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ORIGINAL ARTICLE

Living situation, occupation and health-related quality of life in adult patients with classic galactosemia

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Abstract
Background Galactose-1-phosphate uridyltransferase deficiency is well known as the underlying defect in classic galactosemia. However, little is known about the consequences of this defect beyond physical disease. Aim: To evaluate psychosocial, educational and occupational outcome as well as health-related quality of life (HRQOL) in adult German patients with galactosemia and to compare information with data from patients with phenylketonuria as well as the general German population.
Methods Members of the German patient support group for galactosemia received invitation, informed consent form and questionnaires by regular mail from the patient support group. Participation was voluntary.
Results Forty-one out of 66 invited patients participated in this study. Nearly 2/3 of the patients were singles, and the majority of patients were still living with their parents. Frequently, patients had no school leaving certificate, and 30% of the patients had never started or never completed an apprenticeship. Getting along with galactosemia was rated as 'very good' or 'good' although following the diet was a burden. Social well-being and social functioning was lower compared to patients with PKU.
Discussion Patients with galactosemia need a multiprofessional team not only focusing on physical and/or biochemical aspects of disease but including also psycho-social dimensions of life.

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Introduction

Classic galactosemia (OMIM #230400) is an autosomal-recessive inherited metabolic disease caused by deficiency of galactose-1-phosphate uridyltransferase (GALT, EC 2.7.712). At birth affected children are unobtrusive, but soon after onset of milk-feeding they develop a potentially lethal hepatotoxic syndrome. Institution of a milk-free diet leads to rapid clinical improvement, however, long-term outcome is disappointing with impaired cognitive performance (Schadewaldt et al 2010; Schweitzer et al 1993; Shield et al 2000), speech impairment (Hoffmann et al 2011; Potter et al 2008) reduced bone mineral density (Panis et al 2004), and in females hypergonadotropic hypogonadism (Kaufman et al 1986). Since GALT-deficiency is a chronic disease with unfavourable outcome and life-long dietary restrictions, it is plausible that social participation including school education, social relations, living situation and

health-related quality of life (HRQOL) in these patients may be impaired. Despite the relevance of these domains, only limited information gathered from small samples of patients is available. Impaired HRQOL in all age groups (Bosch et al. 2004b) and lower scores in the domains of cognitive function and social function in patients 16 years and older compared to healthy controls (Bosch et al 2009) have been reported. Both studies concluded that investigations on larger cohorts are needed to identify possible difficulties beyond physical or biochemical examinations.

The present study was undertaken to elaborate a comprehensive evaluation of the social and psychological situation of adults with classic galactosemia (incidence ~ 1:40,000 (Suzuki et al 2001)). In particular, the living situation, social relations, educational and occupational achievements, employment status, getting along with the disease, and HRQOL in a group of adult patients with classic galactosemia were assessed. To set this information into a broader context we compared the collected data with respective information obtained from a sample of patients with Phenylketonuria (Simon et al 2008) and with reference data from the German general population. Results of this study may help to inform patients and their families about possible consequences of the disease on different life domains and to develop focussed strategies for supporting the patients on their way towards a better life.

Patients and methods

Patients

All adult patients with classic galactosemia who were members of the German Galactosemia Patient Support Group (n=66) were invited to participate in this study. The patients received questionnaires by regular mail from the patients' organization together with information on the background of the study and an informed consent form.

Methods

Assessed sociodemographic characteristics included age, gender and marital status (single, married, divorced, widowed). Moreover, household composition (living alone, with parents, living in supervised residential group, living with friends/partner, others), and family planning (children, desire for children) was evaluated.

Information on education comprised the highest school degree (no degree, secondary school degree, university entrance diploma, others), professional training (never started/completed professional training, in apprenticeship, professional training completed), and employment status (unemployed, housewife, depending on social welfare, on early retirement, part-time, full-time working).

Disease specific questions within a proprietary, non-validated questionnaire aimed to evaluate how the patients get along with the disease, areas of life that are influenced by the disease, disease burden as well as monthly expenses for keeping the diet. Patients were able to choose answers from a 5-scaled Likert-scale (see supplementary material including disease specific questions).

