ABSTRACT. Objective. Classical galactosemia (McKusick 230400) is an autosomal recessive disorder of galactose metabolism caused by a deficiency of galactose-1-phosphate uridyltransferase (EC 2.7.712). Treatment, consisting of a severe restriction of dietary galactose, is life saving, but most patients develop abnormalities despite this diet. The aim of this study was to study the influence of galactosemia on the patients’ health-related quality of life (HRQoL), on educational levels, and on the specific galactosemia-related concerns of these families.

Methods. Age-specific HRQoL questionnaires, a classical galactosemia-specific questionnaire designed by the authors, and a list of questions regarding educational attainment were handed out or sent to all 75 members of the Dutch Galactosemia Society and their families.

Results. Sixty-three (84%) patients with classical galactosemia from 58 families returned the questionnaire. Concerning HRQoL, significant differences between patients aged 1 to 5 and healthy children were found on the domains of abdominal complaints and communication. Patients aged 8 to 15 years differed from their healthy peers on the domain of cognitive function. Mothers of patients aged 6 to 15 reported a significantly lower HRQoL on the domains of motor and cognitive function. Patients 16 years and older had significant lower scores on the domains of cognitive and social function. The percentage of patients who attend special schools is significantly higher than in the general population, and the educational attainment is significantly lower in patients with classical galactosemia.

Conclusions. This is the first study to describe the HRQoL of patients with classical galactosemia using well-developed and validated instruments in different age groups. The results of the present study indicate that having galactosemia negatively influences the HRQoL. Early and regular evaluation and support of possible cognitive problems should be a major part of the protocol for the follow-up of patients with classical galactosemia.

METHODS

Participants

All 75 patients who have classical galactosemia and are members of the Dutch Galactosemia Society and their families received questionnaires and were asked to return them by mail after completion. All patients were supposed to follow the strict galactose-restricted dietary recommendations as used in the Netherlands. No data about time of diagnosis were available.

ABBREVIATIONS. GALT, galactose-1-phosphate uridyltransferase; HRQoL, health-related quality of life; TAPQOL, TNO-AZL Preschool Children Quality of Life questionnaire; TACQOL, TNO-AZL Children’s Quality of Life questionnaire; TAAQOL, TNO-AZL Adult Quality of Life questionnaire.
Procedure
Most of the questionnaires were handed out with instructions at an annual meeting of the members of the Dutch Galactosemia Society. Members not present at the meeting received the questionnaires and written instructions a few days later by mail.

Of patients aged 1 to 20 years, both parents were asked to complete a questionnaire. Mothers were asked to complete an HRQoL questionnaire, and both parents completed a classical galactosemia-specific survey. All patients 8 years and older completed a questionnaire themselves, including an HRQoL questionnaire and a classical galactosemia-specific survey. In the case of 2 affected siblings in 1 family, mothers were asked to fill out HRQoL questionnaires for each child separately. Patients were asked to complete the questionnaire within 3 weeks. Instructions included completing the entire questionnaire at the same time, to answer the questions without discussion with others, and to assist young children with difficult questions when necessary without influencing them.

Instruments
For the evaluation of the quality of life and the classical galactosemia-related concerns of children and their parents, we used 2 questionnaires: the HRQoL questionnaires and a classical galactosemia-specific survey developed by the authors.

HRQoL Questionnaire
The TNO Institute of Prevention and Health and the Leiden University Hospital (TNO-AZL) designed questionnaires for measuring HRQoL for different age groups: TNO-AZL Preschool Children’s Quality of Life (TACQOL)10,11 for children aged 2 to 6 years old; the TNO-AZL Preschool Children’s Quality of Life questionnaires (TACQOL)10–12 for children aged 6 to 15 years with a child and a parent form, and the TNO-AZL Adult Quality of Life questionnaire (TAAQOL) for 16 years and older.13 The questionnaires focus on health problems in the past 3 months or the last weeks, and, if present, the well-being in relation to this health problem is assessed. The responses are the health-related component of the instrument, which is subsequently reported, with the exception of scales measuring emotional functioning (eg, social functioning TAPQOL, vitality TAAQOL).

