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Recommendations for newborn screening for galactokinase deficiency: A systematic review and evaluation of Dutch newborn screening data

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ABSTRACT

Introduction: Galactokinase (GALK) deficiency causes cataract leading to severe developmental consequences unless treated early. Because of the easy prevention and rapid reversibility of cataract with treatment, the Dutch Health Council advised to include GALK deficiency in the Dutch newborn screening program. The aim of this study is to establish the optimal screening method and cut-off value (COV) for GALK deficiency screening by performing a systematic review of the literature of screening strategies and total galactose (TGAL) values and by evaluating TGAL values in the first week of life in a cohort of screened newborns in the Netherlands.

Methods: Systematic literature search strategies in OVID MEDLINE and OVID EMBASE were developed and study selection, data collection and analyses were performed by two independent investigators. A range of TGAL values measured by the Quantase Neonatal Total Galactose screening assay in a cohort of Dutch newborns in 2007 was evaluated.

Results: Eight publications were included in the systematic review. All four studies describing screening strategies used TGAL as the primary screening marker combined with galactose-1-phosphate uridyltransferase (GALT) measurement that is used for classical galactosemia screening. TGAL COVs of 2200 μmol/L, 1665 μmol/L and 1110 μmol/L blood resulted in positive predictive values (PPV) of 100%, 82% and 10% respectively. TGAL values measured in the newborn period were reported for 39 GALK deficiency patients with individual values ranging from 3963 to 8159 μmol/L blood and 2 group values with mean 8892 μmol/L blood (SD ± 5243) and 4856 μmol/L blood (SD ± 461). Dutch newborn screening data of 72,786 newborns from 2007 provided a median TGAL value of 110 μmol/L blood with a range of 30–2431 μmol/L blood.

Conclusion: Based on TGAL values measured in GALK deficiency patients reported in the literature and TGAL measurements in the Dutch cohort by newborn screening we suggest to perform the GALK screening with TGAL as a primary marker with a COV of 2500 μmol/L blood, combined with GALT enzyme activity measurement as used in the classical galactosemia screening, to ensure detection of GALK deficiency patients and minimize false positive referrals.

1. Introduction

Galactokinase (GALK; EC 2.7.1.6) deficiency (MIM ID 230200) is an autosomal recessive disorder of galactose metabolism, caused by mutations in the GALK1-gene, located on chromosome 17q24 [1]. Newborn screening data demonstrate that worldwide incidence is low, with estimates ranging from 1:150,000 to 1:1,000,000 [2–4]. Due to a founder mutation, the incidence in the Roma gypsy population is

List of abbreviations: CDC, Center of disease control and prevention; COV, Cut-off value; DBS, Dried blood spots; GALE, UDP-galactose-4-epimerase; GALK, Galactokinase; GALT, Galactose-1-phosphate-uridyltransferase; PPV, Positive predictive value; SD, Standard deviation; TGAL, Total galactose

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1:40,000 [4]. As GALK catalyzes the phosphorylation of galactose to galactose-1-phosphate, deficiency results in hypergalactosemia. The accumulating galactose is reduced to galactitol, causing bilateral cataract formation in infants in the first weeks of life after ingestion of breastmilk or infant formula [4–6]. Untreated cataract has severely disrupting consequences on the development of the child and will eventually cause the need for a lensectomy and blindness [4,7]. Besides cataract other clinical abnormalities, such as mental retardation and microcephaly, were reported in GALK deficiency patients, but were considered unlikely to be related to the disease [4,5]. The treatment of GALK deficiency is a lactose free diet and early start of the diet prevents or sufficiently resolves the cataract and thus prevents visual impairment and long-term complications related to eye surgery [7]. The cataract seems irreversible when the diet is introduced beyond four to eight weeks of life [4].

While Gitzelman was the first to describe the disease in 1965, Thalhammer et al. first reported the detection of a patient with GALK deficiency through a newborn screening program [2,8]. In newborn screening blood galactose has been measured since 1964 and screening was mostly aimed at detection of patients with classical galactosemia (MIM ID 230400) caused by galactose-1-phosphate-uridyltransferase (GALT; EC 2.7.7.12) deficiency [9]. In the Netherlands, the screening for classical galactosemia was implemented in 2007 and in the first three months of that year total galactose (TGAL, free galactose + galactose-1-phosphate) in dried blood spots (DBS) was measured in all newborns as the primary screening parameter, with a cut-off value (COV) of 700 µmol/L blood. Because of the high rate of false positive results, the screening protocol was changed to the measurement of GALT enzyme activity as a first tier, with TGAL as a second tier, in April 2007 [10].

