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Long-term outcome following pediatric liver transplantation for metabolic disorders

Even with optimal medical and nutritional support, many inborn errors of metabolism that affect the liver have a guarded prognosis. In some cases, a metabolic crisis may strike at any time, leading to mortality or neurological impairment in survivors. Therefore, liver transplantation has been an increasingly important therapeutic option for many inborn errors of metabolism (1).

Successful liver transplantation has been reported for a variety of metabolic conditions, including α1-antitrypsin deficiency (2, 3), urea cycle disorders (4), tyrosinemia type 1 (5), MSUD (6), organic acidemias (7, 8), glycogen storage disorders (9), primary hyperoxaluria type 1 (10, 11), Wilson disease (12), and mitochondrial respiratory chain disorders (13). In urea cycle defects, MSUD and organic acidemias, the risk of brain injury despite medical therapy is especially high, so the decision to operate in these conditions is often a matter of urgency. Organic acidemia patients tend to show improved metabolic control, growth, and quality of life following liver transplantation, but unfortunately may still experience brain damage despite surgery (7, 14). Other metabolic disorders, such as phenylketonuria, could in theory be treated by liver transplantation, but effective dietary and

Abstract: In order to determine long-term outcome, including survival, growth and development, following liver transplantation in children with metabolic disorders, we retrospectively reviewed charts of 54 children with metabolic disorders evaluated from 1989–2005 for presenting symptoms, transplantation timing and indications, survival, metabolic parameters, growth, and development. Thirty-three patients underwent liver transplantation (12 received combined liver–kidney transplants) at a median age of 21 months. At a median follow-up of 3.6 yr, patient survival was 100%, and liver and kidney allograft survival was 92%, and 100%, respectively. For the group as a whole, weight Z scores improved and body mass index at follow-up was in the normal range. Two yr post-transplantation, psychomotor development improved significantly (p < 0.01), but mental skills did not; however, both indices were in the low-normal range of development. When compared to patients with biliary atresia, children with metabolic disorders showed significantly lower mental developmental scores at one and two yr post-transplantation (p < 0.05), but psychomotor developmental scores were not significantly different. We conclude that, in patients with metabolic disorders meeting indications for transplantation, liver transplantation or combined liver–kidney transplantation (for those with accompanying renal failure) is associated with excellent long-term survival, improved growth, and improved psychomotor development.
medical therapy exist, so in such cases the risks of surgery outweigh potential benefits.

Important advances in immunosuppression, operative procedures, and post-operative intensive care have contributed to improved liver transplantation outcome (15–18). At present, five-yr survival rates between 80–90% are routinely expected following liver transplantation overall (19). Although we are now in an era of advanced surgical techniques (e.g., the use of living donors and reduced-size grafts) and better results, issues of donor availability and risks of long-term immunosuppressive medications still exist (16, 18). Significant factors requiring close examination in these patients include indication for transplantation, timing of surgery, survival, and long-term growth and developmental outcomes. In order to understand these issues more clearly, we carried out a single-center retrospective analysis of pediatric patients who underwent liver or liver–kidney transplantation for metabolic disorders.

Patients and methods

A chart review was performed on 54 pediatric patients with metabolic disorders evaluated at Lucile Packard Children’s Hospital at Stanford for possible transplantation between 1989–2005. The study was approved by the Institutional Review Board at Stanford University. Parameters examined were presenting symptoms, indications and timing of transplantation, patient and graft survival, metabolic laboratory results, liver function, growth and development. Thirty-three children (15 female, 18 male) were transplanted during the time of the study period. Diagnoses were primary hyperoxaluria (n = 9), tyrosinemia (n = 6), citrullinemia (n = 3), OTC deficiency (n = 3), z-1-antitrypsin deficiency (n = 2), glycogen storage disease type Ia (n = 2), methylmalonic acidemia (mut°) (n = 3), CPS deficiency (n = 2), neonatal hemochromatosis (n = 1), ASL deficiency (n = 1), and a mitochondrial disorder with lactic acidosis (n = 1). Twenty-one patients were evaluated by the liver transplant service but were not transplanted during the period of analysis, including children with diagnoses of z-1-antitrypsin deficiency (n = 7), glycogen storage disease (n = 4), urea cycle defects (n = 4), neonatal hemochromatosis (n = 2), tyrosinemia (n = 1), protein C deficiency (n = 1), Crigler-Najjar syndrome (n = 1), and Wilson disease (n = 1). Reasons for not undergoing transplantation included clinical instability, desire to continue medical management, low assigned priority status, and delays in organ availability.

