

348

Liver Transplantation in Children With Biliary Atresia and Vascular Anomalies

By John R. Lilly and Thomas E. Starzl

THE PARTICULAR SUITABILITY of infants and children with biliary atresia as candidates for orthotopic liver transplantation has been pointed out in a number of communications from our institution.¹⁻⁴ Although exacting and meticulous intraoperative and posttransplant care is required, the hardiness and natural resiliency of the young make these children especially favorable recipients for the procedure. Current survival after replacement of the child's own diseased liver with a cadaveric homograft is over 4 yr.

In these earlier communications an increased frequency of vascular anomalies in children with biliary atresia was noted and it was observed that the vascular malformations compounded the technical hazards of the operation. The purpose of this communication is to describe the specific vascular anomalies encountered in children having transplantation for biliary atresia and, additionally, to separate and define a subgroup of patients with a distinctive and highly unusual constellation of vascular anomalies which have made transplantation attempts uniformly fatal. The composite anomaly which was alluded to previously in a text on hepatic transplantation⁴ consists of absent inferior vena cava, preduodenal portal vein, and anomalous origin of the hepatic artery. In all three children having this lethal vascular complex the anomalies were unsuspected prior to transplantation despite earlier surgical exploration. Several simple maneuvers at the time of the initial evaluation of infants with biliary atresia will help to identify this subgroup of patients, whom we feel at the moment are highly questionable candidates for transplantation.

CLINICAL MATERIAL

Of 29 children having liver transplantation for biliary atresia, eight (27.5%) had associated vascular anomalies. In three, the composite vascular anomaly described above was observed (Fig. 1), while in the other five children, single variations of hepatic arterial or venous architecture were found.

(1) Biliary Atresia With the Composite Vascular Malformation of (1) Absent Inferior Vena Cava; (2) Preduodenal Portal Vein; and (3) Anomalous Hepatic Artery (Table 1)

Patient 1, a white female, had an exploratory laparotomy for jaundice 3 mo after birth. Operative cholecystography demonstrated a small gallbladder and no patent extrahepatic biliary ducts. A thorough exploration failed to find a proximal bile duct in the liver hilum.

From the Divisions of Pediatric Surgery and Transplantation, and Department of Surgery, University of Colorado Medical Center, Denver, Colo.

Presented before the Fifth Annual Meeting of the American Pediatric Surgical Association, New Orleans, La., April 4-6, 1974.

Supported by Grants AI-AM-08898 and AM-07772 from the National Institutes of Health; and by Grants RR-00051 and RR-00069 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

Address for reprint requests: John R. Lilly, M.D., Division of Pediatric Surgery, University of Colorado Medical Center, Denver, Colo. 80210.

© 1974 by Grune & Stratton, Inc.

