Lack of Deafness in Crigler–Najjar Syndrome Type 1: A Patient Survey

ABSTRACT. We performed a questionnaire survey about 42 patients with Crigler–Najjar syndrome type 1 who were currently alive. Information was obtained on their age, sex, birth weight, gestation, parental consanguinity, other family members affected, age of onset of jaundice, neonatal and postneonatal bilirubin values, neonatal and postneonatal therapy, problems faced with phototherapy, liver transplantation, current growth status, current neurologic status, and the status of hearing. Patients were between 2 months and 21 years of age. There were 18 males and 24 females. Thirty-nine patients had been born at full term gestation and 3 had been preterm. Jaundice was noted on postnatal day 1 in 34%, between days 2 and 4 in 55%, and after day 11 of life in 11% of patients. In the neonatal period bilirubin values (mean ± SD) were typically 19.8 ± 4.5 mg/dL. Eighty-six percent of patients had neonatal peak bilirubin values of >20 mg/dL. Parental consanguinity was present in 44% and a history of Gilbert’s disease in one parent was present in 10% of patients. Causes of exacerbations of jaundice reported were respiratory infections, febrile illnesses, vaccinations, fasting, surgery, emotional stress, and noncompliance with treatment. Neonatal therapy consisted of exchange transfusion in 28%, phototherapy in 79%, phenobarbital in 20%, and cholestyramine, albumin, infusions, and plasmapheresis in one case each. The mainstay of postneonatal therapy was home phototherapy for 10 to 16 hours, primarily at night during sleep, using blue lights or a combination of blue and fluorescent lights. Some patients used innovatively designed phototherapy units. Problems reported with phototherapy were decreased effectiveness with age, poor compliance, restriction of activity and play, inability to travel or take vacations, irritation from eye shades, difficulty keeping eye protection on, difficulties in temperature maintenance, tanning of the skin, embarrassment from the need to be nearly nude during phototherapy, and difficulty in procuring phototherapy lamps. Other therapies that had been tried included oral agar, albumin infusions, antioxidants, acacetum, bilirubin oxidase, calcium infusions, clofibrate, cruciferous vegetables, cholestyramine, chlorpromazine, flumeceinol, plasmapheresis, tin mesoporphyrin, ursodeoxycholic acid, and urinary alkalization. Fifteen children had undergone liver transplantation (5 auxiliary and 10 orthotopic). All 42 patients are reportedly of normal height and weight. Neurodevelopmental status is said to be normal in 77% of patients. Two patients have kernicterus, 4 have cerebellar symptoms, and 1 each has developmental delay, mild intention tremor, and mild speech delay. Hearing was reported to be normal in 94% of patients. The 2 children with hearing loss have conductive loss from otitis media. With home phototherapy prolonged, survival free of neurologic deficits is possible in Crigler–Najjar syndrome type 1, but there are many problems associated with phototherapy. Avoiding exacerbations of jaundice is an important aspect of management. Liver transplantation offers the prospect of cure but its risk versus benefit ratio is undetermined. Hearing loss was absent in the patients surveyed despite prolonged exposure to high bilirubin levels, which suggests that bilirubin may not be as ototoxic as is commonly believed. Pediatrics 1997;100:5. URL: http://www.pediatrics.org/cgi/content/full/100/5/5e9; Crigler–Najjar syndrome type 1, hyperbilirubinemia, kernicterus, deafness, phototherapy.

ABBREVIATIONS. CN1, Crigler–Najjar syndrome type 1; SNHL, sensorineural hearing loss.

Crigler–Najjar syndrome type 1 (CN1) is a rare genetic disorder with a complete absence of the hepatic enzyme UDP glucuronyl transferase. This results in a lifelong unconjugated hyperbilirubinemia with a significant risk of bilirubin encephalopathy and death attributable to kernicterus. This survey was performed to determine the current clinical status of patients with this syndrome and therapies being used.

METHODS

We obtained information on patients with CN1 by mailing questionnaires to 27 physicians who, based on their publications, were thought to be in contact with CN1 patients. The questionnaire was designed to elicit information about the patients’ age, sex, birth weight, gestation, parental consanguinity, age of onset of jaundice, other family members affected, neonatal bilirubin values, neonatal therapy, postneonatal therapy, problems faced with phototherapy, postneonatal bilirubin values, evidence of hemolysis, liver function tests, liver biopsy, UGT assay, liver transplantation, current growth status, current neurologic status including deafness and current functional status. Only patients currently known to be alive are reported here.

