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Incidence of congenital hypothyroidism in China: data from the national newborn screening program, 2013–2015

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Abstract

Background: Congenital hypothyroidism (CH) is one of the most frequent, preventable causes of mental retardation. Little has been reported on the epidemiological characteristics of CH in China. We aimed to estimate the incidence of CH in China and investigate its geographical variation.

Methods: We analyzed data from the nationwide newborn screening program for CH between 2013 and 2015. Poisson regression was used to generate the odds ratios (ORs) and 95% confidence intervals (CIs) between the rates of CH and selected demographic characteristics and assess the potential association between CH incidence and geographical locations.

Results: A total of 18,666 patients with CH were identified from 45.2 million newborns, yielding an overall incidence rate of 4.13 per 10,000 live births. Compared with those in the remote area, regardless of infant sex, a higher incidence risk for CH was present in newborns in coastal areas and inland areas (females: OR=2.00, 95% CI: 1.86–2.16 and OR=1.74, 95% CI: 1.61–1.87, respectively; males: OR=1.70, 95% CI: 1.59–1.83 and OR=1.52, 95% CI: 1.42–1.63, respectively). Additionally, the highest risk of CH

for thyroid-stimulating hormone (TSH) screening values <40 mU/L was observed among neonates in the coastal areas, while TSH screening values of 70–100 mU/L were observed among those in the inland areas.

Conclusions: The overall incidence of CH is high in China. The significant geographical variations of CH incidence are presented in this study.

Keywords: congenital hypothyroidism; geographical; incidence; newborn screening; thyroid-stimulating hormone.

Introduction

Congenital hypothyroidism (CH) is a common endocrine disorder characterized as a thyroid hormone deficiency present at birth [1]. If treatment is delayed or left untreated, CH may result in impaired neurological development and intellectual disabilities [2–4]. Universal newborn screening programs through early identification have provided an opportunity for prompt thyroid hormone therapy for CH in the early days of life, thus preventing mental retardation and reducing the morbidity of related neurodevelopmental complications.

CH affects approximately one in 2000–4000 live births worldwide [5–10]. A significant variation in the ethnicity-specific incidence of CH has been reported in

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previous studies [5, 9, 11]. There is a female preponderance for CH, with a female-to-male ratio of 2:1 among thyroid dysgenesis but an approximate 1:1 ratio among eutopic thyroid patients [5, 12–15]. In addition, CH has been associated with adverse pregnancy outcomes, including birth defects, low birth weight and preterm birth [5, 11, 16, 17]. Moreover, CH may result from the changes of some environmental factors, including iodine deficiency/excess, and seasonal patterns [18–23]. Recently, a number of epidemiological studies have indicated that the incidence of CH is increasing in multiple regions over the past two decades [5–7, 24–26]. The most predominant causes of an increase in CH may be a reduction of the thyroid-stimulating hormone (TSH) cutoff (CO) levels and a growing number of preterm births. An increased proportion of CH with eutopic glands may also account for this trend. However, other related explanations on this trend, e.g. increasing exposure to environmental risk factors, show inconsistencies.

Although multiple studies have demonstrated that CH is more common among Asian populations than in some Western newborn populations, epidemiological studies regarding the incidence of CH in Asian countries, particularly in China, are relatively limited. The newborn screening program for CH was initiated as a pilot study in the 1980s in two eastern provinces (Beijing, Shanghai) in China. Until 2015, the newborn screening program was implemented throughout the country and performed in 95% of districts/counties of 31 provinces (Hong Kong, Taiwan and Macao not included). A total of 230 newborn screening centers were developed, covering approximately 90% of the newborn population in China (covering nearly 100% in the eastern regions).

Due to scarce nationwide data available on CH incidence, the aim of the present study was to estimate the incidence of CH using the largest dataset from the national newborn CH screening information system during 2013 to 2015 in China. We also described the geographic variation in the incidence of CH.

Materials and methods

Chinese CH newborn screening program

The national newborn screening program in China is centrally administered by the National Health and Family Planning Commission, which is responsible for drafting related neonatal screening policies, plans, and technical standards and norms. In each province, local newborn screening centers (LNBSCs) in charge of sample testing, diagnosis, treatment and follow-up are authorized and

administered by provincial health departments (Figure 1). Subsequently, a provincial newborn screening center (PNBSC) was established to guide and supervise the LNBSCs for all neonatal screening practices. In 2003, the Ministry of Health issued the Technological Guideline on National Newborn Screening (TGNNBS) to advance the administrative management and standardization on neonatal screening.

