Neonatal screening for congenital hypothyroidism and phenylketonuria in China

Jian-Ying Zhan, Yu-Feng Qin, Zheng-Yan Zhao
Hangzhou, China

Background: **Neonatal screening is helpful to prevent serious disabitily and sufferings caused by congenital or inherited disease. This study was to review the status of neonatal screening for congenital hypothyroidism (CH) and phenylketonuria (PKU) in China.**

Methods: **We analyzed data of neonatal screening for CH and PKU in the past two decades which were obtained from the national network of neonatal screening centers collected by the National Center for Clinical Laboratory.**

Results: **Of 18.8 million newborns screened from 1985 to 2007, 9198 were identified with CH, giving a prevalence of 1/2047. In 19.0 million newborns screened in the same period, 1638 had PKU, with a prevalence of 1/11 572. An increasing number of neonates have been subjected to neonatal screening in China annually during this period. Data from Zhejiang Neonatal Screening Center showed that the recall rate of neonates suspected with CH and PKU was 95.52% in 2007. Confirmatory tests were performed and treatments were initiated in most of the neonates with CH and PKU within a month after birth.**

Conclusions: **More governmental support at different levels is needed to make neonatal screening more efficient. The screening should be improved with a satisfactory control system including shorter time of report and a higher recall rate.**

World J Pediatr 2009;5(2):136-139

Key words: **congenital hypothyroidism; neonatal screening; phenylketonuria**

Author Affiliations: Department of Pediatric Health Care, Children's Hospital, Zhejiang University School of Medicine and Zhejiang Key Laboratory for Diagnosis and Therapy of Neonatal Diseases, Hangzhou 310003, China (Zhan JY, Qin YF, Zhao ZY)

Corresponding Author: Zheng-Yan Zhao, Department of Pediatric Health Care, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China (Email: zhaozy@zju.edu.cn)

doi:10.1007/s12519-009-0027-0

Introduction

Neonatal screening is feasible to prevent serious disability and sufferings caused by congenital or inherited diseases.[1-3] As an integral part of maternal and child health care in China, it has so far focused on the detection of congenital hypothyroidism (CH) and phenylketonuria (PKU) to prevent or reduce mental and physical developmental retardation in children. This investigation aimed to assess neonatal screening for CH and PKU in China in the past 20 years.

Methods

The data reported by the national network of neonatal screening centers were collected by the National Center for Clinical Laboratory (NCCL) between 1985 and 2007, which did not include the data from Hong Kong, Taiwan and Macao.[4] The data included the number of neonates screened, neonates identified with CH or PKU, and neonates treated, information on screening methods, and diagnostic criteria. The study population included live births delivered in health care institutions throughout the mainland of China who participated in the neonatal screening program for CH and PKU between 1985 and 2007.

Laboratory methods

In CH screening, blood thyroid-stimulating hormone (TSH) was quantified by radio-immunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzymatic immunofluorescence assay (EFIA) or dissociation enhanced lanthanide fluoroimmunoassay (DELFIA). Reference values were used with the upper cutoff value for TSH varying from 8 to 20 mU/L. Before 1998, laboratories of various screening centers in China employed RIA, which later was replaced by DELFIA. Only a few laboratories still use ELISA and EFIA currently.

PKU screening was originally performed with bacteria inhibition assay (BIA). At present, most laboratories employ fluorometric method or BIA for the measurement of phenylalanine concentrations, whereas

enzymatic colorimetric method is also used in some laboratories. Blood concentrations below 120 μmol/L (2 mg/dL) are considered normal, and concentrations higher than 120 μmol/L require re-examination. Some laboratories in Shanghai and Beijing performed further diagnostic analyses on patients confirmed with PKU, including uropterin spectrum analysis, oral tetrahydrobiopterin load testing, and determination of dihydropterin reductase activity, for the differentiation of classic PKU from tetrahydopterin deficiency.

Quality control

In the past 20 years, neonatal screening system has formed its own standards for quality control in specimen collection and laboratory procedures. Blood samples should be taken between 72 hours and 7 days after birth from adequately fed children. If it is delayed for some reason, it should be done within 20 days after birth. Blood samples should be tested with filter paper at least 8 mm in diameter with the blood permeating naturally into the paper. Each of the samples must be in similar size and placed on the front or back side of the paper without contamination. All samples should be sent to the screening laboratory within 5 workdays. Extra blood samples should be stored for at least 5 years at 2ºC-8ºC for possible re-analysis. All screening laboratories are required to process and analyze the blood samples within 5 workdays after receipt and to report positive cases immediately. Monthly feedback regarding the screening results is given to the units in charge of collecting the blood samples. The NCCL is authorized to hold annual meeting for quality evaluation and monitoring of activities among laboratories. Some laboratories participate in external quality assessment under the supervision of Centers for Disease Control and Prevention (CDC) in the USA.

