CURRENT TOPIC

Diagnosis and management of late complications after liver transplantation

Gabi Noble-Jamieson, Nick Barnes

Liver transplantation is the only effective treatment for end stage liver disease. In recent years the results of this major procedure have improved progressively in adults and children.[1–4] At Addenbrooke's Hospital, Cambridge, the children's liver transplantation programme was started in January 1984. By December 1996, 200 children had received 284 liver grafts. In December 1998, 138 (69%) of these children were alive more than two years after their first liver graft, 120 were alive after more than five years, and 37 were alive after more than 10 years. In the past 10 years the one year survival rate has increased to 87%. After a successful transplant, children can return to full health and activity, with normal growth and development, but have to continue lifelong immunosuppression.

Liver transplantation remains a difficult and dangerous operation. Most of the acute and life threatening problems occur in the first postoperative days and weeks, and therefore during the initial admission, but important later complications develop in as many as one third of children.[3 4] As the number of children surviving transplantation has increased, many general paediatricians and general practitioners have become involved in sharing the care of these children with transplant units. It is therefore important that the local medical team is conversant with the potential late complications of transplantation.

In this paper we review our own and the reported experience of late complications in children after liver transplantation. Guidelines on preliminary investigation and management are summarised in table 1, and fig 1 illustrates possible sites of biliary and vascular strictures and occlusions.

Late hepatic and immunosuppressive drug complications

The average hospital stay after liver transplantation is five weeks, but some children who have an uncomplicated course might be allowed home as early as two to three weeks after surgery, taking immunosuppressive drugs only.

The major immunosuppressive drugs currently in use are cyclosporin and tacrolimus (previously known as FK506); all children receive one or the other after liver transplantation. Cyclosporin is now given as a microemulsion (Neoral; Sandoz Pharmaceuticals, Surrey, UK) because this is absorbed more efficiently than earlier preparations; in most regimens it is initially combined with prednisolone and azathioprine. Tacrolimus has a similar site and mode of action but a more potent immunosuppressive action; it is usually combined with prednisolone only. Most children can be weaned off prednisolone from three to six months after surgery and many transplant units now favour monotherapy with either cyclosporin or tacrolimus, continued lifelong. These drugs are given in twice daily dosage and trough blood concentrations (12 hours after administration), together with liver and kidney function tests, must be measured regularly. After discharge from hospital, close monitoring is essential and these tests are usually checked weekly. As stability is reached, the frequency of routine testing can be decreased to biweekly, monthly, and eventually to three or six monthly. The expectation is that all routine biochemical values, including the liver function tests, should be within the normal range. If this is not the case an explanation is needed. Even after a long period of stability, continued vigilance is essential because drug concentrations and liver and/or renal function can rapidly become deranged. The most frequent causes are nonspecific intercurrent viral illness, which often provokes a flare in transaminase values, and gastroenteritis with vomiting and diarrhoea, which decreases absorption of the immunosuppressive drug. In some children, constipation can increase drug absorption sufficiently to result in toxicity. Therefore, even in children who have been well for a long time it is essential for all those involved in their care to remain aware of the possibility of complications.

Another important consideration is the wide range of potential side effects and drug interactions[5 6] of cyclosporin and tacrolimus. These are summarised in tables 2 and 3, respectively. We include copies of these tables in the written information we give to parents and ask them to remind any doctor prescribing for their child of the possibility of drug interaction. The side effect of both immunosuppressive agents causing most concern is nephrotoxicity because this can cause hypertension and renal failure in some long term survivors.

All transplant recipients show abnormalities of liver function at some time. These are often minor and transient, and might require no

Department of Paediatrics, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK
G Noble-Jamieson
N D Barnes

Correspondence to:
Dr Noble-Jamieson

Table 1 Medium and late term complications after liver transplantation in children

