Systematic Review and Meta-analysis of Intelligence Quotient in Early-Treated Individuals with Classical Galactosemia

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Abstract *Introduction:* Cognitive impairment is a well-known complication of classical galactosemia (CG). Differences in patient characteristics and test methods have hampered final conclusions regarding the extent of intellectual disabilities in CG. The primary aim of this systematic review was to assess intellectual performance in early-treated (≤ 4 weeks of life) individuals with confirmed CG (defined by absent or barely detectable GALT enzyme activity and/or the presence of two null or severe missense

variations), assessed with comparable test instruments. The full-scale IQ (FSIQ) was the variable of interest.

Methods: A clinical librarian developed search strategies, and two independent investigators performed the study selection, risk of bias assessment and data extraction. Individual patient data were pooled for meta-analysis using linear mixed-effect models with a random intercept per study and including covariates (age or gender) as fixed effects where appropriate.

Results: Four articles were included in this meta-analysis. Data of 87 individuals (median age 13 years, range 3–38 years) were used to assess mean FSIQ in CG. The FSIQ ranged from 47 to 122, and the mean score was 87 (95% CI, 81–94). Forty-five percent of individuals attained scores < 85 , almost 40% attained scores of 85–100, and a minority (15%) attained scores above 100. There was no significant correlation between FSIQ and age.

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Conclusions: Results from this meta-analysis fortify conclusions from previous studies that early-treated individuals with CG are at risk for having impaired cognitive abilities. However, IQ varies considerably between affected individuals.

Introduction

Classical galactosemia (CG, MIM 230400) is an inborn error of galactose metabolism, caused by a severe deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT; EC 2.7.7.12). The incidence in Europe and the United States has been estimated for several countries and varies from 1 case per 19,000 to 1 case per 44,000 individuals (Bosch 2006; Ounap et al. 2010; Waisbren et al. 2012; Coss et al. 2013). When exposed to galactose from breast milk or infant formula, affected newborn infants develop life-threatening symptoms that quickly resolve once a galactose-restricted diet is initiated. A very strict life-long galactose-restricted diet is the only available treatment since CG was first reported in more detail (Jones and Leak 1959). Despite good dietary adherence, individuals are at risk for developing long-term complications including speech and language impairment and impaired cognitive abilities (Bosch 2006). Evaluation of cognitive abilities, including measurement of intelligence, is therefore an important aspect of the follow-up of children and adults. Studies show mean IQ scores below average, however, with large interindividual variability (Donnell et al. 1961; Komrower and Lee 1970; Waggoner et al. 1990; Schweitzer et al. 1993; Kaufman et al. 1994, 1995; Hansen et al. 1996; Rasmussen et al. 1996; Badawi et al. 1996; Shield et al. 2000; Widhalm et al. 2002; Antshel et al. 2004; Doyle et al. 2010; Schadewaldt et al. 2010; Coss et al. 2013; Rubio-Agusti et al. 2013), with many patients (45–72%) scoring in the low to very low range (IQ <85) (Schweitzer et al. 1993; Rasmussen et al. 1996; Shield et al. 2000; Hoffmann et al. 2011). Start of treatment after the 8th week of life seems to increase the risk for decreased cognitive abilities (Waggoner et al. 1990; Schweitzer et al. 1993). A negative correlation between age and IQ in individuals is reported in cross-sectional studies (Komrower and Lee 1970; Waggoner et al. 1990; Doyle et al. 2010), but was not confirmed by longitudinal studies (Fishler et al. 1966; Waggoner et al. 1990; Manis et al. 1997; Schadewaldt et al. 2010). Drawing conclusions from the individual studies about the extent of cognitive impairment in CG remains controversial, because many studies did not (1) define the diagnosis of CG, possibly including individuals with a variant form of galactosemia who have a better outcome;

(2) define inclusion criteria (patients may have been tested on indication [cognitive impairment]), resulting in sampling bias; and (3) report age at start of dietary treatment. Patient samples were frequently small, results of different instruments could not be compared, and study results were presented in variable manners. Because results may vary from one study to another, validity of a hypothesis cannot be based on the results of single studies. An individual patient data (IPD) meta-analysis systematically assesses the results of previous studies to derive conclusions about that body of research (Haidich 2010). It pools patient-level data from multiple studies in a statistically responsible manner, including individual patients according to predefined inclusion and exclusion criteria. A meta-analysis can increase power of the results and may include a more precise estimate of the outcome than any individual study contributing to the pooled analysis (The Cochrane Collaboration 2011).