RESULTS

Information was obtained on 42 patients from questionnaires returned by 14 physicians (primarily pediatricians and gastroenterologists) and in three cases, by parents of patients. These patients were located in the United States, Europe, Australia, and Saudi Arabia. Twelve patients from the United States belonged to an Amish community in Strasburg, PA. The age distribution of the patients is shown in Table 1. The youngest patient was 2 months old, and the oldest was 21 years old. There were 18 males and 24 females. Thirty-nine patients had been born at full-term gestation, and 3 had been preterm. The onset of jaundice (38 survey responses) was noted on postnatal day 1 in 34%, between days 2 and 4 in 55%, and after day 11 of life in 11% of patients. The peak neonatal and the typical bilirubin values reported in these patients are shown in Table 2.

Neonatal therapy (39 survey responses) consisted
of exchange transfusion in 28%; phototherapy in 79%; phenobarbitone in 20%; and cholestyramine, albumin infusions, and plasmapheresis in one case each.

There was a history of parental consanguinity in 44% (16/36), an affected first cousin in 21% (8/38), and a history of Gilbert’s disease in one parent in 10% (4/40) of patients. One of the children in the survey had a mild form of Osteogenesis Imperfecta in addition to CN1.

The persistent jaundice in these patients can be exacerbated in several situations. Causes of such exacerbations were reported by the respondents to be respiratory infections, febrile illnesses, vaccinations, fasting, surgery, emotional stress, and noncompliance with treatment.

The mainstay of therapy in these patients has been home phototherapy for 10 to 16 hours a day. This is carried out primarily at night while patients are sleeping. Blue lights or a combination of blue and fluorescent lights were used for phototherapy. Some of the patients had specially designed phototherapy units such as a converted tanning bed, a vertical unit to enable the child to sit up and receive phototherapy from behind, and a net hammock suspended over a bank of lights and surrounded by reflecting mirrors, which could also be dismantled for travel.

Problems reported with phototherapy were decreased effectiveness with age, poor compliance, restriction of activity and play, inability to travel or take vacations, irritation from eye shades, difficulty keeping eye protection on, difficulties in temperature maintenance, tanning of the skin, and embarrassment from the need to be nearly nude during phototherapy. For some families, difficulty in procuring phototherapy lamps and their high cost were major problems.

A wide variety of adjunctive therapies have been tried by these patients, including oral agar, albumin infusions, antioxidants, acupuncture, bilirubin oxidase, calcium infusions, clofibrate, cruciferous vegetables, cholestyramine, chlorpromazine, flumecinol, plasmapheresis, tin mesoporphyrin, ursodeoxycholic acid, and urinary alkalinization. Five children (between 8 and 13 years of age) have undergone auxiliary liver transplants. One patient developed graft atrophy and later had an orthotopic transplant, one had chronic rejection and is awaiting retransplant, and two are doing well (no data available on one).

Ten children (between 2½ and 16 years of age) have undergone an orthotopic liver transplants. One has needed a repeat transplant, one has chronic mild hyperbilirubinemia (possibly because the donor has Gilbert’s disease), and eight are doing well after transplant.

All 42 patients are reported to be of normal height and weight. The neurodevelopmental status (reported in 39 patients) is reportedly normal (with good school performance) in 77% (30/39). Two patients have kernicterus; 4 have cerebellar symptoms; and 1 each has developmental delay, mild intention tremor, and mild speech delay. Descriptions of three of the children with cerebellar symptoms have been published. Hearing status was reported in 36 patients, of whom 8 have undergone auditory brainstem response testing. Hearing was reported to be normal in 94% (34/36). The two children with hearing loss have conductive loss from otitis media.

**DISCUSSION**

This patient survey represents a first crude attempt to gather information on a large number of CN1 patients. It is difficult to evaluate therapies for this very rare disorder. Nearly all experience to date comes from anecdotal reports. The group of Amish patients is the single largest group of patients in a one geographical area. Another large survey of patients with Crigler–Najjar syndrome has been reported recently from The Netherlands, where a registry of patients has been formed. Some patients are common to both that survey and our own.

Before phototherapy was introduced in 1968, most children with CN1 either died in early infancy or developed kernicterus in adolescence or early adulthood. Our survey suggests that phototherapy has changed the natural history of the disease. Prolonged survival free of neurologic deficits is possible. Unfortunately, daily phototherapy for long periods restricts the patient’s lifestyle. It has many problems and becomes less effective with time. Better and more portable phototherapy devices, perhaps using fiberoptic sources, may overcome some of these limitations. Phototherapy also does not ensure the prevention of encephalopathy. Many other therapies have been tried, and varying degrees of success have been claimed. Albumin infusions and plasmapheresis are effective in dealing with acute exacerbations of jaundice, whereas the other therapies have been tried for various periods as adjuncts to phototherapy. Oral calcium phosphate has been reported recently to cause a modest decrease in serum bilirubin in these patients.

