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Clinical Diagnosis and Treatment of 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency in One Infant: A Case Report

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Abstract

Objective: We reviewed the clinical manifestations and examination results of one infant with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBDD), intending to enhance the understanding, diagnosis and treatment of MHBD.

Method: The clinical manifestations and results of laboratory tests, tandem mass spectrometry of the blood sample, gas chromatography-mass spectrometry of the urine sample, chest X-ray, color Doppler examination, brain MRI and EEG as well as the treatment of this case were analyzed retrospectively.

Result: This infant, aged 3 years old, mainly presented the symptoms of diarrhea and vomiting initially, and later lethargy, disturbance of consciousness, dyspnea and incorrigible metabolic acidosis. Brain MRI indicated mild ventriculomegaly and widening of sulci bilaterally. Borderline EEG was observed, with several sharp wave discharges in the frontal and central regions of the brain. Tandem mass spectrometry of the blood sample indicated increased levels of aspartic acid and other amino acids; gas chromatography of the urine sample indicated an obvious increase of 2-methyl-3-hydroxybutyric acid, but the levels of 3-methylcrotonyl-glycine or 2-methyl-acetoacetic acid were basically normally. Gene detection revealed p.R130C mutation in exon 4 of the HADH2 gene.

Conclusion: As a rare disease, MHBDD may be suspected for infants presenting with incorrigible metabolic acidosis and hyperammonemia or neurological symptoms such as lethargy and disturbance of consciousness for unknown reasons. Examination techniques including tandem mass spectrometry, gas chromatography-mass spectrometry of the blood and urine samples and gene detections can be used for early diagnosis and treatment.

Keywords: Inherited metabolic disease; 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBDD); Tandem mass spectrometry; Gas chromatography-mass spectrometry

Introduction

2-Methy1-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBDD) is a rare X-linked recessive disorder presenting as the accumulation of 2-methyl-3-hydroxybutyric acid in the body fluid due to abnormal activity of 2-methy1-3-hydroxybutyryl-CoA dehydrogenase in isoleucine decomposition. Various symptoms may occur, typically neurological disorders in the onset [1]. MHBDD was first reported by Zschocke et al. [2] in 2000, and by now less than 30 cases have been known globally [3]. Shu et al. [4] carried out gene mutation profiling for the first case of MHBDD discovered in China along with the relatives. MHBDD is very likely to be misdiagnosed because of its extremely low incidence and confusing symptoms.

The case reported in this study suffered from diarrhea and vomiting at the start, followed by lethargy, disturbance of consciousness, dyspnea and incorrigible metabolic acidosis. This case was finally diagnosed as MHBDD. Through a retrospective analysis of this case, we hope to find clues for accurate and early diagnosis and treatment of MHBDD.

Data and Method

Clinical information

The male infant, aged 3 years old, suffered from diarrhea and vomiting for 3 days and lethargy and dyspnea for 1 day. He was transferred from the other hospital to Pediatric ICU of our hospital due to aggravated disturbance of consciousness for 1 hour. Repeated blood gas analyses after admission indicated metabolic acidosis, which was basically incorrigible. After two continuous renal replacement therapies (CRRT), metabolic acidosis was reversed, with alleviation of dyspnea and disturbance of consciousness. The infant was weaned from mechanical ventilation on the fifth day, but he began to suffer from cloudy consciousness, swallowing problems, inability to hold the neck erect, low muscular strength and tension in the four limbs. Neurological rehabilitation was started since the eighth day. The infant was the first child of the mother and had a full-term birth with birth weight of 3.4 kg. The infant was in good condition upon birth and breast fed. The complementary food was fed since the eighth month after birth, and the infant had normal motor and language abilities and normal physical and intelligence development. The parents denied the history of unclean diet and uptake of drugs as well as the history of infectious diseases and toxic exposures.