Health related quality of life was evaluated by the use of the 'Quality of Life Profile of the chronically ill' (PLC) (Siegrist et al 1996). The PLC consists of 40 questions regarding the patients' well-being during the last 7 days. Answers are given on a Likert-scale ranging from 0 (minimum satisfaction) to 4 (maximum satisfaction) yielding six dimensions of HRQOL (see Table 1). The questionnaire is validated and has satisfying psychometric properties (Laubach et al 2001).

The study protocol was approved by the Institutional Review Board of the University Hospital Düsseldorf, Germany, and all patients provided written informed consent.

Statistics

Frequencies were calculated for information on sociodemographic characteristics and living situation, school education, apprenticeship and employment status, as well as for disease specific information. Although males and females are similarly affected by GALT-deficiency, testing for group differences between both genders was performed (χ^2-test or Fisher's exact test where appropriate).

Information about sociodemographics, living situation, education and employment status were compared with data obtained from the German census 2005 or the German Health Monitoring 2005, respectively. To maintain best comparability between these groups, only patients with galactosemia aging between 18 and 34 years were included in this subanalysis. This is the overlapping age range between our study and the register based census data.

PLC-scores are given as mean ± standard deviation (SD). Group differences regarding dimensions of the PLC, gender and patient's living situation were calculated by one-way ANOVA. Correlations between disease specific items of the proprietary questionnaire and PLC-scores were calculated by the use of Spearman's rank correlation. One sample t-test was used to compare PLC-results obtained from patients with galactosemia with those of individuals of the general German population as well as with those of patients with PKU (Laubach et al 2001). Following age classification in the PLC-reference population, only answers from patients aging 18–34 years were used for this purpose.

Significance for all tests was assumed with $p<0.05$. All analyses were performed using the IBM SPSS software 19.0.

Table 1 Sociodemographic characteristics, marital status, household composition and family state in 41 patients with galactosemia compared with data from the general population

N	Patients with galactosemia			General population[‡]		
	Total 41	Female 23	Male 18	Total -	Female -	Male -
Age (years, mean ± SD, range)	26.2±7.2 (18.3-49.3)	27.5±8.5 (18.3-49.3)	24.5±4.9 (18.3-33.5)	- -	- -	- -
Marital status						
Single/no stable partnership	26 (63.4%)	10 (43.5%)	16 (88.9%)	(47.6%)	- (35.3%)	- (62.6%)
Married/stable partnership	15 (36.6%)	13 (56.5%)	2 (11.1%)	- (46.3%)	- (45.4%)	- (47.2%)
Household composition						
Alone	5 (12.2%)	2 (8.7%)	3 (16.7%)	- (37.5%)	- (54.7%)	- (45.3%)
With parents	23 (56.1%)	11 (47.8%)	12 (66.7%)	- (3.5[#]-12.5%[$])	- n.a.	- n.a.
Supervised residential group	1 (2.4%)	1 (4.3%)	0 (0.0%)	n.a.	n.a.	n.a.
With friends/partner	10 (24.4%)	9 (39.1%)	1 (5.6%)	n.a.	n.a.	n.a.
Others	2 (4.8%)	0 (0.0%)	2 (11.1%)	n.a.	n.a.	n.a.
Family state						
own children	2 (4.8%)	2 (8.7%)	0 (0.0%)	n.a.	n.a.	n.a.
desire for children	20 (48.8%)	8 (44.4%)	12[§] (66.7%)	n.a.	n.a.	n.a.

[§] One male patient did not answer the question regarding "desire for children"

[‡] Data as provided by the German census 2005

[#] single children aging 18–27 years in parental household

[$] single children aging ≥27 years in parental household

n.a. = data are not available from the German census

Table 2 Information on highest school degree, professional training and employment status in 35 patients with galactosemia compared to data taken from the German census 2005

