J Inherit Metab Dis (2009) 32:706–712
DOI 10.1007/s10545-009-1253-2

ORIGINAL ARTICLE

Remarkable differences: the course of life of young adults with galactosaemia and PKU

A. M. Bosch · H. Maurice-Stam · F. A. Wijburg · M. A. Grootenhuis

Received: 26 May 2009 / Submitted in revised form: 25 June 2009 / Accepted: 10 August 2009 / Published online: 10 October 2009

Summary Although the need for insight in factors influencing the quality of life of patients with an inborn error of metabolism is recognized, psychological adjustment of adults with metabolic diseases has not been properly studied. Adult patients with PKU were demonstrated not to differ from healthy controls in terms of their course of life (CoL) and health-related quality of life (HRQoL). However, adults with galactosaemia had a lower HRQoL with significant lower scores on the domains of cognitive and social function. This study investigated the CoL and the social demographical outcomes in these young adults with galactosaemia, and compared them with the general population and with PKU patients. A total of 15 (88%) adult patients with classical galactosaemia participated in this study. Classical galactosaemia patients had a delayed social and psychosexual development compared to their peers from the general population and to PKU patients. Also, they were significantly less frequently married or living together and significantly less frequently employed than the general population. Our study shows a stark contrast between patients with galactosaemia and patients with PKU, although both are diagnosed in the neonatal period and need life-long dietary restrictions. The observed difference is likely due to the long-term somatic complications frequently seen in galactosaemia and thus not due to the burden of a chronic disease necessitating life-long dietary restrictions. We conclude that it is essential that parents and clinicians encourage children with galactosaemia to participate in peer-related activities in order to stimulate social performance, which may result in a more normal CoL.

Abbreviations

CoL	course of life
CoLQ	course of life questionnaire
HRQoL	health related quality of life
PKU	phenylketonuria

Communicating editor: Gerard Berry

Competing interests: None declared

References to electronic databases: Classical galactosaemia; OMIM#230400. Galactose-1-phosphate uridyltransferase: EC 2.7.7.12. Phenylketonuria: OMIM 261600. Phenylalanine hydroxylase: EC 1.14.16.1.

A. M. Bosch (✉) · F. A. Wijburg
Department of Pediatrics, Academic Medical Center,
University of Amsterdam,
G8205, Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands
e-mail: A.M.Bosch@amc.nl

H. Maurice-Stam · M. A. Grootenhuis
Pediatric Psychosocial Department,
Academic Medical Center, University of Amsterdam,
Amsterdam, The Netherlands

Introduction

In the general paediatric literature, there is growing attention to late psychological consequences in children and young adults with chronic diseases. However, the psychological adjustment of young adults with metabolic diseases has not been studied properly, even though the importance of insight into the factors influencing the quality of life of patients with an inborn error of metabolism has been increasingly recognized, as this knowledge is needed for optimization of treatment and follow-up,

Classical galactosaemia (OMIM #230400) is an autosomal recessive disorder of galactose metabolism caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT; EC 2.7.7.12). Most patients develop a life-threatening illness in the first two weeks of life after ingestion of galactose-containing breast milk or infant formula. Once the diagnosis is suspected, the neonatal crisis can be rapidly ameliorated by a galactose-restricted diet. As galactosaemia has been included in most expanded newborn screening programmes, the diagnosis is currently generally made before the onset of severe disease. However, in spite of a timely diagnosis, even in cases of asymptomatic diagnosis by newborn screening and a life-long strict diet, many patients develop long-term complications. Frequently, abnormalities are found in motor function, speech development (verbal dyspraxia), cognition, and hormonal function (hypergonadotrophic hypogonadism in girls) (Schweitzer et al. 1993, Waggoner et al. 1990).