Physical examinations revealed T36.7°C, P159 beats/min, R36 beats/min, and BP102/62 mmHg. The infant had the complexion typical of critically ill patients, with active position, cloudy consciousness, but no subcutaneous bleeding, generalized edema or superficial lymph node swelling upon palpitation. The conjunctivas were normal and the

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pupils were equal and round and reactive to light, with the size of 3 mm. The nose wings flapped and the lips were red and moist. Pharyngeal congestion and grade I tonsil inflammation were found, but no herpes or secretions were found. There was negative neck resistance, bilateral respiratory movements, deep breath, positive three-depression syndrome, slightly coarse breathing sound, but no dry or wet rales. The heart beat was regular and powerful without murmurs. The abdomen was soft, and the liver and spleen were not palpable beneath the rib cage. Babinski syndrome and Kernig syndrome were both negative.

Diagnosis

Routine blood test, blood gas analysis, blood glucose and ammonia test, coagulation test, procalcitonin test, blood culture, sputum culture, cerebrospinal fluid test, chest X-ray, Doppler echocardiography, tandem mass spectrometry/gas chromatography-mass spectrometry, EEG and brain MRI were performed.

Treatment

The infant received mechanical ventilation upon admission along with the following treatment: sodium bicarbonate for anti-acid treatment, Mepem for anti-infective treatment, dexamethasone for anti-inflammatory treatment, milrinone for cardiac strengthening, mannitol for diuresis, infusion of fresh frozen plasma for correcting coagulation function, gamma globulin infusion, vitamin k1 administration to prevent bleeding, creatinine phosphate sodium for cardiac protection, coenzyme complex administration to protect the major organs, levocarnitine and coenzyme Q10 administration, correction of electrolyte disturbance and other symptomatic therapies. After screening for inherited metabolic disorders, cefoperazone sodium and tazobactam sodium for injection were given as the anti-inflammatory therapy, ganglioside and B vitamins for neurotrophic effect, and creatine phosphate sodium for cardiotropic effect.

Result

Laboratory tests

WBC 16.25*10^9/L↑, N 71.9%↑, L 24.3%, HB126 g/L, PLT 340*10^9/L, and WBC count and percentage of neutrophils indicated inflammation. PH 7.040↓, PCO_2 1.6 KPa↓, PO_2 29.1 KPa↑, BE -25.4 mmol/L↑ and HCO_3 - 3.2 mmol/L↓, indicating metabolic acidosis, which was found incorrigible after repeated tests. Blood ammonia 40.3 umol/L↑, PT 17.2 s↑, APTT 45.2 s↑, TT 17.6 s, DDI 0.64 mg/l, Fg 216 mg/dL, PCT2.55 ng/mL↑. No bacteria grown in blood culture at 48 h or 5 d, so sepsis was excluded. No abnormalities were found in sputum culture, markers of myocardial injury, random blood glucose, transfusion testing and routine stool test. No abnormalities were found in two detections of enterovirus nucleic acid, so hand-foot-mouth disease was excluded. CSF analysis indicated CSF glucose 4.6 mmol/L↑ and chlorides 151.2 mmol/L↑, showing no abnormalities. Reexaminations at 11 d after admission indicated normal routine blood and urine tests (WBC6.6*10^9/L, N 42.8%, L 40.3%), normal liver and kidney function and normal electrolytes. The PCT level was also normal (0.02 ng/ml), with metabolic acidosis (PH 7.499, PCO_2 3.53 KPa, PO_2 13.92 KPa, BE2.525 mmol/L, HCO_3 25.6 mmol/L).

Chest X-ray

Chest X-ray in anteroposterior position at 3 d after admission indicated increased and obscure texture of bilateral lungs, and bilateral pneumonia was suspected (Figure 1).

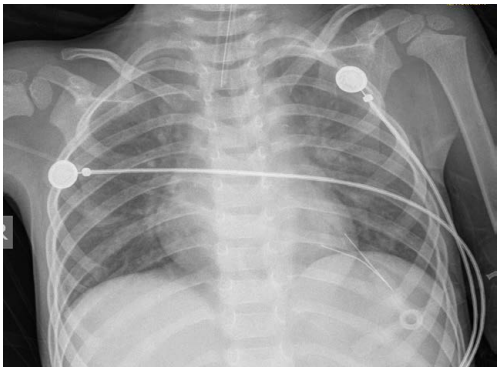

Figure 1: Chest X-ray in AP position: Increased and obscure texture of bilateral lungs.

