Case Reports in Gastroenterology

Case Rep Gastroenterol 2021;15:296–304

DOI: 10.1159/000513281
Published online: March 11, 2021

Case Series

The First Two Liver Transplantations in Syria

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Keywords
Liver transplantation · Living donor · Syria

Abstract
Liver transplantation (LT) is the only curative therapy for the end-stage liver diseases and some metabolic disorders which affect the hepatic cell like the Crigler-Najjar syndrome type 1 (CNSI). Although the LT is a routine procedure in many centers worldwide, the postoperative complications such as rejection, arterial thrombosis, and infection remain serious challenges even in big centers. In our paper, we demonstrate the first two LTs in Syria. The first one was performed on 6 February 2016 for an 11-year-old boy suffering from CNSI using an auxiliary LT, but unfortunately, he had a hepatic artery and portal vein thrombosis, so we removed the necrotic graft on the fifth postoperative day, and he survived. The second LT was for a 9-year-old boy, who had cryptogenic liver cirrhosis, and he lived for 31 days after the transplantation. In both transplants, grafts were obtained from living relative donors.

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Introduction

Solid organ transplantation began in 1954 with a successful kidney transplantation between identical twin brothers [1]; as for liver transplantation (LT), it began in 1963, when T.E. Starzl performed the first three LTs in humans, and his patients stayed alive for 0, 7, and 22 days, respectively [2], but the first successful LT was in 1967 for a 19-month-old girl with hepatocellular carcinoma, who died 13 months after surgery because of a metastatic disease [3]. In 1984, Bismuth reported the first left-lobe LT in a child [4], then in 1988, Pichlmayr performed the first split-LT [5]. The next year, Silvano Raia described the first attempt at a living donor graft in a child [6], but the successful procedure was performed by Strong in 1990 [7]. Since that time, the greatest experience with living donor grafts was in 2017, when more than 6,000 (about 20% of all LT) living donor LTs were performed worldwide [8]. LT is the only curative therapy for liver cirrhosis caused by hepatitis or metabolic disorders such as Wilson's disease, tyrosinemia, alpha-1-antitrypsin deficiency, and Crigler-Najjar syndrome type 1 (CNSI) [9–12], and liver replacement in these cases corrects the metabolic effect, in addition to resolving the problems posed by the cirrhosis. It is worth mentioning that some liver-based metabolic disorders do not cause structural damage of the liver but result in severe or life-threatening extrahepatic complications, and LT is used successfully to replace the defective enzyme or receptor site in such disorders [12]. The aim of this paper is to describe the first two LTs in Syria, and to highlight the existing challenges.

Case Presentation

The first recipient was an 11-year-old boy; he was referred to our institution with CNSI. He was mentally and physically retarded with a poor compliance to phototherapy. His general condition was not poor. Total bilirubin was 30 mg/dL, serum glutamic oxaloacetic transaminase was 26 U/L, and INR was 1.1. After the preoperative preparation of the recipient and the donor, who was his 34-year-old uncle with the same major blood group (O+), we started the donor's operation by isolating the porta hepatis (Fig. 1) and left hepatic vein. After this step, we started the recipient's operation by Mercedes incision, we prepared the hepatic hilus, resected the left liver, and prepared the vena cava inferior (VCI), portal vein, and hepatic artery. The donor's operation took about 300 min without blood transfusion. We continued the hepatic parenchyma dissection with Cavitron ultrasonic surgical aspirator (CUSA), then left lateral hepatectomy (liver segments II, III) was done. The graft was perfused by histidine tryptophan ketoglutarate (HTK) solution via portal vein (about 400 mL), the bile duct (about 200 mL), and the very thin artery (about 200 mL). After that, the left lateral graft was transplanted orthotopically as the following steps:

(a) VCI and hepatic vein were anastomosed with continuous prolene 3/0.

(b) Portal vein was anastomosed with continuous prolene 5/0.

(c) Then, the reperfusion demonstrated a good color (Fig. 2) (Before the reperfusion, it is allowed to draw about 100 mL of blood from the VCI anastomosis).

(d) Graft's artery was reconstructed with the recipient's common hepatic artery end-to-side with prolene 6/0.

(e) The biliary tree of the graft was reconstructed by a bilio-jejunostomy anastomosis using vicryl 5/0.