Phenylketonuria (PKU; OMIM 261600) is an autosomal recessive disorder of phenylalanine metabolism caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH; EC 1.14.16.1). Untreated PKU results in severely retarded development and neurological abnormalities. Since 1974, more than 99% of all newborns have been screened for PKU in the Netherlands in the first two weeks of life. Patients with PKU are treated with a life-long phenylalanine-restricted diet and supplementation of all amino acids except phenylalanine. Plasma phenylalanine levels are frequently evaluated. With the introduction of newborn screening and the early institution of the diet, mental retardation due to PKU has been eliminated, with the exception of very rare cases of false-negative screening results or of extreme lack of dietary compliance. Intellectual performance in patients with early-treated PKU has been reported to be in the normal range, albeit slightly lower than in the general population (Gassio et al. 2005; Lundstedt et al. 2001; Weglage et al. 1992).

In a previous study we evaluated the course of life (CoL), sociodemographic outcomes and health-related quality of life (HRQoL) in young adult patients with PKU identified on newborn screening who were continuously treated (Bosch et al. 2007). We showed that PKU patients did not differ significantly from healthy controls in terms of their CoL and HRQoL. In a study of galactosaemic patients aged 16 years and older we reported a lower HRQoL with significant lower scores on the domains of cognitive and social function (Bosch et al. 2004). Because fulfilling developmental tasks and achieving developmental milestones in youth (such as search for contacts outside the family, or acquisition of independence), referred to as the 'course of life' (CoL), are of significant importance to adjustment in adult life (Garber 1984; Lewis and Miller 1990), we decided to study the CoL of young adults with galactosaemia as well. The purpose was to explore the CoL as well as the social demographical outcomes in young adults with galactosaemia, and to compare the results with those of peers from the general population as well as with PKU patients as another group of patients with a metabolic disorder necessitating life-long dietary restrictions.

Methods

Participants and procedure

All patients with classical galactosaemia aged 18 years and older who were members of the Dutch Galactosaemia Society (n=17) were asked to complete the course of life questionnaire (ColQ). They were sent questionnaires and were asked to return them by mail after completion. The patients were instructed to complete the questionnaire within 3 weeks, to complete the entire questionnaire at the same time and to answer the questions without discussion with others. All patients were supposed to follow the strict galactose-restricted dietary guidelines as used in the Netherlands at that time. No data about time of diagnosis were available. A total of 53 PKU patients who were diagnosed by newborn screening and were treated early and continuously were asked to complete the CoLQ. Their recruitment method and instructions were similar to those of the galactosaemia patients (Bosch et al. 2007).

Instrument

The ColQ, a Dutch questionnaire, was used to assess the achievement of developmental milestones retrospectively. The Psychosocial Department of the Emma Children's Hospital/Academic Medical Center developed this ColQ in order to be able to investigate the CoL of young adults, aged 18–30, who have grown up with a chronic or life-threatening disease, and to facilitate comparison with the course of life of peers without a history of disease (Grootenhuis et al. 2003). The items, based on the literature and clinical experience, concern behaviours that are characteristic of certain age stages, developmental tasks, and the limitations children might encounter when they grow up with a chronic disease. Most questions ask retrospectively whether the respondent had achieved certain developmental milestones (yes, no) or at what age

(category) the respondent achieved the milestones. The answers are dichotomized, if necessary, before being summed to the scale-score. The items are divided into five scales: (1) development of autonomy (6 items about autonomy at home and outside the home); (2) psychosexual development (4 items about love and sexual relations); (3) social development (12 items about social contacts with peers, at school and in leisure time), (4) antisocial behaviour (4 items about misbehaviour at school and outside school); (5) substance use and gambling (12 items about the use of alcohol, tobacco and drugs, and about gambling). For this study, only autonomy development, psychosexual development and social development are taken into account. A higher score on the scales indicates the accomplishment of more developmental milestones and therefore a more favourable course of life. Apart from the five scales, the questionnaire measures sociodemographic outcomes in young adulthood, such as living situation, education, and employment. The questionnaire covers a total of 74 items. A reference group was recruited through general practitioners (GPs) in a former study (see Stam et al. 2005 for details) and consisted of 508 respondents, 239 men (47.0%) and 269 women (53.0%). Mean age was 24.2 years (SD 3.8, range 18.0–30.9).

The validity of the CoL-scales is good. Firstly, the items are based on the literature and clinical experience. Secondly, the scales seemed to measure distinct constructs because the Pearson's correlation between the scales is not high (r<0.30). Thirdly, the results of the ColQ proved to be in line with several datasets of the Dutch population (Grootenhuis et al. 2003).