According to the TGNNBS, whole-blood TSH was measured as a primary marker for neonatal CH screening. Whole blood, heel-prick samples were collected by well-trained staff in maternity hospitals on filter papers from newborns between 72 h and 7 days after birth. Premature, low birth weight or sick neonates and those who were discharged from the maternity hospitals before 72 h of life were sampled within 20 days after delivery for CH screening. The whole blood samples were dried at room temperature and then sent to the LNBSCs for testing within 5 workdays. All screening laboratories were required to process and analyze the samples within 5 workdays after receiving samples and immediately report the positive cases. TSH was qualified through dissociation-enhanced lanthanide fluoroimmunoassay (DELFA) in most of the laboratories, while enzyme-linked immunosorbent assay (ELISA) and enzymatic immunofluorescence assay (EFIA) were used in a minority of laboratories, with CO levels varying from 10 to 20 mU/L whole blood. Each laboratory set the TSH CO levels based on their respective TSH percentiles. Any cases showing higher TSH CO levels through double testing were followed-up and subjected to further diagnosis. In each LNBSC, the diagnosis of CH was confirmed by trained pediatric endocrinologists according to the thyroid function on serum (serum TSH elevated and serum-free thyroxine reduced). Further examinations, including thyroid ultrasound and/or scintigraphy, were generally performed to complete the diagnosis of CH. The pediatric endocrinologists were required to follow the above guidelines for the diagnosis of CH. A written informed consent on CH screening was obtained from parents prior to the collection of blood samples from the neonates.

Data collection

The data in the present analysis were derived from the Chinese Newborn Screening Information System (CNBSIS) between 2013 and 2015. This system was performed by the National Office of Maternal and Child Health Surveillance (NOMCHS) for routinely collecting and reporting basic information on the testing, diagnosis and follow-up of infants with CH and was utilized by all screening centers, including PNBSCs and LNBSCs. In every LNBSC, trained staff were assigned to complete the online forms quarterly based on the blood sample cards, laboratory test reports and medical records, including data on the number of neonates screened (total, geographical-specific and sex-specific), the number of neonates diagnosed as CH and the demographic and clinical characteristics of CH infants (geographical location, date of birth, sex, TSH screening values and cases diagnosis). All forms were reviewed at the provincial level by professionals in the PNBSCs responsible for data quality. Incomplete forms and nonspecific records were returned to the LNBSCs and verified quarterly. Additionally, a provincial annual form was collected yearly by trained staff in the PNBSCs. Then, the data were reported to the NOMCHS (national level), where an expert group, composed of pediatric endocrinologists, biostatisticians and epidemiologists, was responsible for diagnosis confirmation, data reviewing and compilation. In the present study, data from Tibet was not included because

Figure 1: Distribution of newborn screening centers in China, 2015.

The number of newborn screening centers in the coastal, inland and remote areas were 84, 104 and 42, respectively. Red: the county in which newborn screening center is located.

CH screening there was initiated in 2015. The study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University, China, and performed in accordance with the Declaration of Helsinki, 1964 and its subsequent amendments or comparable ethical standards.

Quality control

Since 1998, the LNBSCs received annual laboratory quality control for neonatal CH screening by the National Center for Clinical Laboratory (NCCL). The NCCL was authorized to convene an annual conference on the quality evaluation and monitoring of practices among laboratories to ensure their quality on CH screening. Some laboratories also participated in external quality assessment under the supervision of Centers for Disease Control and Prevention (CDC) in the United States [27]. Additionally, field supervision at the LNBSCs under the responsibility of the NMCHSO was performed annually by a national expert group composed of pediatric endocrinologists, laboratory technicians and biostatisticians to evaluate the practice of CH screening and the completeness, accuracy and timeliness of the data in the CNBSIS via medical records reviews and face-to-face interviews with related staff.

