Birth prevalence of tetrahydrobiopterin deficiency in China: data from the national newborn screening program, 2013–2019

Abstract

Background: Tetrahydrobiopterin deficiency (BH4D), a less common form of hyperphenylalaninemia (HPA), can lead to severe developmental retardation if untreated. Little has been reported on the prevalence of BH4D among live births worldwide. This study examined its prevalence across China and between geographical areas within the country.

Methods: We analyzed data from the Chinese national screening program for HPA in newborns between 2013 and 2019. BH4D prevalence was examined by province, region and the entire country. Provincial-level prevalence was estimated from the number of confirmed BH4D cases and screened newborns, after adjusting for HPA-positive recall rate. Regional- and national-level prevalences were estimated by summing provincial-level prevalences after weighting them by the number of live births. A Poisson distribution was assumed in order to calculate 95% confidence intervals (CIs) for prevalence.

Results: Among 107,078,115 newborns screened for HPA in China, 380 with BH4D were identified, corresponding to a total prevalence of 3.8 per 1,000,000 live births. Prevalence was higher in eastern regions (5.9 per 1,000,000) and northern regions (4.1 per 1,000,000) of China than in southern regions (1.6 per 1,000,000) or northwestern regions (1.7 per 1,000,000). Across the entire country, 3.9% cases of HPA were diagnosed as BH4D, and this proportion reached as high as 15.1% in the southern part of the country.

Conclusions: These first insights into BH4D prevalence across China suggest slightly higher prevalence than in other countries, and it varies substantially by region. More attention should be paid to early diagnosis and timely treatment of BH4D.

Keywords: geographical; newborn screening; prevalence; tetrahydrobiopterin deficiency.

Introduction

Hyperphenylalaninemias (HPA) are the most common amino acid metabolic diseases [1], and occasionally they occur as tetrahydrobiopterin deficiency (BH4D) [2], in which deficiency of this essential cofactor leads to decreased metabolism of phenylalanine into tyrosine [3], which can give rise to neurometabolic disorders. BH4D can arise if any of the five enzymes involved in tetrahydrobiopterin
biosynthesis or regeneration is deficient [4]. As for the diagnosis of BH4D, it has no specific clinical manifestation as other HPA [1], and if untreated, the resulting accumulation of phenylalanine in the brain can cause severe intellectual disability as well as behavioral and psychiatric disorders [4]. Besides dietary restriction of phenylalanine, tetrahydrobiopterin, 5-hydroxytryptophan (5-HTP) and L-dopamine are often needed for the treatment of BH4D [1, 4]. However, most of these drugs are unaffordable for patients’ families in low and middle income countries [5].

HPA is an autosomal recessive disorder with varying prevalence among countries, regions and races [4]. In contrast to substantial epidemiological data on phenylketonuria [6, 7], few studies have examined the BH4D prevalence among live births due to the rarity of the disease [4]. Several studies have focused on the prevalence of BH4D among individuals with HPA, and it varied from 1 to 20% [4, 8–12]. Only Brazil and Japan have measured BH4D prevalence among millions of live births, indicating a rate of 0.6–2.1 per 1,000,000 [13–16]. Though geographical differences in BH4D prevalence among individuals with HPA were suggested by previous local studies in China [5, 17, 18], BH4D prevalence among live births and its geographical variation remains unknown.

Here we took advantage of newborn screening for HPA, which was introduced in China in 1981 [19, 20], and for which nationwide coverage increased from 31.0% in 2006 [21] to 97.7% in 2019, in order to estimate the total prevalence of BH4D among live births in the country. We analyzed data for 107,078,115 newborns that had been screened from 2013 to 2019. We examined the prevalence nationally and by region, which may help estimate regional burdens of disease as well as provide insights into the genetic transmission of the condition.

**Materials and methods**

**Data source**

The data used in our study came from the Chinese Newborn Screening Information System (CNBSIS), managed by the National Office of Maternal and Child Health Surveillance (NOMCHS). The data covered the period from 2013 to 2019. Until 2019, a total of 251 newborn screening centers throughout the mainland of China used the system to report basic information on the screening, diagnosis and follow-up of newborns screened for HPA (Figure 1). During this period, around 15,000,000 newborns were screened each year in the whole country, accounting for approximately 93.4% of live births in average.

Data quality and accuracy were checked by experienced professionals in provincial newborn screening centers that are responsible for the information management of newborn screening within the jurisdiction. Incomplete forms and nonspecific records were returned to the local centers, and they need to complete or correct them. The final records and forms were then reported to the NOMCHS for data quality assessment. More details about data collection and quality control have been described elsewhere [22].