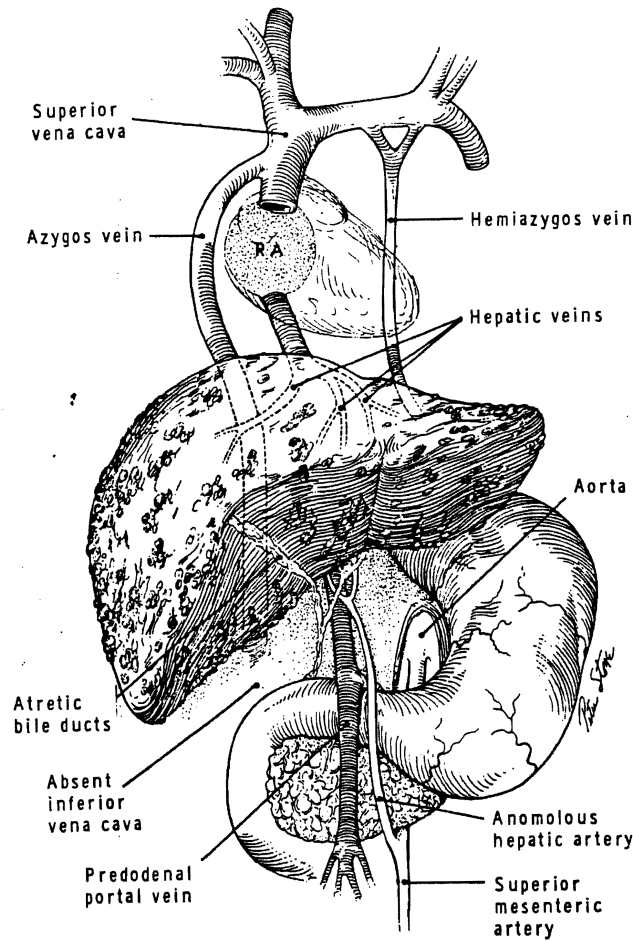


Fig. 1. Artist's depiction of the composite vascular malformation of absent inferior vena cava, preduodenal portal vein, and anomalous origin of the hepatic artery as encountered in the three children with biliary atresia described in the manuscript.

Table 1. Vascular (and Visceral) Anomalies in Three Infants With Extrahepatic Biliary Atresia Having Orthotopic Liver Transplantation

Patient	Age at TX (Mo)	Inferior Vena Cava	Portal Vein	Hepatic Artery	Other Malformations	Result
1	39	Absent	Predodenaal	From superior mesenteric artery	Polysplenia; intestinal malrotation	Died 11 days
2	27	Absent	Predodenaal	From superior mesenteric artery	Malrotation; polysplenia; liver symmetry	Died 7 days
3	16	Absent	Predodenaal	From superior mesenteric artery	Malrotation	Died 2 days

Her condition gradually deteriorated over the ensuing months and she required repeated paracenteses for relief of ascites. When she was 39 mo old, a cadaveric liver donor became available and an orthotopic liver homotransplantation was carried out. At operation, she had severe biliary cirrhosis and, in addition, had the following heretofore unrecognized vascular anomalies: absent inferior vena cava; hepatic artery arising from the superior mesenteric artery; and a preduodenal portal vein.

The reconstructive procedure that was carried out involved mobilizing and rerouting the portal vein and hepatic artery. Apparently satisfactory portal and arterial anastomoses were obtained, but in so doing the first portion of the duodenum was devascularized and had to be resected. A gastroduodenostomy and cholecystoduodenostomy were done. Absence of a recipient inferior vena cava prevented anatomic reconstruction of the infrahepatic vena cava of the homograft which had to be simply oversewn. Postoperatively, the liver homograft functioned poorly. Despite extensive supportive measures including exchange transfusions, the patient died in liver failure 11 days after transplantation. At autopsy intestinal malrotation and polysplenia were noted. The three vascular anastomoses were patent, but the tortuous reconstructed hepatic artery was of tiny caliber, and it was suspected that inadequate hepatic blood flow had been obtained. This impression was supported by the finding of massive necrosis of the homograft.

Patient 2, a white female, had an exploratory laparotomy for jaundice at the age of 7 wk. Extrahepatic biliary atresia was found, and an extensive dissection of the liver hilum failed to reveal a proximal bile duct for drainage.

At 27 mo of age, her diseased liver was removed and replaced with a cadaveric homograft. At the operation, she was found to have an identical triad of vascular anomalies that were described for patient 1. Intestinal malrotation, liver symmetry, and polysplenia were also noted. The homograft was revascularized without rerouting the portal vein or hepatic artery, as had been necessary in patient 1. The donor infrahepatic cava was simply oversewn.

Five hours after operation, she became hypotensive and was reexplored. The liver homograft was discolored, greatly enlarged, and hard consequent to a mechanical outflow block at the suprahepatic vena cava. The anastomosis was redone with some improvement in the vascular mechanics of the graft.

Postoperatively, continued bleeding necessitated reoperation at 16 hr and again at 4 days after transplantation. On each of these occasions, there was widespread vascular oozing from areas of previous dissection, and no single major bleeding vessel was found. Liver homograft function, which had never been good, deteriorated, and she died on the 7th posttransplant day. There was frank necrosis of the liver homograft at autopsy.