An important aspect of management of these patients is avoiding exacerbations of jaundice, because these can precipitate bilirubin encephalopathy in a previously stable patient. In addition to the list of causes above, open liver biopsy and crush injury

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**TABLE 1. Age Distribution of Patients**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 Year</td>
<td>2</td>
</tr>
<tr>
<td>1-5 Years</td>
<td>13</td>
</tr>
<tr>
<td>6-15 Years</td>
<td>21</td>
</tr>
<tr>
<td>&gt;15 Years</td>
<td>6</td>
</tr>
</tbody>
</table>

**TABLE 2. Bilirubin Values in Crigler-Najjar Syndrome Type 1**

<table>
<thead>
<tr>
<th>Bilirubin Level mg/dL*</th>
<th>Neonatal Period</th>
<th>Postneonatal Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak (n)</td>
<td>Typical (n)</td>
</tr>
<tr>
<td></td>
<td>Typical (n)</td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15-19</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>20-29</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>≥ 30</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Survey responses</td>
<td>38</td>
<td>36</td>
</tr>
</tbody>
</table>

*Mean ± SD bilirubin values were 26.6 ± 5.8 (peak), 19.8 ± 4.5 (typical) in the neonatal period, and 20.5 ± 5.5 (typical) in the postnatal period.
have also been reported to cause decompensation.\textsuperscript{6,7} The use of tin mesoporphyrin to prevent such dangerous rises in bilirubin level needs to be studied.\textsuperscript{5}

Liver transplantation offers the prospect of cure. It is, however, a very invasive, expensive procedure for which the complications can be serious. It requires prolonged immunosuppression. The patient ends up trading one set of problems for another. The risk: benefit ratio, the best type of transplant (complete vs auxiliary), and the best age for transplant remain unresolved issues. The current therapeutic options are all unsatisfactory. This crisis is likely to persist until gene therapy becomes feasible.

It is reassuring that most of the patients surveyed were reported to be neurodevelopmentally normal. However, these data may not reflect the true natural history of the disorder. All patients had hyperbilirubinemia for many years, beginning in the neonatal period. We did not collect detailed data about the duration of exposure to different levels of hyperbilirubinemia; hence, the mechanisms of encephalopathy, the timing of its occurrence, and the timing of liver transplantation to prevent it are still speculative.

A striking finding in this survey was that none of the patients had sensorineural deafness despite having prolonged exposure over several years to bilirubin levels $>20$ mg/dL. This is contrary to the belief that the auditory system is the most sensitive neural system to clinically overt bilirubin injury\textsuperscript{9} and that hearing loss is the most common neurologic abnormality in children with chronic bilirubin encephalopathy.\textsuperscript{10}

Hearing loss came to be widely accepted as one of the manifestations of bilirubin neurotoxicity after the association between neonatal hyperbilirubinemia, and sensorineural hearing loss (SNHL) was described in the 1950s in relation to hemolytic jaundice, primarily Rh incompatibility.\textsuperscript{11,12} A review of this early literature reveals that these infants with hemolytic jaundice also had multiple other risk factors for deafness such as asphyxia, exposure to streptomycin and dihydrostreptomycin, and low birth weight. They could also have had undetected cytomegalovirus infection, a leading cause of deafness.\textsuperscript{13}

More recently, Valaes et al reported a significantly higher incidence of SNHL (9.2\%) in infants with moderate or marked neonatal jaundice (hemolytic and nonhemolytic) than in the children with slight or no jaundice (1.1\%).\textsuperscript{14} De Vries et al reported an association between hearing loss and hyperbilirubinemia in very low birth weight infants.\textsuperscript{15} None of these studies accounted for potentially confounding variables that could contribute to SNHL or that could increase the risk of bilirubin neurotoxicity. One study, which used multivariate analysis, reported high serum bilirubin to be a significant predictor of hearing loss.\textsuperscript{16} In contrast, studies in full-term infants without hemolysis have not found a relationship between high bilirubin levels and hearing loss.\textsuperscript{17} In the Collaborative Perinatal Project, SNHL was not associated with high bilirubin levels.\textsuperscript{18} In the CN1 patients described in this report, hearing loss was not noted despite exposure to high levels of bilirubin for periods much more prolonged than in any of the infants in the studies noted above. This represents an intriguing finding and leads us to speculate that bilirubin itself is not ototoxic as is usually thought. Alternatively, these patients could have been protected by some unidentified mechanism. Why bilirubin might be ototoxic in some situations and not in others is puzzling. Much remains to be learned about the mechanisms and risk factors for hearing loss after hyperbilirubinemia.

Because of the rarity of CN1 and the wide geographic scatter of patients, an international registry of patients would be useful in tracking the clinical courses of patients and in coordinating trials of proposed therapies. It would also help the families of these children share information and form support groups. We are currently evaluating the feasibility of starting such a registry for this condition in the United States to complement the registry in The Netherlands.\textsuperscript{2}

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