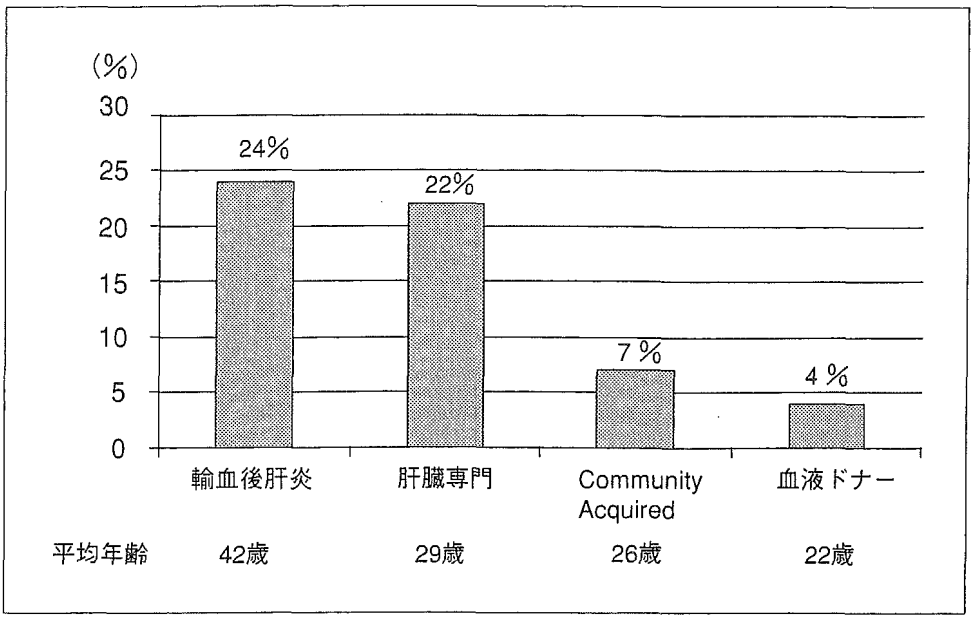

図4　HCV感染後20年で肝硬変に進行する割合(文献[10]より引用改変)

1)肝臓病専門クリニックにおける断面調査(cross-sectional)
2)輸血後肝炎の長期経過観察
3)血液ドナーのスクリーニングの際にHCV感染を指摘された断面調査
4)Community-basedの長期経過観察

に分けて分析した．図4に示すようにHCV感染20年後に肝硬変が出現する頻度は輸血後肝炎のコホートでは24%(感染者の平均年齢は42歳)，肝臓専門クリニックにおけるコホートでは22%(平均年齢29歳)であった．一方，community-basedでは7%(平均年齢26歳)，血液ドナーでは4%(22歳)と低率であった．

肝線維化進展速度

慢性肝炎では肝障害の持続，すなわち肝組織の壊死・炎症の持続とともに線維化が進展し，肝硬変さらには肝癌発症へと至る．慢性肝炎から肝硬変に至るまでの進展度を正確に評価するための指標として，肝組織所見が重要である．肝炎の活動性は肝組織における壊死・炎症の程度を表し，進展度は肝線維化の程度すなわちF因子で表され，F0～F4の5段階に分類されている．F0は肝線維化がなく，慢性肝炎では通常軽度の線維化であるF1ないしは高度線維化のF3と表し，肝硬変はF4に相当する．つまり肝線維化の程度で慢性肝炎の進展度を判断しており，肝線維化の程度の評価は重要である．

Poynardらは感染時期を輸血や薬物使用の時期と推定したうえで，肝生検の線維化の程度から年間の肝線維化の進展率を計算したところ，C型慢性肝炎全体では0.133単位/年，男性；0.154単位/年，女性；0.111単位/年，アルコール飲酒者；0.167単位/年，非飲酒者；0.125単位/年であった．これらの値は1回の肝生検と病歴からの推定の感染期間に基づいている[21]．一方，Shiratoriらは，同一症例で2回の肝生検の線維化の程度の違いを両肝生検の期間で除して計算し，本邦における肝線維化進展率は0.10単位/年と報告している[22]．

肝線維化と発癌率

信州大学第二内科の検討から，C型慢性肝炎における肝線維化の進展度別に年間発癌率を計算したところF1では0.5%，F2で1.5%，F3で2.6%，F4で5.8%であった(図5)[23]．また，YoshidaらもC型慢性肝炎490例の検討からもそれぞれ0.4%，2%，5%，8%とほぼ同様の成績が報告されており[24]，C型肝炎ウイルス群では肝硬変がもっとも強い危険因子であることが分かる．

現在までに慢性肝疾患の進展や肝発癌に影響

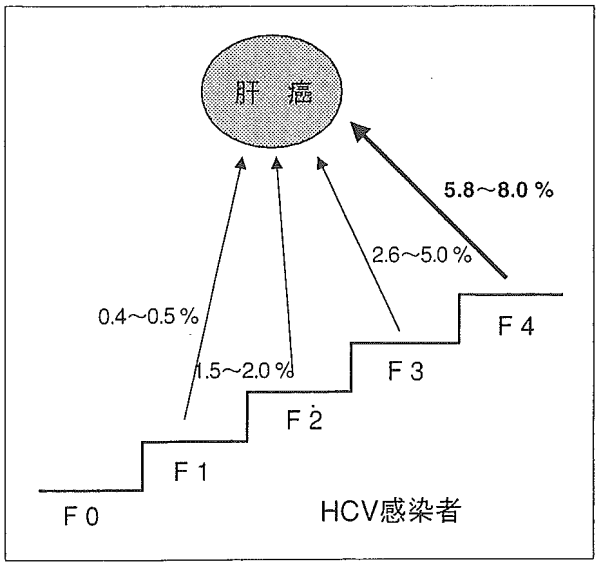

図5 C型慢性肝炎の自然経過と肝線維化

を及ぼしている因子がいくつか報告されている[14]．

宿主側の要因：高齢者や感染時年齢が高齢の場合は進展が早い．性差(男性)，人種差(黒人)も重要な要因である．糖尿病，肥満の合併なども進展を早める．肝線維化の進展度(肝硬変)も発癌に影響を与える．

ウイルス側の要因：われわれは以前，genotype 1に感染した群はgenotype 2に感染した群より肝癌患者が多いと報告したがgenotype 1と慢性C型肝炎の進展の関連性には否定的な報告もあり明らかとなっていない．ウイルス量，超可変領域(Hypervariable region)のquasispeciesが線維化の進展に関与するという報告は現在までにない．HBVやHIVとの重複感染は慢性肝炎の進展に関与するという報告もされている．

環境因子：大量のアルコール摂取は進展を早めることが報告されている．

おわりに

C型肝炎の自然史としてC型慢性肝炎の経過，肝線維化の進展，肝発癌の危険因子について概説した．従来，線維化の評価は肝生検によって行われてきた．しかし，肝生検は危険が0でないこと，時にサンプリング・エラーや読み違いなどが起こる可能性もある．感度の高い線維化の血清マーカーは存在しないため，簡単に線維化の状態を推定する計算式や最近では肝臓の“硬さ”を非侵襲的に測定できるFibroscan®の開発も行われてきている[25)26)]．しかし，感度，特異度，コストなどに問題がある．肝線維化の進展を正確に評価できるマーカーの開発は今後の重要な課題である．2004年，アメリカではNational Institutes of Healthが中心となって“Action Plan for Liver Disease Research”(http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm)を発表している．肝臓病を16の分野に分けておのおのの専門家たちがその分野において現在までに明らかになっていること，今後明らかにしなくてはならないことについて優先順位を示している．肝線維化の分野では血清マーカーの開発が最重要プロジェクトとしてあげられている．また，今後の研究はC型肝炎の進展に関する病態を明らかにし，線維化の進展に寄与しているかもしれない未知の因子の同定などにも力を入れる必要がある．