Statistical analysis

In the present analysis, 30 provinces were categorized according to the geographical locations and socioeconomic status into the coastal area (Beijing, Tianjin, Shanghai, Liaoning, Shandong, Jiangsu, Zhejiang, Fujian and Guangdong), inland area (Heilongjiang, Jilin, Hebei, Henan, Shanxi, Anhui, Hubei, Hunan, Guangxi, Shaanxi, Jiangxi, Hainan and Chongqing) and remote area (Inner Mongolia, Ningxia, Gansu, Xinjiang, Qinghai, Yunnan, Guizhou and Sichuan). The incidence of overall CH by geographical locations (coastal area, inland area and remote area), infant sex (female and male) and the year of infant birth (2013, 2014 and 2015), expressed as the number per 10,000 live births, was calculated as the number of diagnosed cases divided by the number of screened newborns. The 95% confidence intervals (CIs) of CH incidence were estimated based on a Poisson distribution. Poisson regression was used to generate the odds ratios (ORs) and 95% CIs between the rates of CH and selected demographic characteristics and assess the potential association between CH incidence and geographical locations while controlling for other demographic factors. To further analyze the geographical variation of CH, cases were grouped by the TSH screening values at an interval of 10 mU/L. Poisson regression was also used to assess the geographical difference of

CH based on the TSH screening values. All tests of hypotheses were two-tailed with a type 1 error rate fixed at 5%. Statistical analyses were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

From 2013 to 2015, approximately 45.2 million newborns were screened in China. The percentage of screened newborns was highest in the coastal area (90%), followed by the inland area (88%). A total of 18,666 cases were identified as CH, yielding an overall incidence rate of 4.13 per 10,000 screened newborns. Among the identified CH cases, 9364 cases occurred in males (overall incidence 3.87 per 10,000), whereas 9294 cases were in females (overall incidence 4.44 per 10,000). The female-to-male ratio for CH cases was 0.99. However, females were more likely to have CH than males (OR=1.15; 95% CI: 1.12–1.18) (Table 1).

Table 1 also presents the geographical and annual incidence of CH between 2013 and 2015. During the 3-year study period, the CH incidence predominated in the coastal area, followed by that in the inland area. Compared with that in the remote area, a higher incidence risk of CH was observed in the coastal area and the inland area (OR=1.84, 95% CI: 1.75–1.93 and OR=1.62, 95% CI: 1.54–1.70, respectively). According to the years of birth, the incidence rates of CH were 4.05, 4.15 and 4.20 per 10,000 live births in 2013, 2014 and 2015, respectively. There was no statistically significant difference for CH incidence among different groups by years of birth.

Table 2 shows the incidence of CH according to infant sex and geographical locations between 2013 and 2015. Females located in coastal areas had the highest CH incidence, at 5.02 per 10,000 newborns screened, followed by males in coastal areas (4.49 per 10,000) and females in inland areas (4.49 per 10,000). Compared with that in remote areas, regardless of infant sex, a higher incidence of CH was present in newborns in coastal areas and in

Table 1: Incidence rates of CH by sex, geographical locations and years of birth in China, 2013–2015.

	n (%) ^a	CH ^b	Incidence per 10,000 screened newborns (95% CI)	OR (95% CI)
Total	45,151,947 (90)	18,666	4.13 (4.08–4.19)	
Sex ^c				
Male	24,183,956 ^d	9364	3.87 (3.79–3.95)	Ref.
Female	20,913,113 ^d	9294	4.44 (4.35–4.54)	1.15 (1.12–1.18)
Geographical locations				
Remote area	7,042,884 (80)	1814	2.58 (2.46–2.70)	Ref.
Inland area	20,760,725 (88)	8646	4.16 (4.08–4.25)	1.62 (1.54–1.70)
Coastal area	17,348,338 (99)	8206	4.73 (4.63–4.83)	1.84 (1.75–1.93)
Years of birth				
2013	14,705,320 (90)	5959	4.05 (3.95–4.16)	Ref.
2014	15,356,369 (89)	6368	4.15 (4.05–4.25)	1.02 (0.99–1.06)
2015	15,090,258 (92)	6339	4.20 (4.10–4.31)	1.04 (1.00–1.07)

^an, the number of newborns screened; %, the number of screened newborns per 100 live births. ^bThe number of cases diagnosed among screened newborns. ^cA total of 54,878 newborns (eight cases included) were excluded from our analysis because information on sex were missed or unknown. ^dThe percentages of screened newborns by sex were unknown because the number of sex-specific live births were missed in the present system. CH, congenital hypothyroidism; OR, odds ratio; CI, confidence interval; Ref., reference group.

