

CASE REPORTS

Tyrosinemia

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Received: November 1, 2012
DOI: 10.14725/dcc.v2n1p7

Accepted: December 2, 2012
URL: <http://dx.doi.org/10.14725/dcc.v2n1p7>

Online Published: March 15, 2015

Abstract

A case of pediatric tyrosinemia in the Third Affiliated Hospital of Inner Mongolia Medical University was collected and analyzed on the basis of diagnosis, physical examination and treatment. Misdiagnosis of tyrosinemia is very common due to the low incidence, rare clinical cases and diagnosis difficulty. So this paper aims to arouse the doctors' awareness of tyrosinemia during clinical practice.

Key Words: Tyrosinemia, Diagnosis, Treatment, Pediatric

1 Medical record

1.1 General information

A 3-month-old female infant was admitted to our hospital on May 18, 2012 for more than two months of skin stained yellow. She was the first and single baby of her mother, was given a natural birth of 38-week after the pregnancy, weighing 2,500 g on her birth, and no other injuries and asphyxia occurred during the delivery. Skin stained yellow appeared the third day after birth, while there was no obvious increasing or reducing of the weight on her, so her parents did not take it seriously. She had been given breastfeeding exclusively, and her weight gained normally. Then a normal dose of hepatitis B vaccination was obtained on the very day of the first month of her birth. However, the symptom of jaundice aggravated ten days prior to her admission as the baby had systemic skin stained yellow with skin color bright yellow. Thus, she was taken to a traditional Chinese medicine clinic for oral administration of Chinese herb medicine in the following three days and stopped taking the medicine thereafter jaundice alleviated. She was brought to our hospital due to sneezing, running nose, milk choking, occasional cough and progressive jaundice 4 days before her admission. In the course of the disease, no symptoms of fever, convulsions, vomiting and diarrhea appeared, she was with

normal excrement and urine, eating and sleeping were normal as well.

1.2 Physical examination

Data on the physical examination revealed her T 36.6°C, P 125 beats/minute, R 28 times/minute, weight 5 kg, poor spirit and reaction, steady breathing, normal development, common complexion, moderate jaundice on the whole body skin, with dark yellow, black hair, no rash, anterior bregma (1.0 cm × 1.0 cm) soft, yellow sclera, pharyngeal congestion, lung breath sounds rough, no rales sounded, heart rate 125 beats/min, showing regularity in the force and rhythm of the heartbeat, no murmur from valves sounded, abdomen soft, liver was 4 cm under the ribs, and spleen was 3 cm under the ribs, both with medium texture, no dull resonance. No limb deformities or abnormalities in neurological examination.

1.3 Auxiliary examination

Blood routine test showed that WBC $4.3-10.99 \times 10^9/L$, hemoglobin 73-129.0 g/L, platelets $93-235.0 \times 10^9/L$, retic-

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ulocyte count 0.012-0.024. Urine and stool routine normal, urine bilirubin positive, urobilinogen positive. Blood biochemistry: K⁺ 2.54-4.90 mmol/L, Na⁺ 132.0-146 mmol/L, Cl⁻ 106.0-114 mmol/L, Ca²⁺ 2.09-2.25 mmol/L, P 1.09-1.35 mmol/L, Mg²⁺ 1.02-0.88 mmol/L, glucose 2.33-6.2 mmol/L. Creatine kinase 52.0-340 U/L, creatine kinase isoenzyme 43.9-324.3 U/L, lactate dehydrogenase 319.0-457 U/L, hydroxybutyrate dehydrogenase 231.0-330 U/L, complement C₃ 0.22, C₄ 0.15. C-reactive protein, lipids, renal function and thyroid function were all normal. Blood gas analysis: PH 7.407, PCO₂ 20.1 mmHg, BE -13.8, HCO₃⁻ -13.1 mmol/L. CMV-IgM was positive in her, but CMV-IgM was negative in her mother. Herpes simplex virus antibodies, rubella virus and toxoplasma virus antibodies were