The TACQOL contains 43 items in 12 scales divided over 4 domains: 1) physical function, 2) social function, 3) cognitive function, and 4) emotional function. Scales that measure motor function, social function, and communication are applicable only to children 1.5 years and older.

The TACQOL contains 7 scales of 8 items: 1) physical symptoms, 2) motor function, 3) autonomy, 4) cognitive function, 5) social function, 6) positive emotions, and 7) negative emotions. Maximum domain scores are 32 for the first 5 domains and 16 for the emotional scales.

The TAAQOL comprises 12 scales: gross motor function, fine motor function, cognitive function, sleeping, pain, social function, limitations of daily activities, sexuality, vitality, happiness, depressive moods, and aggressiveness. In all scales, except in the scales concerning vitality, happiness, depressive moods, and aggressiveness, each item consists of 2 questions. For the TAPQOL and TAAQOL, the scale scores are obtained by adding item scores within scales and transforming crude scale scores to a 0 to 100 scale. For all questionnaires, higher scores indicate a better quality of life.

Galactosemia Quality of Life Survey
This unvalidated questionnaire was developed to obtain an impression of the effects of the disorder on the daily lives of the patients and their families. Item lists were developed from clinical experience and from parent interviews. A team of researchers (A.M.B, M.A.G., and B.F.L) collaborated on item development.

RESULTS
Sixty-three (84%) patients with classical galactosemia returned the questionnaire. Patient ages and the questionnaires completed by them and their families are shown in Table 1. As 5 pairs of affected siblings participated, 63 patients from a total of 58 families participated in the study. Because classical galactosemia is a relatively rare disease with an average of 6 new cases per year in the Netherlands, the patient group participating in this study is small. When calculated from Dutch incidence and birth rate, we included 73% of Dutch patients aged 1 to 5 (n = 22), 58% of patients aged 6 to 7 (n = 7), and at least 35% of patients aged 8 to 15 (n = 7). Two (17%) patients aged 16 to 17 and 15 patients over 18 were included. As in the recent past, many patients died before the proper diagnosis was made; this percentage is likely to be much higher in the older age groups.

There were 24 (38%) male and 39 (62%) female
patients. Ages ranged from 1 to 41 years. Ninety-seven parents completed the questionnaire: 51 mothers and 46 fathers. One patient aged 8 was not able to complete the questionnaire because of mental retardation, and 2 mothers and 1 patient returned the questionnaire incomplete for unknown reasons.

HRQoL

Twenty-one mothers of children aged 1 to 5 years completed the TAPQOL questionnaire. Significant differences between patients with classical galactosemia and healthy control subjects were found on 2 domains: abdominal complaints (higher frequency of abdominal pain and colic) and communication (more problems with understanding what others say, problems with speaking clearly, and more difficulties with active and passive use of language). Mean scores are presented in Table 2.

Sixteen children aged 8 to 15 years completed the TACQOL questionnaire, and they differed from their healthy peers on the domain of cognitive function (understanding, learning, reading, mathematics, memory, concentration) showing impaired HRQoL (Table 3). Twenty-three mothers of patients aged 6 to 15 reported a significantly lower HRQoL on the domains of motor function (walking, running, standing, ascending stairs, balance, endurance, playing, handiness) and cognitive function (learning, concentration, reading, writing, mathematics, memory, verbal expression; Table 3). Quality of life measured with the TAAQOL showed that patients of 16 years and older had significantly lower scores on the domains of cognitive function (memory, concentration, attention) and social function (visiting other people, talking to other people, having fun with other people, having meaningful conversations; Table 4).

Educational Level

Of the age group 6 to 11 years, 16 mothers completed the questions regarding educational levels. According to their report, 44% of the children in this group attend special schools as opposed to 3% of the general population (data from Ministry of Education Culture and Science). As levels in Dutch secondary education are much more differentiated, almost everyone is able to attend a regular school.