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SURGERY TODAY

Improved Quality of Life and Unchanged Magnetic Resonance Brain Imaging After Living Donor Liver Transplantation for Late-Onset Ornithine Transcarbamylase Deficiency: Report of a Case

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Abstract
We report the case of a 7-year-old girl with ornithine transcarbamylase deficiency whose quality of life (QOL) improved greatly after a living donor liver transplantation (LDLT). Ornithine transcarbamylase deficiency had been diagnosed when she was 2 years old and she finally underwent LDLT, with her father as the donor, when she was 7 years old. The patient had suffered episodes of hyperammonemic encephalopathy ranging from lethargy to coma, treated by hemodialysis twice before LDLT, and her intelligence quotient was borderline for her age. Preoperative magnetic resonance imaging (MRI) showed an atrophic area in the subcortical white matter of the frontal lobe. After LDLT, the patient suffered acute rejection with hyperamylasemia, but not hyperammonemia. Postoperative MRI and quantitative MR spectroscopy showed no changes in the subcortical lesion. She has been followed up carefully for 16 months and has had no further complications or any sign of hyperammonemia.

Key words Living donor liver transplantation · Ornithine transcarbamylase deficiency · Magnetic resonance imaging · Brain atrophy · Quality of life

Introduction

Ornithine transcarbamylase deficiency (OTCD) is one of the most common inherited disorders of the urea cycle in Japan.[1] It is an X-linked disorder characterized by signs and symptoms of encephalopathy caused by the accumulation of precursors of urea, principally ammonia and glutamine, in the blood. The incidence of OTCD is 1:80000 and it can manifest as the early-onset type or the late-onset type. In boys, the early-onset type of OTCD manifesting during the neonatal period is often fatal, although the late-onset type is milder. On the other hand, heterozygous girls may be normal or have episodes of hyperammonemic encephalopathy with a consequent decline in cognitive function.[1] The treatment for this disease is directed at minimizing the requirement for urea biosynthesis by decreasing dietary nitrogen intake and by increasing waste nitrogen excretion with sodium phenylbutyrate.[2] However, this conservative therapy does not completely prevent hyperammonemic coma and deterioration on cognition, and liver transplantation is necessary if the hyperammonemic attacks are frequent.[3] We report a case of living donor liver transplantation (LDLT) for OTCD which resulted in improved quality of life (QOL) and no further sign of deterioration on cranial magnetic resonance (MR) images 16 months after transplantation.

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Case Report

A girl born after an uncomplicated gestation and delivery was taken to a nearby hospital at the age of 2 years 3 months for investigation of general fatigue, vomiting, and emotional instability. She was diagnosed as having OTCD at the age of 2 years 9 months based on the following findings: hyperammonemia, orotic aciduria, and elevation of plasma glutamine. Protein restriction and medication with sodium benzoate, citrulline, lactulose, carnitine, and arginine were begun, despite with she suffered several episodes of hyperammonemia, which developed into fulminant hyperammonemia,

Table 1. Peak levels of orotate and uracil (mmol/g creatinine) in the urine of the patient and her parents after an allopurinol load

	Orotate (μmol/g Cr)	Uracil (μmol/g Cr)
Patient		
Before LDLT	1691.6	1220.2
1 year after LDLT	29.5	86.0
Father	54.5	59.0
Mother	90.4	119.8
Normal range	<98 (child), <211 (adult)	<254

After oral allopurinol (5 mg/kg), four consecutive 6-h urine collections were taken over the next 24 h.[4] Normal range data were obtained from previous studies[5,6]
LDLT, living donor liver transplantation

Table 2. Changes in serum ammonia, glutamate, glutamine, urine orotate, and urine uracil in the patient

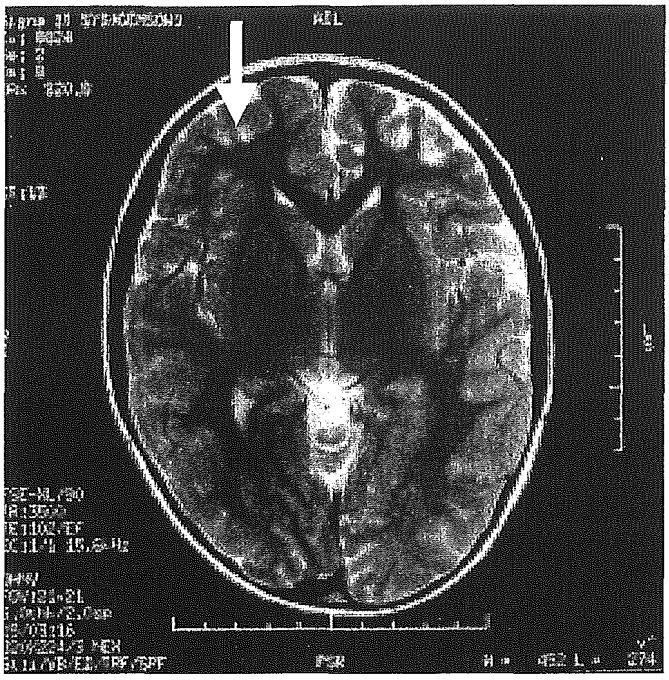
	NH_3 (μg/dl)	Glutamate (μmol/l)	Glutamine (μmol/l)	Orotate (μmol/g Cr)	Uracil (μmol/g Cr)
1 day before LDLT	74	35	371	29	614
Start of LDLT	86	41	358	749	543
Ahepatic period	78	14	332	5	571
Declamping	138	50	376	3	351
End of LDLT	47	NA	NA	4	94
POD 1	94	15	196	3	34
POD 3	82	25	213	14	98
POD 6	44	14	178	15	112
POD 31	63	14	126	NA	NA
1 year after LDLT	34	4	172	4	51
Normal range	<85	15–72	420–700	5–31	<105

Normal range data were obtained from previous studies[4,5]
LDLT, living donor liver transplantation; NH_3, ammonia; POD, postoperative day; NA, not available

twice necessitating hemodialysis. At the age of 7, she was referred to our hospital for LDLT. Her parents were evaluated as potential volunteer donors. The allopurinol loading test, which is used to determine latent carriers of OTCD, showed no abnormalities in either parent (Table 1).[4–6] Thus, the genetic origin of the disease in the patient was considered to be a new mutation. The father decided to be the donor because his blood type was identical to that of the patient.

At the time of admission, the patient was alert and asymptomatic. Physical examination revealed no abnormalities in her abdomen and the superficial lymph nodes were not palpable. The palpebral conjunctivae were not anemic and the bulbar conjunctivae were not stained yellow. The patient showed a normal growth pattern and her intelligence quotient (IQ) was at the borderline of normal for her age (IQ = 76: Tanaka Binet Scale of Intelligence). Laboratory data showed a slightly low prothrombin time (51.0%, international normalized ratio 1.73), an increased serum ammonia level (174 μg/dl), and normal aspartate aminotransferase (AST, 33 IU/l), alanine aminotransferase (ALT, 36 IU/l), and albumin (4.3 g/dl) levels. Her serum was positive for anti-cytomegalovirus and anti-Epstein–Barr virus antibodies. Contrast-enhanced computed tomography (CT) of the abdomen showed a normal-sized liver and a spleen within the normal range of vessel variation. Doppler ultrasonography showed normal blood flow through the intrahepatic portal vein and hepatic vein. Magnetic resonance imaging (MRI) of the brain revealed spotty T1 and T2 prolongations in the subcortical white matter of the frontal lobe. Based on the results of these preoperative examinations we concluded that there were no contraindications to LDLT, which we performed using the left lobe of her father's liver.

