GLOWiNG study

GLucOse in Well babies and their later Neurodevelopment

Waikids
WAIKATO CHILD AND YOUTH HEALTH
Waikato District Health Board

Protocol

Glucose in Well Babies and their later Neurodevelopment (GLOWiNg)

Steering committee

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GLOWiNg Protocol

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Research summary

The Glucose in Well Babies (GLOW) cohort is a unique group of healthy newborn babies who had blood glucose, lactate and beta-hydroxybutyrate concentrations measured and interstitial glucose monitoring over the first five postnatal days. Babies were mostly in their own homes being cared for by their parents, who were also asked to collect information about all the feeds (Glucose in Well Babies Protocol, Version 3 Dated 19th September 2016 (available online http://hdl.handle.net/2292/32066)).

The purpose of the Glucose in Well Babies and their later Neurodevelopment (GLOWiNg) study is to assess the later development of children who participated as babies in the GLOW Study.

The GLOWiNg study has two phases. The first, when the children are 36 months old, involves parent/caregiver questionnaires only.

The second phase, when the children are 4.5 years old, will involve assessment of neurocognitive function, vision, growth and neurological status, and include parental questionnaires. This will be detailed in a separate protocol.

Research objective

To identify relationships between neonatal blood glucose, lactate, and beta-hydroxybutyrate concentrations and interstitial glucose concentrations from healthy term babies and the child's development at 36 months and 4.5 years of age.

Hypothesis

That metabolic fuels measured in the first five postnatal days are related to neurodevelopmental outcomes at 36 months and 4.5 years.

Specific aims

To assess the developmental outcomes of children who completed in the GLOW study, when they reach 36 months of age.

Background and rationale

Neonatal hypoglycaemia has been linked with brain injury and neurodevelopmental delay in at risk children.[1-3] Further, it has been shown that children who as babies had just one blood glucose concentration < 2.6mmol/L have poorer executive and visual-motor function at 4.5 years, and impaired school performance[3, 4].

Data regarding glucose concentrations in healthy newborns are few. Previous reports have included hospitalised babies and used different methods of analysis and timing intervals for measuring blood glucose concentrations. None have included continuous glucose monitoring, or measured alternative cerebral fuels [5, 6]. Importantly, there are no long-term follow-up studies relating neonatal glycaemia to later outcomes in normal babies.

It is possible that the combination of glucose and alternative fuel concentrations is more important than blood glucose concentration alone. Babies have been shown to use both lactate and ketones as cerebral fuels when blood glucose concentration is low[5]. Little is known about the role of alternative metabolic fuel sources during neonatal hypoglycaemia in relation to neurodevelopmental outcome.

The Glucose in Well Babies Study (GLOW)
The aim of the GLOW study was to describe the normal blood glucose, lactate and beta-hydroxybutyrate concentrations, using standard blood testing and also continuous interstitial glucose monitoring over the first five postnatal days.

All families were recruited antenatally. Eligible babies were singletons, term, appropriately-grown and with English-speaking parents. Mothers had normal body mass index, no antenatal history of diabetes or drug dependence and were not using medications that could potentially influence the blood glucose concentrations.

Babies were born at Waikato Women's Hospital, one of the local primary birthing centres, or at home. After discharge from hospital or birthing centre, babies were cared for in their own homes for majority of the study.

A total of 67 children who were born between November 2015 and August 2017 completed the study. The findings are yet to be published, but show that many healthy babies have episodes of hypoglycaemia which would meet the current clinical thresholds for treatment.

Research plan

Inclusion criteria
All parents or caregivers of children who have completed the GLOW study will be invited to join this follow-up study.

Exclusion criteria
Those who withdrew from the GLOW Study (n=3) due to clinical diagnoses.

Contact with families
The GLOW study team have had ongoing contact with GLOW families, most of whom still live within the Waikato region. Parents/caregivers who participated in GLOW were aware that a follow up study was a possibility. All families gave written consent to be contacted by the researchers following the completion of GLOW. In addition, families gave alternative contact addresses of close family or friends, and their general practitioner.

The GLOW Facebook page has also remained active and many parents continue to page by posting photos and messages. We will use the GLOW Facebook page as an additional means to inform families about GLOWiNg. A parent information sheet explaining what is involved will be posted on the Facebook page.

Informed consent
Completion of the questionnaires will be considered to be consent to taking part in GLOWiNg.

Withdrawal
Parents can withdraw their child at any time from the GLOWiNg study without the need to provide a reason.

Procedures
One month before each child's third birthday, we will post a parent information pamphlet to the family and this will be followed up by a phone call from the research nurse to discuss participation in GLOWiNg. If we are unable to trace families we will initially contact the alternative addresses and if necessary, contact their primary health provider. Interested families will be sent the questionnaires and a stamped addressed envelope. They will be asked to complete the questionnaires and return them to the research team using the envelope provided.

Parents will be contacted by phone at weekly intervals for a maximum of three phone calls; the first to confirm that the questionnaires have been received and to ask if any assistance is required, and the second and third contacts as reminder calls if required.

The Ages and Stages Questionnaire
The Ages and Stages Questionnaire (ASQ-3) is a parent-completed developmental screening tool which has been validated in children who have been born both preterm and term, in different countries and settings [7]. It is a standard screening tool and has been shown to promote early detection of neurodevelopmental delay and therefore the opportunity for early intervention.

The ASQ was used in an observational study of children (n= 832) born preterm (32 to 35^{6} weeks' gestation), who were later assessed between 43 and 49 months of age. That study showed neonatal hypoglycaemia to be the only factor independently associated with poorer neurodevelopmental outcome (OR 2.42 (95%CI 1.23 to 4.77)[2].