Fifteen patients over the age of 18 completed the additional questions about their educational level. Of these patients, 28% attended special schools, significantly different from the general population as described above. Current educational attainment is significantly lower than the attainment of the general population with 61.5% completing basic school and low vocational training only, compared with 27.2% of the general population (Table 5).

Specific Concerns

All questions regarding experience of the disease are listed in Table 6 (parents) and Table 7 (patients 8 years and older). Ninety-seven parents completed the questionnaire. Although most parents reported treating their child with galactosemia the same way as their healthy children (69%) and raising their child with galactosemia in the same way as their healthy children (77%), many parents (73%) believe the galactosemia influences their contact with the child. Sixty percent of the parents believe that it is a burden to take care of a child with galactosemia. Most parents of girls (55%) frequently worry about possible infertility, and almost 40% of the parents report that their child experiences speech problems. Still, 86% believe that one can live a good life with this disorder.

Thirty-three patients aged 8 and older completed the questionnaire. Galactosemia is seen as a burden by 39% of patients. Some (34%) feel different because of having galactosemia, and 22% believe that their disease is not well understood by others. However,
TABLE 4. Mean HRQoL Scores (TAAQOL) for Children With Galactosemia and for the General Population

<table>
<thead>
<tr>
<th>Scale</th>
<th>Patients With Galactosemia (n = 17)</th>
<th>Mean General Population (n = 350)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical symptoms</td>
<td>26.1 (6.0)</td>
<td>24.5 (5.7)</td>
<td>.05</td>
</tr>
<tr>
<td>Motor function</td>
<td>28.6 (3.4)</td>
<td>29.8 (2.9)</td>
<td>.13</td>
</tr>
<tr>
<td>Autonomy</td>
<td>30.7 (3.2)</td>
<td>31.5 (1.3)</td>
<td>.11</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>23.5 (5.9)†</td>
<td>28.5 (3.9)</td>
<td>.01</td>
</tr>
<tr>
<td>Social function</td>
<td>28.3 (3.3)</td>
<td>29.3 (3.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Positive emotions</td>
<td>12.6 (3.7)</td>
<td>13.4 (2.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Negative emotions</td>
<td>12.8 (2.6)</td>
<td>11.8 (2.6)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Higher scores indicate a better quality of life. SD indicates standard deviation.
* P < .05.
† P < .01.

TABLE 5. Educational Attainment (Completed) of Patients, Compared With the General Dutch Population

<table>
<thead>
<tr>
<th>Scale</th>
<th>Patients (n = 15)</th>
<th>Dutch Population (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic school and low vocational training†</td>
<td>61.5</td>
<td>27.2</td>
</tr>
<tr>
<td>Intermediate vocational training†</td>
<td>30.8</td>
<td>47.0</td>
</tr>
<tr>
<td>High vocational training†</td>
<td>7.7</td>
<td>25.9</td>
</tr>
</tbody>
</table>

* Dutch population 20–40 years of age: data from the Dutch National Bureau of Statistics (Centraal Bureau voor de Statistiek: www.cbs.nl); see statistical analysis for text on schooling system.
† P < .001.

DISCUSSION

This is the first study to describe the HRQoL of patients with classical galactosemia using well-developed and validated instruments in different age groups. The results of the present study indicate that having galactosemia negatively influences the HRQoL. In all age groups, we found a consistently lower reported HRQoL, most strikingly on the cognitive domain but also on the domain of communication and social function. The consistently low scores on the cognitive domain correspond well with the finding that these patients have much lower educational levels and educational attainment than their healthy peers. Our results are consistent with the reports of late complications in patients with classical galactosemia in the literature. Two large long-term outcome studies show below-average IQ scores for patients with galactosemia as a group with a decline in group scores in groups of increasing age.6,8 However, no consistent decline in IQ was shown in patients who had been tested repeatedly with the same IQ test.8

Other effects of galactosemia on the reported specific concerns of the patients and their families were found. The majority of parents and of patients of all ages believe that patients with galactosemia can live a good life. However, many patients feel different from other people as a result of their disease. Most parents believe that galactosemia affects their contact with the child, and many frequently worry about their child’s future and their fertility.