Two intra-abdominal drainages were placed, one near the porta hepatis and the other in the pouch of Douglas. The donor patient left the hospital on the fifth postoperative day (POD) without any complications, and he returned to his work as a truck driver 6 weeks later. The recipient's operation, which took 720 min, needed 6 units of red blood cells and 4 units of frozen fresh plasma. After this long procedure, the patient was referred to the intensive unite care ICU, and after 2 h, he was extubated. The clinical examination on the first POD showed a stable hemodynamic status, so the patient got out of his bed and walked in the room. Of course, the patient was followed up carefully by laboratory investigations and clinical condition monitoring (Table 1), with medications including immunosuppressant, and radiological investigations, where the daily postoperative color Doppler ultrasound (CDUS) of the graft's vessels (hepatic artery, portal vein, and left hepatic vein) showed a good signal. On the fifth POD, the DUS demonstrated an arterial and portal vein thrombosis. The abdomen MCT scan confirmed the CDUS finding in addition to show a graft necrosis, so we had to perform a laparotomy in order to remove the necrotic graft. The patient was discharged from the hospital after 33 days in a good general status. Now, 1,620 days after that unsuccessful auxiliary LT, our patient is still alive, and his status is as before the operation.

The second recipient was a 9-year-old boy who suffered from unknown liver cirrhosis. He was admitted to pediatric hospital in a poor general condition, with hepatosplenomegaly and jaundice. The laboratory findings included bilirubin which was 49 mg/dL, platelets 117×10^9, PT 32%, albumin 4 g/dL, and creatinine 0.5 mg/dL. The Pediatric Model for End-Stage Liver Disease (PMELD) score was 30. We completed the recipient preparation by transfusion of the fresh-frozen plasma FFP, cryoprecipitate, and platelets. We made a molecular adsorbent recirculating system in order to reduce the serum bilirubin level, and the patient was ready for the transplantation.

The donor was his 34-year-old aunt, who has the same major blood group (A+). We started her operation with a right subcostal Kocher incision which extended vertical up to the xiphoid. The liver showed a very good color and consistency. After we prepared the hepatic hilus and isolated the portal vein, left hepatic artery, and the left hepatic vein, we dissected the parenchyma with CUSA, and the left liver lobe was resected. This procedure took about 150 min without any blood transfusion. The graft weight to the recipient weight (GW/RW) was 1.2%. The graft was perfused via HTK with 500 mL via the portal vein, 300 mL via the hepatic artery and 200 mL via the biliary duct (Fig. 3). When donor's hepatectomy started, the recipient's operation began. We performed a hepatectomy via a Mercedes incision, but at the last step of the hepatectomy, a massive bleeding occurred from the VCI; fortunately, it was under control. The graft was implanted with the piggy-back technique, and the following steps were done:

1 Side-to-end cava-left hepatic vein anastomosis using 3/0 polypropylene running suture.

2 End-to-end portal vein reconstruction using 5/0 polypropylene running suture.

3 Reperfusion and some blood was drawn from the VCI anastomosis.

4 The arterial anastomosis was fashioned with 7/0 polypropylene running suture using a saphenous vein conduit between the very thin graft artery and the recipient's hepatic artery.

5 End-to-end left hepatic duct – common hepatic duct reconstruction using 5/0 PDS suture.

After reperfusion, the graft demonstrated a good visual color, and the bile began to flow out during the reconstruction of the biliary tree. The patient was transferred to the ICU and he was extubated 6 h later. Of course, the patient was followed up carefully by laboratory investigations and clinical condition monitoring (Table 2). When reviewing the table, we noticed that the patient remained in a good state (clinical, laboratory, and radiological) until the eighth POD. On the 15th POD, the patient suffered from wound dehiscence which was repaired in the operation room. And the liver biopsy which was taken intraoperatively showed a focal necrosis. At that time, the laboratory findings began to worsen, and the microbiological examination of the abdominal drainage showed *Pseudomonas* and *Staphylococcus aureus*, which were treated intensively with suitable antibiotic. On the 22nd POD, the patient developed a severe pneumonia and was referred to the ICU, and finally, he developed acute respiratory distress syndrome (ARDS). Unfortunately, he died on the 30th POD.