During the operation we monitored her serum ammonia levels and had prepared for hemodialysis in case hyperammonemia developed. However, as her serum ammonia levels decreased after declamping, we did not need to carry out acute blood purification during or after transplantation (Table 2). The graft weight/recipient weight ratio was 1.4. The operation time was 12 h and the total blood loss was 889 ml. The patient was given tacrolimus, methylpredonisolone, and mycophenolate mofetil (MMF) as immunosuppressive



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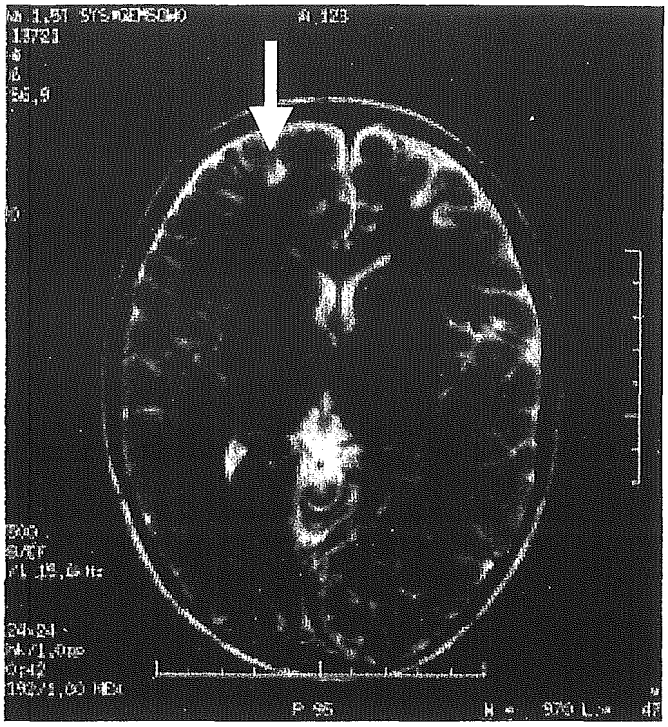

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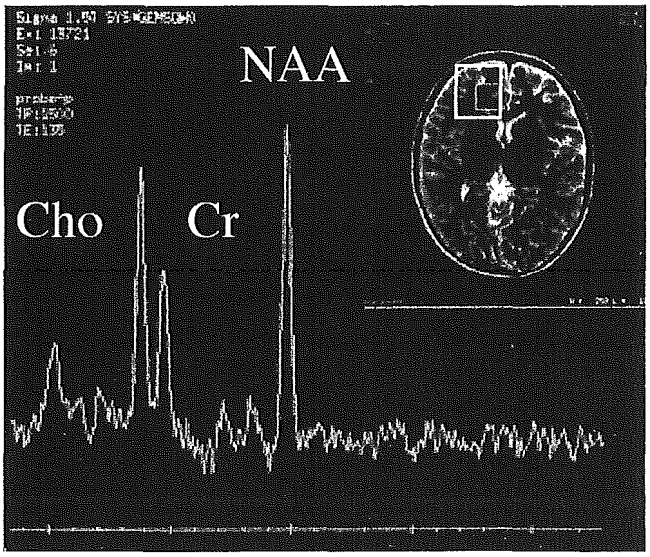

c

Fig. 1. Brain magnetic resonance imaging (MRI) and MR spectroscopy before and after living donor liver transplantation (LDLT). There were some spotty lesions in the subcortical white matter of the frontal lobe (**a**). The lesion in the subcortical white matter was unchanged 1 year after LDLT (**b**). MR spectroscopy (repetition time 1500/echo time 135) 1 year after LDLT showed no abnormal pattern (**c**). *N*-Acetylaspartate (*NAA*) peak was 2.0 ppm, creatine (*Cr*) peak was 3.1 ppm, and choline (*Cho*) peak was 3.2 ppm

therapy. Her post-transplant course was unremarkable, apart from symptoms of acute rejection and mild acute pancreatitis, and she was discharged from hospital on the 76th postoperative day.

At the time of writing this report, 16 months after LDLT, her serum ammonia level and allopurinol loading tests were within the normal range (Tables 1 and 2) and there has been no further evidence of hepatic encephalopathy. Magnetic resonance imaging of the brain still showed the same spotty lesions in the subcortical white matter of the frontal lobe observed before LDLT, and the size of these lesions was also unchanged (Fig. 1a,b). Magnetic resonance spectroscopy after LDLT showed on abnormal peak of *N*-acetylaspartate, creatine, and choline (Fig. 1c). The patient's IQ was still at the borderline of normal for her age (IQ = 75: Tanaka Binet Scale of Intelligence). The patient attends a normal elementary school and is not on a restricted diet. She is followed up in our outpatient clinic every 6 weeks.

Discussion

We reported a case of late-onset OTCD initially treated by protein restriction with sodium benzoate, carnitine, and arginine, and finally cured by LDLT after the development of hyperammonemic encephalopathy, when the patient was 7 years old. Before LDLT, this patient was frequently in hospital and she had to follow a strict diet;

however, after LDLT she could eat what she wanted and her QOL was greatly improved. The patient also had focal brain atrophy caused by the continuous hyperammonemia, and MRI showed no further progression of this after LDLT. Up until 2003, only 14 cases of LDLT for OTCD had been reported in Japan,[7] but these cases constitute important evidence of the usefulness of LDLT to cure OTCD.

Ornithine transcarbamylase deficiency is an X-linked genetic disorder of the urea cycle, which is not uncommon in Japan.[1] The signs and symptoms of encephalopathy are related to the accumulation of the precursors of urea, principally ammonia and glutamine, in the blood.[2] Ornithine transcarbamylase deficiency occurs at an incidence of 1:50000 to 80000,[1,8] and it is a life-threatening disease in hemizygote male neonates with lethargy, vomiting, coma, and serious hyperammonemia and hyperglutaminemia soon after birth.[9] These babies have a poor prognosis. Mild forms of OTCD may present later, even during adulthood. The symptoms and signs include coma, mental retardation, protein avoidance, headache, bizarre behavior, and episodic hyperammonemia.[3,10] The clinical manifestations in girls carrying an OTC mutation vary, and are a reflection of both allelic heterogeneity and the variable pattern of X-chromosome inactivation in hepatocytes.[11] Partial OTCD and the ever rarer partial recessive urea cycle disorders may be difficult to diagnose in girls because they have few, if any, biochemical changes while they are asymptomatic.

Ornithine transcarbamylase deficiency is diagnosed by hyperammonemia, hyperglutaminemia, hypoarginemia, hypocitrullinemia, mild liver dysfunction, and increased urinary orotic acid levels. Performing a liver biopsy to measure the enzymatic activity of hepatocytes is also informative, but there may be a variety of activity in each hepatic cell. Provocative testing, such as the allopurinol challenge, has been used in girls.[12,13] This test measures the excretion of orotic acid and orotidine derived from a cytosolic pool of carbamyl phosphate, thereby monitoring a pathway of pyrimidine synthesis that is only indirectly influenced by metabolic events within the urea cycle itself. Moreover, this challenge test is a safe diagnostic method even for infants.[13] Our patient had a high level of urinary orotic acid before LDLT, which decreased to within the normal range after LDLT.