Because of the severe developmental consequences of untreated cataract, and the easy prevention and rapid reversibility of cataract with early diagnosis and treatment, the Dutch Health Council advised to expand the Dutch neonatal screening program with screening for GALK deficiency [11]. This advice was adopted by the Dutch Ministry of Public Health, Welfare and Sports and screening for GALK deficiency is expected to be implemented in the foreseeable future [4–7]. Because measurement of TGAL is already implemented as a second tier test for classical galactosemia in the Dutch screening laboratories, the introduction of TGAL as a screening parameter for GALK deficiency would be relatively easy. When implementing this screening it is of utmost importance to choose the optimal screening parameters and COVs, to prevent false negative screening results (causing severe visual problems in untreated patients) and false positive results (as they have been demonstrated to cause psychological problems in parents, including anxiety, depression and altered perceptions of the health of their child [10,12]).

With this study, we aim to establish the optimal screening method and COVs for GALK deficiency newborn screening, using two approaches and combining the findings. Firstly, we have performed a systematic review of the literature describing screening strategies for GALK deficiency and of TGAL values measured in GALK deficiency patients at time of diagnosis in the first two weeks of life. Secondly, we have evaluated TGAL values in blood, measured as a screening parameter in the Dutch population in 2007 in the first week of life. Based on these data we formulate a recommendation for a screening strategy for GALK deficiency in the newborn screening program of the Netherlands.

2. Methods

2.1. Systematic review

2.1.1. Research question

Primary outcomes for our systematic review were the screening methods, assays and COVs used in GALK deficiency screening worldwide, TGAL values of GALK deficiency patients measured in the first two weeks of life, both with newborn screening and for clinical reasons, and diet at the time of blood sampling. The secondary outcome was the method of diagnosis confirmation.

2.1.2. Search strategy

This systematic review was conducted and reported according to the protocol specified in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. An experienced information specialist performed a broad search in OVID MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) and OVID EMBASE from inception to August 8, 2017 to find studies on GALK deficiency, using controlled terms, including MeSH, and text words. Animal studies were safely excluded by double negation. No language, date or other restrictions were applied. Reference lists and the citing articles of the identified relevant papers were cross-checked in Web of Science. The records retrieved were imported and de-duplicated in ENDNOTE X7. The complete search strategies are presented in Appendices A and B.

2.1.3. Inclusion and exclusion criteria

We searched for randomized controlled trials, cross-sectional studies, cohort studies, case-control studies, case series and case reports on [1] GALK deficiency screening or [2] TGAL values in GALK deficiency patients measured within the first two weeks of life. Articles reporting on animal and cell studies and articles published in a language different from English or Dutch were excluded.

2.1.4. Study eligibility

Two authors (AMB and KS) independently screened all titles and abstracts. If an article was excluded, the reason was documented. In case of a discrepancy in the selection of studies between the two reviewers, considerations were discussed until consensus on eligibility was reached.

2.1.5. Data collection

Data collection was performed by two separate researchers (AMB and KS) using the predefined criteria.

2.1.6. Data analysis

The origin of the data was considered to be too heterogeneous and thus not suitable for meta-analysis. Therefore, our results are presented in a descriptive manner, divided per publication. To evaluate the precision of the assays used, we consulted data from the Newborn screening quality assurance program from the Center of disease control and prevention (CDC), https://wwwn.cdc.gov/NSQAP/Public/Default.aspx.

2.2. Retrospective study on Dutch newborn screening data

2.2.1. Research question

Outcomes for this study were number of screened newborns in whom a TGAL was measured in 2007, the range of TGAL values in this cohort, and the number of GALK deficiency patients detected in this period.

2.2.2. Data collection and analyses

In the Netherlands, DBS on filter paper are collected between 72 and 168 h after birth and screening is performed in five laboratories located throughout the country. In 2007 TGAL was measured using the colorimetric Quantase Neonatal Total Galactose screening assay (Bio-Rad Laboratories Inc., California, USA) [10]. The TGAL assay has a measurement uncertainty of 20% (average values ± 2× coefficient of variation) in the range from 100 to 2300 µmol/L blood. TGAL screening results were collected from all five screening laboratories and the data were analyzed using IBM SPSS Statistics 24.0.