Patient 3, a white female, underwent exploratory operation for jaundice at 3 mo of age. Complete extrahepatic biliary atresia was found. Over the next 13 mo she developed progressively severe malabsorption and steatorrhea and had significant retardation in developmental landmarks.

When she was 16 mo old, an orthotopic liver transplantation was attempted. There was severe biliary cirrhosis and massive ascites. In addition, she had the same triad of vascular anomalies described for patients 1 and 2. Attempts at revascularization of the homograft were attended by recurrent anastomatic clotting. At no time did the liver homograft develop a normal color. Postoperatively, she never fully regained consciousness, developed profound hepatic coma, and died 36 hr later.

(II) Biliary Atresia and Single Vascular Anomalies (Table 2)

There were five additional children with biliary atresia who had co-existing vascular malformations distinct from the composite group just described. These consisted of four children with anomalous hepatic arterial vasculature and one with a malformation of the hepatic veins. In two children with anomalous hepatic arterial vasculature, the hepatic artery arose exclusively from the superior mesenteric artery. The other two children had a double hepatic artery. In one, the aberrant artery was the left hepatic branch arising from the left gastric artery. The second child having a double hepatic artery had an aberrant right hepatic branch which originated from the superior mesenteric artery. In both children with double hepatic arteries, one of the branches arose normally from the celiac axis.

Homograft arterial reconstruction in these childhood recipients has been detailed in a recent publication.⁴ In every instance, arterial revascularization could be satisfactorily accom-

Table 2. Aberrations of Normal Hepatic Artery: In Seven Children With Biliary Atresia Having Orthotopic Liver Transplantation and in Three "Normal" Cadaveric Liver Donors

	Common Hepatic Artery From Superior Mesenteric Artery	Double Hepatic Artery: Right Branch From Sup. Mesent Artery Left Branch From Celiac Artery	Double Hepatic Artery: Right Branch From Celiac Artery Left Branch From Left Gastric Artery
Recipient (7)	4	2	1
Donor (3)	1	1	1
Total (10)	5	3	2

plished. In one infant, direct anastomosis of the homograft celiac axis to the recipient aorta was necessary because of the diminutive caliber of the anomalous recipient arteries.

The remaining child in this group had an anomalous hepatic venous drainage of her native liver. A large right phrenic vein drained directly into the right hepatic vein instead of the vena cava. The transplant suprahepatic anastomosis was accomplished satisfactorily.

DISCUSSION

Extrahepatic biliary atresia, in contradistinction to other lethal congenital anomalies, has been reported almost exclusively as an isolated malformation.⁵⁻⁸ The paucity of co-existing anomalies lends credence to recently advanced contentions that biliary atresia may be an acquired condition rather than one due to an embryologic fault, as had traditionally been ascribed.⁹⁻¹¹ Indeed, many investigators have now taken the position that biliary atresia and neonatal hepatitis are simply different manifestations of a single disease process.^{6,12} Our findings of a major incidence of vascular malformations in children with biliary atresia do not necessarily contradict this point of view but do incriminate a defect in embryogenesis at an exquisitely early prenatal period. Formation of the inferior vena cava, for example, occurs at 3-4 wk of gestation,¹³ and absence of the inferior vena cava in infants with biliary atresia suggests a common teratogenic factor may be operative in this early gestational time frame. Whether an acquired disease or embryologic fault, a legitimate theory of the etiology of biliary atresia must account for its high numbers of associated vascular malformations.

The individual vascular anomalies found in our series of infants have also been described in conditions other than biliary atresia and even in normal subjects.¹⁴⁻¹⁷ Absence of the inferior vena cava has been reported in the past most extensively in patients with congenital heart disease.¹⁸ Embryologically the malformation results from a failure of union of the hepatic and subcardinal veins and, consequently, there is partial or total retention of the primitive cardinal system. In this situation, venous blood from the lower half of the body reaches the heart via azygous and/or hemiazygous pathways. The anomaly is of little clinical importance unless operations on the vena cava such as a portacaval shunt or ligation are planned.

