

# *Analysis of the Influence of Clinical Symptoms on the Results of Tandem Mass Spectrometry*

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**Keywords:** Newborn, Tandem mass spectrometry, Screening positive rate, Influencing factors

**Abstract:** Objective To collect the basic clinical symptom data of NICU from 2018 to 2019, and to explore the influence of clinical symptoms on the positive results of neonatal tandem mass spectrometry screening. Methods After the informed consent of the parents of the newborn, the basic symptoms of the newborn were collected by the self-administered questionnaire method, sorted out by excel2013, and analyzed by spss19.0. Results Among 720 NICU newborns, 134 were positive. The positive rate of screening was 18.61%. There were 5 kinds of confirmed diseases, 8 cases in total, the rate of diagnosis was 1.11%. 447 male newborns were screened, the positive rate was 19.24%; 273 female newborns were screened, the positive rate was 17.58%. There was no significant difference between the male and female groups by chi square test. In this study, 412 newborns were screened at 2-7 days, with a positive rate of 20.63%; 236 newborns at 8-28 days, with a positive rate of 17.80%; 72 newborns at more than 28 days, with a positive rate of 9.72%. There was no significant difference between groups by chi square test. In this study, 64 normal newborns were screened, the positive rate was 23.44%; 256 premature infants were screened, the positive rate was 7.81%. The difference between the preterm and the normal group was statistically significant by chi square test. There was no significant difference between other factors group and normal control group. Conclusion The positive rate of tandem mass spectrometry screening of neonates with clinical symptoms in NICU is significantly higher than that of normal newborns. Gender and three months have little influence on the results of tandem mass spectrometry, and preterm infants have influence on the results of tandem mass spectrometry. Special attention should be paid to the results of the screening of preterm infants.

## 1. Introduction

Tandem mass spectrometry (MS / MS) is a technology of high sensitivity, high specificity, high selectivity and fast detection, which can detect dozens of metabolites in a sample within 2 minutes, that is, detect dozens of IMD at the same time, and achieve the requirement of “one experiment to detect multiple diseases”. In recent years, tandem mass spectrometry technology has been applied to neonatal disease screening, which has increased the disease types of neonatal disease screening, expanded the scope of screening, and opened up the way for neonatal disease screening. However,

because the sensitivity and specificity of the screening experiment have not been unified, the positive rate of the screening in different regions is quite different, and the positive rate of the initial screening is also high. It has been reported that there are many factors affecting the screening experiment, such as the storage conditions of dry blood spots, laboratory temperature and humidity, etc., but there are few studies on the influence of the newborn with basic diseases or clinical symptoms on the results of tandem mass spectrometry screening<sup>[1]</sup>. In this study, we collected the basic clinical symptoms of newborn with clinical symptoms in our hospital from 2018 to 2019 to explore the clinical effects. The influence of bed symptoms on the positive results of neonatal screening by tandem mass spectrometry lays a theoretical foundation for improving the screening experiments by tandem mass spectrometry and enhancing the specificity of screening experiments in this region.

## **2. Objects and Methods**

### **2.1 Research Object**

The subjects of the study were 720 newborns hospitalized in NICU from 2018 to 2019. The basic clinical symptoms of newborns (including premature delivery, hypoglycemia, fever, hyaline membrane disease, pneumonia, diarrhea, hyperbilirubinemia, convulsion, wet lung, feeding difficulties, asphyxia and other diseases) were collected (Disease) and the results of tandem mass spectrometry screening, to analyze the influence of clinical symptoms on the positive rate of tandem mass spectrometry screening.

### **2.2 Research Method**

After the informed consent of the parents of the newborn, the basic symptoms of the newborn were collected by the self-administered questionnaire method, sorted out by excel2013, and analyzed by spss19.0. The chi square test of four grid table and R \* C contingency table or Fisher exact probability method were used for the comparison between groups, with  $\alpha = 0.05$  as the test level.

### **2.3 Quality Control**

The questionnaire was designed independently by experts in related fields, and was carried out after preliminary investigation in NICU. All investigators are trained in research, and special personnel are responsible for data entry and sorting, and the expert group is responsible for regular supervision of the investigation. The tandem mass spectrometry screening laboratory passed the quality assessment of the clinical test center of the Ministry of health, and the test results were reliable.