	Patients with galactosemia			Normal population		
	Total	Female	Male	Total	Female	Male
Highest school degree‡						
N[#]	37	20	17	-	-	-
No school degree	4 (10.8%)	2 (10.0%)	2 (11.8%)	-(3.5%)[+]	- (3.4%)[+]	- (3.5%)[+]
Secondary school degree	30 (81.1%)	17 (85.0%)	13 (76.5%)	- (59.5%)[+]	- (59.5%)[+]	- (59.6%)[+]
University entrance diploma	3 (8.1%)	1 (5.0%)	2 (11.8%)	- (28.6%)[+]	- (28.1%)[+]	- (28.6%)[+]
Professional training						
N[§]	37	21	16	-	-	-
Never started/completed apprenticeship	11 (29.7%)	9 (42.9%)	2 (12.5%)	n.a.	n.a.	n.a.
In apprenticeship	9 (24.3%)	5 (23.8%)	4 (25.0%)	n.a.	n.a.	n.a.
Professional training completed	16 (43.2%)	7 (33.3%)	9 (56.3%)	n.a.	n.a.	n.a.
Employment status[†]						
N[$]	33	20	13	-	-	-
Unemployed/depending on social welfare/on early retirement	8 (24.2%)	5 (25.0%)	3 (23.1%)	n.a.	n.a.	n.a.
Part-time/Full-time working	18 (54.5%)	10 (50.0%)	8 (61.5%)	-(68.2%)	-(61.9%)	-(74.4%)
In apprenticeship/studying at university	7 (21.2%)	5 (25.0%)	2 (15.4%)	n.a.	n.a.	n.a.

[+] data provided by the German Health Monitoring for the year 2005 (http://www.gbe-bund.de) for subjects >15<50 years of age

[#] Four patients (3 female, 1 male) did not provide information regarding their highest school degree.

[§] Four patients (2 female, 2 male) did not answer the questions regarding "professional training"

[†] data provided from the German Census 2005 (http://www.destatis.de) for subjects >15<50 years of age

[$] Five patients were still in school, three patients did not provide information on their employment status.

[‡] 0.5% of the persons in the German census did not provide information on their school degree

n.a. = data are not available from the German census

Table 3 Disease specific information reported by 41 patients with galactosemia

N	Patients with galactosemia		
	Total 41	Female 23	Male 18
Getting along with galactosemia			
Very good/good	32 (78.1%)	18 (78.3%)	14 (77.8%)
Partly good, partly bad	7 (17.1%)	3 (13.0%)	4 (22.2%)
Bad/very bad	2 (4.9%)	2 (8.7%)	0 (0%)
Following the diet is a burden			
Very much	2 (4.9%)	1 (4.3%)	1 (5.6%)
Partly	15 (36.6%)	10 (43.5%)	5 (27.8%)
Not at all	24 (58.5%)	12 (52.2%)	12 (66.7%)
Informing other people about the disease is a burden			
Very much	4 (9.8%)	3 (13.0%)	1 (5.6%)
Partly	14 (34.1%)	6 (26.1%)	8 (44.4%)
Not at all	23 (56.1%)	14 (60.9%)	9 (50.0%)
Living situation compared to others' is a burden			
Very much	7 (17.1%)	4 (17.4%)	3 (16.7%)
Partly	9 (21.9%)	6 (26.1%)	3 (16.7%)
Not at all	25 (61.0%)	13 (56.5%)	12 (66.7%)
Galactosemia impairs company with other people			
Absolutely	4 (9.8%)	1 (4.3%)	3 (16.7%)
Partly	12 (29.3%)	8 (34.8%)	4 (22.2%)
Not at all	25 (61.0%)	14 (60.9%)	11 (61.1%)

Results

Sociodemographics and living situation

Altogether, 66 questionnaires were sent to members of the German patient support group for galactosemia ≥18 years of age who have a proven GALT-deficiency (< 5% compared to healthy controls). Of these, 41 patients (62.1 %; 23 females, 18 males) participated (mean age 26.2±7.2 years, range 18.3-49.3 years, see Table 2).

The majority of patients were singles, with males more than twice as often as females ($p<0.005$; Fisher's exact test). Of note, only two males out of our cohort were married or living in a stable partnership compared to 13 females ($p<0.005$; Fisher's exact test), and more male patients were still living with their parents or under supervised living conditions compared to female patients (66.7 % vs. 52.1%; $p<0.005$, Fisher's exact test). Moreover, only one male patient but nine female patients with GALT-deficiency were living with their partner or with friends. Consistent with this, own children were reported by two patients only. However, desire for children was reported by nearly 50% of the patients, with a higher proportion in males than in females (66.7% vs. 44.4%; $p<0.05$, χ^2-test).

