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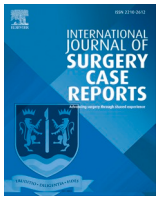

Case report

Intraoperative management during liver transplantation in the child with mitochondrial depletion syndrome: A case report

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ABSTRACT

Introduction: Mitochondrial DNA depletion syndrome (MDS) is a kind of autosomal recessive genetic disorder associated with a reduction in mitochondrial DNA (mtDNA) copy number caused by mutations in nuclear genes during nucleotide synthesis, which affects the energy production of tissues and organs. Changes in hemodynamics during liver transplantation may lead to high energy-demanding organs and tissues being vulnerable. This report described the intraoperative management during liver transplantation in a child with MDS. Ultimately, the child was discharged smoothly without any complications.

Presentation of the case: A five-year-old boy was diagnosed with mitochondrial depletion syndrome preoperatively and scheduled for living donor liver transplantation. The incidence of postreperfusion syndrome (PRS) could not be avoided for 30 min after opening, despite our best efforts to aggressively prevent it before opening. While ensuring hemodynamic stability, we actively prevented and adopted high-energy-demand organ protection strategies to reduce the incidence of postoperative complications. Finally, the child was discharged 28 days after the operation, and no other complications were found.

Discussion: Liver transplantation can be performed for liver failure in this disease to improve the quality of life and prolong the life of patients. As this child has mitochondrial DNA depletion syndrome, the disruption of cellular energy generation caused by mitochondrial malfunction puts high-energy-demanding organs and tissues at risk during surgery. It motivates us to pay closer attention to the prevention and treatment of PRS in anesthetic management to minimize damage to the child's organs and tissues with high energy demands.

Conclusions: This report describes the intraoperative management during liver transplantation in a child with mitochondrial depletion syndrome. To increase the safety of perioperative anesthesia and reduce mortality in patients with mitochondrial disease, for such patients, maintaining an acid-base balance and a stable internal environment is essential. We should also pay attention to protecting body temperature, using vasoactive drugs beforehand to lessen the incidence of PRS, and protecting high-energy-demanding organs afterward.

1. Introduction

Mitochondrial DNA depletion syndromes (MDS) are a group of autosomal recessive genetic disorders in which the mutation of the nuclear gene encoding mitochondrial DNA (mtDNA) leads to the serious reduction of the number of mitochondrial DNA synthesis, resulting in the disorder of mass production of tissues and organs. MDS are divided into five types according to clinical manifestations: myopathy, encephalomyopathy, liver-cerebral, neuro-gastrointestinal, and cardiomyopathy [1]. At least 12 nuclear genes have been reported, including POLG, POLG2, PEO1, SLC25A4, TYMP, DGUOK, TK2, SUCLA2, SUCLG1, MPV17, OPA1, and RRM2B genes [2]. MDS is exceedingly rare, with only a small number of cases reported. Postreperfusion syndrome (PRS) is one of the most common complications in the perioperative period of liver transplantation. It is generally defined as a $>$ 30 % decrease in mean arterial pressure from baseline within 5 min after reperfusion of the transplanted liver and persists for $>$1 min. However, Nashima et al. [3] believed that PRS is the completion of the

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anastomosis of the donor's liver, and the mean arterial pressure after blood reperfusion decreased to <70 % of the pre-opening, and the duration was >5 min, accompanied by a decrease in peripheral vascular resistance and cardiac output, and an increase in pulmonary capillary wedge pressure and central venous pressure. Changes in hemodynamics during liver transplantation may lead to disruption of cellular energy production associated with mitochondrial dysfunction, leaving high energy-demanding organs and tissues (i.e., brain, heart, and skeletal muscle) vulnerable [4]. This article introduced intraoperative management during liver transplantation in a child with mitochondrial depletion syndrome during liver transplantation. This case report has been presented in accordance with SCARE Criteria [24].