Twenty-one children underwent liver transplantation ≤42 months of age and were evaluated using the BSID (20) before transplantation and then at 12 and 12 months post-transplantation. Two-yr post-transplantation developmental data were available for 14 of these 21 patients. The BSID generates an MDI and PDI (X = 100, SD = 15). A subset of seven school-age urea cycle patients aged seven months to nine yr at transplantation were evaluated with either the WPPSI or WISC, standardized assessments designed to measure intellectual abilities in children from two to 16 yr of age. All developmental assessments were conducted in an outpatient clinic as part of ongoing medical care during periods of clinical stability.

MDI and PDI mean scores were analyzed for significant change over time (pre-transplantation, three, 12, and 24 months post-transplantation) and also compared with biliary atresia patients (n = 31) transplanted at ≤42 months of age (mean age at transplantation 11 months; range 5–22 months; 12 females and 19 males). Both biliary atresia patients and metabolic patients were transplanted during the same time frame and cared for by the same medical and surgical team as the metabolic patients. T-tests were used to determine significance of change in mean MDI and PDI scores over time, as well as between different diagnoses at designated points in time (SAS STATVIEW 5.0).

Results

Isolated liver transplantation was performed in 21 patients and combined liver–kidney transplantation was performed in 12 patients (nine with primary hyperoxaluria type 1 and three with methylmalonic acidemia). These 33 children received a total of 48 organ grafts (36 livers, 12 kidneys at an average age of 49.3 ± 59.5 months [or a median age of 21 months]) (Table 1).

Overall, a diagnosis was established at an average age of 18.6 ± 38.6 months (median age 4.5 months; range, <1 month–192 months). One or more of the following presenting signs and symptoms (listed most common to least) were noted at diagnosis: altered mental status, liver dysfunction, renal dysfunction, poor nutrition, hyperammonemia, metabolic acidosis, poor weight gain, poor growth, hyperbilirubinemia, hypoglycemia, infection, liver tumor, and dysmorphic features. The most common presenting symptoms among the 33 transplanted children were altered mental states (21/33 [64%]) and liver dysfunction (15/33 [45%]) (Table 2).

<table>
<thead>
<tr>
<th>Type of metabolic disease</th>
<th>Age at transplantation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperoxaluria (n = 9)</td>
<td>18.5 (28.1 ± 31.9)</td>
</tr>
<tr>
<td>Urea cycle defects (n = 9)</td>
<td>68 (66.8 ± 64.3)</td>
</tr>
<tr>
<td>Citrullinemia (n = 3)</td>
<td>7 (29.8 ± 44.2)</td>
</tr>
<tr>
<td>OTC deficiency (n = 9)</td>
<td>84 (70.3 ± 57.7)</td>
</tr>
<tr>
<td>CPS deficiency (n = 2)</td>
<td>139.5 (139.5 ± 91.2)</td>
</tr>
<tr>
<td>Arginosuccinic aciduria (n = 1)</td>
<td>63</td>
</tr>
<tr>
<td>Tyrosinemia (n = 6)</td>
<td>10 (16.8 ± 17.4)</td>
</tr>
<tr>
<td>Methylmalonic acidemia (n = 3)</td>
<td>130 (161.7 ± 76.6)</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency (n = 2)</td>
<td>25 (25.0 ± 19.8)</td>
</tr>
<tr>
<td>Glycogen storage disease (n = 2)</td>
<td>85 (85.0 ± 72.1)</td>
</tr>
<tr>
<td>Hemochromatosis (n = 1)</td>
<td>3</td>
</tr>
<tr>
<td>Mitochondrial disease (n = 1)</td>
<td>11</td>
</tr>
<tr>
<td>All patients (n = 33)</td>
<td>21 (49.3 ± 59.5)</td>
</tr>
</tbody>
</table>

The median age of transplant (in months) for each subgroup of transplanted patients is indicated in the right-hand column; the mean ± standard deviation follows in parentheses.
All patients (n = 11) with α1-antitrypsin deficiency, neonatal hemochromatosis, glycogen storage disease, or tyrosinemia presented with liver dysfunction (elevated AST and ALT levels or liver cirrhosis). Altered mental status, hyperammonemia, or both were the major presenting features in patients with urea cycle defects (100% [9/9] of the children with urea cycle disorders had altered mental status). Additional presenting features included poor nutrition (36% [12/33]), hyperammonemia (27% [9/33]), renal dysfunction, including renal failure, kidney stones, and abnormal serum creatinine levels (36% [12/33]), acidosis (21% [7/33]), poor weight gain (12% [4/33]), poor growth (bone age and height) (12% [4/33]), hyperbilirubinemia (9% [3/33]), hypoglycemia (9% [3/33]), infection (6% [2/33]), hepatocellular carcinoma (6% [2/33]), and dysmorphic features (3% [1/33]).