Preduodenal portal vein is the least common of the triad of vascular anomalies. It has been associated frequently with intestinal malformations of various kinds and in about one-third of reported cases has produced a partial duodenal obstruction necessitating operative correction.¹⁹ The anomaly is thought to result from a reversal of the usual sequential degenerative obliteration of the vitelline anastomotic veins around the duodenum.²⁰

Considerable variation of both the origin and branches of the hepatic artery exist in normal individuals.^{16,17} The most common deviation from usual anatomy is a right hepatic artery originating from the superior mesenteric artery. Other variations include a left hepatic artery commencing from the left gastric artery and the superior mesenteric artery serving as the source of the common hepatic artery. All of the common variants of hepatic arterialization were encountered in normal donor liver specimens (Table 2), testifying to the frequency of arterial anomalies of the liver.

In the performance of orthotopic liver transplantation, these usually innocuous vascular anomalies assume major importance. Function of the liver homograft after revascularization must be almost instantaneous to provide vital hepatic-based homeostatic compounds, such as coagulation factors. This critical requirement of transplant function demands technical perfection in the execution of liver homograft revascularization. Pure anomalies of hepatic arterialization, though requiring some ingenuity in reconstruction, have been satisfactorily managed. The technical problems of anomalous hepatic venous drainage also appear negotiable. The composite vascular anomaly of absent inferior vena cava, preduodenal portal vein, and anomalous hepatic artery, however, presents the surgeon with a situation in which all of the vascular connections to the native liver are abnormal. Since, in most instances, the vascularity of the donor liver is normal, a transplant situation exists which is incapable of solution. In all three children, inability to reestablish normal vascularization of the donor liver resulted in poor perfusion of the homograft, frank hepatic ischemia, and, finally, liver failure and death.

Twenty-nine infants and children with extrahepatic biliary atresia have had orthotopic liver transplantation in the Denver series. Extended survival has been achieved in a number of these patients—the longest survivor now $4\frac{1}{2}$ yr since transplantation. The absolute shortage of cadaveric donors in childhood makes judicious recipient selection mandatory. Single variations of hepatic arterial or venous architecture should not preclude candidacy. On the other hand, children with the composite triad of perihepatic vascular malformations described here should not be considered as potential recipients of orthotopic liver homografts and, therefore, efforts to identify this group in advance are of paramount importance.

Characteristic findings on plain chest films are an absent inferior vena cava, which is manifest by a distinctive loss of the normal retrocardiac caval shadow on lateral films (Fig. 2A and B) and often a right mediastinal bulge from the tremendously enlarged azygous vein.²¹ These highly specific roentgenographic findings, however, are not commonly seen before 6 mo of age, at which time most infants with obstructive jaundice have already had exploratory surgery. Of more help in the identification of infants with vascular anomalies is the finding of a co-existing visceral abnormality. In a large series of infants with biliary atresia reported earlier, it was noted that in every instance those patients with vascular anomalies had visceral malformations as well.²² The manifestations of the visceral anomaly consisted of intestinal malrotation, situs inversus, polysplenia, and liver symmetry. A similar collection of visceral anomalies were noted incidentally in the cases described in this series (Table 1). In the earlier