Complication	*Incidence (approx)*	*Commonly raised LFTs*	*Typical time course*	*Further investigations*	*Management*
Infection					
Viral	Specific: up to 20% Non-specific: very common	ALT	Any time	Viral serology and PCR studies liver biopsy	Some specific treatments available; most cases resolve spontaneously; rarely progression to subacute hepatic failure
Bacterial	Cholangitis: up to 20% Sepsis: < 5%	Bilirubin	1 month to years later; often underlying biliary problem	Septic screen, US, cholangiography	Antibiotics ± antifungal treatment; look for predisposing factors: biliary obstruction, hepatic ischaemia, overimmunosuppression
Fungal, parasitic	< 5%	Bilirubin	Any time	Septic screen, US, cholangiography	Look for predisposing factors: biliary obstruction, hepatic ischaemia, overimmunosuppression
Biliary tract obstruction					
Intrahepatic stricture(s) Extrahepatic stricture(s) Bile stones	Up to 20%	ALP, GGT, (bilirubin)	1 month to years later	US, cholangiography	Prompt referral to specialist centre; dilatation, stenting, or reconstructive surgery for single strictures; multiple strictures are usually ischaemic in origin and eventually lead to graft failure
Vascular compromise/ischaemia					
PV stenosis or occlusion HA stenosis or occlusion HV stenosis or occlusion	Up to 10% overall	LFTs usually normal	Usually present from early post-op. but clinical presentation often late with portal hypertension ± ascites	US/Doppler, MRA, angiography	PV: ballooning, stenting, or surgical reconstruction HA: usually asymptomatic but may cause biliary strictures and slow graft failure HV: ballooning or stenting; eventually retransplantation
Rejection					
Late acute rejection	5–10%	Bilirubin, ALT	1 month to years later	Liver biopsy for histology	Prompt referral for biopsy and enhanced immunosuppression; delay in treatment might increase risk of progression to CR
Chronic rejection	Up to 10%	Bilirubin	3 to 12 months	Liver biopsy for histology	Early forms might reverse but more often progress to graft failure
Autoimmune hepatitis	Up to 5%	ALT	Months to years (median 2 years)	IgG, autoantibodies, liver biopsy	Referral for liver biopsy; most cases show a good biochemical and histological response to enhanced immunosuppression
Lymphoproliferative disease					
Lymphadenopathic Systemic Lymphomatous presentation	Up to 10%	LFTs usually normal	First 12 months but up to years later; EBV susceptible children and heavily immunosuppressed most at risk	EBV serology and PCR, US, CT, EBV nuclear antigen and immunocytochemistry on tumour tissue	Reduction or discontinuation of immunosuppression; chemotherapy (see UKCCSG protocol)
Recurrence of original disease (such as autoimmune hepatitis)	30–60%	LFTs may be normal	Months to years later; recurrence risk increases with time after transplantation	Biochemical and/or immunological tests; liver biopsy	Referral for liver biopsy and immunosuppressive treatment

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CR, chronic rejection; CT, computed tomography; EBV, Epstein Barr virus; GGT, γ-glutamyl transferase; HA, hepatic artery; HV, hepatic vein; LFTs, liver function tests; MRA, magnetic resonance angiography; PCR, polymerase chain reaction; PV, portal vein; UKCCSG, UK Children's Cancer Study Group; US, ultrasound scan.

more than a follow up blood test, but they can be the first indication of a serious problem. About half the children found to have abnormal liver function tests will need readmission to hospital for further investigation, and of these about two thirds are found to have a potentially serious complication requiring active medical or surgical management.

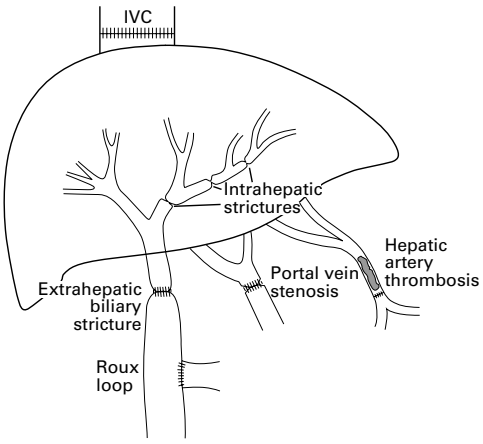

Figure 1 Biliary and vascular complications after liver transplantation. IVC, inferior vena cava.