At a mean follow-up of 5.4 ± 4.4 yr (median 3.6 yr), overall patient survival was 100%, and overall liver and kidney allograft survival was 92% and 100%, respectively (n = 33). Three out of 36 liver grafts were lost in three patients. Two patients with primary hyperoxaluria and one with citrullinemia required replacement of their first liver allografts due to hepatic artery thrombosis between eight and 21 days after the initial transplantation. There were no grafts lost to acute or chronic allograft rejection.

All patients showed durable correction of metabolic parameters. Liver allograft function (mean serum bilirubin 0.73 ± 1.03 mg/dL, mean AST 38.1 ± 18.8 U/L, and mean ALT 36.9 ± 34.6 U/L) was excellent. The three patients with methylmalonic acidemia showed improvement in plasma MMA concentrations. At four to six months post-transplantation, plasma MMA fell to a mean of 270 ± 58 μmol/L from a baseline of 3430 ± 1847 μmol/L.

Post-transplantation infectious complications occurred in 58% of patients (19/33) within one yr following transplantation, with 27% of patients (9/33) having EBV infection. Overall, 9% (3/33) developed EBV-associated PTLD presenting as adenopathy, cat-scratch disease, or chronic airway obstruction (Table 3). These complications resolved with reduction of immunosuppression and anti-viral therapy. A single case of worsening renal function was documented in a patient with methylmalonic acidemia who received combined liver–kidney transplantation and native nephrectomy, following non-adherence with medications and restricted diet (Table 3).
Weight was evaluated 35 ± 3.3 months after transplantation. For the group as a whole, weight Z scores improved 0.72 ± 1.44 from 0.53 ± 1.61 at the time of transplantation to 0.18 ± 1.47 at follow-up (n = 31). For the non-urea cycle disorder patients (n = 21), weight Z scores improved 1.14 ± 1.39 (from 0.77 ± 1.56 to 0.20 ± 1.38) (p = 0.03). For urea cycle patients (n = 9), weight Z scores improved 0.07 ± 1.56 (from 0.06 ± 1.81 to 0.29 ± 1.75). Height was not adequately recorded at the time of transplantation for comparison between time of transplantation and three yr post-transplantation. However, 35 ± 3.3 months after transplantation the study group as a whole had height Z scores of −0.64 ± 1.73; the non-urea cycle patients had height Z scores of −0.89 ± 2.08 and the urea cycle patients had scores of −0.07 ± 1.37. BMI at follow-up was in the normal range (18.26 ± 3.39).

Mental (MDI) and psychomotor (PDI) functioning for metabolic patients transplanted ≤ 42 months of age (n = 21) improved over time. Before transplantation, MDI (82 ± 15.2) and PDI (70 ± 17) mean scores were delayed at −1 SD and −2 SD, respectively. Three months post-transplantation, mean scores decreased significantly for both MDI (75 ± 13, p < 0.001) and PDI (59 ± 13, p < 0.01), but returned to pretransplantation baseline by one yr post-transplantation (MDI 83 ± 17; PDI 74 ± 15). Patients (n = 14) evaluated two yr post-transplantation showed significant increases in mean scores for psychomotor skills (PDI 87 ± 24, p < 0.01), but not mental skills (MDI 87 ± 15) (Table 4).

When compared to patients with biliary atresia matched for age at transplantation (n = 31), metabolic disorder patients demonstrated significantly decreased mental development before transplantation and at one and two yr post-transplantation (p < 0.05) (data not shown). A comparison of psychomotor indices found that metabolic disorder patients had significantly decreased scores pre-transplantation (p < 0.01) and three months post-transplantation (p < 0.05). At one yr, the developmental gap closed somewhat (p < 0.07), but by two yr after transplantation there was no difference between PDI scores for the biliary atresia group (87 ± 12) and the metabolic disorders group (86 ± 15). A summary of intellectual capabilities for urea cycle patients (n = 7) indicates that, 2–6 yr after transplantation, four children were functioning in the normal range, one child achieved an IQ score 1 SD below normal and two children obtained IQ scores 2 SD below normal. Current school status by parental report ranged from age appropriate classroom placement (n = 2) to self-contained special education classroom (n = 3). An additional two children had age appropriate classroom placement, but required additional educational support services (Table 5).

