

Assessment of potential donors for living related liver transplantation

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Background: Living related liver transplantation has been developed as an important potential source of organs for treatment of children with acute and chronic liver disease. A single UK centre performing living related liver transplantation was established in 1993.

Methods: Parents who were potential donors for their children for living related liver transplantation were assessed for suitability according to a protocol based on one developed and published by the University of Chicago Transplant Group. Records kept by the transplant coordinators were retrieved and data were extracted.

Results: Of 64 potential donors for 32 potential recipients ten were excluded at a preliminary stage. Fourteen ultimately became donors. Of 54 parents who began evaluation 23 were finally considered to be suitable. There were 19 non-disease-related reasons for unsuitability: blood group mismatch (eight cases), size discrepancy (six), pregnancy (two), oral contraceptive medication (one), vascular anatomy variant (one) and age (one). Sixteen were unsuitable because disease was found, namely fatty liver (four), thyroid disease (two), hepatitis B positivity (two), cardiac murmur (one), anaemia (one), glucose-6-phosphate dehydrogenase deficiency (one), diabetes mellitus (one) and psychological problems (one), and three parents were affected by the same disorder as the child (Alagille syndrome, one; mitochondrial disorder, one; recurrent cholestasis, one). Three parents were rejected for more than one reason. Both parents were unsuitable for donation in 21 per cent of cases.

Conclusion: Parents approach living related liver transplantation with enthusiasm. They should be advised of the high chance of unsuitability, including the finding of significant pathology. The limitation of living related liver transplantation as the major source of organs for children is recognized.

502

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Introduction

Survival after orthotopic liver transplantation (OLT) has gradually improved to 90 per cent at 1 year and 80 per cent at 5 years for children with terminal liver disease^{1,2}. This success has led to the widening of indications to include complications causing intolerably poor quality of life rather than likelihood of death. One particular example is intractable pruritus. Consequently, larger numbers of children have been referred for liver transplantation, while the number of paediatric cadaver organs available each year in the UK has declined. Adult transplants have rapidly increased in number over the same period³. There have been three imaginative surgical responses to the resulting shortage of organs, based on the

understanding of the segmental anatomy of the liver. The first is 'liver reduction' in which the left lateral segment, left lobe or right lobe is used and the rest of the liver is discarded⁴. The second is the 'split liver technique' whereby liver is divided *in vivo* or on the back table for one larger and one smaller recipient⁵. Since both techniques imply a preference for paediatric recipients over adults either in terms of numbers of grafts available or receiving preference over division of the portal elements on splitting, there is the potential for conflict between the interests of adult and paediatric recipients. The third possibility, living related orthotopic liver transplantation (LROLT), provides additional organs to the donor pool and has potential advantages in terms of a good-quality organ⁶ at a time planned to suit the medical facilities and

family, and before the recipient can deteriorate, risking a worse outcome at OLT⁷.

LROLT was pioneered by Broelsch *et al.* in Chicago between 1989 and 1991⁸, but has not been the sole source of paediatric organs except in Japan where there has been no cadaveric transplant programme. At the outset, the Chicago workers appreciated that since donation required a major abdominal operation with an attendant risk, there was a conflict of interest between the donor and recipient, whose life could be saved by the operation⁹. They attempted to reconcile these interests by considering the ethics from a utilitarian perspective, i.e. to establish the circumstances when the maximum benefit could accrue with the least risk of harm. They concluded that if LROLT could be accomplished successfully it could be acceptable ethically. The ethics of receiving were considered to be the same as those of receiving a cadaver organ, and the restrictions focused on the donor, whose risk must be assessed and found to be the minimum possible. He/she must donate in a spirit of genuine altruism and without inducement beyond natural feelings which are likely to be strongest when the donor is related to the recipient. The donor must understand the nature and risks of the procedure, and must be physically and psychiatrically healthy¹⁰.

When a LROLT programme was established at this centre in 1993 under the auspices of the Department of Health and the Royal College of Surgeons, the institutional ethics committee accepted the conclusions of the Chicago group. A protocol based on their practice was used to assess parents (Fig. 1). Records of the evaluations

were kept prospectively by the recipient transplant coordinators. Ethical approval was obtained. The aim of this study was to review the records in order to establish the proportion of parents who were unsuitable to be LROLT donors and the reasons for their unsuitability so that better information could be provided when counselling future potential donors, and to establish the limitations of the usefulness of the technique if its fullest application was required by donor shortages.

