetham T. Permanent and transient congenital hypothyroidism in preterm infants. *Acta Paediatr*. 2012;101:e179-e182.
9. Zung A, Yehieli A, Almashanu S. Neonatal hyperthyrotropinemia is associated with low birth weight: a twin study. *Eur J Endocrinol*. 2013;168:263-269.
10. Yaman AK, Demirel F, Ermis B, Piskin IE. Maternal and neonatal urinary iodine status and its effect on neonatal TSH levels in a mildly iodine-deficient area. *J Clin Res Pediatr Endocrinol*. 2013;5:90-94.

11. Temboury Molina MC, Rivero Martin MJ, de Juan Ruiz J, Ares Segura S. Maternal autoimmune thyroid disease: relevance for the newborn [published online January 30, 2014]. *Med Clin (Barc)*. doi:10.1016/j.medcli.2013.10.024.
12. Guerra G, Cinelli M, Mesolella M, et al. Morphological, diagnostic and surgical features of ectopic thyroid gland: a review of literature. *Int J Surg*. 2014;12(suppl 1):S3-S11.
13. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3:76-94.
14. Shi XT, Cai J, Wang YY, et al. Newborn screening for inborn errors of metabolism in mainland china: 30 years of experience. *JIMD Rep*. 2012;6:79-83.
15. Maitusong R, Japaer R, Zhao ZY, Yang RL, Huang XL, Mao HQ. Newborn screening in Zhejiang, China. *Chin Med J (Engl)*. 2012;125:702-704.
16. Haghshenas M, Zahed Pasha Y, Ahmadpour-Kacho M, Ghazanfari S. Prevalence of permanent and transient congenital hypothyroidism in Babol City, Iran. *Med Glas (Zenica)*. 2012;9:341-344.
17. Bekhit OE, Yousef RM. Permanent and transient congenital hypothyroidism in Fayoum, Egypt: a descriptive retrospective study. *PloS One*. 2013;8:e68048.
18. Grasberger H, Refetoff S. Genetic causes of congenital hypothyroidism due to dyshormonogenesis. *Curr Opin Pediatr*. 2011;23:421-428.
19. Muzza M, Rabbiosi S, Vigone M, et al. The clinical and molecular characterization of patients with dyshormonogenic congenital hypothyroidism reveals specific diagnostic clues for DUOX2 defects. *J Clin Endocrinol Metab*. 2013;99:E544-E553.
20. Delange F. Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. *Thyroid*. 1998;8:1185-1192.