Table 2: Incidence rates of CH by infant sex and geographical locations, in China, 2013–2015.

Geographical locations	Male			Female		
	Cases	Rates ^a	OR (95% CI)	Cases	Rates ^a	OR (95% CI)
Remote area	831	2.24	Ref	983	2.95	Ref
Inland area	4316	3.89	1.74 (1.61–1.87)	4324	4.49	1.52 (1.42–1.63)
Coastal area	4217	4.49	2.00 (1.86–2.16)	3987	5.02	1.70 (1.59–1.83)

^aRate is the number of cases per 10,000 screened newborns. OR, odds ratio; CI, confidence interval; Ref., reference group.

inland areas (females: OR=2.00, 95% CI: 1.86–2.16 and OR=1.74, 95% CI: 1.61–1.87, respectively; males: OR=1.70, 95% CI: 1.59–1.83 and OR=1.52, 95% CI: 1.42–1.63, respectively). Additionally, regardless of the infant sex, infants located in coastal areas were more likely to have CH than those in inland areas ($p < 0.0001$).

The incidence rates of CH according to the TSH screening values and geographical locations in China over the study period are shown in Figure 2. A U-shaped distribution was observed between CH incidence and TSH screening values in different regions. Higher incidence rates of CH were observed among newborns with TSH screening values <30 mU/L and >100 mU/L. For any TSH screening value group, the incidence of CH in the remote areas was lower than that in the inland and coastal areas.

Figure 3 presents the ORs of CH by TSH screening values and geographical locations after adjusting for infant sex and years of birth. Compared with infants located in remote areas, those located in inland areas were more likely to have CH for any TSH screening value groups. The same difference was observed among infants located in the coastal area, except for TSH screening values of 70–80 mU/L. For groups with TSH screening values <40 mU/L, infants located in the coastal area had the highest risk of CH, followed by those in the inland area. However, the highest risk of CH was detected in the inland area for groups of TSH screening values of 70–100 mU/L. Additionally, for groups of TSH screening values 40–70 mU/L, an elevated risk of CH was observed in the coastal area compared with that in the inland area, but this difference was not statistically significant ($p > 0.05$) (data not shown).

Figure 2: Incidence rates of CH by TSH screening values and geographical locations, in China, 2013–2015. TSH, thyroid-stimulating hormone.

Figure 3: ORs of CH by TSH screening value and geographical location, in China, 2013–2015.

ORs were adjusted by infant sex and years of birth. The incidence of CH in the remote area was the reference group. TSH, thyroid-stimulating hormone; CI, confidence interval.

Discussion

The present study used the largest national database on newborn screening to investigate an overall incidence of CH of 4.1 per 10,000 live births, and we also observed the geographic variations of CH incidence in China. The CNBSIS, the only nationwide network for routine data collection and reporting on newborn screening, provided a large sample size and a sound representative population to assess the estimates of the incidence of CH.

Previous studies have demonstrated that the incidence of CH varies according to race and ethnicity, with a higher incidence in Asians than in non-Hispanic Whites and non-Hispanic Blacks. A recent report in California during 2001–2007 revealed that CH incidence is more common in Asian Indians (5.7 per 10,000 newborns) and in Chinese and Vietnamese (4.2 per 10,000 newborns) than in non-Hispanic Whites (3.6 per 10,000 newborns) and non-Hispanic Blacks (0.9 per 10,000 newborns) [9]. Similar results were also reported in previous studies [5, 11, 28]. In the present study, the overall incidence of CH in China was similar to the estimates of recent studies conducted in California [9] and New Zealand [29], confirming a higher incidence among Asians. However, similar or even higher results were found in Quebec (4.7 per 10,000 live births in 2009) [15], Italy (5.2 per 10,000 live births between 1999 and 2008) [16] and Greece (6.4 per 10,000 live births between 2000 and 2002) [30].

