Sensorineural Hearing Loss in Children After Liver Transplantation

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Objective: To investigate risk factors for sensorineural hearing loss (SNHL) in children after liver transplantation.

Design: Retrospective medical record review.

Setting: Pediatric tertiary care hospital.

Patients: One hundred twenty-five consecutive children who received liver transplants between March 1, 1987, and June 30, 1996.

Main Outcome Measures: The presence of SNHL (bone conduction threshold of ≥35 dB of hearing loss in at least 1 frequency) and the cause of the liver abnormality in all 125 patients. In addition, among the subset of children who had biliary atresia and underwent transplantation before 2 years of age, the total dose (milligrams per kilogram of body weight) of aminoglycoside antibiotic medications (tobramycin sulfate, gentamicin sulfate, and amikacin sulfate) and of intravenous loop diuretic agents (furosemide) was compared between children with and without SNHL.

Results: Audiologic evaluations were available for 66 of 125 patients, 15 (12%) of whom have SNHL. Of 5 survivors with the short-bowel syndrome, 4 have severe to profound SNHL. Of 46 children who have biliary atresia and who underwent transplantation before 2 years of age, 8 (17%) have SNHL. Among the 26 evaluable children with biliary atresia undergoing liver transplantation before 2 years of age, logistic regression analysis revealed that the most important risk factor for SNHL was the cumulative dose of amikacin (P = .05).

Conclusions: Children receiving liver transplants are at an increased risk for SNHL. Those with the short-bowel syndrome have the greatest prevalence of SNHL. Among the subset of children with biliary atresia receiving liver transplants before 2 years of age, statistical analysis demonstrates a dose-response relationship between the receipt of amikacin and the occurrence of SNHL.

SUBJECTS AND METHODS

Medical records from the organ transplantation service were used to identify 125 consecutive children who underwent liver transplantation from March 1, 1987, to June 30, 1996, at St Christopher’s Hospital for Children, Philadelphia, Pa. Corresponding audiometric evaluations from the Department of Speech and Hearing were reviewed to document the presence of SNHL (n = 15) or normal sensorineural hearing thresholds (47 normal and 4 inconclusive). Audiograms had been obtained when there was a clinical suspicion of SNHL or, when feasible, as children returned for routine follow-up. Audiologic information was unavailable for 58 (46.4%) patients. The cause of the liver abnormality was determined for each of the transplant recipients. A descriptive analysis of these patients is presented in Table 1. Two subsets of the total group were addressed in greater detail: transplant recipients with biliary atresia and transplant recipients with the short-bowel syndrome.

Children with biliary atresia composed 54% of the children receiving liver transplants and therefore made up the largest, most uniform group of patients. All had normal renal function, documented by normal glomerular filtration rates. Data from the 48 consecutive children who underwent liver transplantation before 2 years of age for the management of biliary atresia were analyzed. Audiometric data were available for 31 of these 48 children. Of these 31 children, 3 had inconclusive results on their audiograms and 2, with SNHL, had undergone their initial transplants before 2 years of age, 8 (17%) of 46 have SNHL (Figure 2), and 26 of 46 were evaluable for this study. In these 26 children, a large cumulative dose of amikacin is a statistically significant risk factor for SNHL (P = .05). All 4 children who received the largest cumulative doses of amikacin, greater than 200 mg/kg, had SNHL (Figure 3). In contrast, only 2 of 22 children who received less than 90 mg/kg of amikacin had SNHL. The sample size limited the statistical power of this study, but there was a suggestive association with cumulative doses of intravenous furosemide (P = .10) that might be resolved by a larger study. Four of the 5 children who received the largest cumulative doses of intravenous furosemide had SNHL (Figure 4). Cumulative doses of gentamicin and tobramycin were not statistically significant risk factors for SNHL (Figure 5 and Figure 6).

To our knowledge, this is the first report that children receiving liver transplants are at increased risk for SNHL. They frequently receive aminoglycoside antibiotic medications that are known to have both cochlear and vestibular toxic effects. In general, the most important factors contributing to the risk of ototoxicity seem to be the particular agent used and the duration of administration.5,6 Peak and trough levels do not correlate well with ototoxicity, although they may be useful in avoiding nephrotoxicity; renal dysfunction may then contribute secondarily to ototoxicity.3,7-10 A genetic susceptibility to aminoglycoside-induced ototoxicity also has been documented in several family pedigrees.11-14

Our finding that the cumulative dose of amikacin (milligrams per kilogram of body weight) is the most sig-

Table 1. Cause of Liver Disease in All Children Receiving Liver Transplants and Results of Audiometric Evaluation*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients (Total)</th>
<th>No. Whose Hearing Was Tested</th>
<th>No. With Normal Hearing</th>
<th>No. With Documented SNHL (% of Diagnosis Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilary atresia</td>
<td>67</td>
<td>43†</td>
<td>32</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>12</td>
<td>6</td>
<td>5</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>17</td>
<td>8</td>
<td>6</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Short-bowel syndrome</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4</td>
<td>1†</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>2</td>
<td>0</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>66</td>
<td>47</td>
<td>15 (12)</td>
</tr>
</tbody>
</table>

* SNHL indicates sensorineural hearing loss; ellipses, numbers are unknown.
† Audiometric evaluation was inconclusive in 3 children with biliary atresia and 1 with cirrhosis.

