Living With Classical Galactosemia: Health-Related Quality of Life Consequences

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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.** *Pediatrics* **2004;113:e423–e428. URL: http://www.pediatrics.org/cgi/content/full/113/5/e423;** ***classical galactosemia, galactose-1-phosphate uridyltransferase deficiency, health-related quality of life, educational attainment, cognition.***

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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.

Classical galactosemia (McKusick 230400) is an autosomal recessive disorder of galactose metabolism caused by a deficiency of galactose-1-phosphate uridyltransferase (GALT; EC 2.7.712). Incidence in the Netherlands is 1:33 000 with an average of 6 new patients per year.[1] Most patients present in the neonatal period, after ingestion of galactose, with icterus, hepatosplenomegaly, liver failure, food intolerance, hypoglycemia, renal failure, muscle hypotonia, sepsis, and cataract. Treatment, consisting of a severe restriction of dietary galactose, is life saving.[2] For many years, elimination of galactose from the diet was considered to be an effective therapy to prevent complications. However, long-term follow-up of patients with classical galactosemia has shown that, despite a strict diet, most patients develop abnormalities such as in mental development, language development, cognitive and motor function, and hypergonadotropic hypogonadism.[3–8] Long-term complications have been a target of clinical studies so far; however, the patients' own experience of their disease has not been investigated. The interests of this study were 3-fold: 1) the influence of galactosemia on the patients health-related quality of life (HRQoL), 2) the educational levels of galactosemia patients, and 3) the specific galactosemia-related concerns of these families. Because patients with galactosemia, although having a normal life expectancy, are impaired by late complications that cannot yet be prevented, we believe that it is highly relevant to have better insight into the patients' quality of life, to try to provide better support, and to facilitate a development as normal as possible.

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.

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.

For all of the 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 Quality of Life (TAPQOL)[9] for preschool children, the TNO AZL Children's Quality of Life questionnaire (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 TAPQOL 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. Multiple items were generated for different domains of concern (knowledge of the disease, experience of the disease, diet, family communication, communication with health professionals). Items in each domain were reviewed and discussed by the other team members to ensure appropriateness. Questions were adjusted accordingly.

The final Dutch-language Galactosemia Academic Medical Center instrument has 52 items in the children's (patients') form and 59 items in the parents' form. For the patients of 8 to 15 years and 16 years and older, equivalent versions were used. Items are expressed as statements in the first person and in the present tense. Children and parents were asked to indicate whether they agree with a given statement on 2 different 4-point scales. For this report, we focus on the questions regarding experience of the disease, with 17 items in the patients' survey and 19 items in the parents' survey. Nine items in the patients' survey and 12 items in the parents' survey could be answered by an agreement scale (totally agree, agree, disagree, or totally disagree). A frequency scale (almost never, sometimes, often, or almost always) was used for 8 items in the patients' survey and 7 items in the parents' survey.

Educational Level

Added to the mothers' survey was a short list of questions about the educational level of their child. Patients 18 years and older were asked additional questions about educational level (completed level) and whether patients received special education as a result of learning disabilities.

Statistical Analysis

One-sample *t* tests were performed to test the differences between patients with classical galactosemia and Dutch published norms on the TAPQOL and TAAQOL questionnaires.[9,13] HRQoL of the children with classical galactosemia and their parents on the TACQOL was compared with that of an available norm group of healthy Dutch children. Means on the TACQOL of the healthy children and the patients with galactosemia were compared using *t* tests. For avoiding analyses with a large norm population and possible overrepresentation of younger children, an available random sample of 200 healthy Dutch children was used. Of this group, child and parent data were available.[14] Data were collected in 12 municipal health services spread over the Netherlands.

The Dutch school system is divided into 3 phases. During the first phase (4–12 years), children attend primary school or, in case of learning disabilities, special schools with specially adapted programs. The second "high school" phase consists of preeducational programs for low-skilled professions and intermediate-skilled professions, higher skilled professions, or academic professions. These diplomas give access to schools for low-, intermediate-, and high-skilled professions and to university. Dutch Health Statistics provide reliable data only on the completed levels of schooling for different age groups. Therefore, we categorized the educational attainment according to the highest successfully completed level of schooling: low vocational training, intermediate vocational training, or high vocational training. Differences in educational levels between patients with galactosemia and healthy control subjects were analyzed with χ^2 tests. From the galactosemia-specific survey, all questions in Dutch regarding the experience of the disease were selected and translated for presentation in this article, and frequencies are shown.

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

TABLE 1. Numbers of Patients and of Parents Divided Over Age Groups, With Completed Questionnaires

Age	No. of Patients	% of Dutch Patients*	Questionnaires by Patients	Questionnaires by Mothers	Questionnaires by Fathers
1–5	22	73%		TAPQOL (n = 21)	
				Galactosemia specific (n = 21)	Galactosemia specific (n = 21)
6–7	7	58%		TACQOL (n = 7)	
				Galactosemia specific (n = 7)	Galactosemia specific (n = 7)
8–15	17	35%	TACQOL (n = 16)	TACQOL (n = 16)	
			Galactosemia specific (n = 16)	Galactosemia specific (n = 16)	Galactosemia specific (n = 15)
16–17	2	17%	TAAQOL (n = 2)		
			Galactosemia specific (n = 2)	Galactosemia specific (n = 1)	Galactosemia specific (n = 2)
>18	15		TAAQOL (n = 15)		
			Galactosemia specific (n = 15)	Galactosemia specific (n = 4)	Galactosemia specific (n = 3)

* Percentage of patients from the estimated number of Dutch patients in the age group, calculated from the Dutch incidence and birth rate.

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).