The pathophysiological mechanism of central nervous system injury in urea cycle disorders is not completely understood. It has been reported that high levels of ammonium result in the conversion of large amounts of glutamate to glutamine by glutamine synthetase, mainly in astrocytes, which causes swelling of the astrocytes, leading to brain edema, intracranial hypertension, and cerebral hypoperfusion.[14] Magnetic resonance spectroscopy has made it possible to analyze the biochemistry of the brain and accurately identify and quantify metabolites in well-localized regions.[15] It is important to monitor brain damage quantitatively in patients with OTCD, because hepatic encephalopathy can be very harmful and is one of the crucial predictors of their prognosis. In our patient, MRI of the brain before LDLT showed spotty atrophic lesions in the subcortical white matter of the frontal lobe, but this lesion was unchanged 16 months after the operation, and MR spectroscopy showed no abnormal peak of *N*-acetylaspartate, creatine, or choline.

According to one report, patients with late-onset OTCD who were treated with drugs that activate new pathways of waste-nitrogen excretion had fewer hyperammonemic episodes and a reduced risk of further cognitive decline.[2] However, despite remarkable residual activity, because of the heterozygote status of the liver these patients are always at risk of severe hyperammonemia. Thus, liver transplantation is the only complete treatment even for late-onset OTCD. Our patient and her family acknowledged her remarkable improvement and had no regrets about the LDLT, because they are now enjoying a normal life. From the hereditary point of view, deceased donor liver transplantation is feasible for this type of disease, but in Japan deceased donor sources are very limited, making LDLT the most reliable form of transplantation. Thus, all LDLT donors should be selected using the allopurinol challenge test, analysis of gene mutations, and the usual liver function tests.

In summary, we reported the case of a 7-year-old girl who underwent LDLT for late-onset OTCD. The patient has been followed up by measuring her serum levels of ammonia, liver function tests, the allopurinol loading test, and brain MRI. This case report shows that LDLT can cure and improve the QOL of patients with late-onset OTCD.

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ELSEVIER

New Strategy for ABO-Incompatible Living Donor Liver Transplantation With Anti-CD20 Antibody (Rituximab) and Plasma Exchange

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ABSTRACT

It is more difficult to control humoral rejection in living donor liver transplantations (LDLT) across the ABO blood group barrier than in matched or compatible combinations. We achieved excellent results in ABO-incompatible transplantation with novel immunosuppressive regimens and plasma exchange (PE). Among 82 LDLT were 10 cases of ABO-incompatible recipients, including three who were administered rituximab for rescue or prophylactic therapy. Pretransplantation PE was performed as necessary to maintain hemagglutinin titers below 1:16 and posttransplantation PE was performed when there were signs of hyperacute rejection associated with high titers. Induction immunosuppression consisted of FK506, steroid, mycophenolate mofetil (MMF), and rituximab. The first patient was administered rituximab with deoxyspergualin (DSG), steroid pulse therapy, and PE on postoperative day (POD) 7, because of biopsy-proven humoral acute rejection. The titers and LFTs improved drastically. The second and third patients were administered rituximab just after the operation with other routine immunosuppressants for prophylaxis of hyperacute rejection. The second patient showed a slight deterioration in LFTs with an elevated titer, which normalized after steroid pulse therapy and PE. The third patient had no episodes of rejection. At present, that is 27, 17, and 6 months after the operations respectively, the 3 transplant recipients are in stable condition.

THE DONOR SHORTAGE encouraged us to perform living donor liver transplantation (LDLT) across the ABO blood group barrier. The survival rate among ABO-incompatible recipients used to be much poorer than for ABO-compatible recipients, but the introduction of novel immunosuppressive regimens and plasma exchange (PE) has yielded excellent results in ABO-incompatible transplantation. We have successfully performed ABO-incompatible LDLT in 3 patients using rituximab and PE.

PATIENTS AND METHODS

Among 82 LDLT, 10 cases were ABO-incompatible recipients including three administered rituximab for rescue or prophylactic therapy. The age of the 10 recipients ranged from 7 months to 54 years (median age, 12.8 years). IgM and IgG hemagglutinin titers were measured before and after transplantation by serial dilution in saline. Pretransplantation PE was performed as necessary to maintain hemaggultinin titers below 1:16, and posttransplantation PE was performed when the patient showed signs of hyperacute rejection with high titers. Induction immunosuppression in the 10 recipients consisted of FK506, steroid and mycophenolate mofetil (MMF) or azathioprine (AZ), with MMF or AZ administered for 3 days prior to transplantation.

RESULTS

Nine of the 10 recipients and the 3 recipients who were administered rituximab survived (Table 1). The mean follow-up period of the 10 recipients was 4 years.

Case 1

A 22-month-old girl, whose primary disease was biliary atresia, underwent LDLT using her father as the donor (A to O). She also underwent PE twice before transplantation to reduce the titer to 16 or below. From postoperative day

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Table 1. Profile of the 10 ABO-Incompatible Cases

Patient Age/Gender	Primary Disease	Blood Type (Donor/Recipient)	Primary Immunosuppressants	Rejection Therapy	Outcome
5 y/F	BA	A/O	FK, MP, AZ	Pulse, DSG, PE	Alive
1 y/M	BA	AB/B	FK, MP, AZ	Pulse, DSG	Alive
12 y/F	BA	AB/B	FK, MP, AZ	Pulse	Alive
11 m/M	BA	AB/B	FK, MP, AZ	Pulse	Alive
10 y/F	BA	A/B	FK, MP, AZ	Pulse, DSG, PE	Dead
1 y/F	BA	A/O	FK, MP, MMF	Pulse, DSG, PE, rituximab	Alive
42 y/F	PBC	B/O	FK, MP, MMF, rituximab	Pulse, DSG, PE	Alive
10 m/F	BA	A/O	FK, MP, AZ		Alive
7 m/F	BA	B/A	FK, MP, AZ		Alive
54 y/F	HCC	A/O	FK, MP, MMF, rituximab		Alive

AZ, azathioprine; BA, biliary atresia; DSG, deoxyspergualin; F, female; FK, tacrolimus; HCC, hepatoma; M, male; MMF, mycophenolate mophetil; MP, methylprednisolone; PBC, primary biliary cirrhosis; PE, plasma exchange.

(POD) 3, the titers were high and the LFTs results were elevated despite the PE. On POD 7, a needle biopsy of the graft revealed hyperacute rejection. She was treated with rituximab, deoxyspergualin (DSG), and steroid pulse therapy. A section of the liver biopsy showed erythrocyte sludging in the portal veins, swelling of endothelial cells, and hemorrhagic areas in the periportal areas. Her titers and the LFT results improved drastically; she was discharged on POD 74. Less than 1% CD19-positive lymphocytes were observed in her peripheral blood for 3 months after transplantation. At 2 years and 3 months after transplantation, the girl is in stable condition.

Case 2

A 42-year-old woman, whose primary disease was primary biliary cirrhosis, underwent LDLT with her brother-in-law as the donor (B to O). Because of a high anti-B titer (1:512), she underwent PE 7 times and was administered rituximab as prophylactic therapy just after transplantation. The woman also underwent splenectomy and was administered PGE1 and steroids by intrahepatic artery infusion for 2 weeks. One week after transplantation, the titers elevated and the LFTs showed a slight deterioration; steroid pulse therapy together with PE improved the LFTs. She was discharged on POD 102 due to biliary leakage. CD19-positive lymphocytes in her peripheral blood were less than 1% for over 1 year after transplantation. At 1 year and 5 months after transplantation, the woman is in stable condition.