Early liver disease is usually clinically silent so abnormalities of liver function are detected in most children before any symptoms develop. A rise in bilirubin is the most frequent biochemical indicator of an important problem. When clinical symptoms prompt referral, these are most frequently jaundice, fever, or abdominal distension.

The main problems that can occur more than a month after transplantation fall into six main categories; these will be considered in order of frequency.

Infection

VIRAL

Non-specific

Minor acute viral infections, usually involving either the upper respiratory or gastrointestinal tracts, are often associated with a transient rise in alanine and aspartate transaminase values (ALT/AST), up to about four times the normal value. With most infections of this type the tests return to normal within two to four weeks. When this is suspected clinically, we recommend weekly blood tests to check that the liver

Table 2 Cyclosporin: major interactions and important side effects[5]

Substances that increase concentrations of the drug or are toxic
Grapefruit juice
Macrolides including erythromycin, clarithromycin
Antibacterials including trimethoprim, co-trimoxazole
Antifungals including amphotericin, fluconazole
High dose methylprednisolone
Non-steroidal analgesics
Angiotensin converting enzyme inhibitors, calcium channel blockers
Cimetidine
Tacrolimus
Substances that decrease concentrations of the drug
Anticonvulsants including carbamazepine, phenobarbitone, phenytoin
Octreotide
Rifamycins including rifampicin, rifabutin
Griseofulvin
Main side effects
Cosmetic, especially hypertrichosis and gum hypertrophy
Nephrotoxicity
Hypertension
Neurotoxicity (tremor, convulsions)
Susceptibility to infection
Lymphoproliferative disease (usually Epstein Barr virus induced B cell lymphoma)

function tests are improving. No specific treatment can be offered, but routine measures such as control of temperature are appropriate. As a general rule, if other liver function tests are affected or the transaminases remain noticeably raised for more than four weeks, the child should be admitted for further investigation, usually including a liver biopsy.

Specific

Viral hepatitis is most likely to be caused by cytomegalovirus (CMV), especially after transplantation of a liver from a CMV positive donor into a CMV negative recipient. The donor and recipient status are always checked and when a mismatch cannot be avoided the transplant unit will give prophylactic treatment postoperatively. This usually prevents early symptomatic infection, when the child is most heavily immunosuppressed, but might not suppress later presentation. The symptoms of such late primary infection are usually mild and often confined to fever and malaise, but this can occasionally progress to multisystem involvement with hepatitis, gastroenteritis (sometimes with gastrointestinal tract bleeding), and pneumonitis. In children previously exposed to CMV, reactivation can occur, but this generally causes much less severe illness. In the acute stage, the diagnosis can be confirmed by the polymerase chain reaction (PCR) on blood or urine and sometimes by immunohistochemistry on liver biopsy tissue. Treatment with ganciclovir is usually effective; this drug is given intravenously for severe infections but is now also available as an oral preparation.

Table 3 Tacrolimus: major interactions and important side effects[6]

Substances that increase concentrations of the drug or are toxic
Macrolides including erythromycin, clarithromycin
Quinolones including ciprofloxacin
Non-steroidal analgesics
Antifungals including amphotericin, fluconazole
Cimetidine, omeprazole
Substances that decrease concentrations of the drug
Anticonvulsants including carbamazepine, phenobarbitone, phenytoin
Rifamycin antibiotics including rifampicin, rifabutin
Main side effects
Neurotoxicity (including alteration of mood and behaviour)
Nephrotoxicity
Induction of diabetes (often transient)
Lymphoproliferative disease (usually Epstein Barr virus induced B cell lymphoma)
Susceptibility to infection
Diarrhoea
Thinning of hair

Epstein Barr virus (EBV) infection is common and important. This results either from mismatched transplantation as above or from de novo infection. The diagnostic tests are similar to those for CMV. No antiviral agents effective against EBV are available as yet, but reduction of immunosuppression might be indicated, because primary infection might be associated with uncontrolled proliferation of B lymphocytes and the development of post-transplant lymphoproliferative disease.

Specific viral infections include other herpes viruses such as varicella, herpes simplex, and herpesvirus 6. These respond to treatment with aciclovir.

