Analysis of neonatal screening and recall of 338,680 neonates in Haidian District in Beijing, China: A retrospective observational study

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Abstract

Objective

To analyze neonatal screening and recall of neonates suspected of having congenital metabolic disorders in Haidian District from 2010 to 2017 with the aim of improving the quality of neonatal screening.

Methods

We retrospectively analyzed data on neonates suspected of having congenital metabolic disorders on the basis of findings on neonatal screening in Haidian District from 2010 to 2017. Data on screening findings and recall of affected neonates were drawn from the neonatal screening bulletin in Beijing. The timing of the affected neonates recall was obtained from the Information Management System for Neonatal Disease Screening in Beijing.

Results

From 2010 to 2017, 336,202 neonates from 338,680 live births were screened for abnormalities in Haidian District, the average rate of screening being 99.27%. Of these, 3392 cases were found to have definite abnormalities, 3260(96.11%) of whom were recalled successfully for further testing to establish a diagnosis. Congenital metabolic disorders were diagnosed in 268 of the recalled neonates, 206 of them being found to have congenital hypothyroidism (CH), and 62 phenylketonuria (PKU). The prevalences of CH and PKU were 0.61‰, 0.18‰ respectively. The times to Level-1 and Level-2 recall decreased over the study period from 28.83 days to 11.33 days and from 51.63 days to 41.92 days, respectively, these differences being statistically significant ($P < 0.001$). The number of neonates recalled to establish a diagnosis increased in parallel with a decreasing interval between Level-1 recall and sending names to Haidian District (OR = 0.974, 95% CI: 0.951–0.999).

Conclusions

The rates of screening of neonates and recall rates of neonatal with positive screening result in Haidian District increased progressively from 2010 to 2017. Early recall of neonates suspected of having a disorder contributes to a high recall rate, earlier diagnosis, and earlier therapy.

Background

Mass neonatal screening for inherited metabolic disorders enables early diagnosis and initiation of appropriate treatment, minimizing growth retardation, development of cognitive impairment, and even death as a result of damage to vital organs[1].

In China, mass screening of neonates was started in Shanghai in October 1981 and in Beijing in 1989. Presidential Order 33 was promulgated in October 1994, and Law of the People's Republic of China on Maternal and Infant Health Care took effect on 1 June 1995. Almost all provinces in China have now launched neonatal screening programs, most of them including screening for congenital hypothyroidism (CH) and phenylketonuria (PKU). With progressive increasing screening rates, follow-up of neonates suspected of having an inherited metabolic disorder is particularly important, such follow-up being the main indicator of the quality of screening [2]. To the best of our knowledge, no research on the timing of follow-up of such patients has yet been performed in China. The aim of this study was to review and analyze the

follow-up of neonates suspected of having an inherited metabolic disorder from 2010 to 2017 with the objective of improving the recall rate of such patients in Haidian District, Beijing.

Methods

Subjects

The study cohort comprised 338,680 neonates born in midwifery institutions in Haidian District, Beijing from October 2010 to September 2017.

Specimen collection, preservation, and delivery

After obtaining parental permission, blood samples were collected from the heels of newborns 72 hours after birth. The samples were dripped onto a special filter paper, dried, and delivered to Haidian Maternal and Child Hospital, where they were scanned into a quality control system. They were then sent to the Beijing Neonatal Screening Center's central laboratory by express mail. Appropriately qualified professionals were responsible for sending, receiving, and testing the samples.

Laboratory screening methods

Thyroid-stimulating hormone (TSH) concentrations were measured to screen for CH and phenylalanine (Phe) concentrations to screen for PKU. Time-resolved fluoroimmunoassays were performed to quantitate TSH and a fluorescence quantitative method was performed to quantitate Phe. A filter paper blood TSH ≥ 10 μ IU/mL was considered suspicious of CH and a blood Phe ≥ 2 mg/dL suspicious of PKU.

