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Acute onset of ornithine transcarbamylase deficiency after total anomalous pulmonary venous connection repair to a 2-day-old neonate

Hisashi Yoshida, Yusuke Iwata, Tai Fuchigami and Junko Katagiri

Department of Pediatric Cardiac Surgery, Gifu Prefectural General Medical Center, Gifu, Japan

Brief Report

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Author for correspondence:
H. Yoshida, MD, Department of Pediatric Cardiac Surgery, Gifu Prefectural General Medical Center, 4-6-1 Noisshiki, Gifu, 500-8717, Japan. Tel: +81-58-246-1111;
Fax: +81-58-248-3805.
E-mail: hisa042889@gmail.com

Abstract

Ornithine transcarbamylase deficiency is an X-linked disorder which results in the accumulation of ammonia causing irritability and vomiting. Acute hyperammonemia requires rapid and intensive intervention. However, as those clinical features are non-specific and commonly seen in peri-operative situation, ornithine transcarbamylase deficiency could be difficult to diagnose prior to and post-emergency cardiac surgery. We report a 2-day-old male neonate who was diagnosed with ornithine transcarbamylase deficiency presenting hyperammonemia and severe heart failure after total anomalous pulmonary venous connection repair.

Acute hyperammonemia of a newborn is rare, but it requires urgent and appropriate management to prevent cerebral dysfunction and death. Ornithine transcarbamylase deficiency is an X-linked disorder of urea cycle disorder which results in the accumulation of ammonia and glutamine, and reduction of arginine and citrulline. On the other hand, total anomalous pulmonary venous connection is a rare cardiac malformation, in which all four pulmonary veins connect to the right atrium or its tributaries. It requires emergency surgery in neonates. As a consequence, a lack of adequate peri-operative examination may underdiagnose concealed metabolic disorders. We report an acute onset of ornithine transcarbamylase deficiency after total anomalous pulmonary venous connection repair to a 2-day-old neonate.

Case report

A 2-day-old, full-term male neonate weighting 3055 g was referred to our department for total anomalous pulmonary venous connection. He was born after uneventful delivery with APGAR scores of 8/9. He was diagnosed with total anomalous pulmonary venous connection from fetal period and had no remarkable family history.

His chest X-ray showed typical snowman sign and increased pulmonary vascularity.

A transthoracic echocardiogram revealed Type 1 (supracardiac) total anomalous pulmonary venous connection, a large atrial septal defect, patent ductus arteriosus, and normal left ventricular function. Due to the worsening of tachypnea and total anomalous pulmonary venous connection obstruction with continuous flow pattern by echocardiography, emergency operation was performed on day 2. Total anomalous pulmonary venous connection repair by sutureless technique via posterior approach, patent ductus arteriosus ligation, and atrial septal defect direct closure were accomplished through median sternotomy, using cardiopulmonary bypass with bicaval cannulation. Cardiopulmonary bypass time and aortic cross-clamp time were 188 and 69 minutes, respectively.

He was extubated on post-operative day 2. Breastmilk feeding started from post-operative day 5. Digoxin was administered to treat supraventricular tachycardia on post-operative day 6. He developed vomiting on post-operative day 8. On post-operative day 13, unexplained tachypnea, somnolence, bulging fontanelle, and metabolic acidosis were recognized. Echocardiogram showed severe left ventricular dysfunction with ejection fraction of 40%, no pericardium effusion, and no significant valvular disease. However, on post-operative day 14, due to refractory ventricular tachycardia, extracorporeal membrane oxygenation and continuous hemodiafiltration were introduced, and all feeds were stopped temporarily. In addition, with digoxin concentration of 10.3 ng/ml, digoxin toxicity was diagnosed. On the following day, extracorporeal membrane oxygenation and continuous hemodiafiltration were weaned successfully. On post-operative day 20, breastmilk feeding was resumed. However, on the following day, he developed apnoea, pupil dilation, and absent pupillary light reflex. On post-operative day 21, as repeated vomiting after breastmilk feeding and neonatal screening test was positive for abnormal amino acid metabolism and fatty acid metabolism, amino acid analysis and urine organic acid analysis were applied. On post-operative day 29, with NH3 (ammonia) 463 μg/dl, citrulline

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0.11 mg/dl, glutamine 11,753 nmol/ml, and high level of orotic acid in urine, ornithine transcarbamylase deficiency was additionally diagnosed. He received arginine infusion and lactulose and was placed on non-protein, high-calorie diet supplemented by essential amino acids. On post-operative day 31, NH3 decreased to 230 μg/dl; however, his condition progressively deteriorated. He died on post-operative day 32 due to multiple organ failure.