The primary aim of this systematic review with meta-analysis was to assess cognitive abilities in a large group of individuals with a confirmed diagnosis of CG, who commenced dietary treatment before the age of 4 weeks and who were not tested on because of (suspected) cognitive impairment. The primary variable of interest was full-scale intelligence quotient (FSIQ), determined by comparable test instruments. Secondary aims were to assess a possible correlation between FSIQ and age and to evaluate performance IQ (PIQ) and verbal IQ (VIQ) scores in individuals with this disorder.

Methods

Eligibility Criteria

Inclusion and Exclusion Criteria

In the meta-analysis, these criteria apply to individual patients.

Patients Individuals of all ages with a confirmed diagnosis of CG, defined by a profound impairment of GALT enzyme activity (absent or barely detectable) and/or the presence of two null or severe missense variations. Individuals with reported residual GALT enzyme activity >1%, as well as individuals from the Traveller community, were excluded. To avoid any influence of later treatment on cognition, we decided to include only patients with age at diagnosis/start of dietary treatment ≤4 weeks of life.

Outcome Cognitive testing with any of the following test instruments yielding full/total IQ score: any version of the Wechsler Preschool and Primary Scale of Intelligence

(WPSI), Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scale (WAIS), the McCarthy Scales of Children's Abilities or Stanford–Binet (and any translated, validated versions of these test instruments).

Study Design Randomized controlled trials (RCT), non-RCT, cohort studies, case-control studies, cross-sectional studies and case series were included; case reports and (systematic) reviews were excluded. Only studies in which the majority of patients treated in a specific hospital participated were included, aiming to avoid bias caused by only testing patients because of (suspected) cognitive impairment. Studies published ≥ 1980 were included, as it was not considered feasible to contact authors of the articles published before 1980.

Characteristics Human studies, studies conducted in any year, and articles (including conference abstracts) written in English were included.

It is well known that the Irish Traveller community may have decreased access to full educational opportunities. Traveller pupils are reported to have lower levels of achievement and are more likely to be identified as having special educational needs than pupils from other ethnic groups in Ireland (Wilkin et al. 2010). It was not possible to correct for parental educational or socioeconomic status as they were not reported in any of the original studies. Therefore, to prevent bias caused by reduced access to schooling by members of the Traveller community, we excluded the FSIQ data reported in Coss et al. (2013) from this group.

Identifying Studies

A computerized search was conducted by a clinical librarian and one of the investigators (LW) in EMBASE, MEDLINE, PsycInfo and the Cochrane Library up to June 2015, who also hand-searched reference lists of included articles, conference abstracts and narrative and systematic reviews for additional relevant articles. Search strategies for each database are presented in Supplementary Data 1.

Study Selection Process

Two independent investigators (AMB, LW) performed the initial selection of potentially eligible articles, by screening titles of identified records. Thereafter, these investigators read abstracts (or the whole article in case an abstract was lacking), to make a more precise selection of potentially eligible articles. Of these studies, the full-text articles were read and selected based on predefined eligibility criteria. Study selection process for the meta-analysis of FSIQ

(Fig. 1) and the study selection process of the analysis of PIQ and VIQ were performed separately. Based on the IPD, patients not meeting all inclusion criteria were excluded from the meta-analysis.

Data Collection Process: Individual Patient Data

Authors of all relevant articles were contacted via e-mail with the request to share IPD. Multiple attempts, contacting different authors, were undertaken to obtain IPD.

Data Items: Individual Patient Data

Variables collected at a participant level were sex, age at diagnosis and/or initiation of dietary treatment, age at testing, test instrument used and individual FSIQ. If applicable: if patients were from a Traveller community. If individuals had been tested multiple times, the most recent score was used in the analysis.

Individual Patient Data Integrity

All IPD received from the authors were checked for completeness. If data were incomplete or if data included a sample that differed from the original article, authors were asked to explain these differences. Additional data were incorporated in the dataset only if they met inclusion criteria used for the systematic review, thus preventing selection bias.

Risk of Bias Assessment in Individual Studies

The Scottish Intercollegiate Guidelines Network (SIGN) quality appraisal checklists to assess bias were used (for RCT, non-RCT, cohort study and case-control study designs). For cross-sectional studies and case series, no standardized critical appraisal checklists were available, and risk of bias assessment was performed by systematically judging the study population in terms of reliability of the diagnosis of CG. Two independent investigators performed risk of bias assessment (AMB, LW).

Specification of Outcomes and Effect Measures

The primary outcome investigated in this systematic review is cognitive ability, expressed as a FSIQ. Secondary outcomes are VIQ and PIQ.

