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ORIGINAL ARTICLE

# Psychosocial developmental milestones in men with classic galactosemia

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**Abstract** Patients with classic galactosemia suffer from several long term effects of their disease. Research in a group of mainly female patients has shown that these patients may also have a developmental delay with regard to their social aptitude. To study if male galactosemia patients achieve psychosocial developmental milestones more slowly than male peers from the general Dutch population, we assessed their development with the Course of Life Questionnaire (CoLQ). A total of 18 male galactosemia patients participated in this study (response rate 69%): 11 Dutch patients and seven American patients. We found severe delays in the social and psychosexual scales of this questionnaire, but not on the autonomy axis. These results are comparable to an earlier study with a limited number of male patients. The observed delays could be secondary to less developed social skills, cognitive dysfunction, or disrupted language development. We strongly recommend screening of galactosemia patients for developmental delays, to ensure early intervention through social skills training.

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## Introduction

Classic galactosemia (OMIM 230400) is an inherited disease of carbohydrate metabolism caused by a mutation in the Galactose-1-phosphate uridyltransferase (GALT) gene leading to a complete or near complete aberrance of GALT activity. Its incidence in the Netherlands is about 1:33,000 (Bosch et al. 2005), in the US 1 in about 47,000 live born children is affected (National Newborn Screening and Genetics Research Center 2002). Despite dietary treatment minimizing galactose intake, patients suffer from several long term effects of their disease, such as primary ovarian insufficiency, impaired mental abilities, decreased bone mass and suboptimal growth (Holton et al. 2001). It is becoming more and more clear that social problems may also be part of the spectrum of these complications.

Children with chronic diseases are confronted with their normal age-related development tasks, but must also learn to live with their chronic illness or disability. Performing developmental tasks is important for wellbeing and prevention of adjustment problems later in life (Garber 1984; Lewis and Miller 1990). A chronic condition in childhood could hamper the achievement of milestones, because the disease can lead to an increased dependence on parents and reduced

participation in activities with peers. Cognitive development may be threatened, but also social development as a result of the disease or treatment. A recent publication demonstrated that the developmental trajectory of galactosemia patients is hampered. When compared with both a healthy reference group and a reference group of phenylketonuria patients they achieved fewer psychosocial developmental milestones such as participation in sports activities, going out and initiation of intimate relationships (Bosch et al. 2009).

Women with galactosemia suffer from subfertility, but no conclusive evidence on the male reproductive status in this disease exists. There is a striking lack of published fatherhood in these men, as to our knowledge only one father was ever reported (Panis et al. 2006). We do know that a few more galactosemic men have fathered a child (personal communication European Galactosemia Society), but there appears to be a discrepancy compared to the numerous women that conceived. Our recent study has shown that galactosemic men may face some fertility challenges, although infertility is rare (unpublished data). Young adults with chronic diseases face ongoing challenges to negotiate and obtain normative psychosocial developmental milestones and maintain adaptive functioning. Galactosemics appear to reach their social milestones at a slower pace than their peers, as was shown by Bosch and colleagues (2009), but a limitation of this study was the small number of male patients that took part in the study: only three of the 15 patients were male.

To explore whether the percentage of male galactosemia patients that has achieved psychosocial developmental milestones was lower than the percentage among male peers from the general Dutch population, we have assessed their development with the Course of Life Questionnaire (CoLQ) (Stam et al. 2005).

## Methods

### Patients

The studies were approved by the local IRB of the participating hospitals (Maastricht University Medical Center, Amsterdam Medical Center and Children's Hospital Boston) as part of larger studies. Patients were invited to participate through the Dutch Galactosemia Society (GVN) and Parents of Galactosemic Children (PGC), and volunteered with informed consent. Out of a total of 26 male galactosemia patients that received the questionnaire, 18 participated in this study (response rate 69%): 11 Dutch patients (eight from a study in Maastricht, three other patients from an earlier study in Amsterdam) and seven American patients. As the CoLQ is validated only for patients aged 35 or younger, we included only patients between 18 and 35. The reference group

introduced in an earlier study (Stam et al. 2005) was used for comparison with our patients.

### Course of life Questionnaire

The CoLQ was used to assess the achievement of psychosocial developmental milestones retrospectively (Stam et al. 2005). The CoLQ was developed in order to be able to investigate the psychosocial developmental milestones in young adults, who have grown up with a chronic or life threatening disease, and to facilitate comparison with that of peers without a history of disease. The items, based on the literature and on clinical experience, concern behaviours that are characteristic for 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 psychosocial developmental milestones (yes, no) or at what age (category) the respondent achieved the milestones. The answers are dichotomised, if necessary, before being added up to the scale-score. The items are divided into five domains: (1) development of autonomy (6 items about autonomy at home and outside the home), (2) psycho-sexual 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) anti-social 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). Apart from the five scales, the questionnaire measures socio-demographic outcomes in young adulthood. The American version of the CoLQ was established by a forwards-backwards translation. The backwards translation was cross-checked for inconsistencies by the authors of the original. For some items cultural adaptation was accomplished (e.g. educational system).