Case 3

A 54-year-old woman, whose primary disease was LC(B) with HCC underwent LDLT with her son as the donor (A to O). She underwent PE 3 times before transplantation and was administered rituximab as prophylactic therapy just after transplantation. Because her hepatic artery was dissected during transplantation, she was administered PGE1 and steroid by intraportal infusion for 2 weeks and subjected to splenectomy. At 6 month after transplantation, her LFTs are stable with no signs of rejection. CD19-positive lymphocytes in the woman's peripheral blood are less than 1% at 6 months postoperatively.

DISCUSSION

ABO-incompatible liver transplantation has been associated with poor outcomes and should be indicated only for emergency cases. The main reason for these poor results is the severe hyperacute rejection due to antidonor ABO antibodies during the early postoperative period. The impact of preformed antidonor ABO antibodies and the strategy to reduce their titers play key roles in the success of this transplantation.[1,2] Rituximab has been approved for the treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma. We expected rituximab to reduce complement-dependent and antibody-dependent cellular cytotoxicity induced by antidonor ABO antibodies via B-cells.[3] We had good results without using rituximab for children, but the results for adults in terms of humoral rejection have been poor. Therefore, we used rituximab for the adults and for the humoral rejection cases. Furthermore, PE was also expected to directly reduce the titers of anti-ABO antibodies.[4] We experienced 3 cases of successful ABO-incompatible LDLT by introducing rituximab and PE.

Although rituximab has been used in ABO-incompatible liver transplantation in a limited number of patients,[5] our results indicate that rituximab and PE may become the new strategy for the ABO-incompatible liver transplantation.

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特集 生体肝移植をめぐる諸問題

生体肝移植の現状をめぐる諸問題
(5) 先天性肝疾患に対する肝移植

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Key words：生体肝移植，先天性肝疾患，代謝異常症，胆道閉鎖症

要 旨

先天性肝疾患にはさまざまな疾患があるため，生体肝移植の適応，周術期，長期には各疾患に合わせた幅広い領域からより専門的な見地での管理が必要である．また，遺伝的な背景をもつことが多いことから，ドナーの選択にも遺伝子検索も含めた厳重な検査が要求されることもある．本稿では，本邦における先天性疾患に対する生体肝移植のうち，頻度の高かったものを中心に，胆道閉鎖症，ウィルソン病，家族性アミロイドポリノイロパチーなどについて，当科における経験もまじえて概説する．

はじめに

先天性肝疾患は代謝異常症が含まれるためさまざまな疾患がある(表)．小児のみならず成人発症の代謝異常症もあり，一般的な肝移植の管理とは別に，各疾患に合わせた処置が必要である．したがって小児科，小児外科，内科など幅広い領域からより専門的な見地で症例を検討しなくてはならないのも特徴である．また，遺伝的な背景をもつことが多いことから，ドナーの選択には遺伝子検索も含めた専門的な検査が要求されることもある．

本稿では当科の経験も含め概説する．

表 肝移植の適応となるおもな先天性疾患

胆汁うっ滞性疾患	
胆道閉鎖症	(992)
アラジール症候群	(39)
バイラー病	(23)
代謝性疾患	
ウィルソン病	(60)
家族性アミロイドポリノイロパチー	(42)
シトルリン血症	(30)
オルニチントランスカルバミラーゼ欠損症	(15)
糖原病	(11)
チロシン病	(10)
原発性高シュウ酸尿症	(8)
家族性高コレステロール血症ホモ型	(2)

( )内は2003年までの本邦における生体肝移植数〔日本肝移植研究会[1]による〕．

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Ⅰ．胆汁うっ滞性疾患

この項のポイント

- 胆汁うっ滞性疾患は胆道閉鎖症を筆頭にもっとも生体肝移植数の多い疾患である．

胆汁うっ滞性疾患は大きく肝外性と肝内性に分類されるが，肝移植の適応としてもっとも多いのは肝外性である胆道閉鎖症である．近年，ほかの疾患数の増加により移植数の割合は減少したが，総数では2003年末の時点でもっとも多い適応疾患である[1]．そのほかに，本邦で比較的多く肝移植されているアラジール症候群とバイラー病について述べる．

1．胆道閉鎖症

胆道閉鎖症は，1万～1万5千人に1人の頻度で起こる原因不明の難病である．先天性の構造的奇形，後天的な炎症性硬化性病変などが考えられている．そのため，最近では「先天性」とつけないのが一般的である．肝外胆管の欠損形態から大きく三つに分類される．1968年に当科の葛西らがKasai手術を報告して以来[2]，その治療成績は飛躍的に向上したが，きわめて難治性の疾患であることには変わりがない．当院小児外科の成績では，1980年代以降に限ってみると約70%の症例が10年以上の生存を得ており[3]，20歳以上の長期生存例も40例を超えている[4]．しかし，進行する肝硬変，イレウス，脾機能亢進，食道静脈瘤，胆管炎などで入退院を繰り返す症例も存在する．一方，本邦での胆道閉鎖症に対する生体肝移植は約1,000例にのぼり，5年生存率も80%を超えている[1]．

最近では，顕性の黄疸がなくとも，難治性胆管炎や消化管出血などによる頻回の入退院を繰り返す症例，食道静脈瘤，瘙痒感などの症状がコントロール不可能な症例，成長発育障害を認める症例など，患児のQOLをも考慮した適応が考えられている．当科で生体肝移植術を受けた患者における検討でも，移植後の生存症例と死亡症例で術前の血清総ビリルビン値に有意差はないが，5歳未満に移植をした症例のほうが移植後の発育が良好であることから，胆道閉鎖症の移植適応並びに時期については，ビリルビン値にかかわらず患児のQOLを考慮したうえで肝移植することを提唱している[5]．

2．アラジール症候群

アラジール症候群は肝内の小葉間胆管の欠損による胆汁うっ滞と特徴的な顔貌，心血管系，椎体，眼球の異常などの臨床的特徴をもつ症候群である．特徴的な顔貌とは，広い前頭部，離れた両眼，小顎などである．心血管系の異常としては末梢肺動脈の狭窄がもっとも多いが手術適応となるものは少なく，ほかに心室中隔欠損，大動脈狭窄，ファロー四徴症などを伴うものがある．椎体では，蝶形の椎体，椎間の狭小化などで，眼球では後方角膜周囲混濁，網膜の色素沈着異常，虹彩の異常，近視などがある．末梢血検査では血清ビリルビン値，血清トリグリセリド値，アルカリフォスファターゼ(ALP)の高値などがある．常染色体優性で第20染色体短腕の欠損が報告されている．

予後は非常に良く，肝硬変症まで進行する例は数%であり，薬物療法が中心で，重症例には胆嚢空腸吻合による胆道ドレナージなどが施行される．しかし，著しい成長障害，門脈圧亢進症，肝硬変症による肝不全には肝移植が適応となる．肝移植に際しては，心血管系，腎臓などの異常に注意が必要である．肝移植成績は良好である[6]．

3．バイラー病

バイラー病は，進行性家族性肝内胆汁うっ滞

症とも呼ばれ，常染色体劣性遺伝である．瘙痒感，黄疸などの症状は10カ月から1歳頃に現れることが多い．血清ビリルビン値が40～50 mg/dlになることもまれではないが，血清コレステロール値は正常であることが多い．血清AST，ALT，ALPは高値である．胆道造影では肝内胆管は開存していることから，疾患の本態は毛細胆管レベルでの胆汁うっ滞であると考えられている．

予後は非常に悪く，ほとんどの症例は2～15歳の間に死亡する．まれに25歳まで生きたという報告がある．したがって，薬物療法などの保存的療法には限界があり，肝硬変，肝不全症例には肝移植しか完治の見込みはない．肝移植成績は良好である[7]．

