Enhancing Pediatricians Awareness of MSUD Infants Health in China -What Can We Do?

Xin-lin Hou, MD,PhD

Pediatric Department, First Hospital, Peking University, Beijing, China. 100034

with Karen Dolins

The first case of MSUD in China was reported in 1987 and described a girl in Shanghai whose parents were first cousins. Prior to her birth, three of her brothers had previously died of unknown causes. The diagnosis of MSUD was made at Xin Hua hospital, Shanghai Jiao Tong University by a blood test for branched chain amino acids.

No further cases were reported for 8 years, but 46 cases have been reported since 1994 and several papers describing MSUD diagnosis, treatment and prognosis have been published, including one by our hospital in the *European Journal of Medical Genetics* in 2015. Most diagnoses have been made in the Eastern area of China around Beijing and Shanghai. There are almost no cases reported from mid and Western China, where the economy is less developed. We believe that more children have been born with MSUD but have not been diagnosed.

Clinical features of children with MSUD in China are not unique, but the time of diagnosis and treatment is always relatively late. Most patients were admitted to the hospital with neurological symptoms 7 days after birth, including poor feeding, seizures, coma and respiratory failure. Of the 40 cases of neonatal onset, 28 died, 5 had combined developmental lag and epilepsy, and 7 cases were lost to follow up. Among the 7 children who lived for more than 1 month, 1 has died, and 4 were lost to follow up. All of those diagnosed with MSUD who lived for more than one month have mental retardation and epilepsy.

Treatment for MSUD in China remains difficult as the metabolic formula is not available. Although newborn screening has identified a number of cases, the prognosis is poor. One paper reported on newborn screening at Shanghai Xinhua Hospital, which is the transfer center of inborn metabolic disorders for the whole country. They screened 410,000 newborn babies and found 3 cases of MSUD, but did not mention the prognosis. Another article screened 19,000 newborn babies, found 4 cases of MSUD, but the prognoses were all poor.

We comprehensively analyzed 33 patients diagnosed with MSUD. There were 28 cases of classical type, presenting with dystonia, sleepiness, poor response, poor feeding, seizures, retardation, and varying degrees of metabolic acidosis. Of the 33 cases, 10% of them were Vitamin B sensitive（400mg per day）and 5 cases were intermediate type（2 cases were adult, one is 29 years old, the other is 30 years old).

In 2012, one patient was diagnosed with classic MSUD at 18 days of age. He was initially diagnosed with neonatal pneumonia due to vomiting and feeding difficulties, but soon lapsed into a coma. Gene sequencing identified a *BCKDHA* compound heterozygous mutation with a C.740

A>G mutation on one chromosome and on another chromosome IVS6+1G was missing. The family was able to obtain the MSUD formula through contacts outside of the country. Formula was bought in the UK and shipped to Hong Kong, where it was then brought over to China. The child improved, but several weeks after diagnosis and initiation of the diet severe diarrhea and a rash appeared. We researched the literature and determined that the likely cause was a lack of isoleucine and valine. After adding some ordinary formula milk for 5 days, the diarrhea and rash were cured.

At the age of 1 year and 5 months, he experienced a bout of diarrhea and refused formula. He rapidly decompensated, became hypoglycemic and ketoacidotic, and lapsed into a coma. He was treated with hemodialysis and BCAA levels decreased to the normal range.

This case is unique to us as the parents have been able to cover the cost of care including measurement of BCAA levels, which is not covered by health insurance.

The prognosis of children with MSUD in China is poor for the following reasons：

1. Lack of routine screening. Most children were identified after the appearance of clinical symptoms.

2. Delay of 2-4 weeks in obtaining laboratory results. Also, most laboratories can only assess leucine and valine levels, not isoleucine and alloisoleucine.

3. BCAA free formula, isoleucine and valine, and low protein food for MSUD patients is not available..

4. The vast majority of hospitals can not perform liver transplantation.

Our hospital has treated a total of 8 cases of MSUD since 2012. One case was diagnosed with newborn screening and 7 cases were diagnosed with selective screening upon presentation of neurological disorders.. Of these, 6 cases were classic and 1 case was intermediate. In one mother's second pregnancy, we ran amniocentesis and gene analysis and determined that the fetus was heterozygous. This baby was born healthy. This is the first time we have had a successful prenatal diagnosis. We have also succeeded in performing liver transplantation for two girls, whom are still in follow-up.

We wish that in the near future, the government could provide free routine screening to every neonate, BCAAs-free formula, supplementation and health insurance coverage for treatment

. Overall, for MSUD in China, from the government to the pediatrician, the understanding of MSUD is still in the initial stage. We hope that pediatrician's understanding of MSUD can be improved, early diagnosis and early treatment can be implemented, and the metabolic formula essential to survival will be made available in order to improve survival rates and reduce occurrence of neurological disability.