Education, professional training and employment status

Thirty-seven patients provided information about their highest level of school education (see Table 3).

Of these, 10.8% had no school leaving certificate at all, and the vast majority (81.1%) had graduated from secondary school, while three patients had a university-entrance diploma (8.1%, 1 female, 2 males).

Forty-three percent of the patients in this cohort who provided information on their vocational training had completed a professional training. However, nearly 30% of the patients had never started or never completed an apprenticeship. Of note, the rate of male patients who completed their professional training was 56%, whereas only 1/3 of the females reported this. Consistent with this, the rate of females who had never started/completed an apprenticeship is nearly four times higher as in males (see Table 3).

Thirty-three patients with galactosemia provided information on their current status of employment at the time of evaluation. Of these, 24.2% were not employed at all, and 54.5% were either working part-time or full-time. The remainder of patients were studying at the university or in apprenticeship. No differences were seen between males and females (see Table 3).

Disease specific information

Table 1 summarizes information on disease specific aspects. More than 75% of the patients rated their coping with galactosemia as 'very good' or 'good', but the remainder patients had difficulties in getting along with the disease. Keeping the diet was no problem at all for 58.5% of the patients, but at least partly straining for nearly every third patient. Most patients (56.1%) did not feel burdened to inform other people about the disease, and similarly 61.0% of the patients reported that it does not affect them to compare their life with others'. Nevertheless, nearly every fifth patient reported that it was a burden to compare their living situation with other people's life. More than 60% of the patients reported that galactosemia does not at all impair their company with other people. Nearly 30% of the patients reported that this was in part true, three males and one female patient (altogether 9.8%) reported that the disease impairs their company with other people.

Figure 1 shows the aspects of life that were reported to be influenced by galactosemia. Based on the disease specific information provided by the patients "diet/nutrition" is the primary aspect of life influenced by the disease, followed by "school/work" and "friends/leisure". Affection of family life was reported by three patients only (7.7%). No differences regarding these aspects were observed between females and males.

To follow the diet recommended for patients with galactosemia caused additional expenditures for foods with a mean of 145 €/month (range 0–400 €/month) (data not shown).

Health related quality of life

Figure 2 shows mean values (±SD) of the six dimensions of the PLC-questionnaire in 36 patients with galactosemia aging 18–34 years compared to patients with phenylketonuria (n=67, age range 17–38 years, based on (Simon et al 2008)) and healthy subjects of comparable age (n=526, age range 18–34 years, as reported in (Laubach et al 2001)) from the general German population, respectively.

In galactosemia highest scores were reported for the dimension "negative mood" (2.99±0.76, range 1.13-4.00), followed by "psychological functioning" (2.81±0.61, range 0.80-3.80) and the dimension of "social well-being" (2.79+0.82, range 1.50-4.00). Lowest scores were reported for "positive mood" (2.32+0.73, range 1.00-3.80). No differences for the PLC-dimensions were observed between males and females, therefore no gender stratified results are shown. Compared to the general German population differences in PLC-scores were only small, however, positive mood in patients with galactosemia was reported significantly lower compared to both, the general German population (one sample t-test, $p<0.05$) and the patients with PKU (one sample t-test, $p<0.005$). Moreover, social well-being and social functioning were also lower in patients with galactosemia then in patients with PKU (one sample t-test, $p<0.005$ each).

Regarding associations between HRQOL and how the patients get along with the disease we found a positive correlation between "getting along with the disease" and each of the dimensions of the PLC ($p<0.05$, lowest Spearman's rho 0.365 for "positive mood"; highest Spearman's rho 0.496 for "psychological functioning") (data not shown). This finding clearly shows the impact of galactosemia on the entire spectrum of HRQOL-domains. Moreover, "negative mood" showed good correlation with burden of the diet ($p<0.05$, Spearman's rho 0.43). Patients reporting a burden by following the diet also