all negative, four items for infection check and five items for hepatitis B were normal. Hepatitis A, hepatitis C and hepatitis E antibody was negative, blood cholinesterase 2,412-3,905 U/L (reference value: 4,000-12,220 U/L), adenosine deaminase 27.9-55.9 U/L (reference value: 0-15.0 U/L), α-fetoprotein (AFP) 439.1 μg/L, carcinoembryonic antigen 12.6 μg/L. Liver fibrosis: hyaluronic acid 581.3 μg/L (reference value: 0-120 μg/L), laminin 825.8 μg/L (reference value: 0-140 μg/L), III procollagen amino acid peptide 574.3 μg/L (reference value: 0-120 μg/L), IV collagen 565.2 μg/L (reference value: 0-140 μg/L). Dynamic liver function and blood coagulation results were indicated in Table 1.

Table 1: Liver function, blood coagulation dynamic changes after admission

Admission (day)	ALT (U/L)	AST (U/L)	PA (mg/L)	TP (g/L)	ALB (g/L)	TBIL (U/L)	DBIL (μmol/L)	ALP (U/L)	GGT (U/L)	TBA (U/L)	PT (s)	PTA (%)	INR	APT T (s)	FIB (g/L)
2	166	599	8.6	44.2	31.3	329.3	197.5	1013	31	129.1					
4	118	177	11.9	42.1	32.8	307.7	191.8	702	28	115.9	20.9	43	1.67	60.3	0.625
6	158	266		48.6	37.9	292.2	173.1				25.2	33.6	2.02	69.5	0.441
8	202	330				367.7	201.7				32.3	24.2	2.58	98.0	0.582
10		270				459.2	261.1				24.5	34.9	1.96	73.9	0.768
11	260	305	18.3	49.3	34.1	475.5	301.3	385	48	85.1	24.9	34.1	1.99	69.8	0.663
Reference value	0-40	5-40	200-400	60-80	35-55	0-19.6	0-7	39-117	0-57	0-10	12.5	80-120	0.8-1.2	29.0	2-4

Note ALT: alanine aminotransferase; AST: aspartate aminotransferase; PA: prealbumin; TP: total protein; ALB: albumin; TBIL: total bilirubin; DBIL: direct bilirubin; ALP: alkaline phosphatase; GGT: glutamyl endopeptidase; TBA: total bile acids; PT: prothrombin time; PTA: prothrombin activity; INR: international normalized values; APTT: partial thromboplastin time; FIB: fibrinogen.

Abdominal ultrasound examination of three times: The left lobe of the liver was about the size of 3.8-4.8 × 3.6 cm, and the right lobe was 7.3-8.0 cm thick, about 5.3 cm under the ribs. Volume of caudate lobe increased about 4.8 cm × 4.3 cm, low echo. The diameter of the secondary bile duct in liver was about 1 mm. Diameter of portal vein was about 0.6 cm. Gallbladder size was about 2.1-2.5 × 0.8-1.0 cm, with rough walls, clear fluid inside. Diameter of upper section of common bile duct was about 0.2 cm, and the visible segment was clear. Size and shape of the pancreas were normal, normal echo. Spleen was 3.0 cm thick, diameter 9.4 cm, 4.2 cm under the ribs. There was no clear abnormality in kidneys and ureter. While there were free fluid areas in around periliver, perispleen, intestinal loop, left and right iliac fossa and pelvic in enterocoelia, about 4.6 cm deep in the lower abdomen. Tips: liver volume increasesd and the echo lowered, with splenomegaly and seroperitoneum (of moderate amount). And there was no clear abnormality found in Echocardiography.

Screening for inherited metabolic disease. Test results of blood tandem mass spectrometry showed that tyrosine 424.44 μmol/L (reference value: 20-100 μmol/L), phenylalanine 150.59 μmol/L (reference value: 20-120 μmol/L), methionine 215.8 μmol/L (reference value: 8-35 μmol/L). Urine gas chromatography and mass spectrometry analysis of organic acids: Urinary 4-hydroxy acid, 4-hydroxyphenyl

acetic acid, 4-hydroxyphenyl pyruvate increased significantly (see Figure 1).

1.4 Primary diagnosis

- (1) Infantile hepatitis syndrome: cytomegalovirus hepatitis?
- (2) Liver failure
- (3) Genetic metabolic disease?