Ⅱ．代謝異常症

この項のポイント
- 代謝異常症にはさまざまな疾患があり，ドナー選択も含め十分な術前検討を要する．

代謝異常症のうち肝移植適応となるのは，生命維持のために必要な代謝機能に異常がある疾患が対象となる．ここでは，本邦で行われた生体肝移植のうち，症例数の多かったものを中心に述べる．

1．ウィルソン病

ウィルソン病は，常染色体劣性の遺伝形式をとる銅代謝異常症である．臨床的には慢性活動性肝炎もしくは劇症肝炎で発症するが，5歳以下で臨床所見が出現するものはまれであり，多くは10歳代に発症する．神経学的症状としては，錐体外路への銅の沈着による振戦，精神発達遅延などである．診断としてはKayser-Fleischer輪，血清セルロプラスミンの低値，血清銅の低値，24時間尿中銅の高値であるが，肝臓乾燥組織中の銅含有量が250 μg/gを超えることがもっとも診断に有用である．治療としては，ペニシラミン-D，トリエンチンなどのキレート剤や銅の腸管からの吸収を抑制する亜鉛が用いられる．劇症肝炎になる症例は2：1で女性に多く，クームス試験陰性の溶血性貧血，血清と尿中の銅高値，血清セルロプラスミンの低値，肝逸脱酵素はほかの劇症肝炎に比し低値，Kayser-Fleischer輪は半数以下であるなどの特徴をもっている[8]．

肝移植適応となる病態は，劇症肝炎はもちろんであるが，内科的治療抵抗性の進行性肝障害，繰り返す消化管出血などである．肝障害の程度が軽微で神経症状のみ存在する症例は内科的治療で回復可能なため，肝移植の適応とはならない．肝移植後の長期成績は良好で，神経症状や腎尿細管障害も移植後回復することが多い．Kayser-Fleischer輪も3～4年で消失する．

2．家族性アミロイドポリノイロパチー

家族性アミロイドポリノイロパチーは，常染色体優性の全身性アミロイドーシスである．末梢神経障害または自律神経障害で発病し，最終的には心臓，腎臓を中心にすべての臓器が障害を受ける．この疾患のアミロイド前駆タンパクは肝臓で産生されるトランスサイレチンである．発症年齢は20歳代～40歳代が多い．初発症状は足底から始まる疼痛などの異常感覚，長期にわたる下痢または便秘，嘔気・嘔吐などである．末梢神経障害としては下肢を中心とする感覚障害，筋萎縮・筋力低下であり，自律神経障害としては起立性低血圧，消化管運動障害，膀胱直腸障害である．とくに消化管運動障害は1週間周期で高度な便秘と下痢を繰り返す特徴的な症状である．発病後5～6年で歩行不能，10年前後で臥床状態，その後，多臓器不全で

死に至る．

診断は生検によるアミロイドの証明と，免疫組織学的にアミロイドが抗トランスサイレチン抗体陽性であること，また，トランスサイレチンのアミノ酸変異を確認することである．肝移植が唯一有効な治療法である．

肝移植の適応としては，施設間にやや差があるものの罹病期間が5年以内，多発神経炎が下肢に限局または自律神経症状のみで重篤な心機能異常がない，などである[9]．肝移植後の経過は，術前の状態が軽度の者は2～3年で無症状になるが，術前に進行した排尿障害などは改善しない．本邦での移植後生存率は5年85%ほどである．また，肝移植前に心臓に沈着した変異型トランスサイレチンを核として，野生型トランスサイレチンが肝移植後に沈着し，心機能が障害される症例があり問題となっている．

3. シトルリン血症

シトルリン血症のうち成人型(II型)は日本人の若年男性に多いアルギノコハク酸合成酵素(ASS)の欠損による尿素サイクル酵素欠損症である．遺伝形式は常染色体劣性で，初発年齢は10歳代～60歳代と幅が広い．初発症状は突然の意識障害発作で，異常行動，不穏状態，傾眠傾向などであるが，これらの症状は再発を繰り返し，多くの症例で2年以内に高度な脳障害へと進行する．てんかんや統合失調症と診断されてしまう症例もある．診断は血中アンモニア，シトルリン値の上昇，肝生検組織によりASSの活性低下，責任遺伝子であるSLC25A13遺伝子異常の証明である．

治療としては，低タンパク食，ラクチュロース，安息香酸ナトリウム，カナマイシンなどの血中アンモニアを下げる療法が行われてきたが，多くの症例で脳症の進行は食い止められない．

本疾患は，発病後急激に脳症が進行し，しかも進行した脳症に対しては保存的療法，急性血液浄化療法による改善は期待できないことから，シトルリン血症と診断された時点で肝移植を早期に行うべきである[9]．肝移植後の予後は良好で，移植後速やかに血中アンモニア，シトルリン値は正常化し，脳症状も軽快する．

4. オルニチントランスカルバミラーゼ欠損症

オルニチントランスカルバミラーゼ欠損症(ornithine transcarbamylase deficiency；OTCD)は，尿素サイクル異常症のなかで一番頻度の高い疾患である．男の新生児型は生後数カ月以内に死亡し，生存例も重度の神経障害を残すといわれている．遅発型の発症年齢はさまざまであるが，繰り返す嘔吐，精神錯乱などで発症する．診断は高アンモニア血症，アロプリノール負荷後の尿中オロット酸排泄増加，血中グルタミン，グルタミン酸の上昇などである．

治療としては，高度の高アンモニア血症に対しては血液透析，薬物療法としては安息香酸ナトリウム，フェニール酢酸ナトリウム，栄養療法として低タンパク食などである．日本人の遅発型症例の20年生存率は男女とも40～50%であるが，初発時の血中アンモニア値が360 μmol/l を超える症例は予後が悪い[10]．肝移植の適応は，頻回の高アンモニア血症，知能発育遅延，薬物治療抵抗性などの症例である．肝移植後の成績は良好である．

5. 糖原病

糖原病には12種類あり，そのうち肝移植の適応となるのはおもにIV型とIA型の2種類である．III型も適応となることがある[11]．IV型は常染色体劣性で，栄養療法の効果は期待できず2～3歳で肝硬変へと移行する．また，アミ

ロペクチンが中枢神経，心臓，骨格筋に沈着し障害をもたらす．

肝移植の適応としては，肝硬変による肝不全時を基本とするが高度のアミロペクチン沈着前に行うことも重要である．ＩＡ型は常染色体劣性で，栄養療法に効果が認められる症例もある．しかし，てんかんを伴う重篤な低血糖になる症例では，肝移植が必要になる．また，ＩＡ型には肝内に腺腫を伴うことが多いが，癌化するリスクは不明なため，これ自体が肝移植の適応とはならない．

6．チロシン病

チロシン病は常染色体劣性の fumarylacetoacetate hydrolase 欠損症で，この酵素活性低下により診断される．新生児では劇症肝炎として発症し，慢性に経過する症例では１歳を過ぎたころに肝硬変となり，２歳以降には約３分の１の症例で多中心性の肝癌の発生を見る．ほかに精神障害，呼吸障害，腎障害も出現する．

肝移植適応は新生児劇症肝炎のほか，慢性に経過した２歳以降にも肝癌発生の頻度が高く，しかも多中心性で肝切除が困難であることから，肝移植を施行すべきと考えられている．肝移植後の成績は良好であるが，腎障害が遷延する症例がみられる[12]．