Management of neonatal screening

The Neonatal Screening Center is located in Beijing Maternal and Child Health Hospital. Twenty-four hospitals in Haidian District participated in collecting the required blood specimens. The Beijing Neonatal Screening Center is responsible for testing, diagnosis, recalls, treatment, and follow-up. In this center, neonatal screening is computerized using newborn screening management software to create files for each screened neonate.

Neonates suspected of having a metabolic disorder were recalled through the three-level network of the Beijing Neonatal Screening Center, Haidian Maternal and Child Health (MCH) Hospital, delivery hospitals and communities. The families of these neonates were notified via Short Messaging Services (SMS) and phone call by the Beijing Neonatal Screening Center (Level-1 recall). The names of neonates who were not brought in for reexamination within a certain time after receiving this message were sent to the relevant MCH Hospital by the Beijing Neonatal Screening Center management system at the beginning of each month. After receiving these names, the professional responsible for this task called the relevant neonates' parents (Level-2 recall). The delivery hospital was informed about neonates who again failed to attend for reexamination and asked to assist in ensuring a follow-up visit (Level-3 recall). The local community child health doctor of the small number of neonates who failed to present for reexamination after the above three follow-up attempts was then notified. Professionals in the MCHs of the relevant districts were responsible for recording the results of Level-2 and Level-3 follow-up attempts in the district level information management system and these data were regularly reported to the Beijing Neonatal Screening Center.

Diagnosis

Circulating T3, T4, TSH, FT3, and FT4 concentrations were measured in the neonates suspected of having CH and ultrasound examination was performed to confirm the final diagnosis. Neonates whose blood Phe concentrations

continued to increase after excluding tetrahydrobiopterin deficiency were diagnosed as having PKU. The Beijing Neonatal Screening Center created a file for every neonate diagnosed with CH or PKU. Thyroid hormone replacement therapy was prescribed for those with CH, whereas those with PKU were placed on a low phenylalanine diet

Quality control

The Beijing Neonatal Screening Laboratory is monitored by the National Center for Clinical Laboratories. In addition, newborn screening laboratory quality management software has been established to monitor newborn screening laboratories' blood spot collection, storage, delivery, testing, data-entry processes, and quality control standards

Data sources

The numbers of live births were drawn from obstetric reports submitted by 24 midwifery institutions in Haidian District to the Maternal and Child Information Department of Haidian MCH hospital. The numbers of neonates screened, suspected of having an inherited metabolic disorder, recalled, and with confirmed diagnosis were obtained from the data recorded by the Beijing Neonatal Screening Center from 2010 to 2017;data on follow-up of neonates with suspicious findings were obtained from the Quality Monitoring and Management System of that center.

Statistical analysis

Because blood for screening is collected at least 72 hours after the time of birth, the neonatal disease screening system used by midwifery institutions in Beijing is a stand-alone version. Only the district managers are connected with the screening center's system and the proportion of live births screened is calculated by the Beijing Neonatal Screening Center as follows: identified cases/screened cases×100%. Follow-up data in the neonatal disease screening system were then entered into Excel 2007. The interval to follow-up in different years was compared by analysis of variance or independent sample *t*-test. Statistical significance was set at *P*< 0.05. Data analyses were performed using IBM SPSS, version 20.0(SPSS, Chicago, IL, USA).

Results

Screening and detection rates

From 2010 to 2017, 336,202 neonates from 338,680 live births were screened (screening rate 99.27%). In all, 206 cases of CH, and 62 cases of PKU were diagnosed, making a total of 268 cases of the target metabolic disorders. The incidence of CH was 0.61‰ (1/1632), and of PKU was 0.18‰(1/5422), as shown in Table 1.