Infection with the hepatitis viruses, A, B, C, or G, can occur. The diagnosis can be confirmed by PCR on blood and/or liver tissue and later by specific serology. Hepatitis A and B can be prevented by the administration of killed vaccine before exposure.

Chronic viral hepatitis is a likely cause if there is a predominant rise of ALT or swings to high values occur over a period of months. We have investigated five children with biochemical and histological evidence of a chronic hepatitis in whom we were unable to identify a specific virus. In four of these children the hepatitis progressed to subacute graft failure and required urgent retransplantation; three have done well, without recurrence, but in one child a similar clinical and histological picture of chronic hepatitis recurred after retransplantation and eventually progressed to graft failure and death.

BACTERIAL

Serious bacterial infection is a surprisingly uncommon late complication in children on immunosuppressive drugs after transplantation but, when it occurs, it can be sudden and devastating. During transplantation the spleen is preserved whenever possible, but in the few children in whom splenectomy is necessary, the risk of overwhelming bacterial infection is increased. Such children should receive immunisation with pneumococcal, haemophilus, and meningococcal vaccines, as well as lifelong antibiotic prophylaxis.

Other factors predisposing to bacterial infection include hepatic ischaemia, biliary obstruction, and augmented immunosuppression. In children presenting with bacteraemia or suspected cholangitis, an ultrasound scan to check the patency of the hepatic vessels and biliary tract should be an early investigation. In the presence of serious bacterial infection, especially cholangitis, bilirubin values are often raised.

OTHER

Invasive fungal infection is rare and is usually associated with a serious underlying problem, such as biliary obstruction or hepatic ischaemia. Parasitic infections, such as cryptosporidium of the gastrointestinal tract, rarely cause serious illness but in two of our patients, one with congenital hypogammaglobulinaemia, systemic infection with cryptosporidium followed invasion of the biliary tree.

Biliary tract obstruction

This is a common late complication affecting up to 20% of children.[7] In our experience, biliary strictures can present as early as six weeks or as late as six years after transplantation, but most become apparent within the first six months. Abnormalities of liver function tests are usually the first indication and, as expected, the enzymes derived from biliary epithelium, alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT), are predominantly affected. Episodes of cholangitis are also common and usually present with fever and malaise, sometimes associated with mild intermittent jaundice, diarrhoea, and weight loss. Children with severe biliary obstruction present with pruritus, jaundice, and steatorrhoea. The site of obstruction can be extrahepatic or intrahepatic (fig 1). Extrahepatic biliary strictures usually occur at the site of the surgical anastomosis, and eventually cause sufficient intrahepatic duct dilatation to be visible on ultrasound. With intrahepatic strictures the ultrasound may be normal[8] or may show intrahepatic fluid filled spaces, which are pools of bile within the obstructed ducts. Intrahepatic strictures are often multiple and are probably the end result of ischaemia, which can be the result of hepatic artery stenosis or occlusion, a prolonged graft ischaemic time, or chronic rejection.[7 8]

Extrahepatic strictures can be treated by percutaneous balloon dilatation or surgical revision. Single intrahepatic strictures can sometimes be dilated percutaneously, but a graft with multiple strictures will eventually require retransplantation. Children with liver function tests suggesting cholestasis (raised ALP and GGT, with or without a raised bilirubin), and those who develop cholangitis, should be referred promptly for cholangiography, because prolonged biliary obstruction will result in progressive biliary cirrhosis and subsequent graft failure.

Hepatic ischaemia

Severe ischaemia with acute graft failure in the first few days after transplantation is usually caused by hepatic artery thrombosis or portal vein thrombosis. Acute ischaemic graft failure is a rare late complication, but less severe hepatic ischaemia caused by narrowing or late occlusion of one of the major blood vessels is increasingly recognised. Most children who develop late vascular complications remain asymptomatic at the time, and the liver function tests might also remain normal. The diagnosis is usually made by routine ultrasound/Doppler examination, which is included in the annual assessment of our patients. Stenosis or occlusion of the portal vein eventually leads to portal hypertension. Children with this problem can stay well for years, but eventually develop the haematological markers of hypersplenism and are at risk of variceal bleeding. Transhepatic portal vein angiography is a specialist procedure that should be done in a transplant centre with facilities for balloon dilatation or stenting of portal vein strictures.