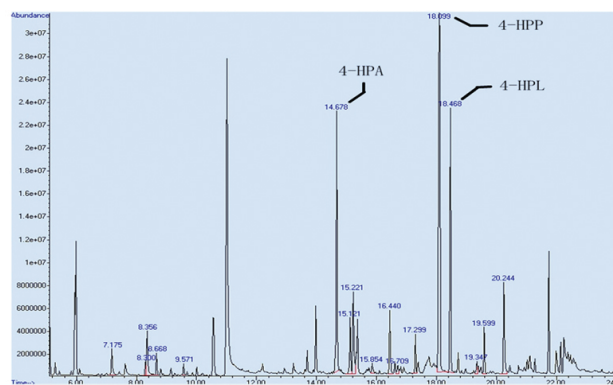


Figure 1: Organic Acid test images on Children with urinary gas chromatography

1.5 Treatment

The patient received conventional liver protecting treatment of Glycyrrhizin, inosine and glucuro lactone tablets. Abdominal distention, abdominal varices, ascites, hepatomegaly, coagulation abnormalities, and CMV-IgM positive appeared four days after admission. She was diagnosed as (1) liver failure, or (2) cytomegalovirus hepatitis during experts consultation. Hence, ganciclovir and glutathione were added to intravenous fluid therapy, together with Vit k1 symptomatically to stop bleeding and to treat diuresis, meanwhile, alternately making albumin and plasma treatment for two weeks (8 times in total), however, the condition didn't get much better. She passed clay-like stools on the seventh day after admission, urine bilirubin urobilinogen were tested to be positive so that hepatocyte growth-promoting factor treatment twice was supplied. On the tenth day, the infant was presented with night crying, irritability, difficult to appease with poor appetite, and jaundice worsened, severe coagulation disorder, PT up to 32.3 s, PTA decreased to 24.2%, liver fibrosis four indicators hyaluronic acid, III procollagen amino acid peptide, laminin, IV collagen increased, alpha-fetoprotein up to 439.1 ng/ml. So that cirrhosis, hepatic encephalopathy, genetic and metabolic diseases were highly suspected. Then liver biopsy was advised but rejected by the parents. She underwent inherited metabolic diseases examination and was discharged automatically on the 13th day when the treatment was quit. Xi'an Golden Field laboratory returned the result about blood and urine amino acid analysis in 5 days, showing that blood tyrosine level reached to 424.44 $\mu\text{mol/L}$, significantly increased; phenylalanine 150.59 $\mu\text{mol/L}$, slightly increased; methionine 215.8 $\mu\text{mol/L}$, increased as well; urine 4-hydroxy acid, 4-hydroxyphenyl acetic acid and 4-hydroxyphenyl pyruvate significantly elevated. The results hinted the diagnosis of (1) secondary to liver damage; (2) tyrosinemia. Measuring blood succinylacetone and testing tyrosinemia genetic were recommended as tyrosinemia type I was highly suspected on the basis of clinical features of the infant. The patient was heard dead over a follow-up visit.

2 Discussion

2.1 Dr. Jinli Hao

Dr. Jinli Hao is a deputy director of pediatric department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in child development, pediatric blood cancer and newborn.

The infant, under 6 months, was initially diagnosed as hepatitis syndrome due to the severe degree of prolonged jaundice, with the increase of liver and serum aminotransferase. The disease is a group of clinical syndrome, of infantile onset, characterized by hepatocellular jaundice, liver enlarge-

ment, abnormal and elevated liver enzymes texture, caused by a variety of factors.^[1] The cause behind the disease is complicated, mainly due to intrauterine and perinatal infections, inherited metabolic diseases and intra-and extra-hepatic bile duct abnormal development.

Infection factors that may lead to the disease. Cytomegalovirus (CMV) infection proves to be the most frequent factor that results in infant liver failure. The baby in the case, three months' old, was with persistent jaundice after birth unnoticed, and progressed into serious liver injury. The physical examination result revealed the condition of hepatomegaly, elevated liver enzymes, and CMV-IgM positive, so that cytomegalovirus hepatitis was suspected. There was no virus infection or medicine taken by her mother during pregnancy. There was no mphilitis, impetigo or after intestinal infections on this bay after birth. Herpes simplex virus, rubella virus, and toxoplasma virus antibodies were all tested to be negative. Four items for infections check and five items of hepatitis B were normal. Besides that, hepatitis A, hepatitis C and hepatitis E hepatitis antibody were all negative, and CMV-IgM was negative as well. Based on these factors, CMV infection was not the main cause.