2. Case presentation

A 5-year-old boy was scheduled for living donor liver transplantation due to liver cirrhosis and liver insufficiency. The donor is the mother of the child, aged 41 years old. The admission height and weight were 105 cm and 15 kg, respectively. 40 days after birth, the child had yellow skin and sclera, accompanied by diarrhea, light-colored stool, and dark-colored urine. It was considered familial intrahepatic cholestasis. Cholecystocolonic anastomosis was performed immediately. After the operation, jaundice disappeared, and the liver function gradually improved. Four months before this operation, the family found that the physical activity of the child was significantly worse than that of children of the same age, and the general weakness was obvious after the activity. Abnormal movements of both lower limbs manifested as easy to fall when running or walking quickly. The liver function became serious. Two compound heterozygous variants of the MPV17 gene, c. 451dupC and c. 293C > t were discovered during genetic testing. The child's mental development was normal. Enhanced CT showed cirrhosis multiple regenerative nodules of the liver, and more intrahepatic nodules than before. Cardiac color Doppler ultrasonography showed a small amount of tricuspid regurgitation and a left ventricular ejection fraction of 69 %. Magnetic resonance imaging of the brain was seen in the bilateral fronto-parietal occipital lobes on magnetic resonance imaging, and there was no aberrant dilatation or constriction in the morphology of the ventricles, sulci, or cisterns. The chest CT scan and other exams revealed no evident abnormalities. Preoperative laboratory workup showed alanine transaminase (ALT) 81 U/L, aspartate transaminase (AST) 97 U/L, total bilirubin 7.1 μmol/L, albumin (ALB) 38.8 g/L, creatinine 26 μmol/L, urea 6.1 mmol/L, and blood glucose 3.5 mmol/L. The preoperative diagnosis was mitochondrial DNA depletion syndrome, liver cirrhosis, and hepatic insufficiency. Sign the consent form for anesthesia and surgery, and plan to perform living-donor liver transplantation under general anesthesia.

This child suffered from the mitochondrial depletion syndrome. Considering the increased incidence of reperfusion syndrome and high-energy tissue and organ damage, we made the following plans before surgery: (1) Intravenous glucose during fasting to reduce hypoglycemia and hypovolemia; (2) Continuous monitoring of the patient's blood gas during surgery, and timely adjustment of the internal environment; (3) Perform active temperature protection measures during the operation; (4)Administer low doses of adrenaline to reduce the occurrence of PRS; (5) Strengthen perioperative cardio brain protection, detect cardio and brain injury markers during surgery, and supplement with sodium creatine phosphate.