Few studies have presented the incidence of CH in China during the past two decades, although CH has been widely studied in Western countries. Two previous studies using data from the national network of neonatal screening centers collected by the National Center for Clinical Laboratory in China assessed the CH incidence of Chinese newborns, yielding the rates of 4.89 per 10,000 newborns from 1985 to 2007 and 4.88 per 10,000 newborns from 2000 to 2007 [27, 31]. However, due to a lower coverage for newborns screened in both studies, a limited representative population may underestimate or overestimate the true incidence rate of CH. Both rates in these studies were higher than our overall rate but similar to the estimate of 4.73 per 10,000 in the coastal area reported in the present study. This discrepancy may be primarily explained by the higher population of newborns located in the eastern region and the lower population of newborns in the midwestern regions in these two studies than in the present study. In other Asian regions, much higher CH incidences were also observed in Taiwan [8] and Japan [32] (5.02 per 10,000 births during 1997–2008 and 6.8 per 10,000 live births during 1994–2002, respectively). These inconsistencies may be caused by the differences among the study populations, neonatal screening program practices and potential environmental risk factors.

Notably, due to unbalanced development, there are significant differences among regions (coastal area, inland area and remote area) in China regarding the progress on economic, culture, education and environment. In general, the coastal area is more developed than the inland and remote areas. The present study also observed a statistically significant geographic variation of CH incidences across regions, showing a higher incidence risk in the coastal area and in the inland area but a lower incidence risk in the remote area. This difference may be the result of several factors. First, some differences among regions, including screening program practices (e.g. TSH CO levels, screening methodology), follow-up of screening positive cases and laboratory testing, may be correlated with case identification and diagnosis for CH. Generally, more improved screening activities are present in the coastal and inland areas than in remote areas. Therefore, cases have a higher chance to be identified and diagnosed from newborns in the coastal and inland areas. Second, the survival rates for preterm births across regions may lead to geographical variations in CH incidence, although there were no data available to support the differences between CH and preterm births by regions in China. Several previous studies conducted in Western countries have indicated that an elevated survival rate for preterm

neonates contributes to an increasing CH incidence over years [9, 16]. Because of more advanced neonatal health care in the coastal area and less advanced care in the remote area, a higher survival rate among preterm births may occur in the coastal area than in the remote area, suggesting a higher CH incidence in the coastal area. However, no data were available to identify whether prematurity contributed to the increased rate of CH in the coastal area. Third, several environmental risk factors may be associated with the incidence of CH, such as iodine deficiency or iodine excess [33, 34]. Although there is no evidence to support the geographical differences in the iodine nutritional status across regions in China, several studies have revealed that an iodine deficiency during pregnancy exists in the coastal areas of China [35, 36]. Additionally, differences in CH incidence in geographic regions may also be related to the distribution of population with CH susceptibility genes.

Furthermore, the present study showed a change in the geographical variation of the incidence according to the TSH screening value. In the present analysis, the geographical variation of the incidence was present among newborns with lower TSH screening values but also among those with higher TSH screening values. Therefore, the geographical variation of CH incidence may be correlated not only with the TSH CO levels and screening assay methods but also with other risk factors, such as preterm births, iodine deficiency/excess and other unknown environmental factors. Future epidemiologic studies are needed to emphasize that it is of great importance to analyze the distributions and identify potential risk factors of CH across regions.

There are some limitations in the present study. First, due to the limited screening ability in some centers, particularly in the remote areas, some mild cases were not detected via neonatal CH screening and some positive cases were not recalled for further diagnosis. Consequently, the rate reported in the present study may underestimate the true incidence of CH in China. Second, because the data on thyroid ultrasound and scintigraphy were not acquired in these systems, we could not analyze the demographic characteristics of thyroid dysgenesis and dyshormonogenesis. In the future, national newborn screening information system is needed to improve data access regarding the CH subtypes. Third, we did not collect more detailed information on neonatal CH screening procedures. Therefore, we could not obtain TSH CO levels and TSH assay methods across centers and could not describe the age at screening and the age at treatment initiation for CH. We could also not, through the long-term follow-up data, identify cases of permanent and transient

CH. Thus, a detailed analysis of the screening procedures was not performed in the present study.

In conclusion, it is of great importance that newborn screening be implemented in China, as long-term neuro-developmental consequences occur when CH is not treated early. There is room for improvement in the newborn screening program in China because not all areas have fully implemented this program. Furthermore, as the incidence of CH seems to be increased in the Chinese population, further studies are needed to identify the causes of the increased incidence of CH in China.

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