Intra- and extra-hepatic bile duct abnormalities. There was no particularity in the onset of the disease, which was mostly believed to be physiological jaundice at the beginning. It then developed into biliary cirrhosis due to inflammation, cholestasis intrahepatic bile capillary, or biliary atresia. The infant was with persistent jaundice after birth, liver enzymes (mainly direct bilirubin) elevated, and urine bilirubin was testified to be positive. The symptom of the stool turned from yellow to yellowish-white after admission, alkaline phosphatase was abnormally increased, serum total bile acid rose, were highly suggestive of cholestatic liver disease. There were some symptoms, however, that did not meet the characteristics of the disease, such as ortholiposis and Gamma-glutamyl transpeptidase (GGT) were normal, gall bladder was checked to be normal by hepatobiliary ultrasound three times, and bile duct and portal vein diameter were normal. The suggestion that radionuclide hepatobiliary imaging, abdominal CT and liver biopsy be performed was rejected by the parents.

Inherited metabolic disease. Damage to liver-based inherited metabolic disease is usually presented with liver enlargement, hypoglycemia and liver dysfunction. The disease of acute onset proceeded rapidly, characterized with severe jaundice, progressive liver enlargement, ascites, coagulation disorders uncorrected, and liver failure. Blood and urine quantitative amino acid analysis showed that abnormally increased, phenylalanine, slightly elevated, methionine increased. Gas chromatography mass spectrometry in urine organic acid detection showed that 4-hydroxyphenyl pyruvic acid, 4-hydroxy phenyl acetic acid and 4-hydroxy benzene lactate excretion increased. Those symptoms complied with the features of acute tyrosinemia type I. The disease

is mostly manifested with abnormal liver function, hypoglycemia, bleeding tendency, ascites and other symptoms in infant about one-month old. In addition to those symptoms, acidosis and low hyperphosphatemia, renal proximal tubule damage and rickets are accompanied. The three-month old infant had not yet experienced hypoglycemia or renal tubular damage so that the diagnosis of tyrosinemia type I was demolished.

2.2 Dr. Xin Wang

Dr. Xin Wang is the director of pediatric department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in respiratory system diseases.

The infant in the case was presented with persistent jaundice after birth, gradually led to bloating, abdominal varicose veins, and progressive enlargement of the liver at the onset of hepatitis syndrome in severe condition with rapid progress. Liver ultrasound showed that liver volume enlarged, mostly seen in hepatic caudate lobe with low echo. Laboratory test result showed that coagulation disorders, alanine aminotransferase, aspartate aminotransferase, γ -glutamyl transpeptidase, alkaline phosphatase, bilirubin, total bile acid, AFP, four indicators of liver fibrosis were abnormally high, the minimum of PTA was 24.2%. The diagnosis of liver failure was established, while the possibility of liver cirrhosis could not be excluded. The symptom in the case was severe liver damage caused by variety of factors, and its etiology and clinical manifestations had great difference from those seen in adult patients. National data confirm the casual relationship between pathogen and age.^[2] CMV infection of unknown origin is the most common cause of the disease among the infant patients. Based on the case analysis, the causes that induce the disease are listed as follows.

Hepatitis viruses and other viral infections. The patient, 3-month-old infant, was with persistent jaundice after birth, enlargement of the liver, bidirectional increase of bilirubin, (mainly seen in bilirubin direct). CMV-IgM was tested to be positive. Cirrhosis and liver failure induced by cytomegalovirus hepatitis were highly suspected. The manifestations that failed to support the diagnosis: no history of severe infection, weight gain at the expected rate, no fever, anemia, bleeding tendencies were presented during the course. No cholestasis, bile duct obstruction, biliary atresia were shown by abdominal ultrasound. Besides that, the mother had no history of severe infection during pregnancy, and CMV-IgM was negative. Urine CMV culture may be a useful tool to aid in the diagnosis.