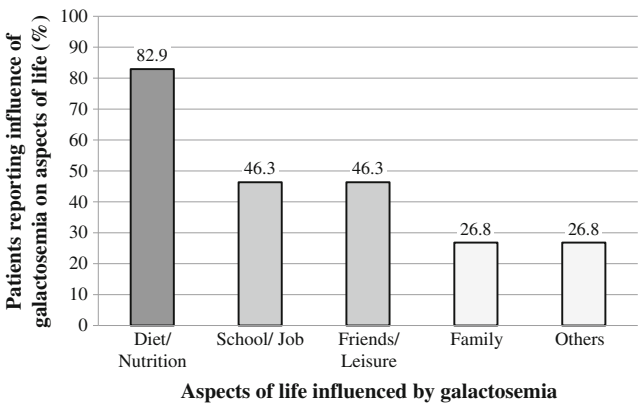

Fig. 1 Percentage of patients reporting influence of galactosemia on different aspects of life (n=41)

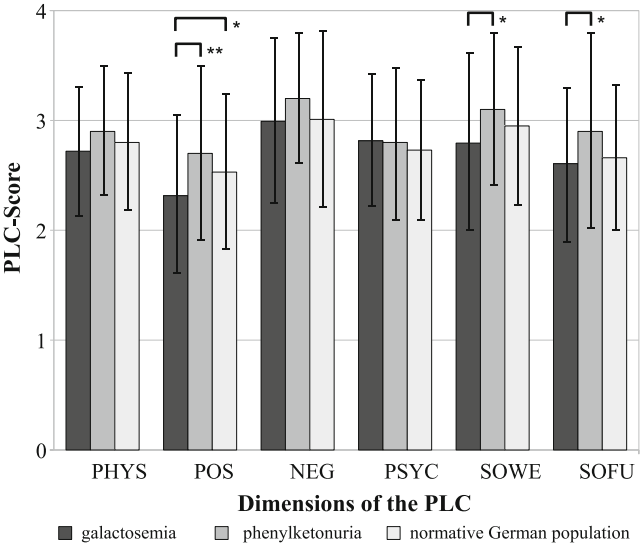

Fig. 2 Mean values (± standard deviation) of the six dimensions of the PLC-scores in 36 patients with galactosemia aging 18–34 years (mean age 23.9 years) compared to patients with phenylketonuria (n=67, 17–38 years of age) and compared to the general population (n=526, 18–34 years of age). PHYS=physical functioning, POS=positive mood, NEG=negative mood, PSYC=psychological functioning, SOWE=social wellbeing, SOFU=social functioning. * indicates significance on a level of 0.05; ** indicates significance on a level of 0.005

reported lower PLC-scores for "positive mood" ($p<0.05$, Spearman's rho 0.44), "social well-being" ($p<0.05$, Spearman's rho 0.41), and "social functioning" ($p<0.05$, Spearman's rho 0.34). There was no difference in the PLC-scores between patients who were still living with their parents or under supervised living conditions and other patients.

Discussion

The present study aimed to improve the understanding of difficulties patients with galactosemia may encounter during their life.

It turned out that only the minority of patients with galactosemia are able to build up strong partnerships outside the core family. The percentage of patients who were single in our sample is lower compared to the report by Bosch and colleagues (63.4% vs. 85.7%)(Bosch et al 2009), a fact that may be explained by the small number of patients (n=15) in their study. Moreover, patients with GALT-deficiency in our study were far more often singles than the general German population (47.6%). These findings are comparable to those reported by Gubbels et al who found social developmental delay in patients with galactosemia (Gubbels et al 2011).

With fewer relations beyond the core family and fewer partnerships the majority of patients with GALT-deficiency were still living with their parents. This frequency was much higher compared to the general German population (Table 2), but similar to observations from PKU, (Simon et al 2008). Living with their parents seems to be suitable for most of the patients with galactosemia (56.1%). Of note, this is in good agreement with a recent study by Waisbren et al where 46% of the patients lived independently (Waisbren et al 2011). However, at least when they survive their parents, patients with galactosemia are expected to need support to manage their life, e.g. within supervised residential groups. In order to allow a smooth transition towards a new lodging, possibilities, concerns and chances should be discussed with the patients and their families in time.

Leaving the family e.g. to a supervised residential living group may support the patients' social relationships as "friends/leisure" are reported to be influenced by galactosemia (Fig. 1), and company with other people often is difficult for these patients. This finding is consistent with Bosch et al. where social functioning was also significantly impaired (Bosch et al 2009).

