Expanded screening for neonatal inherited metabolic disorders by tandem mass spectrometry in an eastern Chinese population

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Research Article

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Abstract

Objective

To analyze the newborn screening results, distribution characteristics and incidence rate for inherited metabolic disorders (IMD) by tandem mass spectrometry (MS/MS) in Huai'an.

Methods

Blood samples were collected from 97410 newborns born in Huai'an from June 2018 to December 2021. Amino acids, acylcarnitines, and succinylacetone in the blood were detected by non-derivatized MS/MS. Gene detection and gas chromatography-mass spectrometry (GC-MS) were carried out to diagnose positive neonates. Data were analyzed using descriptive statistics.

Results

From 2018 to 2021, the screening rate of inherited metabolic disorders detected using MS/MS in Huai'an increased from 21.15–99.53%.Twenty-five cases of inherited metabolic disease were diagnosed, and the overall incidence rate was 1/3896. Among them, there were 9 cases of disorders of amino acid metabolism(1/10823), 10 cases of disorders of organic acid metabolism(1/9741), and 6 cases of disorders of fatty acid oxidation(1/16235). The top three diseases with the highest incidence were phenylalanine hydroxylase deficiency(1/12176), methylmalonic acidemia(1/24352), and primary carnitine deficiency (1/24352). Among the 25 children clinically diagnosed with IMD, 84.00% (21 cases) underwent gene diagnosis. Biallelic mutations were identified in 21 children, which were inherited from their parents.

Conclusion

Our study suggests that newborn screening for IMD by tandem mass spectrometry is necessary, which could improve the quality of patient's life and reduce the burden on family and society. More attention should be paid to the early screening, diagnosis and treatment of neonatal genetic metabolic diseases.

1 Introduction

Inherited metabolic disease (IMD) refers to a large class of diseases with abnormal biochemical metabolic markers. It is categorized as single-gene genetic diseases, most of which are autosomal recessive inheritance diseases [1] . Most children with inherited metabolic diseases have non-specific clinical manifestations at birth and are often not identified if screening is not performed during the neonatal period. Without prompt diagnosis and treatment, genetic metabolic diseases will affect the

functions of multiple organs and systems, cause progressive and irreversible damage to the nervous system, and lead to backward physical and mental development and even death. The disease will severely affects the life quality of the diseased children and brings a heavy burden to the family and society[2].

In recent years, the widespread application of tandem mass spectrometry (MS/MS) technology and gas chromatography-mass spectrometry (GC-MS) technology in clinical practice has greatly promoted the development of screening, diagnosis and treatment of genetic metabolic diseases in China[3]. In this study, we showed the result of 97,410 newborns screened for IMD in Huai'an Newborn Disease Screening Center where we identified 25 IMD cases using tandem mass spectrometry.

2 Materials And Methods

2.1 Study design and subject characteristics

Huai'an Newborn Disease Screening Center is located in Huai'an maternal and child health care center. 97410 of children included in this study were born and recruited at Huai'an city from June 2018 to December 2021 under the principle of voluntary. This study has been approved by the Ethics Committee of Huai'an Maternal and Child Health Hospital (Review No. 2017048) and the informed consent was obtained from the parents/legal guardian. Subject characteristics are shown in Table 1.

2.2 Sample collection

The heel blood was collected from the subjects and 11 types of amino acids, 31 acylcarnitine profiles and 1 succinylacetone concentrations were assessed as the marker of 27 genetic metabolic diseases using non-derivatized MS/MS technology at Huai'an Newborn Disease Screening Center. Within 48 hours-7 days after birth and after full lactation, the heel blood was collected by the blood collection personnel of the delivery institution, and was dripped on filter paper (ScheicherandandSchuell903#) to make blood films. The diameter of each blood spot was not less than 8mm. Dried blood spot(DBS) samples were delivered by cold-chain transportation to the NBS center of Huai'an Maternal and Child Health Hospital within 5 days.

2.3 Instruments, equipment and reagents

The instruments used in MS/MS genetic metabolic disease screening experiment are: Puncher 9 automatic drilling instrument made by PerkinElmer company in Finland; single-channel and 8-channel quantitative sampler and suction pump made by Eppendorf company in Germany; 10ml and 50ml glass pipette; Hangzhou Ausheng MB100-4A incubation oscillator; Shumei KQ-100E ultrasonic cleaner; nitrogen and argon gas; TQ-D ultra-high-performance liquid chromatography-tandem mass spectrometer from Waters company in the USA. PerkinElmer's non-derivative kit was used for the determination of a variety of amino acids, carnitine and succinylacetone.