Doppler echocardiography

Doppler echocardiography found no obvious abnormalities with normal measured values of left ventricular contractility. Color Doppler ultrasound of the kidney showed no abnormalities of bilateral kidneys, ureters and bladder. Tandem mass spectrometry of the blood sample: GLY 1263.82↑, LEU 381.49↑, ORN 424.65↑, PHE 120.86↑, C0 61.17↑, C3/C2 0.28↑, C3DC__C4OH 0.55↑, C5:1 0.23↑, and C0/(C16+C18) 61.17↑. Combining with other tests, beta-ketothiolase deficiency was suspected.

Gas chromatography-mass spectrometry of the urine sample

In the first urine test, 3-hydroxybutyric acid 1440.13↑, acetoacetic acid 1.22↑, 2-methyl-3-hydroxybutyric acid 4.37↑, 3-hydroxyisovalerate 34.68↑, so ketosis was suspected, but β-ketothiolase deficiency could not be excluded. In the second test, 2-methyl-3-hydroxybutyric acid 6.85↑, but the levels of 3-methylcrotonyl-glycine and 2-methyl-acetoacetic acid were normal. Therefore, MHBDD was suspected and β-ketothiolase deficiency was excluded preliminarily.

Brain MRI

Mild ventriculomegaly and widening of sulci bilaterally were observed (Figure 2).

EEG

Borderline EEG was observed with several sharp wave discharges in the frontal and central regions of the brain.

Gene detection

Gene detection using the peripheral venous blood sample indicated p.R130C mutation in exon 4 of the HADH2 gene.

Discussion

MHBDD, a very rare inherited disorder related to isoleucine metabolism, usually involves the nerve system and manifests as a process from static encephalopathy to degenerative changes [4]. Zschocke [2] and Ensenauer et al. [5] reported that MHBDD may show no retarded development or only mild retardation in newborns at the early stage, but retarded mental development will occur later. Shu et al. [4] reported one infant, aged 1 year and a month, who was treated at the outpatient clinic of Department of Neurology due to retarded mental development following hospitalization for pneumonia at 2 d and 2 months after birth, respectively. Our case, a three-year-old infant, showed normal conditions upon birth with normal movement and

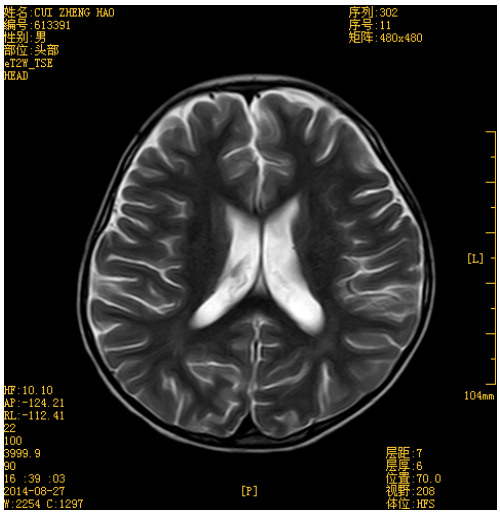

Figure 2: Brain MRI: Mild ventriculomegaly and widening of sulci bilaterally.

language abilities and normal physical and intelligence development. He initially presented the symptoms of diarrhea and vomiting, followed by lethargy and dyspnea 3 days later. The symptoms were aggravated after that, and laboratory tests revealed acidosis. Before that, the infant received treatment at other hospital for supposed encephalitis and acidosis, but achieved no obvious improvement. Instead the infant suffered from lethargy and disturbance of consciousness and aggravated dyspnea. After he was transferred to our hospital, repeated blood gas analyses indicated incorrigible metabolic acidosis with an obvious increase in blood ammonia and chest X-ray indicated bilateral pneumonia. CRRT was given and metabolic acidosis was effectively reversed with alleviation of disturbance of consciousness and dyspnea. However, the symptom of cloud consciousness lingered, and the infant had swallowing problems, inability to hold the neck erect, low muscular strength and tension in the four limbs. As demonstrated above, such cases may be easily misdiagnosed as pneumonia, encephalitis and other common pediatric diseases rather than inherited metabolic disorders. Besides, our case had no abnormal development in the early stage and was combined with incorrigible metabolic acidosis, which conflicts with the existing literature reports [2,4].