Other advantages of the ASQ include the parental/caregiver involvement, ease of completion and scoring of the questionnaire, and also that questionnaire is inexpensive[8].

There are 30 questions in five domains: communication, gross motor, fine motor, problem solving and personal-social.

Home and Family Questionnaire
This questionnaire will contain questions regarding length of breast feeding, eating, allergies, immunisations, illnesses or hospitalisations of the child, family size and the home environment (Appendix). We will also ask if the children have any scars related to the repeated heel pricks and parent views about the GLOW study.

Parents/caregivers will be provided with a brief report summarising the Ages and Stages Assessment findings and offering an opportunity to ask questions.

Adverse outcomes
In the unlikely event of a child scoring < 2 SD below the mean Drs Weston or Harris will meet with the family, discuss parental concerns and then make a referral to an appropriate health agency, usually the family General Practitioner, with the consent of the parents.

Statistical analysis
There are 67 children eligible for the recruitment. We are confident of at least 90% follow-up rate (i.e. 61 babies).

These are hypothesis generating analyses. In standard multivariable analyses 61 observations conveys 80% power at the 5% significance level in an unconditional model with two controlled variables (gestational age and maternal socioeconomic status) and three additional independent variables to detect effects (f^2) of at least 0.21 (defined as a medium to large effect by Cohen). Power analysis was performed using PASS 16 (PASS 16 Power Analysis and Sample Size Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.)

Data analysis will be specified in the Statistical Analysis Plan, which will be finalised before analysis begins, but in broad terms, the analysis will proceed with these steps:

1. Description of the developmental outcomes at 36 months of age.
2. Visual inspection of plots showing relationships between developmental outcomes and neonatal metabolic fuel concentrations.
3. Regression evaluation, linear or non-linear, of developmental outcomes by neonatal metabolic fuel concentrations, with adjustments for covariates and factors as appropriate.

Children who have suffered brain injury through a known postnatal accident or serious illness will be recorded and sensitivity analysis will be performed excluding these data.

Data Management

The ASQ will be independently scored by two investigators. The Home and Family Questionnaire will be double-entered and any discrepancies will be resolved prior to data finalisation.

Data Security

Data identifying each participant will only be on the first page of each questionnaire, which will be separated from the main document and stored separately. The original paper copies will be identified only by study number and stored in a locked cupboard within the locked Newborn Intensive Care Research office. Questionnaires will be scanned and sorted electronically in a password protected central database. All electronic data will be de-identified and linked only by the original GLOW study number. Access to the data will be limited to the investigators. All data quality checks and statistical analyses are performed using Stata Corp 2015, Stata Statistical Software release 14 College Station, TX, USA.

All data and all study records will be retained for 10 years after the age of majority.

Ethics

A full application has been submitted to the New Zealand Health and Disability Ethics Committee. An application has also been submitted to the Kaumātua Kaunihera Research Ethics Committee at Waikato Hospital.

Consultation

GLOW families

When families provided their consented to participate in the GLOW study, researchers discussed the possibility of a follow up study. All families consented to be contacted by investigators in the future. Some families have contacted the GLOW Facebook page to seek information about the possibility of a follow up study and when that may begin. During this follow up at 3 years of age we will discuss with parents the feasibility and acceptability of the proposed 4.5-year-old assessment.

Māori

Two babies within the GLOW cohort are Māori. Consultation with Māori during the development of this protocol included discussion with key members from Te Puna Oranga at Waikato Hospital, and Leanne Colmer the Social Worker within the Newborn Intensive Care Unit at Waikato Hospital. Every attempt will be made to consult with Māori advisors for the more extensive follow up planned at 4.5 years.

Adverse events
If a member of the research team is made aware of an adverse health event for either the participating child or family member unrelated to the study. The Principal Investigator will be informed and with permission appropriate referrals in order to seek any required care will be made.

Significance
The GLOW study has, for the first time, provided a reliable description of the normal glucose, lactate and ketone profiles in the 5 days after birth in healthy term babies cared for according to contemporary practice. Low blood glucose concentrations were common, but none of these babies were diagnosed with or treated for neonatal hypoglycaemia. There has been considerable research to determine the outcome of children following neonatal hypoglycaemia in order to determine if the treatment of this common condition soon after birth improves neurosensory outcome. As yet, there is no evidence that treating transitional neonatal hypoglycaemia improves the neurological outcome for children or adolescents.[9, 10]

Additionally, there have been no investigations following up a cohort of healthy babies who have detailed perinatal blood metabolite concentrations, or continuous glucose monitoring recorded in the first 5 days. Data produced from GLOWiNg will be novel and provide descriptive follow-up outcomes of children who as healthy babies had blood concentrations of cerebral fuels measured. Further, these findings will provide the opportunity to compare neurosensory outcomes with children who as babies were hypoglycaemic and identified as being at-risk. As such this small group of children may contribute to the understanding of the impact of neonatal hypoglycaemia.

Time line

June 2018	Consultation with GLOW Families
June 2018	Consultation with Māori
Aug 2018	Protocol development
Sept 2018	Finalising the GLOWiNg protocol
Sept 2018	Ethics application
Nov 2018	First child's 3rd birthday
June 2019	Data base development completed
June 2019	Statistical Analysis Plan completed
Nov 2019	Decision about 4.5 year follow up
Aug 2020	Last child's 3rd birthday
Sept 2020	Data entry completion
Mar 2021	Data analysis
Apr 2021	Dissemination of findings

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