Letter to the Editor

Living donor liver transplantation combined with splenectomy in a child with Niemann-Pick disease type B: single-centre experience of perioperative anticoagulation regimen

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Niemann-Pick disease (NPD) is a rare and life-threatening disease caused by the deficiency of acid sphingomyelinase activity which is characterized by intracellular accumulation of sphingomyelin within multiple organs (1). At present, few non-surgical treatment options are available for NPD apart from enzyme replacement therapy and allogeneic hematopoietic stem cell transplantation. However, neither surgical nor alternative therapies can modify the progression of neurological disorders, which makes the prognosis of NPD except type B bleak (2). NPD type B (NPD-B), known as one visceral form of NPD, is usually clinically manifested as hepatosplenomegaly but without neurological symptoms. Notably, pulmonary parenchymal involvement secondary to the accumulation of sphingomyelin in alveoli is also a feature of NPD-B (3). Scattered reports (4) indicated that liver transplantation (LT) have shown some preliminary results for NPD-B. Owing to the effect of diseased spleen on operation field and pancytopenia associated with hypersplenism, splenectomy is always performed in conjunction with LT. However, the hypercoagulable state associated with splenectomy which may induce hepatic artery thrombosis (HAT) or portal vein thrombosis (PVT) deserves our attention. Here we report a case of living donor liver transplantation (LDLT) combined with splenectomy in a child with NPD-B along with perioperative anticoagulation regimen review.

The patient was a 7-year-old boy who was diagnosed with NPD-B by enzymology examination, a bone marrow aspiration and a genetic test (mutation in SMPD1) at the age of 1. It is a difficult choice to perform LT before liver failure for the patient with Child-Pugh class B, but persistent hepatosplenomegaly, progressive liver dysfunction, growth retardation and repeated pneumonia caused by NPD-B pushed him to receive LT. We cautiously evaluated the possibility of LDLT with high-accuracy 3D technology and calculated the graft to recipient weight ratio to be 1.78% with expanded left lateral lobe (*Figure 1A*). This LDLT case was approved by the ethics committee of our hospital (No. XHEC-D-2021-125) and all data of the pediatric patient were reported with the consent of his parents. The operation went well with an intraoperative blood loss of 200 mL and without any transfusion. The resected liver and spleen showed hepatic fibrosis stage IV and local splenic infarction accompanied with a large number of characteristic foam cells in pathology (*Figure 1B*). In addition to the recovery of liver function, catch-up growth (height z-score increased from −2.4 to −1.8, weight z-score increased from −1.3 to −0.6), relief of pneumonia (*Figure 1C,1D*) and restored pulmonary function (FEV1 percentage increased from 68% to 84%) were gradually observed during follow-up, possibly because the transplanted liver enhances the acid sphingomyelinase activity and reduces the accumulation of sphingomyelin in other organs.

HAT and PVT after LT is dreaded sequelae that often result in ischemic liver necrosis and graft loss. We strived to reduce the incidence of thrombosis by anastomosing under ×10 magnification microscope, confirming sufficient blood flow by vascular blood flowmeter, avoiding plasma and other anticoagulants transfusion, monitoring the occurrence