Table 1.Rates of screening and diagnosis of neonatal metabolic disorders in Haidian District from 2010 to 2017

Year	Live births(N)	Screening (N)	Screening rate(N)	Total Diagnosed number	Total Detection rate (‰)	Diagnosed number and Detection rate (n/‰)	
						CH	PKU
2010	35151	35081	99.80	17	0.48	12(0.34)	5(0.14)
2011	38610	38257	99.09	26	0.68	21(0.55)	5(0.13)
2012	45943	45060	98.08	33	0.73	22(0.49)	11(0.24)
2013	42636	42714	99.33	35	0.82	26(0.61)	9(0.21)
2014	48180	47490	98.57	35	0.74	29(0.61)	6(0.13)
2015	40916	41031	100.28*	44	1.07	34(0.83)	10(0.24)
2016	43521	42919	98.62	40	0.93	32(0.75)	8(0.19)
2017	43723	43650	99.83	38	0.87	30(0.69)	8(0.18)
Total	338680	336202	99.27	268	0.80	206(0.61)	62(0.18)

*The rate of screening was calculated as follows: number screened/number of live births during the same period. The screening rate for 2015 is more than 100% because blood was collected in early 2015 from neonates born at the end of 2014.

Recall of neonates suspected of having congenital disorders in Haidian District from 2010 to 2017

As shown in Table 2, from 2010 to 2017, 3392 of 233,602 neonates screened (1.01%) in Haidian District screened positive for a congenital disorder. Of these,3260 neonates were recalled, the recall rate increasing from 88.08% in 2010 to 99.61% in 2017. All neonates who tested positive on screening were recalled at Level-1. The Level-1 recall rate increased from 61.92% in 2010 to 90.20% in 2017.Level-2 recalls were sent to the families of 438 neonates, the Level-2 recall rate increasing from 58.89% in 2010 to 95.83% in 2017.

Table 2.Rates of recall of neonates screened in Haidian District from 2010 to 2017

Year	Screening (N)	screening positive		level-1 recall		level-2 recall			Total	
		N	Suspicious rate(%)	Recalled cases(N)	Recall rate(%)	N	Recalled cases(N)	Recall rate(%)	Recalled cases(N)	Recall rate(%)
2010	35081	344	0.98	250	61.92	90	53	58.89	303	88.08
2011	38257	491	1.28	416	79.84	71	47	66.2	463	93.81
2012	45060	394	0.87	340	84.26	50	42	84	382	96.95
2013	42714	621	1.45	546	85.02	73	55	75.34	601	96.78
2014	47490	449	0.95	390	84.19	59	47	79.66	437	97.33
2015	41031	474	1.16	434	90.30	36	30	83.33	464	97.89
2016	42919	364	0.85	326	88.19	35	30	85.71	356	97.8
2017	43650	255	0.58	231	90.20	24	23	95.83	254	99.61
∑	336202	3392	1.01	2933	83.20	438	327	74.66	3260	96.11

Changes in interval to follow-up of neonates suspected of having congenital disorders

There were no significant differences between study years in the timing of collection of specimens, and the average interval was 4.33 days ($F=1.327$, $P=0.236$). The times of Level-1 and Level-2 recalls decreased progressively, from 28.83 days to 11.33 days and from 51.63 days to 41.92 days, respectively. These differences are statistically significant ($P<0.001$). Additionally, the differences in intervals between Level-1 recall and sending the names to Haidian district and between sending the names and Level-2 recall were both statistically significant ($P=0.008$, $P<0.001$), as shown in Table 3.

Table 3. Timing of Level-1 and Level-2 recalls and sending the list to Haidian district according to study year

Year	Specimen collection time(days)	Level-1 recall time(days)	Interval between Level-1 recall and sending names to Haidian District	Interval between sending names to Haidian District and Level-2 recall	Level-2 recall time(days)
2010	4.00±2.160	28.83±6.760	16.76±10.997	2.04±4.779	51.63±13.777
2011	3.85±1.134	24.70±14.775	22.43±10.957	1.35±1.895	52.33±17.430
2012	5.18±7.515	20.02±6.005	19.72±9.252	2.42±4.233	47.34±14.808
2013	4.37±2.342	25.97±8.021	20.10±9.033	1.01±0.858	51.45±11.220
2014	4.07±1.032	17.31±2.507	17.29±11.598	5.05±5.713	43.71±13.575
2015	5.56±6.971	19.89±8.795	23.17±9.620	2.50±1.813	51.11±13.018
2016	3.91±0.570	12.32±2.253	16.94±9.175	4.35±2.436	37.53±10.434
2017	4.17±1.606	11.33±3.306	22.17±15.890	4.25±3.339	41.92±16.960
̄̄	4.33±3.672	21.48±10.084	19.86±10.805	2.57±3.715	48.24±14.848
<i>F</i>	1.327	21.672	2.760	10.223	6.424
<i>P</i>	0.236	<0.001	0.008	<0.001	<0.001