![Figure 1: Distribution of newborn screening centers by province in China in 2019.](image-url)
Data collection

In each center, trained staffs were assigned to complete the online forms based on blood sample cards, laboratory test reports and medical records, including the number of newborns screened, and the demographic and clinical characteristics of infants diagnosed with HPA, which included BH4D and Phenylketonuria. These characteristics included geographical location, mother’s ethnicity and age, sex, number of fetuses, gestational week, birth weight, date of birth and date of diagnosis. The present study considered only live births between 2013 and 2019 that were diagnosed with BH4D. Screened newborns throughout the entire country were included except for Tibet, where newborn screening began in 2015 and the number of live births screened from 2015 to 2019 (20,658 newborns) was too small for even one case of BH4D to be detected, which were not representative.

This study was approved by the Ethics Committee of West China Second University Hospital (No. 20150111, and performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

BH4D diagnosis

The procedure of the disease screening and diagnosis must be conducted in accordance with Technical Regulations For Neonatal Screening issued by Ministry of Health in 2010 [23]. HPA was diagnosed in newborns when the concentration of blood phenylalanine was higher than 120 μmol/L (2 mg/dL) [23]. These newborns were then tested for urinary pterin spectrum and dihydropterin reductase activity in blood to differentially diagnose Phenylketonuria or BH4D. If necessary, the BH4 loading test was performed to assist diagnosis [23].

Statistical analysis

To explore geographic variations in BH4D prevalence, the 31 provinces was divided into the following seven regions based on geography and socioeconomic status: northeastern, eastern, northern, central, southern, northwestern and southwestern [24] (Figure 1, Supplementary Table 1).

Provincial crude prevalence was reported as the number of BH4D cases identified, divided by the number of newborns screened. As the HPA-positive recall rate, defined as the proportion of newborns who had been successfully recalled for diagnosis among the newborns with HPA-positive screening results, was not 100% in most provinces, and different HPA-positive recall rates could affect the number of babies who were ultimately diagnosed, we adjusted for it to yield the adjusted provincial prevalence \( p_i \):  
\[
\frac{\sum_{i=1}^{k} w_i s_i}{\sum_{i=1}^{k} w_i} \times 1000000 = \frac{\sum_{i=1}^{k} w_i s_i}{\sum_{i=1}^{k} b_i} \times \frac{b_i}{s_i}
\]

where \( k \) indicated the number of provinces in the nation or region; \( w_i \), the weight of each province; \( b_i \), the number of live births in each province; \( s_i \), the number of newborns screened in each province; and \( P_{adj} \), the adjusted national prevalence or regional prevalence.

Taking the BH4D prevalence in northern China as the reference, we calculated relative risk (RR) of BH4D in each of the other regions, together with the corresponding 95% confidence intervals (CIs) based on the natural logarithm [25]. The 95% CIs of regional or national proportions of HPA cases that were diagnosed as BH4D were estimated assuming a binomial distribution [26], while 95% CIs of provincial, regional and national prevalences were estimated assuming a Poisson distribution as the following formula [27]:

lower limit of \( p_{adj} \) = \( c \times \left( 1 - \frac{1}{9c} - \frac{1.96}{3 \sqrt{c}} \right) / s \times 1000000 \)

and

upper limit of \( p_{adj} \) = \( (c + 1) \times \left( 1 - \frac{1}{9(c + 1)} - \frac{1.96}{3 \sqrt{c + 1}} \right) / s \times 1000000 \)

The provincial prevalences and proportions of HPA cases that were diagnosed as BH4D were depicted on a map. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, http://www.r-project.org).

Results

A total of 107,078,115 newborns were screened for HPA in China between 2013 and 2019, and 10,553 babies were identified with HPA, of whom 380 (3.9%, 95% CI 3.5–4.3) were diagnosed with BH4D. Among the BH4D cases, 50.5% were males, and 88.7% were Han Chinese. This corresponds to a total BH4D prevalence of 3.8 (95% CI 3.5–4.2) per 1,000,000 live births (Table 1). Only a few babies with BH4D were born before 37 weeks (1.3%) or had low birth weight (7.6%). Most cases of BH4D (87.9%) occurred in women younger than 35 years (Supplementary Table 2).