Routine fasting was performed before surgery, peripheral venous access was established and administered 5 % glucose 100 mL in the ward before surgery. After entering the operating room, vital signs were monitored. The monitor shows the patient's blood pressure (BP) at 90/60 mmHg, heart rate (HR) at 100 beats/min, and SpO_2 at 98 %. Intraoperatively, general anesthesia was induced with midazolam 2 mg, etomidate 4 mg, rocuronium 8 mg, and sufentanil 10 μg. Under the guidance of a video laryngoscope, an ID 5.0 tracheal intubation was inserted, and mechanical ventilation was performed, $FiO_2$50% ~ 60 %, tidal volume 120 mL, respiratory rate 18–23 times/ min, maintain $P_{ET}CO2$ 35–45 mmHg. The left radial artery was cannulated and connected to the Mostcare monitor through a pressure sensor to monitor circulatory indicators such as BP, HR, cardiac output (CO), stroke volume variability (SVV), and cardiac cycle efficiency (CCE). The right internal jugular vein was punctured under ultrasound guidance, and a 5.5F three-lumen central venous catheter was inserted to monitor central venous pressure (CVP). Intraoperative Sonoclot coagulation and platelet function analyzer (Sonoclot analyzer) was used to monitor coagulation function, and blood product input volume was adjusted according to blood gas analysis and coagulation function monitoring indicators. Monitoring the circulation index following anesthesia induction (Table 1): BP 98/56 mmHg , HR 118 beats/min , CVP 5 mmHg , CI 3.29 $L{\cdot}min^{-1}{\cdot}m^{-2}$, SVV 14 % , CCE 0.20. Blood gas analysis revealed (Table 2):PH 7.26, PCO_2 44.6 mmHg, PO_2 346 mmHg, SpO_2 100 %, Hb 131 g/L, BE −7.0 mmol/L, lactate 3.0 mmol/L, blood glucose 3.4 mmol/L, K^+ 3.4 mmol/L. Sonoclot monitoring: activated whole blood clotting time (ACT) 121 s, clotting rate (CR) 11.7, and platelet function (PF) 2.4. Myocardial damage markers: high-sensitivity troponin I (hs-cTnI) 39.6 pg/mL, creatine kinase-MB (CK-MB) 2.2 pg/mL. Anesthesia is maintained by inhalation of 1 %–2 % sevoflurane, intravenous infusion of propofol 8–10 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$, and remifentanil 0.1–0.3 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ to maintain sedation and analgesia, intravenous infusion of cisatracurium 1–2 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ to maintain muscle relaxation. The incision stage lasted 225 min, the blood loss was 130 mL, the urine output was 55 mL, and a total of 610 mL of fluid was infused. Entering the anhepatic stage, the hemodynamics of the child were stable, no vasoactive drugs were used, and the internal environment was generally stable. At this stage, creatine phosphate is given to protect the myocardium. Monitoring of vital signs (Table 1): BP 65/40 mmHg, HR 137 beats/min, CVP 3 mmHg, CI 2.82 $L{\cdot}min^{-1}{\cdot}m^{-2}$, SVV 34 %, CCE 0.14. Blood gas analysis (Table 2): PH 7.28, PCO_2 37.2 mmHg, PO_2 357 mmHg, SpO_2 100 %, Hb 113 g/L, BE −7.7 mmol/L, lactate 5.0 mmol/L, blood glucose 4.4 mmlol/L, K^+ 3.3 mmol/L. Sonoclot: ACT 118 s, CR 10.1, PF 1.9. Myocardial injury markers: hsTnI 56.4 pg/mL, CK-MB 4.9 pg/mL. The anhepatic phase lasted for 49 min, the blood loss was 20 mL, the urine output was 25 mL, and a total of 150 mL of fluid was infused. Immediately after the completion of vascular anastomosis and the opening of the portal vein, the new liver stage is entered. The child presented with a drop in blood pressure, a slow heart rate, a minimum of BP 52/35 mmHg, HR 85 beats/min, and a PRS reaction. After immediate intravenous injection of epinephrine 2 μg and 5 % sodium bicarbonate 10 mL intravenous infusion, blood pressure and heart rate gradually recovered to BP 91/43 mmHg, HR 112 times/min. Half an hour after the portal vein was opened, the blood pressure dropped again to 65/40 mmHg, and a continuous pump of 0.1μg/kg/min of epinephrine was given to boost the blood pressure. Intraoperative infusion heating and warm air blankets and other heat preservation measures were continuously applied, and the body temperature was maintained at 36 °C ~ 37 °C. Vital signs monitoring at the end of surgery (Table 1): BP 98/37 mmHg, HR 125 beats/min, CVP 8 mmHg, CI 4.38 $L{\cdot}min^{-1}{\cdot}m^{-2}$, SVV 7 %, CCE 0.24. Blood gas analysis (Table 2): PH 7.27, PCO2 32.5 mmHg, PO2 320 mmHg, SpO_2 100 %, Hb 97 g/L, BE −8 mmol/L, lactate 10 mmol/L, blood sugar 8.5 mmol/L, K+ 4.2 mmol/L. Sonoclot: ACT 136 s, CR 6.1, PF 1.2. Markers of myocardial injury: hsTnI 93.2 pg/mL, CK-MB 5.4 pg/mL. The operation lasted 605 min, the bleeding was about 200 mL, the urine output was 600 mL, the intraoperative fluid input was 1511 mL, the red blood cells were 0 U, and the plasma was 100 mL. After the operation, the patient's vital signs were stable, and under sufficient sedation and analgesia, the patient was sent to the ICU with tracheal intubation for observation. The tracheal intubation was pulled out 3 h after the operation, and the patient was transferred to the general ward on the second day after the operation. One week after the operation, the blood biochemical tests were rechecked: ALT 76 U/L, AST 48 U/L, total bilirubin 13.9 μmol/L, albumin 42.4 g/L, creatinine 19 μmol/L, urea 4.6 mmol/L, blood glucose 3.5 mmol/L.

Table 1
Intraoperative hemodynamics and myocardial enzyme spectrum changes.

	Entry into operation room	Beforeincision	Anhepatic phase 30 min	Immediate reperfusion phase	Reperfusion phase1h	End of operation
HR (beats/min)	105	118	137	85	124	125
BP (mmHg)	92/50	98/56	65/40	52/35	80/41	98/37
CVP (mmHg)	–	5	3	10	12	8
CI ($L{\cdot}min^{-1}{\cdot}m^{-2}$)	–	3.29	2.82	2.01	3.25	4.38
SVV	–	14 %	34 %	12.5 %	7.6 %	7 %
CCE	–	0.20	0.14	0.06	0.32	0.24
hs-cTnI (pg/mL)	–	39.6	56.4	–	63.6	93.2
CK-MB (pg/mL)	–	2.2	4.9	–	5.1	5.4

Table 2
Arterial blood gases during liver transplantation.