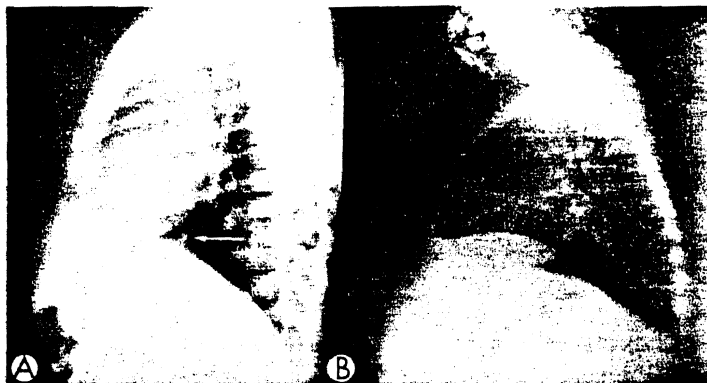


Fig. 2. Lateral chest film in absent inferior vena cava. (A) Normal lateral chest has distinctive retrocardiac shadow from normally located inferior vena cava (Arrow). (B) In absence of the inferior vena cava this retrocardiac space is "empty." Venous blood returns to the heart via azygous and/or hemiazygous venous pathways which drain into the superior vena cava.

report the observation was made that performance of the Kasai portico-
enterostomy procedure²³ might be jeopardized in infants with visceral
malformations but that vascular anomalies were of little consequence. Although a
contrary opinion can be given in the transplant situation, the visceral ab-
normalities do provide valuable clues for the detection of that special group of
infants with vascular malformations. Since intestinal malrotation or abdominal
situs inversus are easily diagnosed by radiologic study of the intestine, a barium
examination of the gastrointestinal tract should be a requisite part of the diag-
nostic work-up of infants with jaundice. Similarly, the finding of polysplenia or
liver symmetry at operative exploration should alert the surgeon to the possi-
bility of co-existing vascular anomalies. A few extra minutes to identify pre-
cisely the hepatic vasculature are fully justified in infants with noncorrectable
extrahepatic biliary atresia.

SUMMARY

Eight of 29 infants and children undergoing orthotopic liver transplantation
for extrahepatic biliary atresia had associated major vascular anomalies. A dis-
tinctive and highly unusual vascular malformation consisting of absent inferior
vena cava, anomalous origin of the hepatic artery, and preduodenal portal vein
was encountered in three of these children. Although at times technically diffi-
cult, single anomalies of hepatic vasculature were satisfactorily handled. In con-
trast, transplantation attempts were lethal in all three infants having the com-
plex vascular malformation. The suggestion is made that this specific subgroup
of patients with biliary atresia be identified in advance and that, at the moment,
children with this composite anomaly are highly questionable candidates for
liver transplantation.

ACKNOWLEDGMENT

The authors wish to thank Dr. Richard L. Wesenberg, the Pediatric Radiologist, UCMC, for
his advice and assistance in illustrating the radiographic findings of absent inferior vena cava;

Dr. John Taubman, who carried out and helped with the interpretation of the donor hepatic arteriograms; and Miss Krene Kozusko for her superb assistance in preparing this manuscript.