The test-retest reliability is good (Last et al. 2000) and the internal consistency of four out of the five scales developed is satisfactory (Grootenhuis et al. 2003). The reliability of the development of autonomy scale is moderate, probably because the items concern diverging aspects of autonomy (Grootenhuis et al. 2003).

Statistical analysis

The Statistical Package for Social Sciences (SPSS) Windows version 16.0 was used for all the analyses. Analyses of variance (ANOVA) followed by Bonferroni post-hoc tests were conducted to test group differences on the CoL-scales. Effect sizes were calculated by dividing the difference in mean scale scores of patients and the reference group by the standard deviation of the scores in the reference group. This procedure was performed for the galactosaemia patients and PKU patients separately. Following Cohen (1988), effect sizes (d) of 0.2, 0.5 and 0.8 were considered small, medium and large, respectively.

To improve reliability, we also performed non-parametric Kruskal-Wallis tests followed by Mann-Whitney U-tests because the distribution of the scores of the CoL-scales was not fully normal.

Furthermore, in order to gain a detailed insight into the CoL of the galactosaemia patients, differences on item level between the patients with galactosaemia, those with PKU and the reference group were also calculated. Therefore, logistic regression analyses were conducted at the frequency distributions of the individual (dichotomized) scale items.

Logistic regression analyses were also conducted in order to trace differences between the groups in sociodemographic outcomes: living situation (living with their parents or not), marital status (married/living together or single) and occupational status (employed or unemployed). Because these outcomes have a known effect of sex, analyses were corrected for sex.

A significance level 0.05 was used, but to compensate for multiple testing a significance level of 0.01 was used at testing the differences on item level.

Results

A total of 15 patients (88%) with classical galactosaemia aged 18 years and older completed the CoLQ. There were 3 male and 12 female patients. The data of one female galactosaemia patient could not be used for analysis because she was too old (41 years) for the CoLQ. Without this respondent ages ranged from 18 to 35 years (mean 24.2, SD 3.9).

A total of 32 PKU patients (60%) who were early diagnosed and continuously treated with a protein-restricted diet with supplementation of amino acids completed the CoLQ; 10 (31%) male and 22 (69%) female. Mean age of the participants was 24.6 years (SD 3.6, range 18.0–30.4) (Bosch et al. 2007).

Course of life

The ANOVA and Kruskal-Wallis nonparametric tests showed significant overall group differences on two of three CoL-scales; Psycho-sexual development (F(2, 540)=14.4, p<0.001; χ^2=22.1, df=2; p<0.001) and Social development (F(2, 511)=13.4, p<0.001; χ^2=19.1, df=2; p<0.001). More specifically, galactosaemia patients achieved fewer developmental milestones (or at older age) in the psychosexual and social domain than PKU patients and the reference group of peers from the general population (Table 1). PKU patients

Table 1 Mean scale scores, standard deviations (SD) and effect sizes (d)[a] of young adults who grew up with galactosaemia or PKU and the reference group, on the three scales of the course of life questionnaire

	Galactosaemia			PKU			Reference	
	N	Mean (SD)	*d*	*N*	Mean (SD)	*d*	*N*	Mean (SD)
Autonomy development	12	9.0 (1.5)	−0.30	31	9.8 (1.5)	0.28	501	9.5 (1.5)
Psychosexual development[b]	14	5.5 (1.3)[cd]	−1.43	30	7.3 (1.0)	0.11	499	7.1 (1.1)
Social development[b]	12	17.4 (2.6)[cd]	−1.43	30	21.6 (2.0)	0.26	472	21.0 (2.5)

[a] Effect sizes for comparison of galactosaemia and PKU with the reference group of peers from the general population.
[b] Group differences at $p<0.0001$ according to ANOVA and Kruskal-Wallis nonparametric test.
[c] Patients with galactosaemia differed significantly from the reference group, according to ANOVA with Bonferroni post-hoc test and Mann-Whitney *U*-test: $p<0.0001$.
[d] Patients with galactosaemia differed significantly from patients with PKU, according to ANOVA with Bonferroni post-hoc test and Mann-Whitney *U*-test: $p<0.0001$.

did not differ from the reference group on any of the CoL scales.