	After induction	Hepatectomy phase	Anhepatic phase 30 min	Reperfusion phase 1 h	End of operation
PH	7.26	7.33	7.28	7.25	7.27
PO2 (mmHg)	346	356	357	345	320
PCO2 (mmHg)	44.6	39.9	37.2	43.4	32.5
Hb (g/L)	131	127	113	109	97
Lac (mmol/L)	3.0	3.4	5.0	7.0	10
SBE (mmol/L)	−7	−7.5	−7.7	−8.2	−8
Glu (mmol/L)	3.4	3.9	4.4	5.2	8.5
K+ (mmol/L)	3.4	3.8	3.3	3.7	4.2

3. Outcome and follow up

The liver function recovered well 28 days after the operation, no other complications were found, and the patient was discharged smoothly.

4. Discussion

Mitochondrial diseases are a group of inherited metabolic diseases characterized by impaired mitochondrial oxidative phosphorylation caused by defects in mitochondrial DNA or nuclear DNA, which are the real cause of several neurological, muscular, cardiac, and endocrine diseases. The genotypes and clinical phenotypes of MDS are complex and diverse. Hepatocerebral MPV17-MDS typically manifests as cholestatic hepatitis, hepatitis, hypoplasia, developmental delay, systemic hypotension, hypoglycemia, and lactic acidemia [5]. Liver dysfunction and neuromuscular diseases usually occur in infants and young children [6]. MDS has a poor prognosis, and there is currently no effective treatment, mainly symptomatic treatment [7]. Liver transplantation can be performed for liver failure in this disease to improve the quality of life and prolong the life of patients [5]. Postreperfusion syndrome (PRS) is a common physiological and pathological process in liver transplantation. The incidence of PRS is approximately 34.7 % [8]. PRS was first reported by Aggarwal in 1987. It is usually defined as a decrease of mean arterial pressure of >30 % from the baseline within 5 min after liver transplantation reperfusion, and it lasts for >1 minute [23]. It not only causes a sharp drop in blood pressure but also a slow heart rate, which can even result in cardiac arrest and is one of the most dangerous complications of pediatric liver transplantation [8]. Moreover, the occurrence of PRS can also induce acute kidney injury (AKI) and myocardial damage, which seriously affects the prognosis of children [9,10].

As this child has mitochondrial DNA depletion syndrome, the disruption of cellular energy generation caused by mitochondrial malfunction puts high-energy-demanding organs and tissues (such as the brain, heart, and skeletal muscle) at risk during surgery [4]. It motivates us to pay closer attention to the prevention and treatment of PRS in anesthetic management to minimize damage to the child's organs and tissues with high energy demands.

There are many causes of PRS after portal vein opening in liver transplantation, and the mechanism is complicated. In recent years, studies have found that the occurrence of PRS is mainly related to the return of a large amount of low-temperature blood containing acidic metabolites and inflammatory mediators to the heart, resulting in dramatic changes in hemodynamics [9]. Some researchers believe that the opening of the portal vein during liver transplantation, low temperature, acidity, and high potassium-containing blood quickly enter the systemic circulation and return to the heart, which is the initial cause of PRS [11]. In addition, the decrease of mitochondrial DNA in children with MDS can lead to energy metabolism disorders in tissues and organs, and are more likely to develop lactic acidosis. Prolonged preoperative fasting leads to hypoglycemia and possible metabolic encephalopathy [12]. Therefore, intravenous glucose is required during the preoperative fasting period to reduce the occurrence of hypoglycemia and hypovolemia. During the operation, we should choose the fluid that does not increase the blood lactate level, maintains the acid-base balance, maintains an appropriate colloid osmotic pressure, can rapidly expand the volume, increases tissue perfusion, and has minimal impact on renal function and coagulation function. The donor perfusate is usually UW fluid, which can cause a transient increase in serum potassium in the early stage of new liver reperfusion, and may even lead to cardiac arrest, seriously endangering the life of the child. The serum potassium level should be closely monitored during the operation, and the high potassium perfusate should be flushed from the donor with protein water before opening. If the blood potassium level is increased during the anhepatic phase, symptomatic therapy with insulin, sodium bicarbonate, or calcium should be administered promptly. Dysfunction of the mitochondrial respiratory chain can cause defects in thermogenesis, and patients with mitochondrial diseases are also at increased risk of hypothermia [13]. Inflatable warming blankets, infusion warming, and radiation warming apparatus irradiation are all effective active-heat preservation measures. Meanwhile, intraperitoneal warm water irrigation is also a fast and effective warming method. For our patient, we made the effort to implement body temperature protection strategies throughout the procedure continuously monitored the arterial blood gas of the child, actively maintained the stability of the internal environment and electrolyte balance, and avoided hyperkalemia and hyperlactatemia induced PRS.