Statistical Analysis

We present age in terms of median and range, with no correction for clustering within studies. We tested for homogeneity of variances of FSIQ across the studies using

Fig. 1 Flow diagram of study selection process for the meta-analysis of full-scale IQ. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic*

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an univariate test for equal distributions (Rizzo and Székely 2010). We used linear mixed models (Zuur et al. 2009) with study as a random intercept, to obtain estimates of overall mean FSIQ with 95% confidence intervals (CI) for the means and *p*-values of differences between subgroups based on dichotomized age and sex. We used similar models to assess the association between FSIQ and age in years as a continuous variable. We considered *p*-values less than 0.05 statistically significant. We used R version 3.2.2015-12-04 (R Core Team 2014) and the packages lme4 (Bates et al. 2014) and energy (Rizzo and Székely 2014) to perform the meta-analysis and IBM SPSS Statistics version 22 for descriptive analyses.

Results

Study Selection Process

A total of 584 articles were identified by our search strategies (without doubles), of which 532 were discarded because they did not address our research question.

Meta-analysis

The study selection process for the meta-analysis is presented in Fig. 1. Of the 26 potentially eligible articles, IPD were sought for a total of 17 articles potentially eligible, and authors of these articles were contacted (see Supplementary Data 2 Data Retrieval, for characteristics of these studies). IPD were not sought for five articles published before 1980 (Donnell et al. 1961; Fishler et al. 1966, 1972; Komrower and Lee 1970; Lee 1972), for two articles in which IPD was already available (Hansen et al. 1996; Rasmussen et al. 1996) and for two articles that reported data also published in an earlier article of the same author(s) (Waggoner and Buist 1993; Hughes et al. 2009). Finally, IPD from four of these 17 articles were included in the meta-analysis (Waisbren et al. 1983, 2012; Antshel et al. 2004; Coss et al. 2013). Due to our inclusion and exclusion criteria, IPD of 87/199 individuals could be included in this meta-analysis. The first and/or last author of each article ascertained that the reported patients were not a selection of individuals tested because of (suspected) cognitive impairment, but were a good representation of the group of patients followed at that time.

Secondary Outcomes

No articles addressing PIQ and VIQ (*n* = 5) met all inclusion criteria, and therefore zero studies were included.

Risk of Bias Within Studies and Quality of Evidence

None of the selected studies had a study design for which a risk of bias checklist from SIGN was available.

Meta-analysis Full-Scale Intelligence Quotient

Four studies were included in our meta-analysis (Waisbren et al. 1983, 2012; Antshel et al. 2004; Coss et al. 2013), with relatively small patient sample sizes in the original studies (varying from 8 to 85 patients tested). Data of 87 individuals were pooled in the meta-analysis, 54 males and 33 females, with a median age of 13 years (range 3–38 years).

Antshel et al. assessed the neuropsychological profile (including FSIQ) in a cross-sectional study in 25 children and adolescents, homozygous for the c.563A>G (p. Gln188Arg) variation in the *GALT* gene (NM_000155.3), and tested with the WISC-III (Antshel et al. 2004). FSIQ scores of two originally tested patients (age 11 and 13 years) were not reported in the article (because the patients were excluded for further neuropsychological testing in that study), but FSIQ scores were provided for the meta-analysis. Therefore a total of 27 children from this study were included, 17 males and 10 females, median age 11 years (range 8–14 years).

In a retrospective study, Coss et al. assessed long-term outcome in 130 individuals (Coss et al. 2013). A total of 85 individuals, aged 6–39 years, were administered IQ tests (32/63 Travellers and 53/67 non-Travellers). Tests used were the WPPSI-III (Third UK Edition) for children aged 2 years and 6 months to 7 years and 3 months, the WISC-IV generally used for children aged 6–16 years and the WAIS-IV for individuals aged 16 years onward. All Travellers were excluded for reasons described in the Methods section. Furthermore, we excluded six non-Traveller individuals who had been diagnosed >4 weeks of life and/or had a variant form of galactosemia. Nine non-Traveller individuals not included in the original article were tested under the same protocol after the study was finished, and one female patient (15 years, FSIQ 90) meeting the inclusion criteria was included in this meta-analysis. A total of 48 non-Traveller individuals were thus included in our meta-analysis, and their median age was 19 years (range 6–38 years). All but three of these 48 individuals were homozygous for the c.563A>G (p. Gln188Arg) variation, two individuals were heterozygous for the known pathologic c.563A>G (p. Gln188Arg)/c.997C>T (p. Arg333Trp), and one individual was heterozygous for c.563A>G (p. Gln188Arg)/c.598delC (p. Gln200Serfs).