The psychometric characteristics of the CoL-scales are satisfactory, including validity (Stam et al. 2005). For this study, only the items of the developmental scales (autonomy development, psychosexual development and social development) were taken into account since internal consistency of sumscores in our small study sample was limited. A reference group was recruited through general practitioners 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%). The male data were used in the current study.

### Statistics

The Statistical Package for Social Sciences (SPSS) Windows version 16.0 was used for all the analyses. Analysis of variance

**Table 1** Characteristics of male patients with galactosemia and the reference group

| Group | N | Age (years) | Mean | SD | Response |
|---|---|---|---|---|---|
| Dutch galactosemia patients | 11 | 18.1-26.6 | 22.8 | 2.8 | 11/14 (79%) |
| American galactosemia patients | 7 | 21.4-35.0 | 26.4 | 5.2 | 7/12 (58%) |
| All galactosemia patients | 18 | 18.1-35.0 | 24.2 | 4.2 | 18/26 (69%) |
| Reference group | 239 | 18.0-30.9 | 24.0 | 3.9 | – |

**Table 2** Social milestones, galactosemia versus reference group

| | Galactosemia | | Norm | | |
|---|---|---|---|---|---|
| | % | N | % | N | Significance[1] |
| Social development | | | | | |
| At least one year competitive sports / sports club in elementary school | | | | | |
| yes | 50.0 | 9 | 87.8 | 209 | < 0.001 |
| no | 50.0 | 9 | 12.2 | 29 | |
| Number of friends in kindergarten through third grade in elementary school | | | | | |
| less than 4 | 83.3 | 15 | 31.6 | 75 | < 0.001 |
| 4 or more | 16.7 | 3 | 68.4 | 162 | |
| Number of friends in fourth-sixth grade in elementary school | | | | | |
| less than 4 | 77.8 | 14 | 27.8 | 66 | < 0.001 |
| 4 or more | 22.2 | 4 | 72.2 | 171 | |
| Best friend in elementary school | | | | | |
| yes | 55.6 | 10 | 71.1 | 170 | 0.19 |
| no | 44.4 | 8 | 28.9 | 69 | |
| Most of time playing with ….. in elementary school | | | | | |
| friends | 38.9 | 7 | 87.2 | 204 | < 0.001 |
| brothers and/or sisters, parents, on your own | 61.1 | 11 | 12.8 | 30 | |
| At least one year competitive sports in middle and/or high school | | | | | |
| yes | 33.3 | 6 | 76.9 | 183 | < 0.001 |
| no | 66.7 | 12 | 23.1 | 55 | |
| Number of friends in middle and/or high school | | | | | |
| less than 4 | 66.7 | 12 | 27.8 | 66 | 0.001 |
| 4 or more | 33.3 | 6 | 72.2 | 171 | |
| Best friend in middle and/or high school | | | | | |
| yes | 44.4 | 8 | 65.4 | 155 | 0.081 |
| no | 55.6 | 10 | 34.6 | 82 | |
| Belonging to a group of friends in middle and/or high school | | | | | |
| yes | 44.4 | 8 | 78.4 | 185 | 0.003 |
| no | 55.6 | 10 | 21.6 | 51 | |
| Leisure time, mainly with ….. in middle and/or high school | | | | | |
| friends | 33.3 | 6 | 81.1 | 193 | < 0.001 |
| brothers and/or sisters, parents, on your own | 66.7 | 12 | 18.9 | 45 | |
| Going to a bar or disco in middle and/or high school | | | | | |
| sometimes / often | 27.8 | 5 | 85.7 | 204 | < 0.001 |
| never | 72.2 | 13 | 14.3 | 34 | |
| At least one year competitive sports / sports club after high school | | | | | |
| yes | 31.2 | 5 | 53.7 | 124 | 0.12 |
| no | 68.8 | 11 | 46.3 | 107 | |

[1] according to $\chi^2$-test or Fisher's exact test

revealed no age difference (at p<0.1) between the patient groups and the reference group so that the analyses could be performed without correction for age. Chi-square tests were used to test differences between patients and the reference group on the dichotomised items of the CoLQ (i.e. on the proportion that achieved the milestone), using Fisher's exact test if the number of observations in the cells was not sufficient. Because chi-square tests showed no considerable differences between the CoL item scores of the Dutch and the American patients, the Dutch and American patients were compared to the reference population as one group. A significance level of 0.002 was used in order to compensate for multiple testing, since we tested group differences on 23 milestones.

## Results

### Participants

The data on the patients and the reference group are summarised in Table 1.