Table 2 shows the individual (dichotomized) items of the social development scale of the CoLQ. Patients with classical galactosaemia differed on 6 of the 12 items from the PKU patients and/or their peers from the general population; according to logistic regression analysis at $p<0.01$. In primary school, significantly fewer galactosaemia patients than PKU patients and peers from the reference group reported membership in a sports club for at least one year. Also, significantly fewer galactosaemia patients than PKU patients had a best friend in primary school. In contrast with PKU patients (in primary school) and the reference group (in primary and secondary school), galactosaemia patients spent most of their time playing with siblings, parents or alone, instead of with friends. Furthermore, in secondary school fewer galactosaemia patients belonged to a group of friends and they went out to a bar or disco significantly less often than PKU patients and peers from the reference group.

With respect to Autonomy development, only one significant difference was found: galactosaemia patients less often had a paid job during secondary school compared with the reference group (50% versus 87.4%, $p<0.001$).

We found significant differences between the galactosaemia patients and the other groups on two of the items of Psychosexual development. Patients with classical galactosaemia were older than the reference group at the time of their first boyfriend/girlfriend; 42.9% versus 80.4% ($p<0.01$) had their first boyfriend/girlfriend at the age of 17 years or younger. They were also older than both the reference group and the PKU patients at the time of their first sexual intimacy: 35.7% versus 96.7% ($p<0.001$) and 83.4% ($p<0.001$), respectively, experienced sexual intimacy for the first time at the age of 18 years or younger.

Sociodemographic outcomes

The percentage of galactosaemia patients living together or being married was significantly lower ($p<0.05$) than that percentage in the reference group of peers from the general population (Table 3). However, galactosaemia patients did not live more often with their parents. Furthermore, patients with galactosaemia were significantly less frequently ($p<0.05$) employed than the reference group. PKU patients did not differ from the reference group with respect to their marital status, living situation and employment.

Discussion

The objectives of the study reported here were to assess the CoL of patients with classical galactosaemia and to compare their CoL with the general population as well as with a cohort of young adults with phenylketonuria. Knowledge about possible gaps in the CoL can be useful in clinical practice because it enables health care providers to aim at a most favourable CoL in children throughout their development. Comparing the CoL in patients with two different metabolic disorders, but all needing life-long dietary restrictions, may provide more information regarding the specific factors that contribute to a normal CoL.

The adults with galactosaemia in this study had a significantly delayed CoL. They achieved fewer milestones than their peers from the general population and than patients with PKU with respect to Social development and Psychosexual behaviour. Patients with galactosaemia were significantly less frequently employed than the general population. A delayed CoL, in which patients do not fulfil age-specific developmental tasks in childhood, may hamper adjust-

Table 2 Percentages and differences between young adults grown up with galactosaemia, PKU and the reference group with respect to the milestones of social development

	Galactosaemia		PKU		Reference	
	N	%	N	%	N	%
At least one year of membership in a sports club (primary school)						
Yes[a*]	6	42.9[b**c*]	30	93.8	427	84.2
No	8	57.1	2	6.2	80	15.8
Number of friends in 1–3 grade (primary school)						
<4	9	64.3	10	31.2	187	37.0
4 or more	5	35.7	22	68.8	319	63.0
Number of friends in 4–6 grade (primary school)						
<4	9	64.3	8	25.0	156	30.9
4 or more	5	35.7	24	75.0	349	69.1
Best friend (primary school)						
Yes	7	50.0 [c*]	28	87.5	377	74.2
No	7	50.0	4	12.5	131	25.8
Most of time playing with(primary school)						
Friends[a*]	7	50.0[b**c*]	28	87.5	436	87.6
Siblings, parents, alone	7	50.0	4	12.5	62	12.4
At least one year of membership in a sports club (secondary school)						
Yes	6	42.9	25	80.6	373	73.6
No	8	57.1	6	19.4	134	26.4
Number of friends (secondary school)						
<4	9	64.3	9	29.0	154	30.4
4 or more	5	35.7	22	71.0	352	69.6
Best friend (secondary school)						
Yes	9	64.3	27	87.1	372	73.5
No	5	35.7	4	12.9	134	26.5
Belonging to a group of friends (secondary school)						
Yes[a*]	6	42.9[b*c*]	29	93.5	403	80.6
No	8	57.1	2	6.5	97	19.4
Leisure time mainly with(secondary school)						
Friends	8	57.1[b*]	27	90.0	430	85.1
Siblings, parents, alone	6	42.9	3	10.0	75	14.9
Going out to a bar or disco (secondary school)						
Sometimes/often[a**]	5	35.7[b**c*]	24	77.4	430	84.8
Never	9	64.3	7	22.6	77	15.2
At least one year of membership in a sports club (after secondary school)						
Yes	6	50.0	18	58.1	243	48.9
No	6	50.0	13	41.9	254	51.1