TABLE 2. Mean HRQoL Scores (TAPQOL) for Children With Galactosemia and for Healthy Children

Scale	Mean Children With Galactosemia (n = 21)	Mean Healthy Children (n = 251)	P Value
Sleeping	79.1	83.1	.36
Appetite	80.6	85.9	.08
Lungs	94.3	97.2	.40
Stomach	79.8	92.6	.00*
Skin	94.6	92.8	.42
Motor function	95.3	98.8	.12
Social function	95.6	91.4	.05
Problem behavior	67.7	67.7	.93
Communication	80.9	91.7	.03†
Anxiety	73.0	79.2	.28
Positive mood	97.6	98.9	.57
Liveliness	96.8	98.1	.64

High scores indicate better quality of life.
* $P < .01$.
† $P < .05$.

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 3. Mean HRQoL Scores for Children Aged 6 to 15 With Classical Galactosemia and Healthy Children

	Children		Mothers	
	Galactosemia (Mean [SD]; $N = 16$)	Healthy Children (Mean [SD]; $N = 200$)	Galactosemia (Mean [SD]; $N = 23$)	Healthy Children (Mean [SD]; $N = 200$)
Physical symptoms	26.1 (6.0)	24.5 (5.7)	27.1 (3.6)	27.2 (4.0)
Motor function	28.6 (3.4)	29.8 (2.9)	29.2 (3.4)*	30.5 (2.5)
Autonomy	30.7 (3.2)	31.5 (1.3)	30.1 (3.6)	31.5 (1.5)
Cognitive function	23.5 (5.9)†	28.5 (3.9)	22.8 (6.4)†	29.0 (3.6)
Social function	28.3 (3.3)	29.3 (3.2)	28.3 (3.8)	29.6 (2.5)
Positive emotions	12.6 (3.7)	13.4 (2.8)	14.6 (2.1)	14.2 (2.6)
Negative emotions	12.8 (2.6)	11.8 (2.6)	11.6 (2.9)	11.7 (2.5)

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

TABLE 4. Mean HRQoL Scores (TAAQOL) for Children With Galactosemia and for the General Population

Scale	Mean Patients With Galactosemia ($n = 17$)	Mean General Population ($n = 350$)	P Value
Gross motor	89.7	93.7	.28
Fine motor	95.2	97.9	.30
Pain	75.0	81.0	.47
Sleeping	77.2	79.5	.70
Cognitive function	72.4	84.0	.04*
Social function	76.8	89.0	.04*
Daily activities	90.8	84.1	.05
Sexuality	89.7	90.9	.82
Vitality	58.8	68.0	.11
Happiness	67.6	73.3	.25
Depressive moods	80.4	81.5	.70
Aggressiveness	92.2	86.5	.09

High scores indicate better quality of life.
* $P < .05$.

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

	Patients (%; $N = 15$)	Dutch Population (%)*
Basic school and low vocational training†	61.5	27.2
Intermediate vocational training†	30.8	47.0
High vocational training†	7.7	25.9

* 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.
† $P < .001$.

few patients worry frequently about their future, and most patients (91%) believe that one can live a good life with galactosemia. Most patients (80%) report being treated by their parents the same way as their healthy siblings. Worries about possible infertility are reported by 28% of the girls aged 8 and older ($n = 22$).

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 are 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

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

Experience of the Disease	Totally Agree	Agree	Disagree	Totally Disagree
Galactosemia as a genetic disease is a burden to our family	14	32	43	11
The care of my child with galactosemia is a great burden	19	41	30	10
I feel isolated as a parent of a child with galactosemia	4	17	57	22
It bothers me that my child suffers from galactosemia	54	32	13	1
One can live a good life with galactosemia	22	64	12	2
I treat my child with galactosemia the same way as my healthy child	37	32	30	1
I watch over my child with galactosemia more than over my healthy child	17	42	32	9
Galactosemia affects the contact with my child	41	32	18	9
I raise my child with galactosemia in a different way than my healthy child	3	20	41	36
My child's friends know what galactosemia is	8	43	39	10
My child suffers from unclear speech	13	25	42	20
Hospital visits are a burden to our family	2	33	45	20
	Almost Always	Often	Sometimes	Almost Never
It bothers me to go to the hospital for follow-up	10	16	46	28
I find it difficult when my child needs to have a blood test	30	20	30	20
My child with galactosemia is jealous of his/her healthy sibling		8	47	45
I worry about the future of my child	15	23	47	15
I worry about the results from blood tests and urine tests	11	7	32	50
I worry that my child may become ill	4	7	48	41
I worry that my female child might suffer from infertility	20	35	35	10

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

Experience of the Disease	Totally Agree	Agree	Disagree	Totally Disagree
It bothers me that I have galactosemia	18	21	40	21
I can live a good life with galactosemia	65	26	3	6
I feel different because I have galactosemia	6	28	41	25
I feel nobody understands my disease	6	16	50	28
I have unclear speech	6	22	34	38
My parents treat me the same way as my healthy siblings	49	31	10	10
My parents watch over me more than over my healthy siblings	7	22	39	32
At school they understand I have to visit the hospital sometimes	39	55	6	
I explained to my friends what galactosemia is	42	43	12	3
	Almost Always	Often	Sometimes	Almost Never
I am jealous of my healthy siblings	3	4	55	38
I worry about my future		6	24	70
I worry that I may become ill as a result of the galactosemia		9	9	82
It bothers me when I have to draw blood for follow-up	9	9	27	55
It bothers me when I have to visit the hospital	9	3	33	55
I worry about the results of my blood tests and urine tests		3	18	79
I am bullied by other children at school			9	91
I worry about possible infertility problems (girls n = 22)	14	14	45	27

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.

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