PEDIATRIC LIVER TRANSPLANTATION: PROSPECTS FOR LINEAR GROWTH

Andrew H. Urbach, M.D., J. Carlton Gartner, Jr., M.D., J. Jeffrey Malatack, M.D., Basil J. Zitelli, M.D., and Thomas E. Starzl, M.D.

The first attempt at liver transplantation in humans was made in 1963 (1). The first long term survivor was transplanted on July 23, 1967. She was a one-and-one-half-year-old girl who lived for 13 months before she succumbed to the hepatocellular carcinoma for which she was treated. During the years 1963-1979, Dr. Thomas Starzl performed liver transplantation on 170 patients including 86 children (2). Survival at five years was less than 30% with younger patients, showing a 10% survival advantage over adults. Not until the discovery of cyclosporine (3, 4) and the initiation of clinical trials did survival increase significantly. As a direct result of this success, the number of patients who underwent the procedure climbed and an innovative and aggressive procedure became accepted therapy for end-stage liver disease (5); however, a multitude of questions remain about the quality of life of these patients. The purpose of this review is to address one aspect of this issue, linear growth.

OVERALL SURVIVAL

From May 1981 to May 1986, 229 children received 303 liver transplants at the Children's Hospital of Pittsburgh. Overall survival rate as of May 1986 was 71%. Table 1 shows overall survival rates for each year while Table 2 reviews survival rates of children undergoing retransplantation compared with those of children receiving only one transplant.

GROWTH

From May 1981 to June 1983, 49 children received liver transplants and 29 survivors were evaluated for growth potential (6). Their average age at the time of transplant was five-and-one-half years (7 mo. - 13 years) and all were Tanner Stage I. Transplantation was performed for a wide variety of liver diseases. Nearly half of the patients had biliary atresia. Metabolic disorders such as alpha$_1$ antitrypsin deficiency and tyrosinemia

accounted for the next largest group. Immunosuppression was accomplished with an average dose of 9.4 mg/kg/day of cyclosporine and 0.21 mg/kg/day of prednisone (6, 7). Twenty-five of 29 patients were on less than 5 mg of prednisone per day. Average length of follow-up was three years (24 - 52 months).

TABLE 1

Yearly survival rates at the Children's Hospital of Pittsburgh from May 1981-May 1986.

DATES	NUMBER OF TRANSPLANTS	NUMBER OF CHILDREN	DEATHS	OVERALL SURVIVAL FOR COHORT
5/81-6/82	30	25	9	64%
7/82-6/83	38	25	10	60%
7/83-6/84	63	50	8	84%
7/84-6/85	79	57	14	75%
7/85-5/86	93	72	25	65%
Overall	303	229	66	71%

TABLE 2

Survival rates bases on need for retransplantation at the Children's Hospital of Pittsburgh from May 1981-1986

NUMBER OF CHILDREN	NUMBER OF TRANSPLANTS	DEATHS	OVERALL SURVIVAL
166	1	38	77%
51	2	24	53%
11	3	4	64%
1	4	0	100%

Twenty-eight percent (8/29) crossed percentiles in an upward direction (had greater than normal growth velocity for age) and were also above the fifth percentile on a standard growth curve at the end of the study. Fourteen percent (4/29) were above the fifth percentile prior to transplantation and maintained a normal growth pattern with no change in percentile. Forty-five percent (13/29) were below the fifth percentile prior to surgery and remained less than the fifth percentile following surgery. Within this group, however, 10 of 13 (77%) attained normal or accelerated growth velocity. Fourteen percent (4/29) began above the fifth percentile and fell to below this level at the time of their last evaluation. Of the seven patients with poor growth, the majority suffered from chronic rejection or a recurrence of the disease for which the transplant was performed (8). Overall, 76% of our patients achieved normal or accelerated growth velocity.

DISCUSSION

A great deal of the concern about growth in renal transplant recipients has centered around the effects of steroids on the developing child. Many mechanisms for steroid-induced growth failure have been suggested. These include abnormalities of calcium and phosphorus metabolism, a direct effect on cell metabolism, and inhibitory effects on growth hormone and somatomedin activity (9, 10, 11). Specifically, linear growth seems to be related to prednisone dosages and scheduling intervals. Lilly (12) and DeShazo (13) showed that with prednisone dosages between 0.2 and 0.3 mg/kg/day, good growth could occur. Better growth is felt to occur when alternate day therapy is utilized (14, 15), particularly in patients with a bone age of less than 12 years (16, 17, 18). Concerns, however, have been raised about the immunosuppressive efficacy of an every-other-day steroid regimen (14, 15, 19, 20) and many authors reserve this therapy for a child with poor growth whose graft function is excellent on daily prednisone. Data on graft survival with administration of every-other-day prednisone is not available for liver transplantation.

Detailed growth studies with the use of cyclosporine and prednisone for immunosuppression are limited to renal transplant patients. Conley (21) and Klare (22) report optimism, but of the 10 patients discussed, the latter report (22), four children received no prednisone at all. The other six children received low dose prednisone, 8.5 mg/1.73m^2/day. Ellis (23), on the other hand, reports more disappointing results with growth, using the same immunosuppressive drugs. Utilizing a mean dose of 0.25 mg/kg/day of prednisone, growth was suboptimal or poor in seven of eight patients.

Linear growth failure is a prominent feature of end-stage liver disease (24). In the pre-cyclosporine era, some authors (25) expressed reluctance to perform transplants in pediatric patients. Much of their hesitancy revolved around the growth retardation and the multitude of side effects of high dose corticosteroids. With the advent of cyclosporine as a potent immunosuppressive agent (3, 4), the necessity to utilize high dose prednisone in liver transplant patients lessened. Until recently no data were available on growth following liver transplantation in the cyclosporine era. Two articles (26, 27) briefly referred to the observation that good growth could be achieved; however, these impressions were limited in scope because of the short length of follow-up.