Statistical analysis

The data were collected, processed and stored on MS Excel spreadsheets. Statistical analysis was made with the SPSS 13.0 software package for Windows.

Results

Prevalence of CH and PKU

Between 1985 and 2007, around 19 million newborns were screened for CH and PKU. The number of subjects screened in 2007 was 100 times more than that in 1985. In the last 20 years, 9198 neonates were diagnosed as having CH with a prevalence of 1 per 2047, and 1638 newborns were diagnosed to have PKU with a prevalence of 1 per 11 572 (Table 1). The prevalence of CH increased in recent years especially after 1998, but the prevalence of PKU was relatively stable in the same period.

Status of neonatal screening

In China neonatal screening was conducted sporadically in Shanghai and Beijing in 1981. In March 1982, a PKU screening cooperation was established as a collaboration of 11 provinces, including Beijing, Tianjin, Hebei, Liaoning, Shandong, Shanghai, Zhejiang, Jilin, Heilongjiang, Sichuan and Shanxi. Provincial screening programs have been implemented since 1985. In October 1994, the law on *Maternal and Infant Care in China* was issued, which provided a legal basis for neonatal screening as an integral part of preventive medicine. Since then, the national screening has undergone rapid development. Presently, most provinces in China have launched neonatal screening programs, mostly screening for CH and PKU.

Since 1998, laboratory quality control in neonatal screening has been carried out by the NCCL. In 2002, there were only 46 centers for screening, but by the end of 2007, 143 centers in 28 provinces have conducted neonatal screening (Table 2). Some provinces prefer one major screening center for the whole province

Table 1. Neonatal screening for CH and PKU in China from 1985 to 2007[4]

Year	Congenital hypothyroidism (*n*)			Phenylketonuria (*n*)		
	Screened	Confirmed	Prevalence	Screened	Confirmed	Prevalence
1985	-	-	-	52722	5	1/10544
1986	-	-	-	69506	2	1/34753
1987	-	-	-	83262	5	1/16652
1988	-	-	-	67535	5	1/13507
1989	-	-	-	65722	2	1/32861
1990	-	-	-	49033	3	1/16344
1991	150801*	37	1/4076	50113	4	1/12528
1992	75836	16	1/4740	117904	6	1/19651
1993	121103	18	1/6728	121106	10	1/12111
1994	130875	19	1/6888	126141	4	1/31535
1995	123494	25	1/4940	121227	24	1/5010
1996	173707	31	1/5603	164509	13	1/12655
1997	292583	65	1/4501	280891	22	1/12768
1998	400653	137	1/2924	385297	35	1/11008
1999	477282	189	1/2525	471405	59	1/7990
2000	686777	308	1/2229	686075	55	1/12474
2001	851855	319	1/2670	852605	76	1/11218
2002	949495	474	1/2003	950960	95	1/10010
2003	1427596	886	1/1611	1367541	155	1/8822
2004	1911349	998	1/1915	2021541	156	1/12959
2005	2511814	1282	1/1959	2632419	213	1/12358
2006	2944022	1701	1/1730	2929236	221	1/13254
2007	5603451	2693	1/2081	5289471	468	1/11302
Total	18832693	9198	1/2047	18956221	1638	1/11572

*: including the cases before 1991. The data from the national network of neonatal screening centers collected by the NCCL.

Table 2. The number of screened neonates, provinces and laboratories

Year	Screened neonates (*n*)		Province	Laboratories	Mean
	PKU	CH	(*n*)	(*n*)	(×1000)
1998	385297	400653	16	18	22
2002	950960	949495	24	46	21
2005	2632419	2511814	28	109	23
2007	5289471	5603451	28	143	39

Table 3. Measurements of quality control in Zhejiang Neonatal Screening Center

Year	Screening (*n*)	Coverage (%)	Disqualified specimen (‰)	Recall rate (%)	Notified day (mean)	Over 21 days (%)
2003	272815	76.79	7.19	94.79	nd	nd
2004	342707	84.19	6.20	92.65	23.50	50.4
2005	410534	86.50	4.90	93.44	21.04	38.4
2006	417049	89.01	1.33	93.91	18.55	26.5
2007	470047	93.02	0.56	95.52	16.81	18.3

nd: no data available.

while other provinces have more than one center, each of them in charge of only the local screening program. Unfortunately, even in those provinces with several testing centers, there are still regions uncovered by the neonatal screening program. The average number of samples tested per year in each center is 39 000. Less than 40 000 samples are tested per year in more than half (54.5%) of the centers, while the largest center measures more than 400 000 samples a year.