Damage to the liver-based inherited metabolic diseases.

(1) Pompe's syndrome: hepatomegaly, hypoglycemia, hypotonia; feeding difficulties, drowsiness, convulsions and other non-specific performance may also occur among new-

borns at the onset of the disease. Lactic metabolic acidosis, hyperlipidemia and hypertriglyceridemia urea were testified. There was no hypoglycemia or metabolic acidosis in the case, and blood lipids, muscle tone were normal so that the possibility of pompe's syndrome was excluded. (2) Galactosemia: jaundice dissipated delay, gradual enlargement of liver, texture hard, elevated liver enzymes and bilirubin, mild reduced albumin and mild to moderate coagulation abnormalities, progress quickly into cirrhosis, ascites, were in line with the present case. Galactosemia is more likely to be characterized by renal tubular dysfunction, such as full-acid urine, metabolic acidosis and phosphorus in urine.^[3] In addition to that, nuclear cataract might be discovered by slit lamp examination a few days or weeks after birth. Cataract was not found in the case after eye examination, the routine urine test results were normal. So the possibility of Galactosemia was also denied. (3) Tyrosinemia type I: congenital amino acid metabolism caused by a shortage of the enzyme fumarylacetoacetate hydrolase. It usually appears in the first 2-3 months of life with high mortality, manifested as severe liver disease or liver failure among 6-month-old infants. Laboratory tests proved that moderately elevated transaminase and bilirubin posed serious damage to the blood coagulation function. Prothrombin time and partial thromboplastin time was prolonged, while levels of alpha-fetoprotein increased simultaneously. Metabolic disease screening revealed abnormal increase of blood tyrosine, and a significant increase of urine 4-hydroxyphenylpyruvate, 4-hydroxy phenylacetic acid and 4-hydroxyphenyl lactic acid. The characteristics of the disease and auxiliary examination of this case were highly suggestive of tyrosinemia type I. A further genetic testing of blood succinylacetone and tyrosinemia was needed to clarify a diagnosis.

Other factors. Infants with liver failure of unknown origin accounts for 40.6% of all the reported 120 cases of liver failure in children in China.^[4] Robert, *et al.* reported that acetaminophen poisoning accounts for 14% at abroad.^[5] There were no congenital abnormalities of extrahepatic bile duct or biliary atresia in the patient, and it had no dark yellow urine or pale stool prior to its admission. Repeated liver function tests demonstrated that both glutamyl endopeptidase and blood lipids were normal. The possibility of biliary cirrhosis, thus, was denied. The diagnosis of drug-induced liver failure was also excluded as no acetaminophen phenolic drugs had been taken before the onset of the disease.

Hepatocellular carcinoma. The symptoms of progressive jaundice, abdominal varicose veins, ascites, coagulation disorders, liver failure, and a significant increase of AFP 439.1 ng/ml are the clues of the disease. The symptoms that demolished the diagnosis includes: the age of onset was young, no fever, anemia, leukopenia, nor thrombocytopenia was presented, hepatic ultrasound showed enlargement of liver volume, mostly seen in hepatic caudate lobe with low echo, which coincided with pediatric cirrho-

sis. Abdominal CT is needed for the exclusion of malignant tumor.

2.3 Dr. Hong Cui

Dr. Hong Cui is the director of digestive system department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in digestive system diseases.

Currently, unified and definite diagnosis and treatment of pediatric cirrhosis and liver failure remain to be determined in our country. There are different types of liver failure according to various factors. It is usually divided into Acute liver failure, subacute liver failure, acute-on-chronic (subacute) and chronic liver failure according to "liver failure treatment guidelines" compiled in China in 2006, comprehensive analysis of medical history, clinical manifestations and laboratory examinations. While, it is also staged into early, interim and late phase according to the degree of clinical manifestations, state of jaundice, mobility of prothrombin and the occurrence of hepatic encephalopathy.^[6] The patient was diagnosed as subacute liver failure (middle phase) on the basis of its medical history, symptom features and laboratory examinations. Pathological features of this period includes that the liver tissue is presented as old or new blocked shaped structure, bridging necrosis, collagen deposition, stump varying degrees of liver cells regeneration, small bile duct hyperplasia and cholestasis.