Late occlusion of the hepatic artery might also occur without clinical or biochemical signs. This is a more common event in children who received a donor graft with hepatic arterial anomalies and in those in whom the arterial anastomosis required the use of a conduit.[9] With late arterial occlusion, there might be little ischaemic damage to the liver as long as the portal vein flow is good, but hepatic artery thrombosis can result in the development of ischaemic biliary strictures[7] or late graft failure.[10] In skilled hands ultrasound/Doppler provides a sensitive and non-invasive test for the detection of vascular problems and, if available, magnetic resonance angiography can be used. Direct angiography might still be needed to make a definitive diagnosis.[11]

Hepatic vein stenosis or occlusion can occur and cause venous outflow obstruction; this occurs more commonly after the "piggy back" operation in which the recipient superior vena cava is preserved. With the conventional operative technique, venous obstruction can result from stenosis of the upper caval anastomosis. Venous obstruction usually causes gross ascites; the blood tests typically show hypoalbuminaemia and deranged clotting. The diagnosis may be suspected on ultrasound examination but requires confirmation by direct angiography, during which ballooning or stenting of the obstructed vessel can also be attempted. Failure requires retransplantation.

Late acute rejection

Late acute cellular rejection occurs in > 10% of children.[12 13] Liver function tests are variable but characteristically show raised bilirubin, ALP, and ALT values. Some children develop a fever, which can mislead the medical team into treating for a presumed bacterial or viral infection. Late acute rejection often follows a reduction in immunosuppression. This can be the result of transient malabsorption from a gastrointestinal upset, biliary obstruction or, of course, it can be the result of inadequate dosing or non-compliance. In our experience, non-compliance is most often seen in teenagers, particularly those who are completely well and who received their transplant in early childhood. These patients need intensive counselling, with much time spent talking about the original reason for transplantation and in reinforcing the absolute need for regular, lifelong immunosuppression. All children with suspected late acute rejection should be referred promptly to a specialist centre for a diagnostic liver biopsy. The rejection can be difficult to reverse and only 50% of children are reported to respond fully to the first line rescue

treatment, a course of high dose methylprednisolone.[12] Our experience is even less encouraging, with 10 of the 12 patients who presented with late acute rejection eventually requiring retransplantation. The recently available immunosuppressive agent mycophenolate mofetil has been used as rescue treatment in resistant acute rejection and preliminary reports are encouraging.[14]

Chronic rejection

This serious complication, also called "ductopenic rejection", is characterised histologically by more than 50% loss of interlobular and septal bile ducts, with or without associated arteriopathy.[15] In general, it occurs from six weeks to six months after transplantation, and has been described with a remarkably variable incidence ranging from 2% to 17%.[15] Although chronic rejection can sometimes be reversible in its early stages, most affected grafts eventually fail. The pathogenesis remains obscure; it has been postulated that chronic rejection might be the end result of persistent local endothelial activation by a number of factors, including inflammatory mediators that might be induced by acute rejection, viruses, and drugs.[16 17] Because the main structures affected are the bile ducts, liver function tests usually first show a rise in bilirubin, ALP, and GGT. This pattern of tests is therefore an indication for prompt referral for investigation and liver biopsy. There is no specific treatment for chronic rejection, but the diagnosis must be confirmed to exclude more treatable problems, and immunosuppression should be optimised by more frequent monitoring and adjustment of doses to ensure high enough blood concentrations, even in the presence of cholestasis.[18 19] Some patients with chronic rejection develop biliary strictures and can present with cholangitis. These children may still benefit from dilatation of accessible strictures because this might prevent recurrent cholangitis.

Autoimmune hepatitis

It has been recognised recently that, whatever may have been the initial problem, a chronic autoimmune hepatitis can develop de novo after liver transplantation in children. This complication was first described in five children from Kings College Hospital, London,[20] and has occurred in our patients. In spite of full immunosuppression, an immune response against the transplanted liver can occur, which presents as a hepatitic process months to years (median two years) after transplantation. Typically, transaminase and IgG values are raised and autoantibodies are present. A liver biopsy is needed for histological proof. In the children followed to date, there has been a biochemical and histological response to the addition of high dose prednisolone and azathioprine to the basic immunosuppressive regimen. This can delay, and possibly prevent, the need for retransplantation. Unfortunately, autoimmune hepatitis can recur after retransplantation.