Relationship between recall time and recall outcomes

Table 4 summarizes the results of multiple logistic regression assessment of recall outcomes (N= 438). The interval between Level-1 recall and sending the list to Haidian district decreased in parallel with increases in the number of cases of neonates suspected of having congenital disorders successfully recalled to establish a diagnosis (OR=0.974, 95% CI:0.951–0.999).

Table 4. Results of multiple logistic regression analysis of outcomes of recall of neonates identified by screening as positive for congenital disorders and requiring Level-2 recall (N=438)*

Variable	β	Wald χ^2	<i>P</i> value	OR	95% CI for OR	
					Lower	Upper
Interval between Level-1 recall and sending names to Haidian District	-0.026	4.279	0.039	0.974	0.951	0.999
Year						
2010	Reference					
2011	0.819	4.004	0.045	2.268	1.017	5.058
2012	1.283	6.454	0.011	3.608	1.341	9.712
2013	1.180	7.367	0.007	3.256	1.388	7.636
2014	1.720	9.800	0.002	5.586	1.903	16.399
2015	1.640	7.356	0.007	5.155	1.576	16.860
2016	1.979	7.243	0.007	7.235	1.712	30.572
2017	2.866	6.677	0.010	17.561	1.998	154.356

*The model was adjusted for times of specimen collection (days), Level-1 recall(days),Level-2 recall(days),interval between Level-1 recall and sending names to Haidian District, interval between sending the names and Level-2 recall, season, and year.

Discussion

The incidence of CH is estimated at 1:1714 to 1:3500 newborns worldwide[3]and varies by geographic location, with a higher incidence in Italy (1:1940)[4],which is surrounded by ocean, than in landlocked countries, such as the Czech Republic(1:2877)[5].There are also geographic variations in CH incidence within certain countries. A USA study showed a higher incidence in the southwest, Great Lakes region, and Hawaii [6]. There are similar geographic variations across China, with a 1.3 times higher incidence in newborns in coastal and inland areas[7, 8]than in remote provinces[8, 9, 10].Furthermore, differences in CH incidence between cities in the same province can reach as much as 1.5-fold[11, 12]. The higher incidence of CH in Asian individuals may be partially explained by genetic and hereditary factors.

The incidence of CH (1/1632) in Haidian Districts considerably higher than the national incidence (1/2047)[13], but similar to that in ZheJiang Province from 1999–2009 (1/1678)[14]. These differences are similar to those found in a retrospective study based on 92 million newborns screened in 2013–2018[15]. Neonates in central (risk ratio = 0.84, 95% CI: 0.82–0.85) and western region of China (risk ratio = 0.71, 95% CI: 0.69–0.73) reportedly have a lower probability of having CH cases than those in the eastern region [15];Beijing is classified as being in the eastern region. Possible explanations for these differences include the followings :**(1)** High screening and recall rates (99.27% and 96.11%, respectively): these are likely to more accurately reflect the true incidence of congenital disorders in neonates. In the Songkhla area of Thailand, the incidence of CH was 1/5021 from 1995 to 2004. A national TSH screening program was implemented nationwide in Thailand in 2005, after which the incidence of CH increased to 1/2238 in 2013 [16].**(2)** Different screening methods: these differ between various provinces and regions in China. The high-sensitivity time-resolved immunofluorescence method for CH screening was reported improves the detection rate greatly [17].**(3)** Different cutoff values: Many of the screening values in children who were subsequently found to have definite CH were only slightly higher than the cutoff value. Reducing the cutoff for screening TSH concentrations can result in a large difference in the incidence of diagnosed CH [18].