In our study, no data were available on the neonatal symptoms and the age of the start of dietary treatment of the included patients. However, previous studies showed no significant correlation among mean IQ, development and the neonatal history, and initiation time of dietary treatment, except for patients in whom treatment was started after the age of 8 weeks.4,6,8 In addition, siblings with galactosemia, of whom the oldest had experienced clinical symptoms whereas the younger siblings were detected antenatally, had the same outcome of IQ and development.8 We know that classical galactosemia in 81% of the Dutch patients who were born in 1992–1997 was diagnosed within the first 2 weeks of life, and in all but 1 patient, who was homozygous for a mutation known for its mild presentation, within 40 days.15 We do not suspect a later start of dietary treatment in patients who were younger than 18 years and were born before 1992 or after 1997, and therefore we do not expect our data to be affected by differences in time of the start of dietary treatment.

As classical galactosemia is a relatively rare disorder with an average of 6 new cases per year in the Netherlands, the patient group participating in this study is small. However, we included >50% of the Dutch patients under age 16. We do not know
whether the fact that all participants were members of the Dutch Galactosemia Society creates a bias. Potentially, patients with a lesser outcome are more likely to become a member of such a society. However, most patients who participated in the study are too young to draw conclusions about their long-term outcome, and most members joined the society in the neonatal period.

We believe that the strong correlation of the HRQoL over the different age groups and the correlation with the educational attainment strongly validates our results. The cognitive problems in all ages as well as the social problems reported by the patients over 18 should be a major factor of concern for medical specialists who are involved in the care of patients with classical galactosemia. As survival in patients with classical galactosemia is high, we now are confronted with an increasing group of patients who experience late complications that cannot be prevented with the present medical knowledge. In the Dutch protocol for the follow-up of patients with classical galactosemia, evaluation of cognitive skills and educational possibilities does not have a prominent place. We now believe that the attention should not be only on biochemical evaluation but that the focus during follow-up should shift to supporting the patients to attain the best achievable quality of life. Although patient numbers are small, the severe effects of classical galactosemia on the cognitive skills of the patients demand additional research on the effects of early intervention on the late effects of classical galactosemia.

REFERENCES


TABLE 6. Specific Concerns Reported by Parents (n = 97) in Percentages

<table>
<thead>
<tr>
<th>Experience of the Disease</th>
<th>Totally Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Totally Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactosemia as a genetic disease is a burden to our family</td>
<td>14</td>
<td>32</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>The care of my child with galactosemia is a great burden</td>
<td>19</td>
<td>41</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>I feel isolated as a parent of a child with galactosemia</td>
<td>4</td>
<td>17</td>
<td>57</td>
<td>22</td>
</tr>
<tr>
<td>It bothers me that my child suffers from galactosemia</td>
<td>54</td>
<td>32</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>One can live a good life with galactosemia</td>
<td>22</td>
<td>64</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>I treat my child with galactosemia the same way as my healthy child</td>
<td>37</td>
<td>32</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>I watch over my child with galactosemia more than over my healthy child</td>
<td>17</td>
<td>42</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Galactosemia affects the contact with my child</td>
<td>41</td>
<td>32</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>I raise my child with galactosemia in a different way than my healthy child</td>
<td>3</td>
<td>20</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>My child’s friends know what galactosemia is</td>
<td>8</td>
<td>43</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>My child suffers from unclear speech</td>
<td>13</td>
<td>25</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td>Hospital visits are a burden to our family</td>
<td>2</td>
<td>33</td>
<td>45</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experience of the Disease</th>
<th>Almost Always</th>
<th>Always</th>
<th>Often</th>
<th>Sometimes</th>
<th>Almost Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>It bothers me to go to the hospital for follow-up</td>
<td>10</td>
<td>16</td>
<td>46</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>I find it difficult when my child needs to have a blood test</td>
<td>30</td>
<td>20</td>
<td>30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>My child with galactosemia is jealous of his/her healthy sibling</td>
<td>8</td>
<td>47</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I worry about the future of my child</td>
<td>15</td>
<td>23</td>
<td>47</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>I worry about the results from blood tests and urine tests</td>
<td>11</td>
<td>7</td>
<td>32</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>I worry that my child may become ill</td>
<td>4</td>
<td>7</td>
<td>48</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>I worry that my female child might suffer from infertility</td>
<td>20</td>
<td>35</td>
<td>35</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 7. Specific Concerns Reported by Patients Aged 8 and Older (n = 33) in Percentages