Waisbren et al. (1983) reported IQ scores in eight individuals, two males and six females, in a cross-sectional study (Waisbren et al. 1983). This was the complete group of children, identified at an early age (by NBS) and followed in their hospital at that time. Tests used were the McCarthy Scales of Children's Abilities, the Stanford-Binet (ages 3–6 years) and the WISC (ages 7 years and older). One patient was excluded because of a 5% residual GALT activity compared to virtually no residual activity in the other individuals. Thus, seven individuals (with a median age of 6 years, range 3–11 years) were included in our meta-analysis.

Waisbren et al. (2012) assessed the adult phenotype, including FSIQ, in a cross-sectional study including 33 individuals aged 18–59 years. All had absent GALT activity and two severe or null variations in the *GALT* gene and were administered the WAIS. Of these patients, only five could be included in this meta-analysis, because age at diagnosis was not known for the others. Their median age at testing was 20 years (range 18–23 years).

Full-Scale Intelligence Quotient in CG

The mean FSIQ in the four separate studies, calculated with the obtained IPD, were Antshel et al. (2004) mean 82 (SD 11.6), Coss et al. (2013) mean 83 (SD 18.0), Waisbren et al. (1983) mean 95 (SD 14.5) and Waisbren et al. (2012) mean 100 (SD 20.6). The univariate test of equal distributions with FSIQ data of all individuals included from the four studies indicated that the distribution of FSIQ scores across the four studies was not homogeneous ($p = 0.02$), justifying the use of linear mixed models to obtain mean FSIQ scores.

Following correction for the grouping of patients within studies, data from 87 individuals (median age 13 years, range 3–38 years) from these four studies revealed FSIQ range from 47 to 122 and a group mean of 87 (95% CI, 81–94). In all, 13 individuals (15%) attained scores lower than two standard deviations below the general population mean (FSIQ <70), 27 individuals (31%) performed between one and two standard deviations below the population mean (FSIQ 70–84), 34 individuals (39%) attained scores within one standard deviation below the population mean (FSIQ 85–100), and 13 individuals (15%) attained scores above 100.

Males and Females

The mean FSIQ score of 54 males (median age 13 years, range 3–35 years) was 92 (95% CI, 81–103). The mean FSIQ score of 33 females (median age 16 years, range 8–38 years) was 81 (95% CI, 77–86). The difference in

mean FSIQ between males and females was not statistically significant (5.5 points, 95% CI –1.4 to 12.5, $p = 0.1241$). The estimate of the difference between mean FSIQ in males and females is different from the difference between the estimates for males and females, because of the correction for the difference between the studies in the meta-analysis.

FSIQ Score and Age

There was no statistically significant association between FSIQ and age (increase of 0.4 points/year, 95% CI –0.1 to 0.9, $p = 0.1146$).

Performance and Verbal IQ Scores in Early-Treated CG Individuals

No studies addressing PIQ and VIQ scores that met all our inclusion criteria were identified.

Discussion

In this systematic review and meta-analysis, we demonstrate, to our knowledge in the largest and most homogeneous sample with early-treated individuals with a confirmed diagnosis, that individuals with the classical form of galactosemia are at risk for cognitive impairment. The mean FSIQ in pooled data of 87 children and adults with CG was found to be 87, which is at the 19th percentile of the general population and substantially lower compared to the general population mean. Compared to the general population, a large percentage of individuals perform in the borderline to low average intellectual range (FSIQ 70–85) and in the range of intellectual disability (FSIQ <70). Slightly more individuals perform within one SD below the general population mean (FSIQ 85–100), and fewer individuals attained a FSIQ score above 100. The range of FSIQ in patients is remarkably wide. Thus, developmental and neuropsychological assessments are important in clinical follow-up to identify individuals in need of early intervention, special education or other supportive services. No statistical difference was found between mean FSIQ in males and females (5.5 points, 95% CI –1.4 to 12.5, $p = 0.1241$). However, the sample sizes were small, consequently the confidence interval was relatively wide, and therefore such a difference between males and females cannot be ruled out. Biological factors (hereditary traits) and environmental factors may influence cognitive development, such as perinatal factors, individual and parental educational opportunities and socioeconomic status. One very important factor was taken into account in this study, by excluding patients who started treatment after the first

month of life. Because the other environmental factors were not reported in the original studies, these could not be accounted for in this meta-analysis.