MHBDD shares some similarities with beta-ketothiolase deficiency (BKT) and therefore may be confused with the latter [6]. BKT is a rare autosomal recessive disorder related to isoleucine metabolism. With the defect of acetoacetyl-CoA thiolase, abnormal metabolites are discharged with the urine together with a large amount of carnitine. But the accumulation of intermediates will lead to abnormal metabolism and organ dysfunction or even retarded mental and motor development. Zhou et al. [7] reported the following symptoms in infants with BKT: retarded growth, poor appetite, vomiting, dyspnea, circulation disorders, reduced muscular tension, and disturbance of consciousness, hyperammonemia, and severe metabolic acidosis. The infant reported in this study also had the symptoms of vomiting, disturbance of consciousness, hyperammonemia, and severe metabolic acidosis. BKT usually features a high level of C5 and C5-OH in the blood or urine. As shown by the gas chromatography-mass spectrometry, the levels of 2-methyl-3-hydroxybutyric acid, 3-methylcrotonyl-glycine and 2-methyl-acetoacetic acid were increased, based on which BKT might be diagnosed. However, MHBDD usually involves the increase of 3-methylcrotonyl-glycine and 2-methyl-3-hydroxybutyric acid, but not 2-methyl-acetoacetic acid. We found in this present case that the levels of organic acids increased obviously in the screening test for inherited metabolic disorders, including C5-OH and C5:1. In the first gas chromatography-mass spectrometry of the urine sample, the levels of 3-hydroxybutyric acid, acetoacetic acid, 2-methyl-3-hydroxybutyric acid and 3-hydroxyisovalerate all increased significantly. In the second test after treatment, the level of 2-methyl-3-hydroxybutyric acid was higher significantly, but the levels of 3-methylcrotonyl-glycine and 2-methyl-acetoacetic acid was basically normal. Therefore, MHBDD was considered. Combining with the clinical manifestations and screening test for inherited metabolic disorders, BKT was excluded and MHBDD was diagnosed finally.

So far 7 mutations in the HADH2 gene are considered to be related to MHBDD, all being missense mutations, among which p.R130C mutation is the most common [8-11]. Shu et al. [4] carried out gene mutation profiling for the first case of MHBDD discovered in China along with the relatives. The p.R130C mutation was found in this infant, whose mother was heterozygous at this locus. This confirmed the existence of mutation at this locus among Chinese population. We also found p.R130C mutation in exon 4 of the HADH2 gene, which agrees with the existing reports.

Low-isoleucine diet is usually adopted for patients with MHBDD along with anti-infective therapies to reduce mitochondrial stress and maintain mitochondrial balance and vitamins and cofactor administration [4,12]. Initially the present case showed the symptoms of lethargy, dyspnea, severe metabolic acidosis, disturbance of consciousness, poor swallowing, inability to hold the neck erect, low muscular strength and tension in the four limbs, which were signs of subsequent brain injury. The infant received anti-infective and anti-inflammatory therapies, mechanical ventilation, sodium bicarbonate administration as anti-acid therapy and two CRRT. After the screening test for inherited metabolic disorders, cefoperazone sodium and tazobactam sodium for injection were given as anti-inflammatory therapy, ganglioside and B vitamins as neurotrophic medication, and creatine phosphate sodium as cardiotropic medication. In spite of these therapies, the infant still had tremor of both hands, especially in object handling, and unsteady standing. But these symptoms were much improved as compared with the conditions upon admission. The infant had no fever, spasm, disturbance of consciousness, cough, diarrhea and vomiting with moderate spiritual well-being and appetite. After neurological rehabilitation for some time, the infant was discharged.

This study reported one infant with MHBDD through a retrospective analysis of the clinical manifestations, laboratory tests, tandem mass spectrometry of blood sample and gas chromatography-mass spectrometry of the urine sample. Particular emphasis was laid upon differentiation with other metabolic disorders. For infants with neurological symptoms for unknown reasons, including incorrigible metabolic acidosis, hyperammonemia, lethargy and disturbance of consciousness, MHBDD can be considered. Tandem mass spectrometry and gas chromatography-mass spectrometry of blood and urine are recommended for such cases to achieve early diagnosis and treatment. For those with family history of MHBDD, prenatal diagnosis or tandem mass spectrometry and gene detection for the newborns are preferred.

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