## **3. Results**

### **3.1 General Situation of Tandem Mass Spectrometry Screening**

In this study, 720 cases of NICU newborn were screened, 134 cases were positive, the positive rate was 18.61%, 5 kinds of IMD were diagnosed, 8 cases in total, the rate was 1.11%. There are five kinds of genetic metabolic diseases including amino acid metabolic disease, fatty acid metabolic disease and organic acid metabolic disease. Three cases of PKU were diagnosed, with a diagnosis rate of 0.42%; one case of MMA, with a diagnosis rate of 0.14%; one case of IVA, with a

diagnosis rate of 0.14%; two cases of PCD, with a diagnosis rate of 0.28%; one case of MDH, with a diagnosis rate of 0.14%.

### 3.2 Tandem Mass Spectrometry Screening Results

The MS / MS screening results of MMA showed that the specific indexes were C3, C3 / C2, C5, c5dc, C5 / C2, C0, C0 / (C16 + C18), C8, C10, C12, and Phe, Phe / Tyr.

### 3.3 The Influence of Sex and Birth Time of Newborn on the Positive Rate of Tandem Mass Spectrometry

In this study, 447 male newborns were screened, 86 were positive, the positive rate was 19.24%; 273 female newborns were screened, 48 were positive, the positive rate was 17.58%. There was no significant difference between the male and female groups by chi square test ( $P > 0.05$ ). In this study, 412 newborns from 2 to 7 days were screened, 85 were positive, the positive rate was 20.63%; 236 newborns from 8 to 28 days were screened, 42 were positive, the positive rate was 17.80%; 72 newborns from more than 28 days were screened, 7 were positive, the positive rate was 9.72%. There was no significant difference between the groups by chi square test ( $P > 0.05$ ).

### 3.4 The Effect of Clinical Symptoms of Newborn on the Results of Tandem Mass Spectrometry

According to the purpose of the study, the normal newborns were taken as the control group and compared with the corresponding newborns with clinical symptoms. The results showed that 64 normal newborns were screened, 15 were positive, the positive rate was 23.44%; 256 premature infants were screened, 20 were positive, the positive rate was 7.81%. The difference was statistically significant between the preterm group and the normal control group by chi square test,  $P < 0.05$ . There was no significant difference between the other groups and the normal control group ( $P > 0.05$ ).

## 4. Discussion

### 4.1 General Situation of Tandem Mass Spectrometry Screening

In our province, the level of prenatal screening and diagnosis technology is not mature, and neonatal screening technology started late, especially IMD screening, which was first carried out in 2015. In this study, 720 newborns with NICU in our hospital were screened. The positive rate of screening was 18.61%, 8 cases were diagnosed with diseases, and the diagnosis rate was 1.11%. Compared with the results of genetic and metabolic disease screening in Zhengzhou and Ningbo, the positive rate of screening was significantly higher. In the 2011 IMD screening study in Hebei Province, the screening objects were high-risk IMD newborns, and the positive rate (11.6%) was significantly lower than this study. Compared with Xining study, the positive rate of screening is also higher. The main reason is that the subjects in Hebei Province and Xining city may be normal newborns. Most of this study has clinical manifestations, which may affect the level of amino acids and acyl carnitine in the blood, leading to the increase of the positive rate of screening. 8 cases of IMD were confirmed in this study, including 3 cases of PKU, 1 case of MMA, 1 case of IVA, 2 cases of PCD and 1 case of MCAD. As early as 2004, Gu xuefan and other researchers reported the application of MS / MS technology to screen IMD. Among 104 suspected positive high-risk infants, 10 IMD patients were confirmed. The confirmed diseases were tyrosinemia, homocystinemia, oat,

MMA, PA, hmgcl, MCAD and CACT. Yuan's research in Dongguan showed that in 1206 cases of IMD screening, 12 cases of CTLn, 4 cases of citrin deficiency, 4 cases of PA, 2 cases of IVA, 3 cases of hyperargininomy, 6 cases of fatty acid metabolism abnormality, 2 cases of multiple amino acid metabolism abnormality, 2 cases of urea cycle disorder, 1 case of homocysteinuria, 5 cases of hypermethioninemia and 5 cases of PKU were screened. Compared with this study, although there are fewer cases screened in this study, there are more types of metabolic diseases screened out, which indicates that our province is a high incidence area of metabolic diseases, and the screening rate is high, so we should pay attention to the prevention of metabolic diseases<sup>[2-3]</sup>.