Patients and methods

Subjects

Between June 1992 and August 1997, 32 children were considered for LROLT with their 64 parents as potential donors. Being a single parent was not considered a contraindication but no single parent requested assessment. Of the 32 potential recipients, 20 had biliary atresia, two α -1-antitrypsin deficiency, two tumours, two metabolic diseases, two intrahepatic cholestasis, two cryptogenic liver disease, one Alagille syndrome and one cystic fibrosis. Their median age was 14 (range 5–114) months and median weight was 9 (6–27) kg. Fourteen children received LROLT, 16 received cadaveric organs and two died while waiting for transplant. There was no significant difference in diagnosis between those receiving LROLT or cadaver organs. Median time between listing and OLT was not significantly different between LROLT and cadaver recipients: LROLT, 34 (range 10–310) days; cadaver, 50 (range 4–315) days. The median age of donors considered was 31 (range 17–46) years.

Methods

An initial approach was made to all parents when the need for OLT was first discussed, although many parents introduced the possibility themselves and six children were referred specifically for LROLT assessment, because it was not available in their transplant centres. Families received initial information verbally and by a handout. They were advised that LROLT could provide an organ for their child, would enable the time of operation to be chosen to suit the family's needs and before the child deteriorated with increased risk at operation or prolonged suffering. Early organ function might be better. The disadvantages were described as risk of death of the donor quoted at one in 250 operations, being a conservative estimate based on the single death known at that time. Lesser complications such as abdominal pain and dyspepsia were quoted to occur in 10–20 per cent of donors. Other problems cited included one parent being

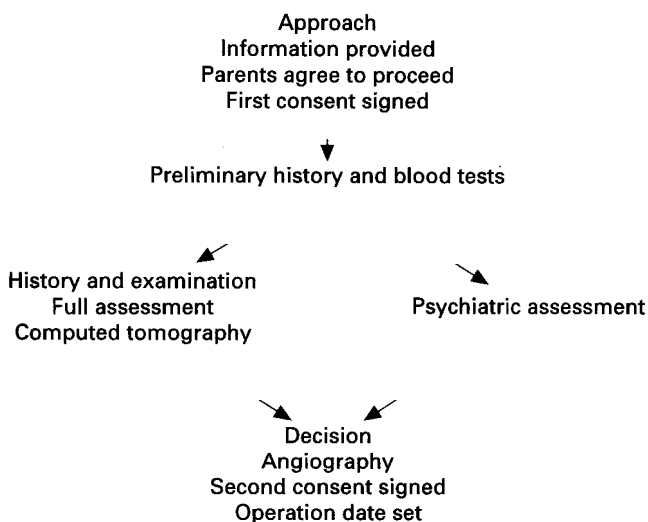


Fig. 1 Protocol for evaluation of donors used at King's College Hospital, based on the Chicago protocol

Table 1 Medical evaluation of prospective living related liver transplant donors

Medical history	Liver disease
	Needles/blood exposure
	Viral infections
	Pregnancy/contraception
	Thrombotic episodes/family history
Medical examination	Blood pressure
	Height and weight
	Abdominal circumference
Blood tests	Full blood count and film
	Blood group
	Urea and electrolytes, creatinine, cholesterol
	Liver function tests
	Thyroid function tests
	Pregnancy test
	HLA 'hot testing'
	Hepatitis B and C
	Human immunodeficiency virus
	Cytomegalovirus
	Epstein-Barr virus
	Abdominal ultrasonography
Other tests	Doppler ultrasonography of the liver
	Abdominal computed tomography
	Chest radiography
	Electrocardiography
	Echocardiography
Independent psychiatric assessment	
Aortoportography*	

*Of chosen donor after second consent obtained. HLA, human leucocyte antigen.

emotionally unsupported during the perioperative period, loss of income particularly for those in self-employed manual work and risk of rendering life insurance void. The risk of acute rejection was estimated to be the same as that for cadaveric organs.

Potential donors were evaluated to establish that the medical risk was not increased. The genetic relationship of donor and recipient was also established by a designated laboratory according to the specification of the Human Organ Transplants Act 1989¹¹. If the parents wished to proceed, consent forms were signed and the tests shown in *Table 1* were performed. The adult hepatologists were responsible for assessment of the donors' risk. Liver biopsy was not performed. One parent was chosen by the transplant surgeons based on minimum risk and liver size and anatomy from computed tomography images. Independent psychiatric assessment was obtained. Two weeks after the first consent, a second consent form was signed and angiography was performed in the selected parent. If this was satisfactory a date was set for transplantation. All recipients were simultaneously listed for living related and cadaver organ transplantation. An organ was accepted from a cadaver if it became available to reduce any sense of coercion on the parents. They were advised that they

could withdraw without explanation up to the moment of anaesthesia.