2.4 Laboratory testing

Filter paper with a diameter of 3.2 mm was taken at the blood spot from the blood films by the automatic punching instrument and placed in a 96-well U-shaped reaction plate. The blood was pretreated using a non-derivatization method by adding100μl/well of pretreat solution containing pre-prepared extract and internal standard. The plate was sealed with a transparent film and placed in a 45 ℃ constant temperature oscillator to oscillate for 45 minutes. A low and high concentration standard was provided in the kit and included in each measuring plate to ensure the accuracy of detection. After cooling to room temperature, 90μl of supernatantwas transferred to a 96-well V-shaped measuring plate for MS/MS measurement.

2.5 Instrument parameter setting

The tandem mass spectrometer uses electrospray positive ion scanning and multi-reaction monitoring mode to collect data. The injection volume of each sample was 20 μl and the determination time was 3min. MasslynxV4.1 software was used to process data. The ionization voltage was 3.5kV and the temperature of dissolvent gas was 350℃.

2.6 Result judgment and follow-up

The normal range of metabolite concentration and the related ratio was established by percentile combined with the receiver operating characteristic (ROC) curve. Clinicians interpret primary screening as positive when the detection index of tandem mass spectrometry exceeds or is lower than the normal value. The blood was re-collected immediately from the positive subjects identified in primary screening and a second tandem mass spectrometry analysis was performed. The dropout subjects who did not get blood re-collected were recorded (and excluded in the subsequent analysis). Subjects who are identified as positive in both primary and secondary screening were referred to confirmatory tests.

3 Results

3.1 Screening of MS/MS genetic metabolic diseases

From 2018 to 2021, the screening rate of MS/MS genetic metabolic diseases in Huai’an area increased annually, from 21.15–99.53%, and the recall rate of positive cases also showed an annual increase, from 93.10–98.51% (Table 1).

Table 1
Screening forgenetic metabolic diseases using MS/MS in Huai'an area

Year	Deliverymechanism The number of live births (n)	Number of people screened (n)	Screeningrate(%)	Positive number of screening (n)	Number of recalls(n)	Recall rate(%)
2018	45333	9589	21.15%	29	27	93.10%
2019	40231	29622	73.63%	74	71	95.95%
2020	32647	30830	94.43%	84	82	97.62%
2021	27498	27369	99.53%	67	66	98.51%
Total	145709	97410	66.85%	254	246	96.85%

3.2 Distribution of disease spectrum in children with genetic and metabolic diseases

A total of 97410 newborns were screened in Huai'an area, and 25 cases of 11 kinds of genetic metabolic diseases were diagnosed. Among them, there were 9 cases of two kinds of amino acid metabolic diseases, 10 cases of six kinds of organic acid metabolic diseases, and 6 cases of three kinds of fatty acid metabolic diseases. In addition, there were 4 cases of maternal carnitine deficiency. The three most prevalent diseases were phenylalanine hydroxylase deficiency (1/ 12176), methylmalonic acidemia (1/24352) and primary carnitine deficiency (1/ 24352) (Table 2).

Table 2
Disease spectrum distribution of 25 cases of genetic metabolic diseases identified in 97410 newborns

Disease name	Number of confirmed cases	Morbidity	Constituent ratio (%)
Amino acid metabolic disease	9	1:10823	36.00
Phenylalanine hydroxylase deficiency	8	1:12176	32.00
Hypermethioninemia	1	1:97410	4.00
Organic acid metabolic disease	10	1:9741	40.00
Propionic acidemia	1	1:97410	4.00
Methylmalonic acidemia	4	1:24352	16.00
Glutaric acidemia type I	2	1:48705	8.00
3- methylcrotonyl-CoA carboxylase deficiency	1	1:97410	4.00
Isobutyrylglycinuria	1	1:97410	4.00
beta-ketothiolase deficiency	1	1:97410	4.00
Fatty acid metabolic disease	6	1:16235	24.00
primary carnitine deficiency	4	1:24352	16.00
Short-chain acyl-coenzyme A dehydrogenase deficiency	1	1:97410	4.00
Medium-chain acyl-coenzyme A dehydrogenase deficiency	1	1:97410	4.00

3.3 The results of MS/MS in 25 children with genetic metabolic diseases

The results of MS/MS primary screening and secondary recall examination of 25 children with genetic and metabolic diseases exhibited abnormal disease characteristic indexes and corresponding index ratioswas shown in**Table 3**.