[a] Significant group differences according to logistic regression analysis.
[b] Patients with galactosaemia differed significantly from the reference group, according to logistic regression analysis.
[c] Patients with galactosaemia differed significantly from patients with PKU, according to logistic regression analysis.
*$p<0.01$; **$p<0.001$.

ment in adult life (Garber 1984; Lewis and Miller 1990). These results from the CoLQ in patients with classical galactosaemia correspond well with the finding of a lower social and cognitive health-related quality of life in this age group (Bosch et al. 2004). In that previous study we also reported a significantly lower educational attainment in adult patients with classical galactosaemia. Cognitive function and social function appear to be problems in all age groups of patients with galactosaemia (Bosch et al. 2004). Lambert and Boneh (2004) report frequent problems in interaction with others, such as feeling different and being bullied, in a small cohort of Australian patients with classical galactosaemia and of different ages.

Remarkably, in a cohort of young adults with phenylketonuria who were diagnosed early and treated continuously we found a normal CoL and a normal HRQoL (Bosch et al. 2007). Although a higher percentage of PKU patients received special education in primary school compared with controls, the educa-

Table 3 Percentages and differences between young adults grown up with galactosaemia, PKU and the reference group with respect to living situation, marital status and employment

	Galactosaemia						PKU						Reference					
	Male		Female		Total		Male		Female		Total		Male		Female		Total	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Living with their parents																		
No	1	33.3	6	66.7	7	58.3	2	80.0	16	72.7	24	75.0	138	57.7	190	70.6	328	64.6
Yes	2	66.7	3	33.3	5	41.7	8	20.0	6	27.3	8	25.0	101	42.3	79	29.4	180	35.4
Marital status																		
Married/living together[a]	0	0.0	2	18.2	2	14.3	2	20.0	11	50.0	13	40.6	71	30.9	121	46.4	192	39.1
Single	3	100	9	81.8	12	85.7	8	80.0	11	50.0	19	59.4	159	69.1	140	53.6	299	60.9
Employment status[b]																		
Employed[a]	2	100	5	62.5	7	70.0	7	87.5	13	92.9	20	90.9	148	97.4	147	89.1	295	93.1
Not employed	0	0	3	37.5	3	30.0	1	12.5	1	7.1	2	9.1	4	2.6	18	10.9	22	6.9

[a] Patients with galactosaemia differed significantly ($p<0.05$) from the reference group, according to logistic regression analysis of the outcome predicted by group and sex.
[b] Students excluded.

tional attainment and the employment was comparable to that of controls.

Our results show a striking difference in CoL and HRQoL between patients with galactosaemia and PKU. We had previously assumed that some part of the problems we detected in classical galactosaemia were caused by the burden of having a chronic disorder and life-long dietary restrictions. However, PKU patients also suffer from a chronic disorder and their dietary guidelines are considerably more strict than those in galactosaemia. Still, their CoL and HRQoL are normal. From these findings we conclude that the lower HRQoL and the hampered CoL in classical galactosaemia are due to the long-term somatic effects of the disorder, such as cognitive impairment and speech problems, and not to the dietary restrictions or the burden of having a chronic disease.