7．原発性高シュウ酸尿症

原発性高シュウ酸尿症（primary hyperoxaluria type Ⅰ）は，腎臓，骨，心臓などに過剰産生によるシュウ酸が沈着する常染色体劣性の遺伝性疾患である．肝臓の alanine-glyoxylate aminotransferase 欠損による．乳児期の腎不全が死因となることが多いため，腎機能が悪化する前に早期の肝移植が推奨されている[13]．腎機能障害が出ている症例に対しては，肝腎同時移植を施行し，良好な長期成績であったという報告があり，また，本邦での異時性生体肝腎移植も報告されている[14]．

8．家族性高コレステロール血症ホモ型

LDL レセプター欠損症である家族性高コレステロール血症ホモ型は，常染色体劣性で約100万人に１人の割合である．高コレステロール血症，腱黄色腫，冠動脈疾患を主症状とする．多くの症例は LDL アフェレシスで治療され，30歳以上の生存はまれである．欧米での肝移植の成績は良好であるが，本邦では当科においてヘテロの親からホモの子に肝移植した２例が最初であり，現在，薬物療法を併用し経過順調である[15]．

おわりに

このほかにもさまざまな先天性肝疾患が肝移植の適応になると考えられる．先天性疾患では遺伝的素因も大きく影響すると考えられることから，ドナーが近親者であることが多い本邦での生体肝移植では，長期にわたって原疾患の再発に厳重な監視が必要である．

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Summary

Living Donor Liver Transplantation for Congenital Liver Disease

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Congenital liver diseases, which are indicated for liver transplantation are represented as cholestatic and metabolic diseases. There are many liver diseases and we must treat them in a variety of ways. Particularly metabolic diseases often have genetic back ground, we must also check the genetic status of the donor before transplantation. In this article we describe congenital liver diseases for which we have performed living donor liver transplantation (LDLT) in Japan. Biliary atresia is the most frequent disease requiring LDLT and the number of these cases treated with LDLT in Japan totals 1,000. The most frequent indications for LDLT were failed Kasai operations and developmental retardation. However, the indications became wider when considering the quality of daily life for the patient. Other diseases such as Wilson's disease, familial amyloid polyneuropathy and citrullinemia are described. We also describe our experiences with two homozygous for familial hypercholesterolemia (FH) who received LDLT from their parents, who were heterozygous for FH.

Key words: congenital liver disease, biliary atresia, liver transplantation, living donor, indication

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SHORT REPORT

Liver Laceration Associated With Severe Seizures After Living Donor Liver Transplantation

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Hemorrhagic complications commonly occur early after liver transplantation (LT), sometimes requiring emergent relaparotomy. However, active bleeding from the liver graft itself is a rare but life-threatening complication after living donor liver transplantation (LDLT). We report an unusual case of liver laceration with massive bleeding, associated with severe epileptic seizures as a result of tacrolimus-induced leukoencephalopathy, after LDLT. The patient was successfully rescued by conventional surgical management without a second transplantation. In conclusion, to our knowledge this is the first reported case of graft rupture due to immunosuppression-associated leukoencephalopathy after LT. ***Liver Transpl 12:152–155, 2006.*** © 2005 AASLD.

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In spite of significant technical advances, living donor liver transplantation (LDLT) still carries a high incidence of complications. Among the various post-transplant complications, immunosuppression-associated leukoencephalopathy is a well-recognized but uncommon complication. However, the etiology of immunosuppression-associated leukoencephalopathy is uncertain.

Graft rupture after LDLT is also very unusual, and most cases are associated with the handling of the graft during operation.[1,3,4] The severity of parenchymal injury can range from subcapsular hematoma, with or without active bleeding, to massive disruption. Most cases are salvaged by a second liver graft.[1-3] We report what we believe is the first case of liver laceration after LDLT associated with severe generalized tonic-clonic seizures, followed by successful management without a second liver transplantation.

CASE REPORT

The patient, a 14-year-old girl who suffered from biliary atresia, had undergone Kasai's portoenterostomy procedure at Tohoku University Hospital in Sendai, Japan, at 52 days of age. She then suffered several episodes of esophageal variceal bleeding and biliary tract infection. In August 2003, the patient underwent LDLT using a graft from her 42-year-old mother's left-lobe liver with middle hepatic vein. The patient was 1.54 m tall and weighed 40 kg. The actual donor liver graft weighed 480 g, which corresponded to 50.5% of the recipient's standard liver volume, or 1.14% of her body weight. The total ischemic time from clamping of the portal vein in the donor to portal reperfusion in the recipient was 148 minutes. At the end of the operation, there was neither subcapsular hematoma nor congestion in the liver graft. The graft was then fixed to the abdominal wall with the falciform and round ligaments to prevent rotation of the graft and hepatic outflow block. After closure of the abdomen, Doppler ultrasound showed patency and a normal flow pattern in all vessels with the normal velocity of the portal vein.

Initial immunosuppression consisted of tacrolimus, methylprednisolone, and basiliximab. She was extubated on the first postoperative day. Five days after LT, she had 2 focal seizures consisting of loss of consciousness and decreased oxygen saturation. She developed respiratory failure requiring intubation and was treated with intravenous phenytoin as anticonvulsant therapy.

Abbreviations: LDLT, living donor liver transplantation; LT, liver transplantation.

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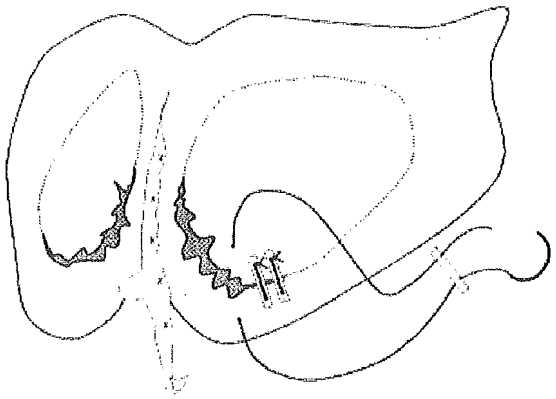

Figure 1. Schematic view of the lacerations on the bilateral anterior surface of the left liver graft with an expanding subcapsular hematoma along the juncture of the falciform ligament. The 2/0 absorbable sutures using a needle (3.5 cm in diameter) were placed with 40 × 7 mm Teflon felt, including on parenchyma around the bleeding point. The knot was tied to gently squeeze the liver tissue together.

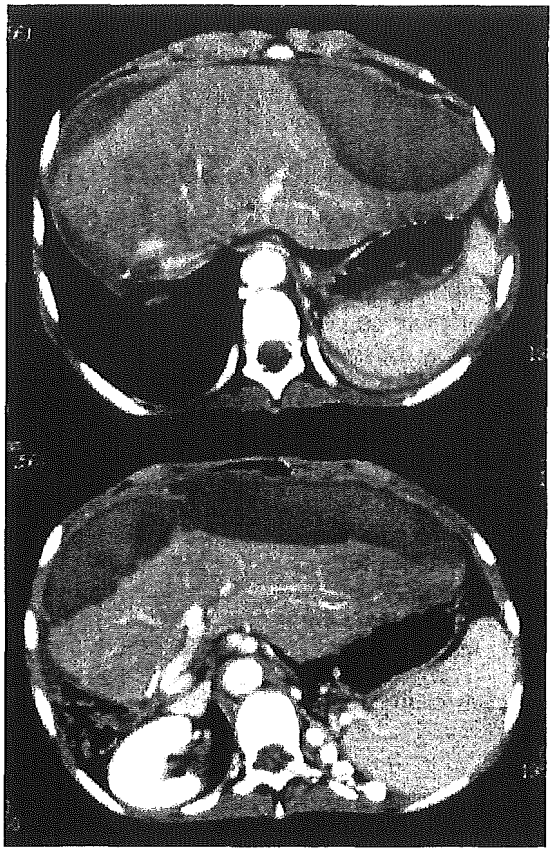

Figure 2. Contrast enhanced computed tomography scan at 35 days after LT shows subcapsular hematoma with nonperfused areas equivalent to 36% of the extended left lobe liver graft.