Table 3
Results of MS/MS detection in children with genetic metabolic diseases (μ mol/L)

Disease name	N	MS/MS characteristic anomaly index	reference value	Readouts in primary screening[X(min ~ max)]	Readout in secondary screening and reviewing[X(min ~ max)]
Phenylalanine hydroxylase deficiency	8	Phe	25.00 ~ 90.00	629.53(109.06 ~ 1870.4)	825.52(147.37 ~ 2723.03)
		Phe/Tyr	0.2 ~ 1.56	10.29(1.42 ~ 39.74)	10.2(1.17 ~ 40.99)
Hypermethioninemia	1	Met	7.50 ~ 40.00	81.88	239.36
		Met/ Phe	0.15 ~ 0.77	1.8	7.24
* Propionic acidemia	1	C3	0.4 ~ 3.90	14.39	/
		C3/C2	0.04 ~ 0.24	1.31	/
		C3/C0	0.02 ~ 0.18	1.24	/
Methylmalonic acidemia	4	C3	0.4 ~ 3.90	10.04(4.16 ~ 15.41)	4.33(2.86 ~ 6.31)
		C3/C2	0.04 ~ 0.24	0.70(0.42 ~ 1.08)	0.75(0.39 ~ 0.96)
		C3/C0	0.02 ~ 0.18	0.43(0.23 ~ 0.78)	0.23(0.14 ~ 0.4)
Glutaric acidemia type	2	C5DC + C6OH	0.04 ~ 0.20	2.47(2.31 ~ 2.62)	1.38(0.98 ~ 1.78)
		C5DC + C6OH/ C8	0.6 ~ 4.5	55.85(46.2 ~ 65.5)	69(49 ~ 89)
		C5DC + C6OH/ C4DC + C5OH	0.18 ~ 1.1	9.86(9.24 ~ 10.48)	6.10(4.45 ~ 7.74)
3- methylcrotonyl-CoA carboxylase deficiency	1	C4DC + C5OH	0.08 ~ 0.48	9.43	10.24
		C4DC + C5OH/C0	0.00 ~ 0.03	2.97	4.15

Phe: (phenylalanine; Tyr: (tyrosine);Met methionine C3 propionylcarnitine C2 acetylcarnitine C0 free carnitine C5DC + C6OH (glutarylcarnitine C4DC + C5OH methylmalonyl/3 -hydroxy-isovalerylcarnitine

Disease name	N	MS/MS characteristic anomaly index	reference value	Readouts in primary screening[X(min ~ max)]	Readout in secondary screening and reviewing[X(min ~ max)]
		C4DC + C5OH/C8	0.9 ~ 13	471.5	1024
beta-ketothiolase deficiency		C4DC + C5OH	0.08 ~ 0.48	1.1	1.02
		C3DC + C4OH	0.02 ~ 0.32	0.66	0.25
		C5:1	0.00 ~ 0.02	0.38	0.34
primary carnitine deficiency	4	C0	9.00 ~ 49.00	7.61(6.15 ~ 8.91)	5.25(3.03 ~ 7.41)
Maternal carnitine deficiency	4	C0	9.00 ~ 49.00	4.09(3.02 ~ 6.33)	5.40(2.51 ~ 11.44)
Short chain acyl-coenzyme A dehydrogenase deficiency	1	C4	0.1 ~ 0.48	0.8	1.1
		C4/C2	0.00 ~ 0.05	0.06	0.13
		C4/C3	0.05 ~ 0.4	1.11	1.59
Medium-chain acyl-coenzyme A dehydrogenase deficiency	1	C8	0.01 ~ 0.15	0.45	0.33
		C8/C2	0.00 ~ 0.01	0.04	0.04
		C8/C10	0.4 ~ 1.5	3.0	4.13
Isobutyrylglycinuria	1	C4	0.10 ~ 0.48	1.52	1.9
		C4/C3	0.05 ~ 0.4	1.77	2.75
		C4/C8	1.21 ~ 10.67	38.0	31.67
Phe: (phenylalanine; Tyr: (tyrosine);Met methionine C3 propionylcarnitine C2 acetylcarnitine C0 free carnitine C5DC + C6OH (glutarylcarnitine C4DC + C5OH methylmalonyl/3 -hydroxy-isovalerylcarnitine					

C8: (octanoylcarnitine);C3DC + C4OH malonylcarnitine C4 butyrylcarnitine C10 decanoylcarnitine ;All ratios have no units.