To date, no consensus exists regarding whether CG is a progressive disorder, with deteriorating cognitive abilities. This systematic review and meta-analysis provided no indication of deterioration of FSIQ over time. However, information about FSIQ after the fourth decade of life is lacking. Our finding contradicts results from other cross-sectional studies, which reported a correlation between age and cognition, and supports results from longtinal studies demonstrating that FSIQ does not correlate with age (Fishler et al. 1966; Waggoner et al. 1990; Manis et al. 1997; Schadewaldt et al. 2010). This difference may be explained by a cohort effect in these cross-sectional studies, whereby patients born before a certain date did not have access to the modern standard of care and diagnosis techniques. This may have resulted in later diagnosis and start of treatment in the elder patients in these studies, possibly negatively affecting cognitive outcome. In these studies, age at diagnosis and start of treatment was frequently not taken into account or not reported. This may falsely result in the impression that cognitive abilities regress over time. In our study, this effect was eliminated by applying strict inclusion criteria, with all patients being treated soon after birth. Furthermore, additional studies are needed to assess potential differences in VIQ and PIQ.

This study has several strengths and limitations. Strengths are the large number of patients included compared to previous studies assessing cognitive abilities and the homogeneous sample of early-diagnosed individuals with a confirmed diagnosis of CG, increasing power and precision of the results. Our results confirm and, importantly, fortify the conclusions of previously published studies, settling controversies arising from these previous studies. By only including studies that did not test patients because of (suspected) cognitive impairment, the risk of sampling bias was kept as small as possible. The results of this study are likely the most representative published to date. Limitations are the small patient sample sizes of the included studies, and in some cases not all patients reported in the original paper could be included in our review. We used mixed-effects models to estimate group mean FSIQ. Occasionally, these models may produce biased parameter estimates when the number of groups or individuals within groups is very small (Maas and Hox 2005). However, we feel that using random effects to account for the group structure is more appropriate than using fixed effects, as the patient selections may have been subtly and functionally different between studies, though studies that tested patients on indication were excluded (Borenstein et al. 2009). The small patient sample in Waisbren et al. (1983) is most likely the cause of the smaller range of FSIQ demonstrated in that

group of patients and it is unlikely that this is caused by selection bias because all patients met our definition of CG. Since only cross-sectional data were used in this review and the majority of adult FSIQ scores were from one study, conclusions about FSIQ scores over time must be interpreted with caution.

Future research is needed to determine the factors that contribute to the broad variability in cognitive functioning in CG, predicting which patients are at risk for a low FSIQ (Coss et al. 2014). This could lead to interventions or modifications in treatment that may allow each individual to reach his/her full cognitive potential. Neuropsychological testing incorporated in regular clinical follow-up will identify infants and toddlers in need of early intervention and school-age children in need of special education or other supportive services.

Conclusions

Early-treated individuals with confirmed classical galactosemia, defined by a profound impairment of GALT enzyme activity (absent or barely detectable) and/or the presence of two null or severe missense variations, with age at diagnosis/start of dietary treatment ≤ 4 weeks of age, are at risk for having impaired cognitive abilities, with almost two-thirds of individuals performing more than a standard deviation below the normative mean of 100 (FSIQ range ≤ 85), a quarter performing in the low average to average range (FSIQ 85–100) and a minority (15%) attaining scores ≥ 100 . These results confirm the wide range in cognitive functioning in individual patients. There is no indication that FSIQ deteriorates over time, as assessed in patients up to 38 years of age, but prospective longitudinal studies following FSIQ in individual patients, also after the third decade of life, are needed to confirm this impression.

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Take-Home Message

Early-treated individuals with classical galactosemia are at risk for having impaired cognitive abilities, but FSIQ scores vary considerably between affected individuals.

Contributions of Individual Authors

All authors participated in analysis and interpretation of data and drafting the article and revising it critically for important intellectual content. Annet M. Bosch, Johanna H. van der Lee, Susan E. Waisbren and Lindsey Welling

participated additionally in conception and design of the study.

Guarantor

Annet M. Bosch.

Conflict of Interest

Annet M. Bosch is in receipt of research grants from Nutricia and was a member of an advisory board for Nutricia, Merck Serono and BioMarin.

Kevin M. Antshel declares that he has no conflict of interest.

Hugh-Owen Colhoun declares that he has no conflict of interest.

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Stephanie Grünewald declares that she has no conflict of interest.

Rebecca Holman declares that she has no conflict of interest.

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