Tacrolimus serum level was 14.8 ng/mL and was discontinued at that point. Brain and abdominal computed tomography shortly after the seizure was normal. Blood flow for the graft was good and no parenchymal abnormality was observed by Doppler ultrasound. Laboratory profiles of the patient were as follows: aspartate aminotransferase, 59 IU/L; alanine aminotransferase, 117 IU/L; prothrombin time, 12.8 seconds (international normalized ratio, 1.60); activated partial thromboplatin time, 27.8 seconds; and platelets, $9.4 \times 10^4/\mu L$. One day later (posttransplant day 6) she had another severe generalized tonic-clonic seizure lasting several minutes during a magnetic resonance imaging examination. Subsequently, a large amount of fresh blood was observed to be draining from the right subphrenic drainage tube. Tachycardia and hypotension proved refractory to aggressive fluid resuscitation. Resuscitation with blood products was begun, and she was brought to the operating room. During an urgent operation after aspiration of hemorrhagic fluid and evacuation of clots, we found long lacerations on the bilateral anterior surface of the liver graft with an expanding subcapsular hematoma along the juncture of the falciform ligament. The fixation of the graft to the abdominal wall using the falciform and round ligament was divided. There were two lacerations of less than 3 cm in parenchymal depth and about 5 and 7 cm in length, both with active bleeding. Hepatic hemorrhage was controlled temporarily with surgical gauze pads to compress bleeding lesions. However, after abdominal closure, Doppler ultrasonography showed the blood flow in the portal vein decreased and that it remained reversed. Relaparotomy was again performed; after removing the packing, the blood flow in the portal vein was restored without thrombosis. To control bleeding from the liver graft, an alternative surgical procedure was needed; this time, nonabsorbable Teflon felt pledget sutures were placed across the site of the liver laceration (Fig. 1). This procedure was repeated until the hemorrhage stopped. The abdomen was closed without fixation of the graft to the abdominal wall. Eighteen units of packed red blood cells were transfused, and large amounts of fresh frozen plasma and several packs of platelets were used during and after the reoperation. Hemoglobin remained stable 4 days postoperatively, but serum aspartate aminotransferase/alanine aminotransferase levels rose to a peak of 1,390/1,634 IU/L after the reoperation and then decreased gradually.

The patient was managed in our surgical intensive care unit with prolonged mechanical ventilation requiring tracheotomy due to methicillin-resistant staphylococcus aureus pneumonia. A computed tomography scan at 35 days after LDLT revealed massive subcapsular hematoma around the falciform ligament (Fig. 2). Fortunately, the patient developed neither biliary complication nor a liver abscess in spite of the prolonged increase in serum bilirubin and persistent coagulopathy.

Three months after LDLT, the patient's liver function returned to a normal range (total bilirubin, 0.9 mg/dL; aspartate aminotransferase, 38 IU/L; alanine aminotransferase, 29 IU/L), and she was discharged from our

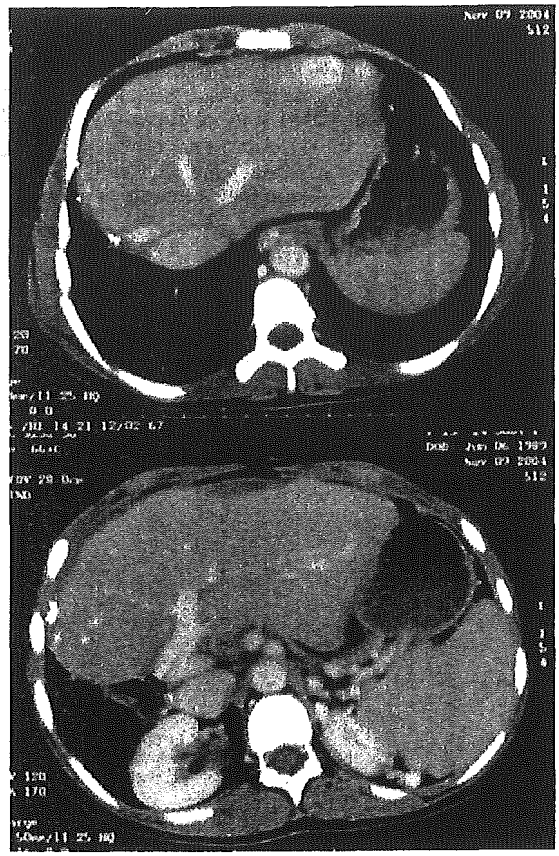

Figure 3. Follow-up computed tomography imagings performed 1 year after LT. The subcapsular hematoma has decreased in size with attenuation over time, and it is seen to be completely resolved.

hospital. She remains well with good liver function after 2 years' follow-up, without liver hematoma or necrosis, and with gradually resolving subcapsular lesions (Fig. 3).

DISCUSSION

Active bleeding of a liver graft rupture after LT is an uncommon event. Solimann et al. reported that parenchymal liver injuries in whole LT can be treated with no adverse effect on the patient or graft survival.[5] However, active bleeding of liver lacerations can lead to a life-threatening event after LDLT.[1-3] It has been suggested that the factors responsible for bleeding are portal hypertension due to a small-for-size graft, liver regeneration after partial LT, superficial liver injury during intraoperative manipulation, and preexisting morphologic donor liver abnormality.[1-4]

The fixation of the graft to the abdominal wall is an important technique and is routinely undertaken to avoid hepatic outflow obstruction in left-lobe liver transplant procedures.[6,7] In our case, the absence of evidence of hematoma or other intrahepatic abnormalities on computed tomography imaging at the first episode of convulsion, suggested that severe generalized tonic-clonic seizure was the cause of the graft rupture. The mechanism of graft rupture is uncertain but is considered to be a tear of the liver capsule at the juncture of the falciform ligament, which is fixed to the abdominal wall due to contractions of the diaphragm and abdominal muscles. Lacerations along the juncture of the liver graft and the falciform ligament are not frequently involved. Interestingly, only 1 similar case, a result of a falciform ligament tear of the liver secondary to vomiting, has been reported.[8]

Immunosuppression-associated leukoencephalopathy is also a rare complication after LT. Leukoencephalopathy is a complication of tacrolimus or cyclosporine use, and it is usually reversible after discontinuation or dose reduction.[9,10] In this patient, the neuroradiologic abnormality was bilateral white matter lesions, notably in the parieto-occipital regions. After discontinuation of tacrolimus, a switch to low-dose cyclosporine in combination with mycophenolate mofetil was started after reoperation. Introduction of mycophenolate mofetil was thought useful for low-dose cyclosporine administration to prevent acute rejection and its adverse effects.

To achieve hemorrhage control using conventional surgical methods, there are some techniques such as suture ligation, liver suture, and packing. In this patient, liver sutures with Teflon felt were useful to avoid tearing through the friable parenchyma. If the hemorrhage of this patient could not have been controlled with liver sutures, portocaval shunting would have been a final therapeutic option for achieving hemostasis of the liver. This procedure is a new surgical technique; however, it does necessitate a second liver graft for successful outcomes.[1] In some countries, particularly in Japan, because of the scarcity of available deceased donor organs, the decision to undertake this procedure is made only if conventional surgical techniques have failed to control hemorrhage.

In summary, we presented the successful management of a unique case of liver graft rupture after LDLT associated with severe generalized tonic-clonic seizures due to tacrolimus-related leukoencephalopathy.

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