*No data from secondary screening is available as propioninemia is a fatal disease and all subjects died before secondary screening”

3.4 Gene diagnosis of 25 children with genetic metabolic diseases

Among the 25 children clinically diagnosed with genetic metabolic diseases, 21 were diagnosed by genetic diagnosis. The rate of genetic diagnosis in all diagnosis methods was 84.00%. The parents of 4 children refused to do genetic testing (1 case of phenylketonuria, 1 case of isobutyrylglycine urinuria, 2 cases of primary carnitine deficiency). Biallelic mutations of the gene Phenylalanine Hydroxylase (PAH) were found in 7 children with phenylalanine hydroxylase deficiency, which came from their parents (one of them also found a heterozygous mutation at one site of the gene 6-Pyruvoyltetrahydropterin Synthase (PTS), which was inherited from the mother), and biallelic mutations of Methionine Adenosyltransferase 1A (MAT1A) gene were also found in another case of hypermethioninemia, which came from the parents. Biallelic mutations were found in 9 children with organic acid metabolic disease (1 case of methylmalonic acidemia not only detected a compound heterozygous mutation of Metabolism Of Cobalamin Associated C (MMACHC) gene but also carried a heterozygous mutation of methylmalonyl-CoA Mutase (MUT) gene and 1 heterozygous mutation of Transcobalamin Receptor (CD320) gene, respectively from the parents). Biallelic mutations were found in 4 children with fatty acid metabolic disease, which were from their parents.

4 Discussion

There are many kinds of genetic metabolic diseases, and the total number of diagnoses may exceed thousands. Although the prevalence rate of a certain type of IMD is low with the incidence rate from ten in thousands to hundreds in thousands, if all genetic metabolic diseases are added together, the overall prevalence rate will be higher than the above data[1].

4.1 Progress in the screening of Neonatal MS/MS genetic Metabolic Diseases

MS/MS technology has been used in the screening of neonatal genetic metabolic diseases since the early 1990s. By detecting the levels of multiple amino acids, free carnitine and acylcarnitine at the same time to screen the genetic metabolic diseases of oxidative disorders of amino acids, organic acids and fatty acids, the transformation from "one disease detected in one test" to "multiple diseases detected in one test" has been accomplished. In recent years, the National Clinical Laboratory Center has formulated and issued relevant consensus to ensure the standardization of the operation process from sample collection, laboratory testing, report interpretation, recall, diagnosis to treatment, as well as to the entire chain of follow-up management to ensure the quality of laboratory screening work in new screening centers across the country[5–7]. MS/MS technology is currently widely used in the screening of neonatal genetic metabolic disease screening due to its relatively low screening cost, high sensitivity (99%) and

specificity (> 99.8%) [8]. Screening for genetic metabolic diseases of MS/MS newborns has been carried out in Huai'an since 2018, and the screening rate has increased year by year, from 21.15–99.53%. The recall rate of positive cases has also increased annually, from 88.64–97.96%. Our data fully showed that with the collaborative efforts of screening personnel, the screening of genetic metabolic diseases of newborns using MS/MS in Huai'an area is very effective, which has made significant contributions to the diagnosis, treatment and prevention of genetic metabolic diseases in the area.

4.2 Overall incidence and diagnosis of genetic metabolic diseases screened by MS/MS technique

At the moment, the majority of genetic metabolic diseases diagnosed using MS/MS screening technology at home and abroad are organic acids, amino acids and fatty acid metabolic diseases. There are great differences in neonatal genetic metabolic diseases and incidence reported in different countries or regions. About 40 kinds of diseases are screened in Italy, and the incidence rate is about 1 in 6041 [9]; there are 13 kinds of diseases screened in Spain with an incidence rate of about 1 in 2577 [10]. There are 24, 18 and 24 screening diseases in Germany, Japan and Korea, and the incidence rate is 1/2200, 1/8557 and 1/13205 respectively [11].Currently, there are more than 27–40 kinds of MS/MS genetic metabolic diseases that can be screened by the neonatal disease screening centers in various regions of China. In this study, a total of 97410 newborns were screened in Huai'an area, and 25 cases of genetic metabolic diseases were clinically diagnosed. The incidence rate is 1/3896, which is close to the average incidence rate of China (3.13/10,000) [12] and the Guangzhou area in Guangdong Province (1/3444), Shanghai area (1/3483) and Beijing area (1/3666) [13–15].Of note, the incidence rate in Huai’an area is significantly lower than that in Quanzhou area in Fujian Province(1/2826) [16], Jining area in Shandong Province (1/1941) [17],as well as Nanjing (1/2835) and Suzhou in Jiangsu Province (1/2910) [2,18].In addition, we found that the top three genetic metabolic diseases with the highest incidence in Huai’an area are phenylalanine hydroxylase deficiency, methylmalonic acidemia and primary carnitine deficiency, which was consistent with the domestic research report [12].