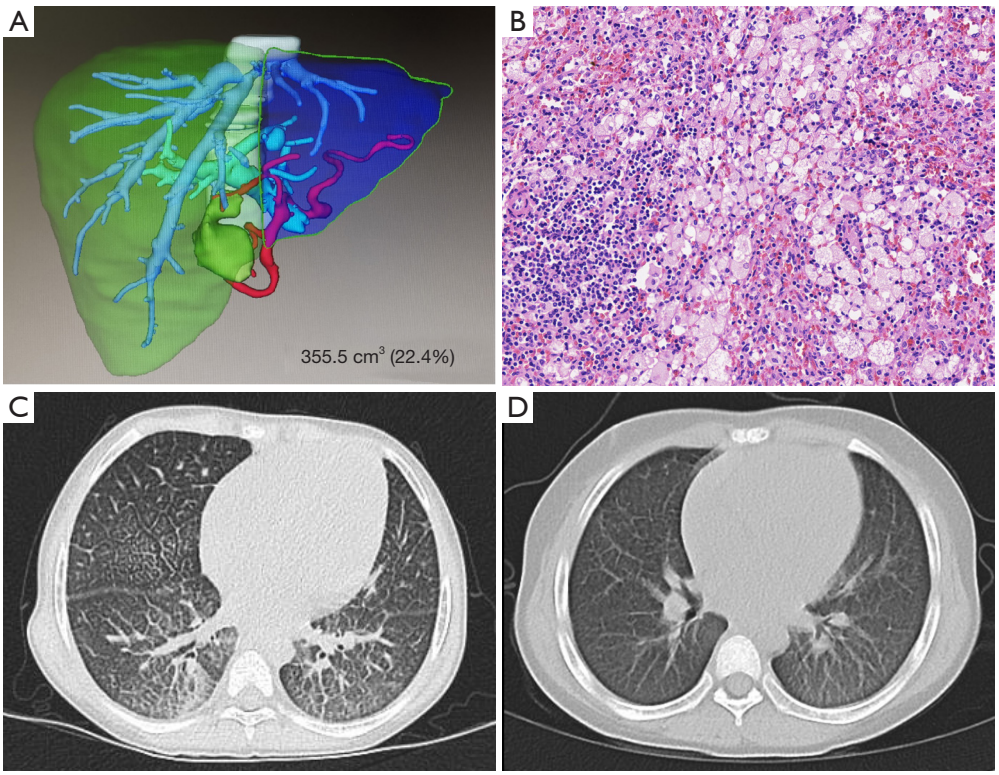

Figure 1 Clinical characteristics of the child with NPD-B. (A) Volume calculated with expanded left lateral lobe as a graft. (B) Foam cells in spleen. Staining method: hematoxylin-eosin staining. Magnification: ×10. (C) Chest CT scan indicated diffuse pulmonary interstitial fibrosis before LT. (D) Chest CT scan indicated relief of pneumonia after 8 months of postoperative follow-up. NPD-B, Niemann-Pick disease type B; LT, liver transplantation.

of HAT/PVT frequently with ultrasonography and actively applying anticoagulants after operation.

Given the lack of guidelines for anticoagulation following pediatric LDLT combined with splenectomy, we extrapolated the clinical management from the inhibition scheme of platelet activation after splenectomy and therapies across Studies of Pediatric Liver Transplantation Registry centers (5). Our routine anticoagulant protocol was the early use of intravenous heparin (5 IU/kg/h), alprostadil (10 μg q.d.), dextran-40 (6 g q.12h.) and sequential oral aspirin (100 mg q.d.). We planned to administer heparin infusions for at least 7 days and chose 60–80 and 130–160 s as the target range of activated partial thromboplastin time (APTT) and activated clotting time (ACT) respectively (6). Before POD 5, the dosage of heparin was adjusted according to ACT in pediatric intensive care unit. On POD 5 in the general ward, when the dosage of heparin reached the peak according to APTT rather than ACT, we observed bleeding fluid from the patient's drainage tube and a significant decrease in hemoglobin. The same bleeding event occurred on POD 7 when we increased heparin again according to APTT. We analyzed the coagulation index on POD 5 and found that although the ACT value was 257 s which was much higher than target range, we still increased the heparin dosage to 25 IU/kg/h according to the APTT value of 31 s. On POD 7, when we increased the heparin dosage again according to the APTT value of 28.7 s, the bleeding event occurred again. Therefore, we realized that it might not be safe to adjust the dosage of heparin according to APTT, as pharmacokinetics and pharmacodynamics of heparin are highly unpredictable for various reasons, especially age (7). Although the pediatric patient had been 7 years old, growth retardation and low weight caused by NPD-B were noteworthy. Moreover, heparin concentration over 1 unit/mL would prolong APTT beyond the linear monitoring range while ACT shows a dosage-response relationship with heparin concentration (8). In summary, we believe that ACT is more reliable than APTT in

monitoring application of heparin after pediatric LDLT for patients with NPD-B.

On POD 13, we had to take oral clopidogrel (75 mg q.d.) and dipyridamole (25 mg t.i.d.) due to the continuous increase of platelet count. Although the platelet count of the patient never fell below 700×10^9/L and even reached $1,636\times10^9$/L on occasion, no thrombotic adverse events occurred during follow-up. The reason may be that the formation of PVT was not only related to the platelet count, but also related to the quality of platelets. In our case, the MA value of thrombelastogram/platelet count on POD 16 and the third month after operation were 42.5 mm/876×10^9/L and 47.8 mm/732×10^9/L respectively. So we reduced the dosage of clopidogrel and dipyridamole successively and no thrombotic events were observed. Low preoperative platelet count and mean platelet volume were considered to be independent risk factors for PVT after splenectomy (9,10), possibly because of stronger aggregation capacity after splenectomy and more thrombus precursors released by larger platelets when activated. Fortunately, the preoperative platelet count and mean platelet volume of the patient were 94×10^9/L and 10.3 fL, respectively. Our antiplatelet aggregation therapy has been maintained for 1 year, but the platelet count is basically in the range of $700–800\times10^9$/L without significant reduction. We speculate that this range may have become the normal level for this patient and even be associated with a lifetime. It is actually difficult to maintain a balance between thrombosis and drugs withdraw, but we have been committed to perfecting our anticoagulation regimen through regular follow-up.

In conclusion, we reported a successful case of LDLT combined with splenectomy in a child with NPD-B, which had ameliorated the liver and pulmonary function, pancytopenia and growth retardation. Careful surgical procedure and proper anticoagulation regimen can effectively reduce the incidence of thrombosis after LDLT, although the thrombocytosis caused by splenectomy is always difficult to be corrected.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-454/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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