As shown in Table 1, lower prevalence of BH4D among cases of HPA was observed in southern China (1.6 per 1,000,000) and northwestern China (1.7 per 1,000,000), while the highest prevalence was in eastern China (5.9 per 1,000,000), followed by northeastern China (5.7 per 1,000,000). After adjusting for HPA-positive recall rates and provincial-level HPA screening rates, we found that babies in eastern region were three times as likely to have BH4D as those in southern region (RR 3.7, 95% CI 2.5–5.4).

The total proportion of BH4D cases among HPA cases was 3.9%, and this proportion varied significantly across
Table 1: BH4D prevalence among live births and among HPA cases in China, 2013–2019.

| Region     | BH4D prevalence per 1,000,000 live births | BH4D proportion among HPA cases |
|------------|------------------------------------------|--------------------------------|
|            | n | Rate, 95%CI | RR, 95%CI | HPA cases | %, 95%CI | χ², p |
| China      | 380 | 3.8 (3.5, 4.2) | – | 10,553 | 3.9 (3.5, 4.3) | – |
| Region     |            |            |            |          |            |      |
| Northern   | 25 | 5.7 (3.7, 8.3) | 3.5 (2.1, 5.9) | 884 | 2.8 (1.7, 3.9) | 166.9 (<0.05) |
| Eastern    | 184 | 5.9 (5.1, 6.8) | 3.7 (2.5, 5.4) | 3,485 | 5.3 (4.6, 6.0) | – |
| Northern   | 45 | 4.1 (3.0, 5.4) | 2.5 (1.6, 4.0) | 2,219 | 2.0 (1.4, 2.6) | – |
| Central    | 57 | 3.4 (2.6, 4.4) | 2.1 (1.4, 3.3) | 1,248 | 4.6 (3.4, 5.8) | – |
| Southern   | 25 | 1.6 (1.1, 2.3) | 1.0 | 166 | 15.1 (9.7, 20.5) | – |
| Northwestern | 10 | 1.7 (0.9, 2.8) | 1.1 (0.5, 2.0) | 1879 | 0.5 (0.2, 0.8) | – |
| Southwestern | 34 | 2.8 (2.0, 3.8) | 1.8 (1.1, 2.8) | 672 | 5.1 (3.4, 6.8) | – |

BH4D, tetrahydrobiopterin deficiency; HPA, Phenylalanine hydroxylases.

regions (Table 1). The highest proportion occurred in southern region (15.1%), followed by eastern (5.3%) and southwestern (5.1%) regions. The lowest proportion was observed in northeastern region (0.5%).

BH4D prevalence among all live births varied substantially across the provinces of China (Figure 2). Six provinces had rates >6.0 per 1,000,000, among which Jiangxi in eastern China had the highest rate of 10.6 per 1,000,000. Three provinces had prevalence <1.0 per 1,000,000. Similarly, the proportion of HPA cases that were BH4D varied substantially across the provinces. Nine provinces showed BH4D proportions >6.0%. Proportions were higher in southeastern and southwestern China than in northeastern and northern China.

Of the 380 babies diagnosed with BH4D during the study period, most (73.4%) were diagnosed within the second month of life, and 29.7% were diagnosed within the first month of life (Table 2). Age at diagnosis varied substantially across regions. The proportion of cases diagnosed within the first month of life were higher in southern China and lower in southeastern and northeastern China.

**Discussion**

This is the first study to describe the prevalence of BH4D in China using the largest national database on newborn screening for HPA in the country. We also investigated geographical variations in BH4D prevalence across regions. BH4D appears more likely to affect babies in eastern and northeastern China.

Few studies have examined BH4D prevalence. A study published in 1996 estimated the global prevalence of BH4D

![Figure 2: (A) BH4D prevalence among live births and (B) proportion of HPA cases that were diagnosed as BH4D during 2013–2019, by province in China.](image-url)
to be 1 per 1,000,000 live births by using an international database [8]. However, it is poorly representative, as the BH4D cases in this database depended on voluntary registration by clinicians in several countries. Most of them (68%) were Caucasian, while only 32% of them were from other countries, such as Chinese (9%) and Japanese (6%) [8]. A study in Minas Gerais, Brazil based on data for 1993–2012 estimated BH4D prevalence to be 2.1 per 1,000,000 live births in that state [13]. Our study estimated a BH4D prevalence of 3.8 per 1,000,000 live births for the period 2013–2019, which may be higher than that reported for Minas Gerais, Brazil. Besides, we also found the BH4D prevalence in China was higher than that in Japan from 1977 to 1982 (0.6 per 1,000,000 live births). In addition to the important fact that the genetic background are different among Brazilians, Japanese and Chinese, the difference in the screening and diagnostic methods of BH4D among these countries could also help to explain such differences in BH4D prevalence. For example, the identification of BH4D in Brazil was performed only based on clinical evaluation of patients with phenylalanine-restricted diet before 2006 [13]. In Japan during 1977–1982, HPA was diagnosed in newborns when the concentration of blood phenylalanine was higher than 8 mg/dL, and the differential diagnosis of BH4D was only made in patients with HPA when the effect of adequate dietary control of the blood phenylalanine level was not ideal [14]. Whereas in China, newborns with a concentration of blood phenylalanine of over 2 mg/dL would be diagnosed as HPA, and the differential diagnosis of BH4D was conducted then [23]. The reported prevalence of BH4D in Japan might be underestimated, as our data showed that approximately 29% of BH4D had a blood phenylalanine concentration of 2–8 mg/dL in the neonatal period.