The 25 children in this study who were clinically diagnosed with genetic metabolic diseases were abnormal in different degrees and were still being identified by MS/MS, indicating that MS/MS is a reliable approach and plays an important role in the early screening and diagnosis of neonatal genetic metabolic diseases. Among the 25 children, only 21 cases were diagnosed by genetic analysis, as 4 cases dropped out due to refusing genetic testing. Thus, the rate of gene diagnosis was 84.00% which is expected to be improved. Gene detection can help parents to decide whether to give birth to a child with genetic metabolic diseases. Gene detection can help parents discover the gene mutations of children with genetic metabolic diseases and their parents. In addition, the gene test results can also help doctors to design individualized clinical treatments for diseased children. Therefore, we believe that genetic diagnosis should be performed for all children with genetic and metabolic diseases.

4.3 Prevalence and diagnosis of three kinds of genetic metabolic diseases

There are great differences in the prevalence of organic acids, amino acids and fatty acids among different countries, regions and races.

4.3.1 Amino acid metabolic disease

A study that included 246 cases of neonatal disease screening centers in China [19] showed that the average prevalence rate of amino acid metabolic disease was 17.14 / 100000, which was similar to that in Austria (1/4980)[20] and Portugal (1/5856) [21]. The prevalence rate of amino acid metabolic disease in Carolina in the United States was lower(1/25000)[22], and the prevalence in Europe (1/10000) [23] is in the middle. A total of 9 cases of two kinds of amino acid metabolic diseases were detected in Huai'an area. the prevalence rate is1/10823, which is similar to that of Zhejiang Province(1/11349)[24], Taiwan(1/11236)[25] and Europe but significantly lower than the national average level [19]. In this study, 8 cases of phenylalanine hydroxylase deficiency were diagnosed, and the prevalence rateis1/12176, which counts for the majority of amino acid metabolic diseases in this area. The prevalence was consistent with the China domestic research report which showed that the prevalence rate of phenylalanine hydroxylase deficiency in China is 1/(3000 ~ 16000), which is higher in the north than in the south [26] . The prevalence rates of phenylalanine hydroxylase deficiency in the Guangzhou area of Guangdong Province [14], Zhejiang Province [24], Jining area of Shandong Province [17] and Xinxiang area of Henan Province [27]were 1/30235, 1/22400, 1/9183 and 1/3341, respectively. The analysis of this data shows that the prevalence rate in Huai'an area is in line with the characteristics of "high in the north and low in the South". The lowest and highest values of serum phenylalanine and phenylalanine/tyrosine ratio in 8 patients with phenylalanine hydroxylase deficiency detected by MS/MS were 109.06 μ mol / L and 1870.4 μ mol / L, respectively. There were significant differences in serum phenylalanine concentration and ratio among different cases, which were related to the residual degree of phenylalanine hydroxylase activity. Among the 9 cases of the amino acid metabolic disease diagnosed clinically, one case of phenylalanine hydroxylase deficiency refused to do genetic testing. We found two inherited pathogenic mutations in PAH gene in7 cases of phenylalanine hydroxylase deficiency. Moreover, one of the phenylalanine hydroxylase deficiency subjects also has a heterozygous variation at a site of PTS gene, inherited from his mother. In addition, two mutations in MAT1A gene were found in 1 case of hypermethionemia, which was inherited from both parents.