Lymphoproliferative disease

This serious complication occurs in 5–10% of children.[21] It is most frequently diagnosed from three to 12 months after transplantation. The children most at risk are EBV negative at transplantation but develop primary EBV infection, either from a mismatched graft or from de novo infection. The risk is increased if augmented immunosuppression is needed for acute rejection, particularly if antilymphocyte antibodies are used. Immunosuppression decreases the population of EBV specific cytotoxic T cells and thus allows increased viral replication and infection of circulating B cells. The persistent EBV infection is controlled by natural immune mechanisms in most patients but when it is not lymphoproliferative disease develops. Common modes of presentation include lymphadenopathy, which can be localised or generalised, and systemic illness with fever, respiratory distress, and gastrointestinal bleeding. The liver graft may be spared so that liver function tests can remain normal. Children with suspected lymphoproliferative disease should be referred to the transplant centre for a full diagnostic investigation and treatment. The UK Children's Cancer Study Group has produced a protocol for diagnosis and treatment. Lymphoproliferative disease can regress fully with reduction of the immunosuppression alone, but there is then a risk of rejection and graft loss. The prognosis of this form of lymphoproliferative disease is poor, with a 50% mortality.

Recurrence of the original disease

This is a risk for some of the more unusual indications for liver transplantation in childhood. It is rare, but should be considered in children who received transplants for sclerosing cholangitis, viral hepatitis, and especially autoimmune hepatitis, which can recur in as many as two thirds of patients by the fifth year after transplantation.[22] For early diagnosis, prospective monitoring of biochemical and immunological markers is indicated and annual liver biopsy has been suggested.

Late retransplantation

Retransplantation might be the only recourse for some children with serious late complications. In our 15 year experience, retransplantation more than one year after the initial graft was necessary in 15 children (7.5%). Some of these patients had remained well with normal liver function tests for as long as 10 years after transplantation when they rapidly developed abnormal liver function, which worsened and progressed to liver failure. In these children, histology of the explanted grafts showed either an aggressive hepatitis or established cirrhosis of unknown cause. In others the need for eventual retransplantation was predictable for some years because of a known complication, such as multiple intrahepatic strictures. The prognosis after retransplantation remains good, with patient and graft survival reduced by only 10% in our experience.

Discussion

In recent years, improvements in surgical technique, medical care, and immunosuppression have been reflected by progressive improvement in the outcome of liver transplantation in childhood. A five year survival rate of up to 80% is now expected,[3] and much longer survival in good health is increasingly frequent. Therefore, there is reason to hope that the long term prognosis for survivors will also be good. Nonetheless, liver transplantation remains an extremely demanding surgical procedure, with many potential early and late complications. Although the most serious of these usually occur within the first month postoperatively, 50–80% of children require readmission to hospital at some time with transplant related complications. The indications for readmission in Eckhoff and colleagues' series of 100 children[3] were transplant related in 90% and were most commonly related to infection, rejection, or biliary or vascular problems.[23]

It is clear that in some children graft function can be improved or restored to normal if treatable complications are identified early and treated appropriately. Examples of these include the early detection and relief of biliary obstruction, which might prevent the development of cholangitis and progression to biliary cirrhosis; the early detection and dilatation of portal vein strictures, which might prevent progression to portal vein thrombosis and portal hypertension; and the prompt diagnosis and treatment of late acute rejection or de novo autoimmune hepatitis, which might respond well to augmented immunosuppression.

Fortunately, the need for liver transplantation in childhood is finite and, except in some acute emergencies, it should be possible for all children who need grafts to receive them. However, the potential of organ transplantation is great and the number of children receiving single or multiple organ transplants is likely to increase for the foreseeable future. Many of the principles of management are similar irrespective of the organ, or organs, transplanted. There will be increasing need for the involvement of local medical teams and the outlook for these children will, to a considerable extent, depend on their expertise and involvement with this demanding but rewarding area of work.

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