Discussion

Regarding the first case, it is worth mentioning that the first report of Crigler-Najjar syndrome (CNS) was in 1952, which is characterized by unconjugated hyperbilirubinemia since birth [13]. CNSI results from a complete deficiency of the enzyme bilirubin UDP-glucuronosyltransferase (UGT), in contrast to the CNS type 2 which results from a partial deficiency. Bilirubin UGT is a member of the UGT family, which is a group of enzymes encoded by the UGT1 and UGT2 genes on 2 and 4 human chromosomes. UGTs are located in the endoplasmic reticulum of hepatocytes. UGT isoforms present in the intestine, kidney, lungs, adrenals, and other organs [14]. Probably because of an unfavorable body surface:weight ratio and because of a decrease in compliance for the socially inconvenient phototherapy sessions lasting approximately 12 h per day. Skin problems, such as hyperkeratosis, by this intensive phototherapy were also frequently reported. LT is the only definitive, effective therapy for this disease [12, 15, 16].

Auxiliary LT from a living donor, as we all know, is a very complicated procedure, and it is not a good option for a developing country to start an LT project, but the privacy of our community and our social reality does not allow us to lose the first patient, so we decided to perform that unusual operation, and the goal, which did not leave our minds (never and ever) was that if we could not succeed, we should not lose the patient. Of course, the donor's operation was our priority and we spent about 300 min of additional strenuous effort, spiritually and physically. The donor left the hospital without any complications. Unfortunately, the arterial and portal vein thrombosis on the fifth POD was unexpected, and we could not do anything, because we did not have a deceased donor program, and it was unethical to expose someone else to a high risk (living donor hepatectomy) to save a patient, who had no

guarantee of survival. At this point, we would like to refer to the fact that the incidence rate of hepatic arterial thrombosis is around 12%, and portal vein thrombosis is around 4% [17, 18]. His 4 postoperative years were not worse than his preoperative period, although the operation failed. We believe that our decision was not false, at least, from the ethical perspective.

About the second patient who came 3 years and 3 months after the first LT, we decided to do a usual complete LT from a living donor, as there is no deceased donor's program. Every step and every moment we went through in the first experience was engraved in our minds and senses. About 8 weeks was spent in the preparation of the donor and recipient, and the operation's details were discussed many times and every one of the team knew his job exactly. The donor operation took about 150 min (half of the first one) and was performed as usual. The recipient's operation, total hepatectomy, and graft transplantation, took about 300 min (half of the first one too). The patient was extubated 6 h after the operation and everything (clinical, laboratory, and radiological examinations) went well, and the bilirubin began to decrease. The first 14 PODs gave us a great hope to continue what we started in LT among the unhelpful circumstances, but the unexpected and dramatic end held us back strongly. Three lessons were concluded from our experience:

1 Firstly, the unconditional government support is necessary to start the LT program.

2 Secondly, there is no significant progress in transplantation without activating the deceased donor program (except for rare countries).

3 Finally, optimal patient (recipient and donor) selection and transplantation timing are essential factors in a successful operation.

Despite the unsatisfactory results, we are going to learn from our experience and perform a successful LT in the nearest future.

Acknowledgment

The author would like to thank everyone who contributed to the operations: Mohamad Ahmad, Mohamad Ali Nahas, Abdelrahman Ayoubi, Bayan Alsaid, Ahmad Al Khaddour, Ammar Mohamad, Alaa Hanout (surgery team); Najwa Rekmani, Abdellatif AhmadD, Huda Dawood (anesthesia and intensive care team); Ayman Ali, Lina Al Khoury (hepatology team).

Statement of Ethics

In accordance with the Declaration of Helsinki, my performed study has been approved by the ethics committee of the Hospital. The informed consent to participate in our study has been obtained from the parents of the participants as well as to publish the cases.

Conflict of Interest Statement

There is none to declare.

Funding Sources

No funding or grant support.

Availability of Data and Materials

The datasets used during the current study are available from the corresponding author on reasonable request.