<table>
<thead>
<tr>
<th>Experience of the Disease</th>
<th>Totally Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Totally Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>It bothers me that I have galactosemia</td>
<td>18</td>
<td>21</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>I can live a good life with galactosemia</td>
<td>65</td>
<td>26</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>I feel different because I have galactosemia</td>
<td>6</td>
<td>28</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>I feel nobody understands my disease</td>
<td>6</td>
<td>16</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>I have unclear speech</td>
<td>6</td>
<td>22</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>My parents treat me the same way as my healthy siblings</td>
<td>49</td>
<td>31</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>My parents watch over me more than over my healthy siblings</td>
<td>7</td>
<td>22</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>At school they understand I have to visit the hospital sometimes</td>
<td>39</td>
<td>55</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>I explained to my friends what galactosemia is</td>
<td>42</td>
<td>43</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experience of the Disease</th>
<th>Almost Always</th>
<th>Often</th>
<th>Sometimes</th>
<th>Almost Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>It bothers me that I have galactosemia</td>
<td>3</td>
<td>4</td>
<td>55</td>
<td>38</td>
</tr>
<tr>
<td>I worry about my future</td>
<td>6</td>
<td>24</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>I worry that I may become ill as a result of the galactosemia</td>
<td>9</td>
<td>9</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>It bothers me when I have to draw blood for follow-up</td>
<td>9</td>
<td>9</td>
<td>27</td>
<td>55</td>
</tr>
<tr>
<td>It bothers me when I have to visit the hospital</td>
<td>9</td>
<td>3</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>I worry about the results of my blood tests and urine tests</td>
<td>3</td>
<td>18</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>I am bullied by other children at school</td>
<td>3</td>
<td>18</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>I worry about possible infertility problems (girls n = 22)</td>
<td>14</td>
<td>14</td>
<td>45</td>
<td>27</td>
</tr>
</tbody>
</table>


12. Vogels AGC, Bruil J, Stuijbergen M, Koopman HM, Verrips GHW. Validity and reliability of a generic health-related quality of life instrument for adolescents, the TACQOL. *Q Life Res.* 1999;8:630


Living With Classical Galactosemia: Health-Related Quality of Life Consequences
Annet M. Bosch, Martha A. Grootenhuis, Henk D. Bakker, Hugo S.A. Heijmans, Frits A. Wijburg and Bob F. Last

Pediatrics 2004;113:e423
DOI: 10.1542/peds.113.5.e423

Updated Information & Services
including high resolution figures, can be found at:
/content/113/5/e423.full.html

References
This article cites 14 articles, 1 of which can be accessed free at:
/content/113/5/e423.full.html#ref-list-1

Citations
This article has been cited by 4 HighWire-hosted articles:
/content/113/5/e423.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Endocrinology
/cgi/collection/endocrinology_sub
Genetics
/cgi/collection/genetics_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Living With Classical Galactosemia: Health-Related Quality of Life Consequences
Annet M. Bosch, Martha A. Grootenhuis, Henk D. Bakker, Hugo S.A. Heijmans, Frits A. Wijburg and Bob F. Last
Pediatrics 2004;113:e423
DOI: 10.1542/peds.113.5.e423

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/113/5/e423.full.html