It is difficult to predict whether it would progress into liver cirrhosis which usually sustains for 6 months among adult patients. It is defined as diffuse liver fibrosis with abnormal nodules by morphology. Neither diffuse liver fibrosis nor nodules alone is cirrhosis. From the clinical point of view, it usually refers to the symptoms of liver failure and portal hypertension caused by histopathological changes in the liver. Liver biopsy histopathology is widely accepted as "gold standard" of the diagnosis of cirrhosis. Liver failure, a clinical syndrome, is severe liver damage caused by a variety of factors led to its synthesis, detoxification, excretion and biotransformation function impairment or decompensated severe, then progresses to coagulation disorders, jaundice, hepatic encephalopathy, ascites and other performances. The main cause for the disease is hepatitis viruses and drugs, while hereditary metabolic disease is the crucial cause for children with liver cirrhosis. Indicators of hepatic fibrosis are barometer of liver fibrosis, whose normal reference range remains to be determined among children patients. Previous studies show that the younger the patient is, the higher III procollagen peptide, hyaluronic presents. It is the same level as adult as that of 7-year-old child.^[7,8] Abnormal liver fibrosis, to some extent, is associated with liver failure and onset age in the case. Furthermore, III procollagen peptide, one indictor of liver fibrosis, may increase among patients with liver syndrome.^[8] As for the treatment: strengthen basic supportive treatment, add albumin or fresh

plasma, positive correct hypoproteinemia, and prevent all kinds of complications. Besides that, a therapy to promote pHGF, thymosin a1 was suggested to perform and the parents were advised to receive liver biopsy for further diagnosis.

2.4 Dr. Yajing Zhang

Dr. Yajing Zhang is the chief pediatric expert at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in neonatal, children growth and development.

Tyrosinemia is a disorder of amino acid metabolism. It is generally divided into three types (type I, type II, type III) according to the deficiency of one of the enzymes required for the multistep process that breaks down tyrosine. Tyrosinemia type I, also known as hepatorenal tyrosinemia, is the most common of the three types, with the highest incidence, first reported in 1956. It is inherited in an autosomal recessive pattern, about 1 person in 2,000 to 100,000.^[9] The onset is mainly due to fumaroyloxy acetoacetate hydrolase activity decreased or deleted, which then induces metabolism disorder of terminal tyrosine metabolic pathway and an increase of fumaroyloxy acetoacetate. It is chronological combined action that the increase of tyrosine and 4-hydroxyphenyl pyruvic acid (upstream metabolites), 4-hydroxyphenyl-lactic acid, 4-hydroxyphenyl acetic acid (pathway metabolites), maleimide acetoacetate, fumaroyl acetoacetate (intermediate metabolite) contributes to the elevation of succinyl acetoacetate and succinylacetone (pathway metabolites). Succinyl acetoacetate, succinylacetone may be combined with the thiol group of proteins, which is the main cause of liver and kidney damage.

Tyrosinemia type I is clinically divided into acute type (average age < 6 months), subacute type (average age 6 months-24 months) and chronic type (average age > 24 months).^[10] In the acute type, manifestations of neonatal hepatitis predominate, including diarrhea, vomiting, an enlarged liver, failure to grow at a normal rate, yellowing of the skin and whites of the eyes with frequent sepsis and rapid deterioration. The infant usually dies of hepatic failure at 3-9 months. Mild proximal tubular disease is usually present. Subacute type manifests a similar but less severe clinical picture presenting usually with hepatomegaly or hypophosphatemic rickets (due to tubular dysfunction). Late-onset type usually occurs after 1 year after birth, characterized by growth retardation, progressive liver cirrhosis and renal tubular dysfunction, phosphorus rickets, diabetes, proteinuria and amino acids urine, and so on, similar to Fanconi syndrome. Therefore, early diagnosis and treatment is the key to the prognosis of this disease.^[11]