### Psychosocial developmental milestones

#### Social development

Table 2 shows the milestones in the social development scale. Patients with galactosemia scored significantly (p<0.002) lower on 8 of the 12 milestones than the reference group of peers from the general Dutch population. During elementary school and during middle and/or high school, (1) a lower percentage of galactosemia patients than of the reference group reported competitive sports or membership in a sports club for at least one year; (2) patients appeared to have a lower number of friends than the reference group; (3) they spent leisure time less often with friends than the reference group did; and (4) patients went out to a bar or disco less often than the reference group.

#### Psychosexual development and marital status

Patients with galactosemia scored significantly (p<0.002) lower on all four milestones of psychosexual development than the reference group of peers from the general Dutch population (Table 3). The patients were older than the reference group when they fell in love for the first time and when they had their first boyfriend/girlfriend. They were also older than the reference group at their first sexual intimacy and first time of sexual intercourse. Only one of the 18 galactosemic men was married. Although this percentage is lower than that in the reference group this difference did not reach significance.

#### Autonomy development

No significant differences (at p<0.002) were found on the milestones of Autonomy development (details not shown). These milestones concerned: regular chores/tasks in the family, paid jobs, vacation without adults, leaving the parents home.

**Table 3** Psychosexual milestones and marital status, galactosemia versus reference group

| | Galactosemia | | Norm | | |
| --- | --- | --- | --- | --- | --- |
| | % | N | % | N | Significance[1] |
| Psychosexual development | | | | | |
| First girlfriend / boyfriend | | | | | |
| at the age of 17 or younger | 29.4 | 5 | 77.7 | 185 | < 0.001 |
| at the age of 18 or older / never | 70.6 | 12 | 22.3 | 53 | |
| For the first time falling in love | | | | | |
| at the age of 18 or younger | 58.8 | 10 | 91.1 | 215 | 0.001 |
| at the age of 19 or older / never | 41.2 | 7 | 8.9 | 21 | |
| For the first time sexual intimacy | | | | | |
| at the age of 18 or younger | 25.0 | 4 | 82.8 | 197 | < 0.001 |
| at the age of 19 or older / never | 75.0 | 12 | 17.2 | 41 | |
| For the first time sexual intercourse | | | | | |
| at the age of 18 or younger | 17.6 | 3 | 55.9 | 133 | 0.002 |
| at the age of 19 or older / never | 82.4 | 14 | 44.1 | 105 | |
| Marital status | | | | | |
| Married / living together | 5.6 | 1 | 30.9 | 71 | 0.028 |
| Single | 94.4 | 17 | 69.1 | 159 | |

[1] according to $\chi^2$-test or Fisher's exact test

## Discussion

This study shows a significant delay in both psychosexual development as well as social development in young adult men with galactosemia. These findings are comparable to those seen in the whole group of galactosemia patients (Bosch et al. 2009). The delay might in part explain the low number of galactosemic fathers.

These findings indicate that it is important to encourage children (boys) with galactosemia to make friends and to participate in peer activities. Peer relationships are important for social development and self-esteem, especially in adolescents. Adolescents with chronic illnesses may become marginalised by peers, rejected for being different at a time when body image and identity so largely depend on conformity (DiNapoli and Murphy 2002). From previous research we know that social development seemed to be related to psychosexual development (Stam et al. 2005), so that friendships in youth are probably important for later sexual relationships.

This study has some limitations. We included patients in two different countries, whereas the reference group is from the Netherlands only. The comparison between the Dutch and the American patients, however, did not show any significant difference (at p<0.01), so that comparison with the Dutch reference group seemed justified. Another limitation is the small sample size. As a result, we decided to include patients up to 35 years while the reference group was aged up to 30 years. A strength of the study is that, compared to the total number of known Dutch galactosemia patients, and the number of American patients asked to participate, a relatively large number of patients decided to enrol.

Future research is necessary to confirm the results of the present, exploratory study, and to describe the relation between developmental achievements and later adjustment. The underlying reason behind the developmental delay in galactosemic men perhaps could be found in social skills. Generally, galactosemia patients are described as more timid than their peers. Furthermore, cognitive dysfunction, which is another complication of classic galactosemia, can interfere with normal social and psychosexual development as was described for childhood cancer survivors (Gurney et al. 2009). This might make it more difficult for galactosemia patients to develop a healthy relationship and start a family. The known problems with language development might be another contributor to this problem.

Perhaps early intervention, such as the speech therapy and social competence training (Last et al. 2007) that many young galactosemia patients currently receive, could lead to a better outcome for future generations. Furthermore, currently therapeutic strategies aimed at preventing and confining long term complications of classic galactosemia are being developed. For physicians it is very important to be aware of a possible delay in galactosemia patients, as it could be important to address problems that may arise during consultations. Paying attention to quality of life during consultations using patient-reported outcomes could be a valuable addition in clinical care (Engelen et al. 2010 (Epub ahead of print)).

In conclusion, men with classic galactosemia have severe delays in social and psychosexual development, as has been shown in a group of galactosemia patients of both sexes before. We strongly support routine screening for social and psycho-sexual development so that intervention is possible at an early age.

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