The incidence of PKU in Haidian District(1/5422)was significantly higher than the national incidence (1/1144)[19]It was fivefold the incidence of 1/27,391 in the Hengyang area from 2009 to 2014[20], and eightfold that of the Huaihua area(1/40,758) in 2011 to 2016 [21].These large differences are probably attributable to regional variations between Chinese provinces, the incidence of PKU in northern provinces being much lower than in southern provinces and almost 1.7 times that in Beijing from 1989 to 2010 (1/9094) [22]. The regional and environmental factors responsible for the higher incidence of CH and PKU in Haidian District than in Beijing need to be further explored.

In the present study, 438 (12.9%) neonates suspected of having a congenital disorder were subject toLevel-2 recall, which is far lower than the proportion of 21.11% (1439/6818) in Beijing from 2005 to 2010 [17].In Haidian District, the proportion of neonates suspected of having a congenital disorder and subject toLevel-2 recall has been decreasing progressively, the highest percentage being 26.16% in 2010 and the lowest being 7.59% in 2015. These findings indicate that neonates suspected of having a congenital disorder have been followed up efficiently after Level-1recall by Beijing Neonatal Disease Screening Center as a result of the joint efforts of the city, districts, and institutions. After introduction of Level-3 follow-up visits, the total rate of recall of neonates suspected of having a congenital disorder in Haidian District increased progressively from 88.08% in 2010 to 99.61% in 2017, the average being 96.11%. This rate is higher than that in Beijing in the same period and also higher than that in the Chaoyang District, where the rate was 95.16% from 2011 to 2016 [23] This recall rate is similar to that reported by Fengmei and others (96.14%), who provided health education at multiple time points and made repeated follow-up telephone calls [24].

In the present study, Level-1 and Level-2 recalls occurred progressively earlier from 2010 to 2017.In parallel with the decreasing interval between Level-1 recall and sending the list to Haidian District, the number of neonates suspected of having a congenital disorder and recalled to establish definite diagnoses increased (OR = 0.974, 95% CI:0.951–0.999). Timely follow-up optimizes early diagnosis and treatment. Haidian District strictly implements the regulations concerning follow-up of neonates suspected of having a congenital disorder in the program for screening for neonatal genetic and metabolic diseases administered by Beijing Neonatal Disease Screening Center. After receiving the list each month, Haidian District staff make timely follow-up telephone calls, address involved families' questions, and address their concerns about the time, place, cost, and need for follow-up treatment. In cases where the families of neonates suspected of having a congenital disorder cannot be contacted, the birth hospital is asked to check the families' contact details in the delivery medical record or birth certificate issuing office, to facilitate follow-up. Alternatively, the community physician is asked to assist with follow-up.

Conclusion

The rates of screening for neonatal disorders and the recall rate of possibly-affected neonates in Haidian District has been increasing progressively. Recalling neonates suspected of having a congenital disorder in a timely manner contributes to a high recall rate, early diagnosis, and early therapy.

Abbreviations

CH
Congenital Hypothyroidism
PKU
Phenylketonuria
TSH
Thyroid-stimulating hormone
Phe
Phenylalanine

MCH
Maternal and Child Health
SMS
Short Messaging Service
OR
Odd Ratios
CI
Confidence Interval

Declarations

Ethics approval and consent to participate

This study is a retrospective research and based on the requirements of Law of the People's Republic of China on Maternal and Infant Health Care as well as Notice of Beijing Municipal Bureau of Health on further implementing the technical specifications for neonatal disease screening of the Ministry of Health (2010 Edition). So ethics approval was waived by Ethics Committee of Haidian Maternal and Child Health Hospital.

All methods were performed in accordance with Declaration of Helsinki. The study has obtained the informed consent of their legal guardians of all neonates.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Beijing Neonatal Screening Center, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Beijing Neonatal Screening Center.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study design, collection and analysis of data, and manuscript preparation. Suhong Gao analyzed the data and drafted the main article; Suhong Gao, Yu Zhou, Quanlian Yuan, Wen Zhao and Yaping Li reviewed data from all sites; and Yu Zhou revised the article. All authors discussed the results and implications and commented on the manuscript at all stages. All authors reviewed the manuscript.

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