Some limitations of the study should be mentioned. The patient group participating in this study is small. Classical galactosaemia is a relatively rare disease with an average of 6 new cases per year in the Netherlands (Bosch et al. 2005). Until 2007 there was no newborn screening for galactosaemia in the Netherlands. Because in the past a significant number of patients died before the proper diagnosis was made, and because some adult patients may be lost to follow up, we do not know the exact number of adult patients with classical galactosaemia in the Netherlands. However, 88% of the adult members of the Dutch galactosaemia society participated in this study. The fact that the patients with galactosaemia were recruited through the patient society, while the patients with PKU were recruited though four Dutch metabolic centres, might cause bias. Also, the fact that male and female patients did not participate equally in the study may hamper the generalizability of the results. However, our results correlate well with the results from the earlier quality of life study in which over 50% of the younger Dutch patients participated (Bosch et al. 2004). Furthermore, determinants of CoL were not further investigated. For this reason it is important to focus future research on the predictors of hampered development so as to be able to detect the children and adolescents who are at risk at an early stage.

In summary, we have demonstrated in a small cohort of patients that young adults with galactosaemia have delayed social and psychosexual development that is in strong contrast to patients with PKU. This difference is likely to be the result of the long-term somatic complications of the disorder and not due to the burden of a chronic disease or life-long dietary restrictions. It seems of utmost importance that parents and clinicians encourage children with galactosaemia to continue peer-related activities as much as possible in order to stimulate social performance. Health care physicians should be aware of possible developmental problems and be observant and refer for more detailed psychosocial assessment and counselling if necessary.

References

Bosch AM, Grootenhuis MA, Bakker HD, Heijmans HSA, Wijburg FA, Last BF (2004) Living with classical galactosemia, health related quality of life consequences. Pediatrics 113(5):e423–428

Bosch AM, Ijlst L, Oostheim W et al (2005) Identification of novel mutations in classical galactosemia. Hum Mutat 25 (5):502

Bosch AM, Tybout W, van Spronsen FJ, de Valk HW, Wijburg FA, Grootenhuis MA (2007) The course of life and quality of life of early and continuously treated Dutch patients with phenylketonuria. J Inherit Metab Dis 30(1):29–34

Cohen J (1988) Statistical power analysis for the behavioral sciences. New York: Academy Press

Garber J (1984) Classification of childhood psychopathology: a developmental perspective. Child Dev 55:30–48

Gassio R, Artuch R, Vilaseca MA et al (2005) Cognitive functions in classic phenylketonuria and mild hyperphenylalaninaemia: experience in a pediatric population. Dev Med Child Neurol 47:443–448

Grootenhuis MA, Stam H, Destrée-Vonk A, Heijmans HSA, Last BF (2003) Levensloop Vragenlijst voor Jong-Volwassenen. [Course of life questionnaire for young adults]. Gedrag Gezond 31:336–350

Lambert C, Boneh A (2004) The impact of galactosemia on quality of life—a pilot study. J Inherit Metab Dis 27(5):601–608

Last BF, Grootenhuis MA, Destrée-Vonk A, Heymans HSA (2000) De ontwikkeling van een levensloopvragenlijst voor jong-volwassenen (LVJV). [The development of a course of life questionnaire for young adults]. Gedrag Gezond 8:22–30

Lewis M, Miller SM (1990) Handbook of developmental psychopathology. New York: Plenum Press

Lundstedt G, Johansson A, Melin L, Alm J (2001) Adjustment and intelligence among children with phenylketonuria in Sweden. Acta Paediatr 90:1147–1152

Schweitzer S, Shin Y, Jacobs C, Brodehl J (1993) Long-term outcome in 134 patients with galactosemia. Eur J Paediatr 152:36–43

Stam H, Grootenhuis MA, Last BF (2005). The course of life of survivors of childhood cancer. Psychooncology 14:227–238

Waggoner DD, Buist NRM, Donnell GN (1990) Long-term prognosis in galactosemia: Results of a survey of 350 cases. J Inherit Metab Dis 13:802–818

Weglage J, Funders B, Wilken B et al (1992) Psychosocial and social findings in adolescents with phenylketonuria. Eur J Paediatr 151:522–525