Discussion

The patients described in this study were diagnosed with a variety of inborn errors of metabolism (Table 1). Not surprisingly, presenting signs and symptoms corresponded to the underlying pathophysiology of the specific metabolic condition (Table 2). Post-transplantation survival rates of patients who have inborn errors of metabolism appear to be higher, reaching 100%, when compared to survival following transplantation for other indications, such as extrahepatic biliary atresia, acute liver failure, and postnecrotic liver cirrhosis (21–23). The results of the current study reinforce this point, with all 33 patients
undergoing liver or combined liver–kidney transplantation surviving at a mean follow-up of 5.4 ± 4.4 yr. Improved survival in metabolic patients undergoing transplantation may be related to the presence of normal anatomy, the ability to perform surgery electively during periods of relative clinical stability, or other unknown factors.

In children who are treated by liver transplantation for chronic liver disease of any type, poor growth occurs in the first 6–12 months post-transplantation and catch-up growth occurs within 1–4 yr. The post-transplantation growth rate is affected by factors such as pretransplantation height, nutritional status, graft function, and steroid usage (2, 24–28). In children undergoing living donor liver transplantation for metabolic disorders, physical growth retardation is more severe the earlier the age of symptom onset or the longer the duration between symptom onset to liver transplantation (29). Improved growth parameters have been observed post-transplantation in patients with methylmalonic acidemia, hyperoxaluria type 1, glycogen storage disease type 1 and mitochondrial disease limited to the liver (7, 9–11, 30). The children in our cohort showed improved weight by three yr post-transplantation. For unclear reasons, this effect was especially notable in patients who did not have urea cycle disorders. Change of height could not be evaluated because of a lack of height measurements at the time of transplantation. However, overall patient height was 0.64 ± 1.73 at the conclusion of this study, which shows the potential for normal stature (within 2 SD of normal) after transplantation. Therefore, children who have metabolic disorders have the potential for improved and, in some cases, normal growth following transplantation.

Developmental outcome studies of patients with inborn errors of metabolism following liver transplantation are scant. Moreover, these studies are limited by lack of standardized assessment instruments and case presentation format in some instances (5–7, 10, 31–36). In one post-transplantation study, 24 children with mixed diagnoses of metabolic disorders showed varied academic performance, with some children performing at appropriate grade level while others required special education services (3). In another study, normal post-transplantation neurological status was reported for 35 metabolic disorder patients, but these positive findings resulted from inclusion of diagnoses with little significant effect on mental functioning (i.e., citrin deficiency and relatively mild, late-onset urea cycle disorders) (29). For patients with MSUD, cognitive, behavioral and motor deficits may improve significantly following liver trans-

### Table 4. Mental (MDI) and psychomotor (PDI) cores for children with metabolic disorders before and after transplantation

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Pretransplant (n = 22)</th>
<th>3 months post-transplant (n = 22)</th>
<th>12 months post-transplant (n = 22)</th>
<th>24 months post-transplant (n = 15)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental score (MDI)</td>
<td>82 ± 15 (50–103)</td>
<td>75 ± 13 (50–92)</td>
<td>83 ± 17 (50–110)</td>
<td>87 ± 24 (50–114)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Psychomotor (PDI)</td>
<td>70 ± 17 (50–102)</td>
<td>59 ± 13 (50–86)</td>
<td>74 ± 15 (50–95)</td>
<td>87 ± 15 (73–115)</td>
<td>&lt;0.01† &lt;0.001‡</td>
</tr>
</tbody>
</table>

Results reported as means ± SD (range).

†Significant for Δ Pretransplant to three months post-transplant.

‡Significant for Δ 3 months to 12 months post-transplant.

§Significant for Δ 12 months to 24 months post-transplant.

### Table 5. Summary of IQ scores and school status for children with urea cycle disorders 2–6 yr following liver transplantation

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Age at Transplantation</th>
<th>IQ †</th>
<th>School status by parental report ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTC</td>
<td>9 yr</td>
<td>95 (2 yr)</td>
<td>Grade appropriate school placement (7 yr)</td>
</tr>
<tr>
<td>2</td>
<td>OTC</td>
<td>7 months</td>
<td>85 (6 yr)</td>
<td>Diagnosed with attention deficit disorder; regular classroom with educational support services (7 yr)</td>
</tr>
<tr>
<td>3</td>
<td>OTC</td>
<td>7 yr</td>
<td>65 (2 yr)</td>
<td>Diagnosed with autism; special education placement (5 yr)</td>
</tr>
<tr>
<td>4</td>
<td>Citrullinemia</td>
<td>8 yr</td>
<td>98 (5 yr)</td>
<td>Grade appropriate school placement (5 yr)</td>
</tr>
<tr>
<td>5</td>
<td>Citrullinemia</td>
<td>7 months</td>
<td>103 (4 yr)</td>
<td>Grade appropriate school placement with educational support services</td>
</tr>
<tr>
<td>6</td>
<td>ASL</td>
<td>5 yr</td>
<td>77 (3 yr)</td>
<td>Special education placement (6 yr)</td>
</tr>
<tr>
<td>7</td>
<td>CPS</td>
<td>6 yr</td>
<td>62 (2 yr)</td>
<td>Home schooled with special education support (3 yr)</td>
</tr>
</tbody>
</table>