It is well known, that patients with GALT-deficiency have an overall impaired IQ (Schadewaldt et al 2010; Schweitzer et al 1993) which may impact on school education and employment status. Patients with GALT-deficiency leave school without a degree about four times more often compared to the general German population of similar age, and individuals from the general German population leave school with a university entrance diploma about three times more often compared to patients with galactosemia (Table 3). Comparison with reports from other countries (e.g. with the Netherlands (Bosch et al. 2004b)) is hampered in particular by different schooling systems and different criteria for entering special schools. Independent from schooling systems, patients with GALT-deficiency have lower educational and professional achievements. About 55% of the patients here were part-time or full-time employed, a rate much lower compared to the general German population where more than 2/3 of individuals between 15 and 50 years of age were employed either part-time or full-time.

Moreover, about 1/3 of the patients with galactosemia have never started or completed a professional training and every fourth patient was unemployed, depending on social welfare or on early retirement. Again, this is consistent with Waisbren et al. where 21% of the patients were unemployed (Waisbren et al 2011). Of note, much fewer patients with PKU were unemployed, and in general they attained higher school leaving certificates (Simon et al 2008). This finding may be explained by the fact, that in PKU adherence to the protein-restricted diet is associated with a better cognitive outcome (Burgard et al 1996), whereas in galactosemia dietary compliance does not improve cognitive capacities. Nevertheless, school degrees and cognitive performance are not the only causes for unemployment. About 60% of the patients here were classified as "severely disabled" following German classifications (data not shown), however, this does not necessarily imply that these patients are physically or mentally disabled. Often, acknowledgment as being disabled is requested because of tax relief, rather than true disability. In adults, employers are often cautious to engage "disabled" workers, e.g. because of extended dismissal protection or impaired working capacity. This may also explain the high rate of jobless patients compared to the general German population.

"Following the diet" is a high burden showing a positive correlation with the domain "negative mood" and a negative correlation with the domains "positive mood", "social well-being", and "social functioning" of the PLC. Recent studies suggested a possible tolerance for galactose in patients with GALT-deficiency (Bosch et al. 2004a; Huidekoper et al 2005), and it might be interesting to evaluate HRQOL in galactosemia again under a relaxed diet as soon as this may be implemented in the future.

Evaluation of HRQOL by the use of the PLC showed significantly lower scores for social functioning and social well-being compared to both, the general German population and compared to patients with PKU (Fig. 2). Patients with galactosemia are regarded to follow their diet strictly, and they fairly accept the restrictions of this diet. However, following the diet in PKU improves both, the short-term course of the disease as well as the long-term outcome. Rapid improvement of dietary adhesion in PKU, e.g. leads to short-term improvements

in sustained attention, calculation speed (Huijbregts et al 2002; Schmidt et al 1994), but also in mood (ten Hoedt et al 2011). In contrast to this, adherence to dietary recommendations in galactosemia rapidly improves the neonatal manifestations of the disease, but long-term outcome is disappointing (Hoffmann et al 2011; Kaufman et al 1986; Rubio-Gozalbo et al 2002; Schadewaldt et al 2010). Apart from this, results of the present study indicate that galactosemia impacts also on emotional well-being and mood. The positive correlation seen between sub-scores of the PLC and the reports about how the patients get along with their disease suggests a general influence of galactosemia and its daily burden on HRQOL. It may be interesting to see in further studies, whether or not improvements in getting along with the disease may also improve HRQOL. To achieve this, appropriate treatment strategies for these patients are needed involving pediatricians and internists as disease managers, geneticists, psychologists, dietitians and if possible social workers.

Strength and limitations of this study

Although this study comprises the largest cohort of adult patients with galactosemia so far investigated regarding living situation, education/occupation and HRQOL, it is a relatively small cohort (n=41). Therefore, no multivariate statistics were possible. Volunteer participation may be a bias in this study since it is conceivable that patients with poor education/cognitive abilities/HRQOL may not participate in such a study.

Nevertheless, our findings provide new insights in important aspects of the living situation of patients with galactosemia. The information obtained from these studies underline the importance of a general treatment approach that does not only focus on physical and/or biochemical aspects of disease but that include also psycho-social dimensions of life.

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