Previous studies have revealed the prevalence of BH4D among individuals with HPA varies by ethnicity. For example, proportion of HPA cases diagnosed as BH4D is higher in Italy (10%) [8], Turkey (15%) [8] and Iran (12.3%) [28], but it is lower in France (1.87%) [29] and Brazil (1.71%) [13]. Our study with a predominantly Han Chinese sample shows that even within a single country, the proportion of HPA cases diagnosed as BH4D can vary across regions. The proportion across the entire country was 3.9% in average, which falls within the range of 1–19% reported in other researches [8], and it ranged from 0.5% in northwestern China to 15.1% in southern China. It may imply the differences between southern and northern China in the frequency of gene mutations linked to HPA [30] and in the epidemiology of the disease [31]. It may also reflect geographic differences in the availability of laboratory testing and expertise in differential diagnosis involving such a rare disease, both of which may be especially lacking in the less developed regions of western China.

Diagnosis of BH4D and initiation of treatment within the first month of life may improve prognosis [32], but fewer than 30% of BH4D cases in our system were diagnosed within that period. Given that a study in Hong Kong suggested that the screening and earlier diagnosis and treatment of 6-pyruvoyl-tetrahydropterin synthase deficiency, a subtype of BH4, among newborns can save substantial healthcare costs [33], our results suggest that it is necessary to substantially improve the timeliness of diagnosis of BH4D in China, especially in the regions where the proportion of cases diagnosed within the first month of life is relatively low.

At the same time, we must acknowledge several limitations in our study. First, we could not analyze in detail about the treatment and prognosis of these patients, since the national database did not include such data. Second, as we did not follow up all the screened newborns, the screened newborns with false-negative results could not be included in our database, which may lead to underestimation of the prevalence. Third, HPA-positive recall rate of less than 100% means that the BH4D prevalence may be underestimated. Therefore, we adjusted the prevalence by HPA-positive recall rate based on the hypothesis that the newborns with HPA-positive screening results who had not undergone diagnosis were randomly distributed in the screened newborns. Another factor that may make our BH4D prevalences underestimates is that some newborns

| Age at diagnosis, months | Entire country | NE | Eastern | Northern | Central | Southern | NW | SW |
|--------------------------|----------------|----|---------|----------|---------|----------|----|----|
| ≤1                       | 113 (29.7)     | 3  | (12.0)  | 52 (28.3)| 18 (60.0)| 17 (29.8)| 17 (68.0)| 2  | 4  |
| 1–2                      | 166 (43.7)     | 14 | (56.0)  | 88 (47.8)| 19 (42.2)| 24 (42.1)| 5  | (20.0)| 0  | 16 (47.1) |
| ≥2                       | 101 (26.6)     | 8  | (32.0)  | 44 (23.9)| 8  (17.8)| 16 (28.1)| 3  | (12.0)| 8  | 14 (41.2) |

Values are n, %. BH4D, tetrahydrobiopterin deficiency; NE, northeastern; NW, northwestern; SW, southwestern.
who tested positive for HPA were likely referred to other specialist hospitals for diagnosis. We were unable to acquire data on patients diagnosed at specialist hospitals, so the prevalence of BH4D may have been underestimated. Future research should include analysis of BH4D diagnosis, treatment and follow-up among BH4D patients in newborn screening centers and specialist hospitals.

Conclusion

This study is the first report of nationwide prevalence of BH4D in China. The prevalence is slightly higher than that reported for other countries, and the prevalence within China varies substantially by region. Although rare, BH4D can lead to severe developmental retardation if untreated, so more attention should be paid to its early diagnosis and timely treatment.

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