Quality control

In China, neonatal screening program is authorized by the local health authorities. At this date, it is difficult to gather data about the quality of the system for the whole country. To investigate the quality of the screening, for example, we explored the data from the Neonatal Screening Center of Zhejiang Province, which is authorized to screen newborns for CH and PKU in the whole province. It is capable of dealing with 400 000 samples each year.

The people involved in neonatal screening include specimen collectors, maternal and child care providers, and officials who have been trained to improve the quality of screening. The screening rate increased from 76.79% in 2003 to 93.02% in 2007 and disqualified blood specimens decreased from 7.19/1000 in 2003 to 0.56/1000 in 2007. Still 5% of (123 neonates in 2007) neonates suspected with CH or PKU did not return for confirmatory measurement. Screening time shortened and the mean days for reporting shortened from 23.5 days in 2004 to 16.8 days in 2007. Although most of the neonates with CH or PKU were confirmed and treatment was initiated within a month after birth, 18.3% of them were notified and treated over 21 days after birth (Table 3).

Discussion

Neonatal screening in China has been popularized in recent years because of the improvement of quality control in data collection and the better understanding of the benefits of early screening and timely treatment. Based on our data, it was estimated that about 9000 newborns are diagnosed with CH and 1700 newborns with PKU in China every year. The increased prevalence of CH is probably due to the more sensitive technical methods, lower cut-off value, and including more neonates born in the western China in recent years.[4,5] Early identification and timely treatment of these newborns are critical to improve their quality of life.

The number of newborns screened annually came to 5 million in 2007. However, this accounts for only 25% of the 20 million live births officially reported in China in the same year. Despite the country-wide neonatal screening program, the coverage varies in different regions.[6] High screening rates are only seen in a small number of economically developed regions, such as Shanghai (97%) and Zhejiang (93.02%).[7] In some provinces, the rates are below the reported average rate, for instance, 5.93% in Henan.[8] Screening has not even been introduced in Tibet. These data show that neonatal screening is still not available for the majority of newborns in China. Therefore, priority should be given to neonatal screening in provinces of western China and in provinces with low screening rates.

Screening approach varies in different regions due to different socioeconomic status. Multi-centralized screening approach with multi-centers in charge of the local neonatal screening requires more investment in laboratory equipments and staffing, compared with the centralized provincial screening approach. The quality of multi-centralized screening is seriously affected by technical and medical limitations as well as difficulty in quality control across different laboratories and regions. Many screening centers in China have less than 40 000 newborns screened per year with too low capacity for a large laboratory. It is probably more efficient to send the blood sample to the nearest large testing center and then give the results back to the local units rather than having many small local laboratories testing samples. It is of critical importance to build a provincial or national network to include the newborns in those regions not covered by the neonatal screening, so as to ensure the possibility of early detection of CH or PKU cases.

Neonatal screening is a multidisciplinary program that requires a close coordination of health administration, screening centers, hospitals, laboratories and parents of the children to ensure high recall rates of suspected cases and timely therapy. Parental compliance is a major issue in screening since some parents still do not understand the necessity to treat and follow up their

little, obviously "health-looking" neonates, and fail to return for further diagnosis or treatment. According to reports from neonatal screening centers, the recall rates of children with suspected disease reached 93.8% in Zhejiang,[9] 85.2% in Beijing,[10] and only 48.9% in Zhanjiang of Guangdong.[11]

Delayed diagnosis may affect mental and physical development for CH and PKU children. In our screening center, most neonates with CH or PKU were diagnosed and treatment was initiated in a month after birth. But in developed countries such as the USA, Germany, and other European countries, neonates should be diagnosed and treatment should be initiated before 21 days after birth, and in some countries even before 15 days.[12,13] Our data in 2007 showed that 18.3% of the newborns with suspected CH or PKU were diagnosed and treatment was initiated over 21 days after birth. To shorten the time to identify cases of CH and PKU, time from specimen collection to laboratory report should be shortened.