REFERENCES

1. Starzl TE, Groth CG, Brettschneider L, et al: Extended survival in 3 cases of orthotopic homotransplantation of the human liver. *Surgery* 63:549, 1968
2. Starzl TE, Groth CG, Brettschneider L, et al: Orthotopic homotransplantation of the human liver. *Ann Surg* 168:392, 1968
3. Starzl TE, Giles G, Lilly JR, et al: Indications for orthotopic liver transplantation; with particular reference to hepatoma, biliary atresia, cirrhosis, Wilson's disease, and serum hepatitis. *Transplant Proc* 3:308-312, 1971
4. Starzl TE: Experience in hepatic transplantation. Philadelphia, Saunders, 1969
5. Potts WJ: The surgeon and the child. Philadelphia, Saunders, 1959
6. Mustard WT, Ravitch MM, Snyder WH, et al (eds): *Pediatric Surgery*. Chicago, Year Book, 1969
7. Gross RE: The surgery of infancy and childhood. Philadelphia, Saunders, 1953
8. Swenson O: *Pediatric Surgery*. New York, Appleton-Century-Crofts, 1969
9. Brent RL, Arey JB, Blanc WA, et al: Persistent jaundice in infancy. *J Pediatr* 6:111, 1962
10. Hays DM: Biliary atresia: The current state of confusion. *Surg Clin N Amer* 53:1257, 1973
11. Hanai H, Idress F, Swenson O: Bile duct proliferation in atresia and related hepatic diseases. *Arch Surg* 94:14, 1967
12. DeLorimer AA: Surgical management of neonatal jaundice. *N Engl J Med* 288:1284, 1973
13. Hamilton WJ, Boyd JD, Mossman HW: Human embryology, prenatal development of form and function, (ed 3). Baltimore, Williams & Wilkins, 1962
14. Knight HO: An anomalous portal vein with its surgical dangers. *Ann Surg* 74:697, 1921
15. Dwight T: Absence of the inferior vena cava below the diaphragm. *J Anat Physiol* 35:7, 1901
16. Singh B, Sohal HS: Variations of the hepatic artery and its branches. *Indian J Surg* 14:20, 1952
17. Brown EZ: Variations in origin and course of the hepatic artery and its branches. *Surgery* 8:424, 1940
18. Anderson RC, Adams P Jr, Burke B: Anomalous inferior vena cava with azygous continuation (infrahepatic interruption of the inferior vena cava): Report of 15 new cases. *J Pediatr* 59:370, 1971
19. Bower RJ, Ternberg JL: Preduodenal portal vein. *J Pediatr Surg* 7:579, 1972
20. Marks C: Developmental basis of the portal venous system. *Am J Surg* 117:671, 1969
21. Berdon WE, Baker DH: Plain film findings in azygous continuation of the inferior vena cava. *Am J Roentgenol Radium Ther Nucl Med* 104:452, 1968
22. Lilly JR, Chandra RS: Surgical hazards of co-existing anomalies in biliary atresia. *Surg Gynecol Obstet* 139:49, 1974
23. Kasai M, Kimura S, Asakura Y, et al: Surgical treatment of biliary atresia. *J Pediatr Surg* 3:665, 1968

Discussion

Dr. Kenney (New York): We have transplanted livers to only three children at Memorial Hospital with biliary atresia. We have not observed any of these anomalies just described. However, our last two patients underwent auxiliary liver transplantation and I am sure we would not be aware of these anomalies. In fact, they probably would not interfere with successful auxiliary liver transplantation. Our one survivor in these three patients was a 6-yr-old boy who presented in the fall of 1971 with bleeding esophageal varices. He underwent a distal splenorenal shunt in hopes of controlling his bleeding as well as preserving his portal vein and vena cava. Indeed, his bleeding did stop, but he was admitted 1 yr later with bleeding from esophageal varices. At that time, in December 1972, he underwent heterotrophic liver transplantation. There was room for a second liver in this boy's abdomen because he had developed a large amount of ascites. However, in patients who do not have the ascites we prepare them for weeks ahead of time with pneumoperitoneum.

Dr. P. Altman (Washington): Dr. Lilley recalled our attention to important vascular anomalies in patients with biliary atresia. For most of us who are doing the Kasai procedure, it is the intestinal anomalies that have even greater significance. We found important intestinal anomalies in about one fourth of our patients whom we have explored for biliary atresia. The Kasai procedure does not preclude candidacy for subsequent liver transplantation because the Roux-en-Y loop for biliary drainage is already made.

Dr. P. Kottmeir (New York): I would like to bring up another point which may be more philosophical. We are unable to predict when our biliary atresia patients will die. So, I would like to know how you pick the time when you do a liver transplant?

Dr. J. Lilly (Denver): We have been reluctant to carry out auxillary liver transplantation in infants with biliary atresia for a number of reasons, not the least of which is the very real specter of malignancy in the native liver. Four of our 29 children with biliary atresia have had hepatomas at the time of transplantation. In fact, the little girl, who is now 4 yr old, since orthotopic transplantation had an unrecognized hepatoma discovered in her own liver after its removal. She has no evidence of recurrence at this time and is probably cured. Because of the very real shortage of cadavaric liver donors, I believe children with biliary atresia should be considered for transplantation when a donor of suitable size and blood type becomes available rather than postpone surgery until a terminal stage of the disease is reached.