#### **4.2 Analysis of Screening Results of Tandem Mass Spectrometry**

According to relevant research, the incidence of PKU in Gansu Province ranks first in China, which is five times higher than the national average level. Before the introduction of MS / MS technology in 2015, the main screening diseases of IMD in Gansu Province were PKU. At present, MS / MS technology can not only complete the screening of PKU, but also achieve the screening of 26 kinds of IMD, including amino acid metabolism disorder, organic acid metabolism disorder and fatty acid metabolism disorder. Besides PKU, there are MMA, IVA, PCD and MCAD in Gansu IMD. Among them, the prevalence of MMA varies greatly in different countries. According to relevant research, the prevalence of MMA in the United States is 13 / 100000. Through IMD research in different regions, it is found that MMA is the most common organic acid metabolic disorder in China. In addition to MMA, the screening rate of other IMD found in this study was higher than that in other regions<sup>[4-5]</sup>.

#### **4.3 The Influence of Sex and Birth Time on the Results of Tandem Mass Spectrometry**

According to this study, the positive rate of IMD was 19.24% in male newborn and 17.58% in female newborn. There was no significant difference between male and female groups. IMD is a kind of disease controlled by genetic material change or pathogenic gene, most of which are single gene genetic diseases, also known as Mendelian genetic diseases, in which autosomal recessive inheritance accounts for the vast majority, and very few of them are autosomal dominant inheritance, X-linked concomitant inheritance and linear inheritance. Because X-chromosome genetic diseases related to gender are not detected in this study, so Most of the occurrence of IMD was not related to gender. In this study, the positive rate of neonatal screening was 20.63% in 2-7 days, 17.80% in 8-28 days and 9.72% in more than 28 days. There was no significant difference between groups by chi square test. The possible reason is that the genetic metabolic disease is caused by the abnormal metabolism of amino acid and acyl carnitine caused by the change of genetic factors, which is less affected by environmental factors. After birth, the newborns all advocate breastfeeding, which is less affected by the environment and diet. However, some studies have shown that the content of amino acids and acyl carnitine in the blood of newborn will change with the growth of newborn, which may affect the detection results of tandem mass spectrometry, which is inconsistent with the conclusion of this study. The possible reason is that the observation time of this study is relatively short, resulting in errors in time<sup>[6-7]</sup>.

#### **4.4 The Effect of Clinical Symptoms of Newborn on the Results of Tandem Mass Spectrometry**

Preterm infants were born between 28w and 37W with a birth weight of 1000-2499g and immature organs. The results showed that the difference between the preterm delivery group and the normal control group was statistically significant by chi square test. The possible reasons are that

the premature infant's circulatory system development is not perfect, the blood composition is not normal, platelets, red blood cells and hemoglobin decrease rapidly, the liver function development is not perfect, it is easy to have metabolic disorder, and the related IMD detection analytes such as amino acids, acyl carnitine decompose, which brings difficulties to the screening and diagnosis of IMD. According to the results of the study, the positive rate of preterm birth screening is lower than that of normal screening group, which may be consistent with the above speculation. It may also be due to genetic metabolic diseases that lead to premature birth. At present, there is no relevant research to support this result. We need to further explore the research. In order to prevent serious consequences caused by missed screening, special attention should be paid to the test results of preterm delivery. According to this study, there was no significant difference in other clinical manifestations between the newborn and the normal control group. It is possible that the sample size of this study is too small, or the above clinical symptoms have little effect on the detection results of MS, so we need to further study<sup>[8]</sup>.

## 5. Conclusion

This study is the first time to explore the related influencing factors of tandem mass spectrometry screening for genetic metabolic diseases. There are many influencing factors for neonatal genetic metabolic disease screening. According to this study, preterm delivery will cause significant differences in tandem mass spectrometry detection results, and the screening positive rate will be significantly reduced, which brings us great difficulties in screening experiments. Therefore, in the screening laboratory, we should Considering whether it is preterm or not, targeted screening of genetic and metabolic diseases should be carried out for preterm infants to improve the specificity of screening experiments, avoid missed screening, and improve the quality of the birth population.

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