Among children with biliary atresia who underwent liver transplantation before 2 years of age, 8 (17%) of 46 have SNHL (Figure 2), and 26 of 46 were evaluable for this study. In these 26 children, a large cumulative dose of amikacin is a statistically significant risk factor for SNHL (P = .05). All 4 children who received the largest cumulative doses of amikacin, greater than 200 mg/kg, had SNHL (Figure 3). In contrast, only 2 of 22 children who received less than 90 mg/kg of amikacin had SNHL. The sample size limited the statistical power of this study, but there was a suggestive association with cumulative doses of intravenous furosemide (P = .10) that might be resolved by a larger study. Four of the 5 children who received the largest cumulative doses of intravenous furosemide had SNHL (Figure 4). Cumulative doses of gentamicin and tobramycin were not statistically significant risk factors for SNHL (Figure 5 and Figure 6).

To our knowledge, this is the first report that children receiving liver transplants are at increased risk for SNHL. They frequently receive aminoglycoside antibiotic medications that are known to have both cochlear and vestibular toxic effects. In general, the most important factors contributing to the risk of ototoxicity seem to be the particular agent used and the duration of administration.5,6 Peak and trough levels do not correlate well with ototoxicity, although they may be useful in avoiding nephrotoxicity; renal dysfunction may then contribute secondarily to ototoxicity.3,7-10 A genetic susceptibility to aminoglycoside-induced ototoxicity also has been documented in several family pedigrees.11-14

Our finding that the cumulative dose of amikacin (milligrams per kilogram of body weight) is the most sig-

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significant risk factor for SNHL in children with biliary atresia who underwent liver transplantation before 2 years of age is consistent with previous data. Other studies have found a dose-response relationship between the use of aminoglycoside antibiotics and SNHL and that amikacin is particularly ototoxic compared with other aminoglycoside antibiotics. 3,15,16

In addition, children receiving liver transplants often receive loop diuretic agents, which are potentially ototoxic. 17,18 Although hearing loss has been reported after the oral administration of loop diuretic medications, its occurrence is more common after intravenous administration and is usually reversible. 19-21 The risk of ototoxicity is thought to be related to rapid rates of infusion. 21,22 The rate of intravenous infusion of furosemide administered to the patients with liver transplants could not be determined by retrospective medical record review. Informal discussion with the intensive care unit nurses indicated that many of them administered furosemide as a rapid bolus infusion. Once we began making inquiries, it became impossible to conduct an unbiased survey of nursing knowledge and practices. As awareness of SNHL in the patients receiving liver transplants grew, any factor potentiating hearing loss was scrutinized, and a slow rate of infusion was encouraged.

Although aminoglycoside antibiotic and loop diuretic drugs may act synergistically to cause SNHL, the number of subjects in this study was too small for an analysis of drug interactions. Furosemide was the only loop diuretic administered to these patients, so its ototoxic effects relative to other loop diuretics was not evaluable. Several patients occasionally received other potentially ototoxic medications, such as salicylates and vancomycin hydrochloride. 15 The administration of these medications was too infrequent to allow statistical evaluation of their individual or synergistic effects.

The greatest prevalence of SNHL was among children with the short-bowel syndrome. In general, these