Parents were considered and assessed as a couple because it was felt that the decision to donate affected the family unit. Once a pathological or non-pathological contraindication to LROLT was found no further assessment was undertaken. For example, one mother known to be pregnant signed a consent for evaluation, but was not investigated further; the husband became a successful donor. If a previously unrecognized medical contraindication to LROLT was discovered it was investigated and specialist management was arranged. Records of the evaluation were kept by the transplant coordinators and retrieved for this study.

All donors had hepatectomy performed according to previously described methods⁸. The left lateral segment was removed in all cases. The left hepatic artery, left portal vein and left hepatic vein were isolated before transection. No dissection of the left bile duct was performed until the end of the procedure when it was dissected close to the cut surface. Segment IV was retained in all donors except for the first donor in whom it was removed because it remained dusky. The implantation of the left lateral segment was by 'piggy back' technique using a triangulating technique similar to that practised in the cadaveric programme.

Results

Of 64 parents considered, 54 began assessment but only 23 were found to be suitable and 14 became donors (mean age 32 (range 23–41) years; three men). Of 50 parents who were not donors there were 29 men (mean age 35 (range 25–45) years) and 21 women (30 (range 17–44) years). Thirty-one parents (48 per cent) were found to be unsuitable, 16 (25 per cent) with conditions likely to increase operative risk of whom 11 (17 per cent) had previously unrecognized pathology. Seven couples (21 per cent) were found to be unsuitable, and in only two couples were both parents suitable. Five couples consented but did not start evaluation because a cadaveric organ became available in three, the recipient was too big to receive a left lateral segment in one (donor (father) to recipient weight ratio 82 : 35) and absence of the recipient inferior vena cava was considered a contraindication to LROLT in one.

Of 18 recipients who did not undergo LROLT, eight were accepted but were transplanted from a cadaveric donor, including three before evaluation of the parents could begin, seven had no suitable living donor, one recipient was unsuitable for LROLT because of absence of the inferior vena cava, and two died before evaluation was complete.

Reasons for donor rejection may be divided into non-pathological and pathological. In the first group were wrong blood group (eight cases), parent too big (six), pregnancy (two), oral contraceptive use (one), vascular anatomical variant (one) and one was too young to give legal consent at 17 years of age. Both pregnancies were known about before assessment. Pathological reasons for rejection were fatty liver due to diet or alcohol identified by ultrasonography in four fathers, hypothyroidism or hyperthyroidism in one each; hepatitis B surface antigen positivity in one; hepatitis B core antibody positivity in one; iron deficiency anaemia in one; glucose-6-phosphate dehydrogenase deficiency in one; diabetes mellitus in one; cardiac murmur in one; and psychological reasons in one. Three were considered to have evidence of the same disease as the child: Alagille syndrome (one), raised plasma lactate secondary to probable mitochondrial respiratory chain disorder (one) and severe cholestasis of pregnancy (one). Single cases of thyroid disease, diabetes, glucose-6-phosphate dehydrogenase deficiency, Alagille syndrome and recurrent cholestasis of pregnancy were known before assessment. Three reasons for unsuitability were found in one parent (anaemia, hypothyroid, vascular variant) and two in two parents.

There were no donor deaths. Complications of donation included a single case each of biliary leak managed conservatively, bleeding from the cut surface requiring laparotomy, dyspepsia responding to antacids, muscular pain resolving spontaneously by 1 year and gallstones leading to cholecystectomy 3 years later. At current follow-up of median 32 (range 12–58) months all parents have been able to return to employment. Two donors have subsequently given birth uneventfully.

One recipient died from sepsis 24 h after LROLT. One has been lost to follow-up. The other 12 are well at 12–58 months' follow-up. One has portal hypertension because the portal vein stretched over the inferior surface of the liver as it hypertrophied. The portal vein is patent and conservative management is currently successful. One has a mild cholangiopathy with normal liver function on ursodeoxycholic acid. Two had steroid-resistant rejection treated successfully with tacrolimus (Fujisawa Pharmaceuticals, Japan). One recipient developed tonsillar lymphoproliferative disease which responded to withdrawal of immunosuppression.