Our report (6) indicates that good growth in pediatric liver transplant recipients is possible using cyclosporine with a daily prednisone dose of 0.21 mg/kg/day. We also show that most growth failure was predictable on the basis of poor graft function. The improvement in linear growth is likely to be multifactorial. Factors which account for good growth include disappearance of metabolic bone disease, good nutrition, improved hepatic function and the general state of well being that these patients achieve (27). By allowing lower doses of prednisone to be utilized, the effectiveness of cyclosporine has also contributed to the positive results that we have presented. We further believe that the risks of alternate day steroids on graft survival may not currently warrant every-other-day dosing considering the growth data presented here. These data provide support for our current immunosuppression regimen of cyclosporine and low dose prednisone. Future investigation should emphasize therapeutic methods which enhance growth while preventing chronic rejection.

REFERENCES

1. Starzl, T.E., Marchioro, T.L., VonKaulla, K.N., et al.: Homotransplantation of the liver in humans. Surg. Gynecol. Obstet. 117:659, 1963.

2. Starzl, T.E., Iwatsuki, S., VanThiel, D., et al.: Evolution of liver transplantation. Hepatology 2:614, 1982.

3. Borel, J.F., Feurer, C., Gubler, H.U., et al.: Biological effects of cyclosporin A: A new antilymphocyte agent. Agents Actions 6:468, 1976.

4. Borel, J.F., Feurer, C., Gubler, H.U., et al.: Effects of the new antilymphocyte peptide cyclosporin A in animals. Immunology 32:1017, 1977.

5. National Institutes of Health Consensus Development Conference Statement: Liver transplantation - June 20-23, 1983. Hepatology 4(suppl):107S, 1984.

6. Urbach, A.H., Gartner, J.C., Malatack, J.J., et al.: Linear growth following pediatric liver transplantation. AJDC 1987, in press.

7. Starzl, T.E., Iwatsuki, S., Malatack, J.J.: Liver and kidney transplantation in children receiving cyclosporin A and steroids. J. Pediatr. 100:681, 1982.

8. Gartner, J.C., Bergman, I., Malatack, J.J., et al.: Progression of neurovisceral storage disease with supranuclear ophthalmoplegia following orthotopic liver transplantation. Pediatrics 77:104, 1986.

9. Travis, L.B., Chesney, R., McEnery, P., et al.: Growth and glucocorticoids in children with kidney disease. Kidney International 14:365, 1978.

10. Pennisi, A.J., Phillips, L.S., Vittenbogaart, C., et al.: Linear growth and somatomedin activity in renal allograft recipients. Proc. Dialysis Transplant Forum 6:168, 1976.

11. Pennisi, A.J., Costin, G., Phillips, L.S., et al.: Linear growth in long term renal allograft recipients. Clinical Nephrology 8:415, 1977.

12. Lilly, J.R., Giles, G., Hurwitz, R., et al.: Renal homotransplantation in pediatric patients. Pediatrics 47:548, 1971.

13. DeShazo, C.V., Simmons, R.L., Bernstein, D.M., et al.: Results of renal transplantation in 100 children. Surgery 76:461, 1976.

14. McEnery, P.T., Gonzalez, L.L., Martin, L.W., et al.: Growth and development of children with renal transplants. Use of alternate day steroid therapy. J. Pediatr. 5:806, 1983.

15. Potter, D.E., Holliday, M.A., Wilson, S.J., et al.: Alternate day steroids in children after renal transplantation. Transpl. Proc. 7:79 1975.

16. Grushkin, C.M., Fine, R.N.: Growth in children following renal transplantation. AJDC 125:514, 1973.

17. Hoda, Q., Hasinoff, D.J., Arbus, G.S.: Growth following renal transplantation. Clinical Nephrology 3:6, 1975.

18. Fine, R.N., Malekzadeh, M.H., Pennisi, A.J., et al.: Long term results of renal transplantation in children. Pediatrics 61:641, 1978.

19. Diethelm, A.G., Sterling, W.A., Hartley, M.W., et al.: Alternate day prednisone therapy in recipients of renal allografts. Arch. Surgery 111:867, 1976.

20. Potter, D., Belzer, F.O., Rames, L., et al.: The treatment of chronic uremia in childhood transplantation. Pediatrics 45:432, 1970.

21. Conley, S.B., Flechner, S.M., Rose, G., et al.: Use of cyclosporine in pediatric renal transplant recipients. J. Pediatr. 106:45, 1985.

22. Klare, B., Walter, J.V., Hahn, H., et al.: Cyclosporine in renal transplantation in children. Lancet 2:692, 1984.

23. Ellis, D., Avner, E.D., Rosenthal, J.T.: Renal function and somatic growth in pediatric cadaveric renal transplantation with cyclosporine-prednisone immunosuppression. AJDC 139:1161, 1985.

24. Burgess, D.B., Martin, H.P., Lilly, J.R.: The development status of children undergoing Kasai procedure for biliary atresia. Pediatrics 70:624, 1982.

25. MacDougall, B.R.D., Williams, R.: The indications for orthotopic liver transplantation. Transplant Proc. 11:247, 1979.

26. Malatack, J.J., Zitelli, B.J., Gartner, J.C., et al.: Pediatric liver transplantation under therapy with cyclosporine A and steroids. Transplant Proc. 15:1292, 1983.

27. Gartner, J.C., Zitelli, B.J., Malatack, J.J., et al.: Orthotopic liver transplantation in children: Two year experience with 47 patients. Pediatrics 74:140, 1984.