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Case Rep Gastroenterol 2021;15:296–304
DOI: 10.1159/000513281

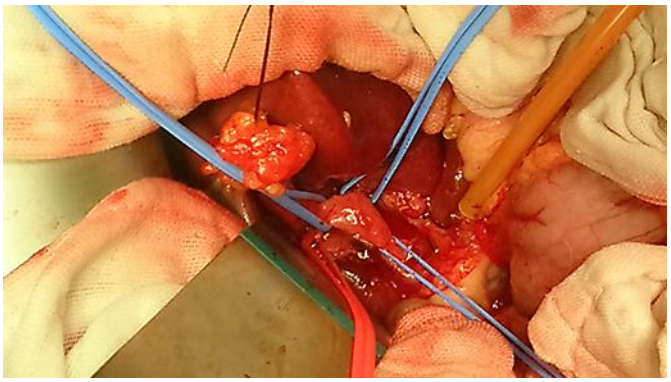

Fig. 1. Intraoperative view showing the left portal vein branches (blue band) and the left hepatic artery (red band).

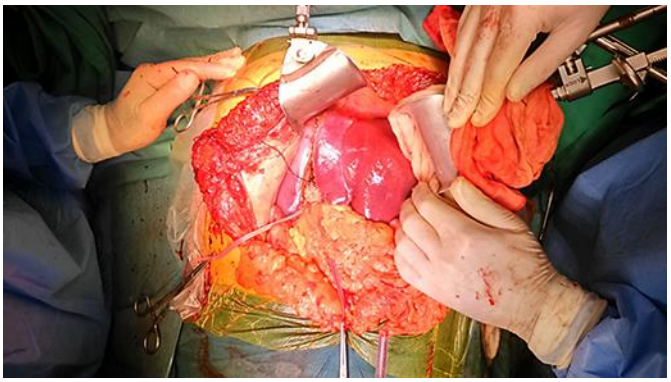

Fig. 2. Intraoperative view showing the reperfusion.

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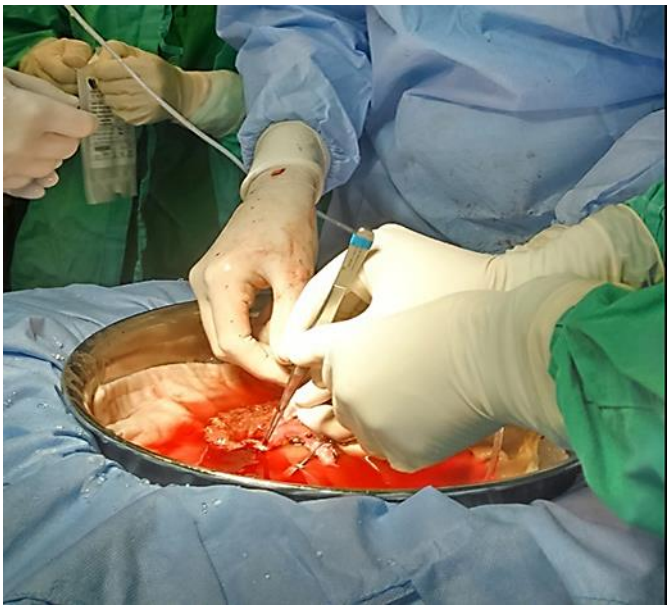

Fig. 3. Perfusion of the graft with HTK.

Table 1. The first patient's follow-up during the hospital stay

POD	Clinical	DUS	WBC	Hb g/dL	Bilirubin mg/dL	GOT/GPT U/L	INR	Creatinine
1	well	good	17,600	12	20	652/1,357	1.8	0.5
2	well	good	13,100	11	22	326/1,008	1.5	0.4
3	well	good	10,900	9.7	26	157/689	1.5	0.5
5	not well	no flow	6,290	9.8	35	75/397	1.4	0.5

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DOI: 10.1159/000513281

Table 2. Second patient's follow-up during the hospital stay

POD	Clinical	DUS	WBC	Hb g/dL	Bilirubin mg/dL	GOT/GPT U/L	INR	Creatinine	Ammonia	FK 506
1	well	good	2,000	7	9.8	354/418	2.4	0.4	54	7
3	well	good	2,600	12	10		1.8	0.4		41
5	well	good	2,300		10.7		1.7		53	36
7	well	good	3,400	13	8.1	52/174	1.4			22
15	fever 39°C biopsy	good	18,000	12	19	277/680	2.9	0.4	65	
18	ok	no hep. arterial flow good portal vein flow	3,000		22		2.9		78	
21		partial necrosis								
22	ICU									

POD, postoperative day; DUS, Doppler ultrasound; hep., hepatic; ICU, intensive care unit; FK 506, tacrolimus level in plasma.