Apart from CH and PKU, glucose-6-phosphate dehydrogenase deficiency is screened in Guangdong and Guangxi in south China. In some regions, such as Shanghai, screening for congenital adrenal cortical hyperplasia has been started.[14] Neonatal screening evolves and its spectrum broadens because new technical and analytical methods are available. Internationally, it is performed with sensitive and reliable tandem mass spectrograph for more than 30 inheritable metabolic diseases, including abnormalities in the metabolism of amino acids, fatty acids and organic acids.[15] Screening centers in Shanghai and Zhejiang have started to collect experiences with this new promising screening method.

In conclusion, neonatal screening for CH and PKU in China has been improved in the last 20 years. Many areas still need to be improved, including establishment of an efficient quality control system, an efficient system for recall, initiating treatment and follow-up, and a cost-effective screening model.

Funding: This study was supported by grant from the Ministry of Science and Technology of China (No. 2006BAI05A07).
Ethical approval: This study was approved by the regional committee for medical research ethics.
Competing interest: None declared.
Contributors: Zhan JY proposed the study and wrote the first draft. Qin YF analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. Zhao ZY is the guarantor.

References

1 Geelhoed EA, Lewis B, Hounsome D, O'leary P. Economic evaluation of neonatal screening for phenylketonuria and congenital hypothyroidism. J Paediatr Child Health 2005;41:575-579.
2 Gu XF, Wang JJ, Ye J, Cheng XM. A cost-benefit evaluation of neonatal screening for phenylketonuria and congenital hypothyroidism. Zhonghua Yu Fang Yi Xue Za Zhi 2000;34:147-149.
3 Therrell BL, Johnson A, Williams D. Status of newborn screening programs in the United States. Pediatrics 2006;117: S212-S252.
4 Xu YH, Qin YF, Zhao ZY. Retrospective study on neonatal screening for congenital hypothyroidism and phenylketomuria in China in the past 22 years. Zhonghua Er Ke Za Zhi 2009;47:18-22.
5 Mao HQ, Xu YH, Cao LP, Yang RL, Zhou XL. The relationship between the value of blood thyroid stimulating hormone on filter paper and the detection rate for congenital thyroidism. Zhejiang Yu Fang Yi Xue 2006;18:48.
6 Gu XF, Wang ZG. Screening for phenylketonuria and congenital hypothyroidism in 5.8 million neonates in China. Zhonghua Yu Fang Yi Xue Za Zhi 2004;38:99-102.
7 Tian GL. Neonatal screening in several regions of Shanghai in the past 18 years. Chin Prev Med 2004;5:484-485.
8 Wang J, Wang BZ, Zhang Z, Hu YL, Zhao DH, Su L, et al. Screening and group distribute regularity of congenital hypothyroidism of neonatal in Henan province. Zhonghua Liu Xing Bing Xue Za Zhi 2006;27:825-826.
9 Chen XX, Yang RL, Shi YH, Cao LP, Zhou XL, Mao HQ, et al. Screening for congenital hypothyroidism in neonates of Zhejiang Province during 1999-2004. Zhejiang Da Xue Xue Bao Yi Xue Ban 2005;34:304-307.
10 Zhang YM. Neonatal screening in Beijing in the past 10 years. Chin Primary Health Care 2001;15:39-40.
11 Huo JP, Cai ZY, Hu DB, Cao XY, Chen HW. Neonatal screening in Zhanjiang area in the past 8 years. Chin J Child Health Care 2006;14:526-527.
12 Toublanc JE. Guidelines for neonatal screening programs for congenital hypothyroidism. Working Group for Neonatal Screening in Paediatric Endocrinology of the European Society for Paediatric Endocrinology. Acta Paediatr Suppl 1999;88:13-14.
13 Korada M, Kibirige M, Turner S, Day J, Johnstone H, Cheetham T. The implementation of revised guidelines and the performance of a screening programme for congenital hypothyroidism. J Med Screen 2008;15:5-8.
14 Gu XF, Zhou JD, Ye J. Neonatal screening for congenital adrenal hyperplasia in Shanghai areas. Zhonghua Yu Fang Yi Xue Za Zhi 2002;36:16-18.
15 Levy HL. Newborn screening by tandem mass spectrometry: a new era. Clin Chem 1998;44:2401-2402.

Received February 5, 2009
Accepted after revision March 30, 2009