4.3.2 Organic acid metabolic diseases

A total of 10 cases of six types of organic acid metabolic diseases were detected in this study. The overall incidence rate of six kinds of organic acid metabolic diseases is1/9741, which is slightly lower than the national average (12.39 / 100000) [19], Jining in Shandong Province(1/3956)[17] and Xinxiang in Henan Province 1/5568 [27], but higher than Guangzhou in Guangdong Province 1/16007 [13] and Zhejiang Province 1/20200 [28]. The prevalence of organic aciduria in Austria was1/13244, the most prevalent subtypes were 3-methylcrotonyl-CoA dehydrogenase deficiency (1/34583 , glutaric acidemia type I 1/69165 and propionemia 1/77811 [20]. The prevalence of organic acid metabolic disease in

Carolina was1/16300. The most common diseases were 3-methylcrotonyl-CoA dehydrogenase deficiency (1/36000), methylmalonic acidemia(1/90000) and isovalerate acidemia (1/130000)[22]. Together, the above studies showed that there are significant differences in the disease spectrum of organic acid metabolic diseases in different countries. was Additionally, weidentified methylmalonic acidemia (1/24352) as the organic acid metabolism disease with the highest incidence which was comparable with the conclusion of multicenter research in China [19]. Among the 9 cases of organic acid metabolic disease that received genetic detection, two pathogenic mutations were found. In one case of the methylmalonic acidemia cases, we found not only a compound heterozygous mutation of MMACHC gene, but also a heterozygous mutation of one MUT gene and one heterozygous mutation of CD320 gene, respectively.

4.3.3 Fatty acid metabolism diseases

In this study, a total of 6 cases of three types of fatty acid metabolism diseases were detected in Huai'an area. The prevalence rate was 1/16235, which is significantly lower compared to the national average level in China (9.16 / 100000) [19]. Compared to other areas and countries, the prevalence of fatty acid metabolism diseases in Huai'an area is similar to that in Jining, Shandong Province (1/15125)[17] and Zhejiang Province (1/15382) [29], significantly lower than in Guangzhou area of Guangdong Province 1/6977 [13], Quanzhou area of Fujian Province (1/7440) [16], Nanjing of Jiangsu Province (1/11718)[2], Suzhou area (1/10041) [18] and Shanxi Province (1/9015) [30], but higher than that of Japan (1/30000) and Korea (1/111000) [11]. Four cases of primary carnitine deficiency were detected, the prevalence rate of primary carnitine deficiency is1/24352 in this study, making it the most common disease of the 3 types of fatty acid metabolic diseases. This finding is consistent with the domestic research report [12,19] . One case of short-chain and one case of medium chain acyl CoA dehydrogenase deficiency was diagnosed, and the prevalence rate for them is 1/97410.Intriguingly, 4 cases of maternal carnitine deficiency were detected. and the level of free carnitine in the corresponding child was lower than that in children with primary carnitine deficiency, which was supported by the results of Yiming Lin et. al. [31]Yiming Lin et. al. showed…..A possible explanation is that the free carnitine in the mother was transported to the fetus through the placenta [32]. Among the 4 children with fatty acid metabolic disease who had the genetic detection, two pathogenic mutation sites were found and the mutations were inherited from the parents.

4.4 Conclusion

Neonatal MS/MS genetic metabolic disease screening has become the mainstream screening method in the field of neonatal disease screening in the international community, which has greatly expanded the ability and capacity of disease screening in the medical care system. Since 2018, MS/MS neonatal genetic metabolic disease screening has been carried out in Huai'an area, and the work has achieved remarkable results. The screening rate and recall rate have increased year by year and have reached the ideal level. Among 97410 newborns in this area, 25 cases of 11 kinds of genetic metabolic diseases were detected. Given that the incidence of overall IMDs and single diseases in Huai'an area are both

comparable to the national average, we believe that the neonatal MS/MS genetic metabolic disease screening system in Huai’an is successfully established. The diseased children were identified and most of them are diagnosed with common genetic metabolic diseases, which are preventable and treatable. The genetic diagnosis rate of children with genetic metabolic diseases in Huai'an area (84.00%) is low. Therefore, we should pay attention to the screening, diagnosis and treatment of neonatal genetic metabolic diseases, and do early screening, early diagnosis and early treatment to improve the quality of patient's life and reduce the burden on family and society. Based on the existing MS/MS genetic metabolic disease screening, further exploring the suitable and optimized screening techniques in this region is needed to reduce the incidence of birth defects, the disability of children with genetic metabolic diseases, and improve the quality of the population, provide a strong guarantee for the implementation of the two-child and three-child policy in our country.

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Huai'an Maternal and Child Health Hospital (Review No. 2017048) and the informed consent was obtained from the parents/legal guardian. All experiments were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are not public, but are available from the corresponding author on reasonable request.

Competing interests

I declare that the authors have no competing interests as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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Authors' contributions

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