Immediately after reperfusion of the transplanted liver, peripheral vascular resistance decreases, and transient hypotension often occurs. If the arterial systolic blood pressure decreases by >30 % for >5 min, PRS is diagnosed. A study by Ryu [14] found that pretreatment with epinephrine or phenylephrine during reperfusion during liver

transplantation significantly reduced the incidence of PRS. Therefore, we administered 2 μg of epinephrine and 10 mL of sodium bicarbonate immediately after the portal vein was opened to prevent the occurrence of PRS. However, the child suffered resistant hypotension 30 min after the reperfusion and we continued to pump 0.05 μg/kg/min epinephrine until the end of the operation to maintain hemodynamic stability. Although the patient in this case actively prevented the occurrence of PRS before opening, and PRS did not appear immediately after opening, unfortunately, The incidence of PRS could not be averted half an hour after the portal vein was opened.

Myocardial injury is one of the common complications of liver transplantation. Our center's study found that the incidence of myocardial injury in children's liver transplantation is as high as 52 % [15]. Huang. et al. [16] found that the incidence of PRS was higher in patients with myocardial injury after liver transplantation. Multivariate logistic regression analysis found that PRS was an independent risk factor for myocardial injury. In addition, mitochondrial diseases due to their genetic defects can cause mitochondrial oxidative phosphorylation disorders, thereby affecting energy production. Patients with mitochondrial disease are prone to cardiac involvement in many conditions [17]. Therefore, we should pay more attention to the protection of myocardial function during the operation. We used the Mostcare monitor to monitor CI, SVV, CCE, and other indicators during the operation. It can better reflect the systolic function of the heart, accurately assess the volume responsiveness, and allow us to quickly grasp the state of cardiac function and take timely and efficient myocardial protection measures. The pressure recording and analysis method (PRAM) is a minimally invasive hemodynamic monitoring method with the advantages of being minimally invasive, no direct or indirect calibration, and suitable for low birth weight infants weighing <20 kg [18]. High-sensitivity troponin (hs-cTn) is a new generation of myocardial markers with higher sensitivity. The sensitivity of the hs-cTn detection method is 100 times that of traditional detection methods [19]. It will facilitate the early detection of myocardial injury. Studies have found that elevated high-sensitivity troponin levels are associated with myocardial dysfunction and short-term mortality, and hsTn measurement can be used as a standard intraoperative monitoring tool in liver transplant patients [20]. Cyclic adenosine monophosphate for injection is exogenous cyclic adenosine monophosphate (cAMP), which can directly play the role of cAMP in vivo. As a second messenger, cAMP plays a role in regulating physiological functions and material metabolism in cells. cAMP can directly or indirectly activate a series of protein kinases, enhance phosphorylation, inhibit the production of free radicals, and prevent ischemia-reperfusion injury [21,22]. Therefore, we gave adenosine to reduce the myocardial injury in the child. Ultimately, the patient recovered well and was discharged from the hospital.

5. Conclusion

In conclusion, to prevent the occurrence of PRS in MDS patients undergoing liver transplantation, we can: (1) Intravenous glucose during fasting to reduce hypoglycemia and hypovolemia; (2)Actively take temperature protection measures during the operation; (3)Continuously monitor arterial blood gas, actively maintain internal environment stability, electrolyte balance, and avoid hyperkalemia and hyperlactatemia; (4) Pretreatment with epinephrine or phenylephrine. After the occurrence of PRS, we should actively prevent and adopt high-energy-demand organ protection strategies to reduce the occurrence of postoperative complications. Further research on the perioperative care of this special population is required in the future.

Ethical approval

Patient gave us informed consent and ethnical approval was not required.

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Author contribution

All authors contributed in writing the paper.

Guarantor

Jiangang Xu is the guarantor for this study.

Research registration number

N/A

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors state that they have no conflicts of interest for this report.

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