†The post-transplantation cognitive assessment testing interval is shown in parentheses.

‡The post-transplantation reported school status interval is shown in parentheses.
plantation, while patients who have organic acidemias or mitochondrial respiratory chain defects remain at risk for continued neurological deterioration following surgery (6, 8, 13, 14, 37). In early-onset urea cycle disorders, which clearly have the potential to impact mental and motor function, transplantation appears to prevent further neurological deterioration and cognitive function may improve in some cases, with neurological outcome correlating with pretransplantation cognitive ability (31, 36, 38, 39). Children transplanted for end-stage liver disease with biliary atresia and other non-metabolic disorders have shown significantly improved development post-transplantation. Such gains in mental development are associated with improved growth and nutritional indices, such as height, weight, and albumin level (24, 25, 40). Overall, the underlying diagnosis and baseline developmental status appear to influence subsequent developmental outcome in children undergoing liver transplantation.

The 21 children described in this paper who were transplanted at ≤42 months of age showed a pattern of “developmental recovery” following transplantation, as has been reported in previous studies (28, 41, 42). Before transplantation, children with metabolic disorders had significant delays in both cognitive and motor development when compared to a norm-based sample. Following a downward trend in both mental and motor scores three months after transplantation, developmental functioning returned to the pretransplantation level one yr after transplantation. When compared to children with biliary atresia at two yr post-transplantation, no difference was found in psychomotor development, suggesting that the deleterious effect of metabolic disorders is confined to mental development. Overall, the group of patients with metabolic disorders showed remarkable gains in both their cognitive and motor skills over time, with low–normal scores at two yr post-transplantation. Given the risk of continued neurological compromise in some metabolic disorders, the fact that mental function was preserved two yr post-surgery may represent a potential benefit of transplantation.

The subset of children with urea cycle disorders (n = 7) demonstrated a wide range of IQ scores following transplantation (62–103), but four of the children were functioning in regular classroom settings (Table 5). These data suggest that disease processes related to metabolic disorders and transplantation can have deleterious effects on both cognitive and psychomotor functioning, but with transplantation developmental gains over time are possible, with some children demonstrating normal or near-normal academic functioning in the post-transplantation period. Further longitudinal study of children with metabolic disorders is needed to determine if developmental gains are maintained or improved over time. In addition, a larger sample size would assist in determining the specific effects of transplantation on the developmental functioning of children with metabolic disorders.

Liver transplantation for patients with metabolic disorders is also associated with significant risks, limitations, and potential adverse events (Table 3), which should be carefully considered before listing a patient for transplantation. EBV or other infections, EBV-related PTLD, and medication reactions may occur. In addition, certain types of immunosuppression (especially steroids) can negatively affect post-transplantation catch-up growth. However, the use of steroid-sparing immunosuppressive regimens has been associated with significant benefits in pediatric transplantation recipients, including improved growth and decreased incidence of hypertension, obesity, and cosmetic side effects (43). A strict regimen of immunosuppression and a carefully managed diet must be followed lifelong. Severe, albeit less common, complications include primary graft failure, abdominal hemorrhage, and the risk of mortality.

Although hepatocyte transplantation is a promising new approach for the treatment of liver-based metabolic disorders, only limited success has been reported to date (44). Gene therapy also holds promise for the treatment of these disorders, but significant hurdles need to be overcome, a fact that is clearly illustrated by the fatal occurrence of systemic inflammatory response syndrome in a urea cycle patient following adeno viral gene transfer (45). Thus, until the aforementioned technologies can be developed for wider application, liver transplantation is currently the only definitive therapy for these patients and has been associated with improvement in patient outcomes. In patients with metabolic disorders meeting indications for transplantation, liver transplantation or combined liver–kidney transplantation (for those with accompanying renal failure) is associated with excellent long-term survival, improved metabolic parameters, and improved growth and developmental functioning.

References

Liver transplantation in metabolic disorders