Discussion

This series reports the UK experience of LROLT which has been performed in a single centre. The numbers are small in comparison to those in centres in the USA,

Europe and Japan^{8,12–14} and are likely to remain limited because of the introduction of a successful cadaveric split liver transplant programme. A higher rate of contraindications to donation was encountered than in other published series. Of 135 potential donors for 120 LROLTs reported by Morimoto *et al.*¹⁵, 11 per cent were not accepted; in an earlier series of 109 donors the same authors found fatty liver in ten and abnormal transaminases in the same number¹⁶. Liver abnormalities necessitated replacement of the first parent by the second in eight couples. Of 73 potential donors 33 per cent were rejected by Sterneck *et al.*¹³, 15 per cent because of adverse risk factors. In a third series, Renz *et al.*¹⁷ found only ten (13 per cent) of 75 potential donors for 38 recipients suitable but contraindications included a significant medical history in 23 per cent and psychosocial reasons in 20 per cent. Twenty-three per cent of potential donors had declined assessment and, if these were removed from the total, 17 per cent were suitable donors and medical contraindications were present in 29 per cent. New pathologies were not recorded. The present authors' high rate of identification of contraindications may have been a result of the sample size or of the careful screening of donors.

Comparisons with other series are dependent on the criteria for assessment of donors, their willingness to volunteer and the availability of organs from other sources. Six of the present cases were referred from other centres specifically requesting LROLT. Because of concerns to allow parents considering donation a free choice, the early pace of the evaluation was often set by the willingness of the parents to contact the paediatricians or liver transplant coordinators to discuss the process, and request formal evaluation after they had been informed of the availability of the technique. Thus there was strong self-selection. Some, feeling under pressure to become donors, may have initiated assessment knowing that health problems would not permit them to donate, but 69 per cent of the health problems uncovered were not previously recognized and therefore could not have influenced the decision to be a donor.

No decision had been taken to exclude single parents but none presented for living related donation. It is unclear why not but it is possible that prospective donors without a partner may have been deterred by literature on LROLT prepared by one of the authors (A.B.). Such literature is published by the Children's Liver Disease Foundation (Digbeth, Birmingham, UK); it is distributed widely to parents of children with chronic liver disease and freely available in outpatient clinics. This emphasized the need for support for the child and donor during the operative period.

The role for LROLT is determined by organ availability and the infrastructural support for transplant programmes. The authors have developed a successful split organ programme resulting in a significant reduction in waiting times for paediatric transplantation. However, larger children who are unsuitable for LROLT are in relative competition with small adults for reduced size and split liver grafts¹⁸. In this centre LROLT is currently recommended only for small children of blood group O or B who may have a long wait for a compatible organ, and who may deteriorate while waiting for a cadaver organ¹⁹, and in those with unresectable hepatoblastoma when OLT has to be performed between courses of chemotherapy.

Parents of young children are typically young and healthy and would expect to be able to donate a piece of liver to their child with minimum risk. Perhaps because of the information provided by the Children's Liver Disease Foundation and self-selection, parents began assessment with considerable enthusiasm. Forty-eight per cent were ultimately disappointed, so it is important to advise parents that both might be unable to be donors and that it is not possible to guarantee donation for every child. Seventeen per cent found that in addition to concerns about their child's liver disease they also had worries about their own health. Discovery of unsuspected medical problems may have profound implications for the family with respect to life insurance or employment, and the consequences of this should be considered before any tests are performed. From this early experience, it is recommended that before starting evaluation of living related transplantation parents are advised that there is a 50 per cent chance of one or other of the parents being unsuitable, a 20 per cent chance of both parents being unsuitable and a 17 per cent chance that significant disease may be identified which may require investigation and treatment. Having discussed the above, parents may choose not to proceed. The very high medical standards set to avoid morbidity and death in donors should not be relaxed even under the pressure of worsening health and liver function in the prospective paediatric recipient.

When patients are at high risk of not receiving OLT in time to prevent death and parents have been excluded as donors, there is no ethical or immunological reason to confine LROLT donation to first-order relatives²⁰. If any genetic relationship or even a long-standing non-genetic relationship can be established, so that it would be reasonable to believe that the donor is acting out of genuine altruism, there can be no objection to considering the family more widely. Uncles, aunts, grandparents and siblings, step and adoptive parents may be assessed as

donors, but they must be over 18 years of age, and able to make the decision to donate on their own behalf²¹.

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