The diagnosis of hereditary tyrosinemia of acute type, in reference to tyrosinemia diagnostic criteria, was established according to clinical manifestations of liver involve-

ment, abnormal increase of blood tyrosine at metabolic disease screening, and a significant increase of urinary 4-hydroxyphenyl pyruvate, 4-hydroxy phenyl acetic acid and 4-hydroxy benzene lactate. The deficiency of the treatment lies in the fact that the parents refuse to have hematuria succinyl acetone measured. Beyond that, no changes appeared in liver biopsy. A variety of studies confirmed that blood or urine succinylacetone increase served as a crucial identifier of tyrosinemia type I.^[12] Liver damage caused by other diseases such as galactosemia, citrin protein deficiency disorders can also lead to the same symptom imposed by tyrosinemia type I, such as blood tyrosine, elevated alpha fetoprotein, urine 4-hydroxyphenylpyruvate, 4-hydroxy phenylacetic acid and 4-hydroxyphenyl lactic acid level increased. So the above factors are not the mere clues to establish the diagnosis of tyrosinemia type I. Blood succinylacetone is employed as an important indicator of tyrosinemia type I screening in many countries. In addition, some transient and secondary high tyrosinemia exist at the same time.^[13] Filter blood screening in this case was performed after liver failure. The results showed that the serum levels of phenylalanine, tyrosine and tryptophan in liver failure were significantly high so that liver failure secondary to hepatic failure should be considered.

2.5 Dr. Hua Chen

Dr. Hua Chen is the director of pediatric department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in kidney-immune diseases, digestive system diseases.

Tyrosinemia type I is a curable inherited metabolic disease, whose primary treatment heavily relies on dietary therapy of nutritional powder formula (tyrosine and phenylalanine were not contained), drug therapy of nitisinone and restriction of natural protein intake. Protein formula milk and breast milk are much referred, in which tyrosine and phenylalanine in those kinds of milk are less half than those in milk. Natural protein intake should be controlled at 1-1.5 g/(kg.d), dietary therapy of nutritional powder formula (tyrosine and phenylalanine were not contained) in an amount of 1.5-2 g/(kg.d). Diet control, however, can merely reduce the risk of kidney complications, pose no effect on liver disease. Neither progression of liver disease nor occurrence of liver cancer could be prevented. Early diagnosis

and treatment of underlying Tyrosinemia type I remains imperative for possible recovery.

Nitisinone is the inhibitor of 4-hydroxyphenylpyruvate dioxygenase. The mechanism of action of nitisinone involves inhibition of tyrosine into 4-hydroxyphenylpyruvate dioxygenase so that accumulation of maleylacetoacetic acid and fumarylacetoacetic acid, which have the potential to be converted to succinyl acetone, was prevented. It was first applied for clinical practice in 1992,^[11] had been reported to lower succinylacetone level, weaken succinylacetone damage to the body, and improve liver function. Ordinary families would not prefer Nitisinone therapy due to its expensive cost and drug resource. Currently, liver transplantation is the primary treatment option for patients in whom nitisinone fails.

3 Conclusion

In all, a rare disease as it is, tyrosinemia is complicated with low incidence and poor prognosis so that a precise diagnosis of tyrosinemia remains challenging. It is easy for misdiagnosis, which aggravate the condition. Ten cases of tyrosinemia had been reported in our country,^[14] 6 cases of which were with CMV infection. The diagnosis of liver failure of unknown origin was established finally. Whether it was complicated with CMV infection or tyrosinemia requires further demonstration. CMV infection is the most common factor that induces liver failure among infant patients, which may initially leads to bile duct fibrosis and progressive biliary atresia, then portal hypertension and even severe biliary cirrhosis. Unfortunately, the parents refuse radionuclide hepatobiliary imaging, abdominal CT and liver biopsy, which impeded an accurate diagnosis of the disease. Therefore, this paper aims to arouse the doctors' awareness of tyrosinemia during clinical practice through case analysis. The doctor should consider this disease a possibility during clinical practice in any infant patients with significant liver involvement or renal impairment shortly after birth. Child with prolonged neonatal jaundice, especially the liver and spleen enlargement, should have urine analyzed, inherited metabolic diseases tested as soon as possible to enable the earliest possible diagnosis and initiation of therapy. We should pay more attention to hepatic failure among child patients and conduct further examination to prevent misdiagnosis.

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