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**Table 2. Cumulative Doses of Aminoglycoside Antibiotics and Loop Diuretics Received by Evaluable Patients With Biliary Atresia Who Received Liver Transplants Before Age 2 Years**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tobramycin Sulfate, mg/kg</th>
<th>Gentamicin Sulfate, mg/kg</th>
<th>Amikacin Sulfate, mg/kg</th>
<th>Furosemide, mg/kg</th>
<th>SNHL</th>
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<tr>
<td>1</td>
<td>134.3</td>
<td>154.1</td>
<td>300.6</td>
<td>283.1</td>
<td>Yes</td>
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<tr>
<td>5</td>
<td>0</td>
<td>98.9</td>
<td>0</td>
<td>39.5</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>70.0</td>
<td>0</td>
<td>13.3</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>5.2</td>
<td>193.1</td>
<td>43.7</td>
<td>60.7</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>51.7</td>
<td>0</td>
<td>68.5</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>107.1</td>
<td>63.5</td>
<td>25.6</td>
<td>162.0</td>
<td>No</td>
</tr>
<tr>
<td>23</td>
<td>0</td>
<td>27.7</td>
<td>0</td>
<td>93.4</td>
<td>No</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>70.5</td>
<td>0</td>
<td>30.8</td>
<td>No</td>
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<tr>
<td>33</td>
<td>40.4</td>
<td>80.0</td>
<td>0</td>
<td>117.5</td>
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<td>35</td>
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<tr>
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<td>0</td>
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<tr>
<td>58</td>
<td>0</td>
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<td>88.1</td>
<td>30.5</td>
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<tr>
<td>63</td>
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<td>65</td>
<td>32.4</td>
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<td>0</td>
<td>20.9</td>
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<tr>
<td>66</td>
<td>31.4</td>
<td>12.4</td>
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<td>71</td>
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<tr>
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<td>244.3</td>
<td>217.0</td>
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<tr>
<td>82</td>
<td>190.4</td>
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<td>93</td>
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<td>203.2</td>
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<tr>
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<td>0</td>
<td>27.4</td>
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<tr>
<td>121</td>
<td>19.6</td>
<td>2.5</td>
<td>303.7</td>
<td>96.9</td>
<td>Yes</td>
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<tr>
<td>124</td>
<td>0</td>
<td>54.4</td>
<td>0</td>
<td>53.5</td>
<td>No</td>
</tr>
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</table>

* SNHL indicates sensorineural hearing loss.
children have more complicated courses than the children with biliary atresia. The children with the short-bowel syndrome receive multiple courses of aminoglycoside antibiotics and diuretics during prolonged periods of critical illness. Although the dosages are adjusted for their hepatorenal dysfunction, they receive large total doses of these drugs. Three of the 4 children with the short-bowel syndrome who have SNHL passed hearing screening tests with the use of brainstem evoked auditory responses in the neonatal intensive care unit, indicating that their hearing loss was acquired rather than congenital.

It is possible that the onset of SNHL precedes liver transplantation. In an effort to determine when SNHL occurs in patients with the short-bowel syndrome, we have begun obtaining prospective audiograms. Two children observed prospectively passed auditory brainstem response hearing screening at 1 month of age, 1 failed auditory brainstem response screening at 5 months of age (the other was not tested), and both demonstrated mild to moderate hearing loss in at least the better ear by behavioral testing at 7 months of age. The caregivers of both patients reported decreased responsiveness to sound. Further audiologic studies were precluded by their deteriorating medical states. Both died at approximately 1 year of age while awaiting transplantation, and they are not included in our calculations. It is not known whether earlier transplantation would decrease the risk of hearing loss.

Future areas for investigation include conducting audiometric evaluations on a prospective, serial basis. This may help to elucidate when during the course of the liver disease and its management the SNHL occurs. It would also allow the earliest habilitation for patients and their families. High-frequency audiometric evaluations (9-20 kHz) may improve early detection because ototoxic damage from aminoglycoside antibiotics begins in the basal end of the cochlea where high-frequency sounds are processed. Otoacoustic emissions may provide more sensitive identification of SNHL, as they rely on the function of the outer hair cells of the cochlea, which are the cells damaged by aminoglycoside antibiotics. Genetic evaluation may identify populations with increased susceptibility to aminoglycoside-induced ototoxicity. The possibility of additional risk factors for SNHL should be addressed.

CONCLUSIONS

Children receiving liver transplants are at an increased risk for SNHL and should undergo baseline and prospec-
tive serial audiometric evaluations. Audiometric evalua-
tions should begin early in the management of chil-
dren with liver disease leading to transplantation, both
to determine when the SNHL occurs and for optimal
habilitation.

Among children with biliary atresia receiving liver
transplants before 2 years of age, a dose-response re-
sationship exists between the use of amikacin and the oc-
currence of SNHL. The relationship between the cumu-
lative dose or rate of furosemide infusion and the occur-
cence of SNHL may require further study.

Sensorineural hearing loss occurs in at least 44%
of children undergoing liver transplantation for the
management of the short-bowel syndrome. Further in-
vestigation is needed to determine whether earlier trans-
plantation would obviate the hearing loss.

Amikacin and furosemide are important medica-
tions for the management of critically ill children. The
risk of ototoxic effects should be factored into the clin-
ic decision of whether, and for how long, these medi-
cations should be administered to a child. The use of am-
okacin should be avoided when less ototoxic antibiotics
may be efficacious.

Collaboration between the liver transplantation team,
otolaryngologist, and audiologist are essential to mini-
mize the use of ototoxic medications, counsel parents,
and monitor and habilitate hearing loss in children re-
cieving liver transplants.

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