Discussion

Ornithine transcarbamylase deficiency is an X-linked urea cycle defect which results in the accumulation of ammonia and glutamine and subsequent irreversible brain damage.[1] The estimated frequency of ornithine transcarbamylase deficiency is 1/80000 in Japan.[2] Protein overtake, decreased energy intake, infection, and surgery are known to be triggering factors.[3,4] Chiong et al. reported late-onset ornithine transcarbamylase deficiency in adult after coronary bypass surgery.[5] They concluded that surgery stress and inadequate calorie intake uncover latent-ornithine transcarbamylase deficiency. In our case, cardiac surgery using cardiopulmonary bypass and post-operative catabolism were thought to be the triggers.

Ornithine transcarbamylase deficiency is suspected in neonates with an undiagnosed lethargy, irritability, and vomiting. However, there are several factors that delayed suspicion of underlying urea cycle disorder in this case. First, those non-specific symptoms are often observed in peri-operative cardiac surgery. In fact, 33.2–82% of children experience post-operative nausea and vomiting.[6] Second, even though there were signs of concealed metabolic disorder such as tachypnea and metabolic acidosis, his high serum digoxin concentration and symptoms misled to focus on only digoxin toxicity. As digoxin toxicity and ornithine transcarbamylase deficiency share common clinical features such as gastrointestinal and neurological symptoms, ornithine transcarbamylase deficiency was underdiagnosed in this case.[7] Moreover, no prior case of acute-onset ornithine transcarbamylase deficiency after cardiac surgery in neonates has been reported. Furthermore, his no remarkable family history excluded congenital metabolism disorder. Subsequently, his mutation analysis confirmed de novo mutation since the analysis showed c. 472C>T (p.P158S) mutation in ornithine transcarbamylase Exon 5 which was not identified in his mother and brother.

Management of ornithine transcarbamylase deficiency in neonate is difficult; mortality rate is 74%.[4] Recommended treatments of ornithine transcarbamylase deficiency are early diagnosis and rapid treatment with glucose injection, protein restriction, intravenous arginine and citrulline, and administration of sodium phenylbutyrate and/or sodium benzoate. Mattke et al. reported successful treatment of a neonatal case with deteriorating cardiac function using extracorporeal membrane oxygenation and continuous hemodiafiltration.[8] Likewise, continuous hemodiafiltration and extracorporeal membrane oxygenation were used in our case; however, underdiagnosis of ornithine transcarbamylase deficiency and deteriorating condition resulted in poor response to intensive care. Routine measurement of plasma ammonia level and examination of organic acid in urine in neonates before and after emergency cardiac surgery may prevent underdiagnosis of ornithine transcarbamylase deficiency.

Severe cardiac dysfunction is thought to be rare in ornithine transcarbamylase deficiency. However, Mattke et al. reported that our case also presented severe left ventricular dysfunction. Mattke et al. proposed that NH3, metabolic acidosis, and oxidative stress might be the cause of severely dilated left ventricular dysfunction. In addition to Mattke's hypothesis, since ornithine transcarbamylase deficiency is known to cause carnitine deficiency, carnitine may have also played an important role in cardiac function and arrythmia in this case.[9,10] Carnitine transfers long-chain fatty acids to mitochondria for β-oxidation. Since long-chain fatty acids are an essential energy source for myocardium, deficiency of carnitine is expected to affect cardiac muscle and results in cardiac dysfunction. Although factors that lead to the development of heart failure are unknown, echocardiogram may be recommended in neonates with ornithine transcarbamylase deficiency.

Conclusion

This case illustrates the difficulty of diagnosing ornithine transcarbamylase deficiency in neonates prior to and after emergency of cardiac surgery with no family history. In addition, it suggests that patients with ornithine transcarbamylase deficiency may develop severe heart failure. In conclusion, emergency surgery in neonates require careful attention to concealed congenital metabolic disorder. Keeping in mind that de novo mutation may occur, neonates with acute onset of unexplained gastrointestinal and neurological symptoms require immediate metabolic investigation and treatment.

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Conflicts of interest. None.

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