15-Year Follow-Up of Recurrent “Hypoglycemia” in Preterm Infants

WHAT'S KNOWN ON THIS SUBJECT: It has been widely thought for the past 20 years that recurrent low blood glucose levels $\leq 2.5$ mmol/L (45 mg/dL), even in the absence of any suggestive clinical signs, can harm a preterm infant’s long-term development.

WHAT THIS STUDY ADDS: This prospective study showed the outcome at 2 and 15 years later for the preterm infants who had a blood glucose level this low in the first 10 days of life did not differ from that of matched controls.

abstract

BACKGROUND: Observational study of 543 infants who weighed $<1850$ g, published in 1988 reported seriously impaired motor and cognitive development at 18 months in those with recurrent, asymptomatic hypoglycemia (plasma glucose level $\leq 2.5$ mmol/L on $\geq 3$ days). No study has yet replicated this observation.

AIM: To quantify disability in a similar cohort of children followed up throughout childhood.

POPULATION: All children born at $<32$ weeks’ gestation in the north of England in 1990–1991 and had laboratory blood glucose levels measured daily for the first 10 days of life.

RESULTS: Forty-seven index children of the 566 who survived to 2 years had a blood glucose level of $\leq 2.5$ mmol/L on $\geq 3$ days. All of these children and hypoglycemia-free controls, matched for hospital of care, gestation, and birth weight, were assessed at age 2. No differences in developmental progress or physical disability were detected. The families were seen again when the children were 15 years old, and 38 of the index children (81%) and matched controls agreed to detailed psychometric assessment. Findings in the 2 groups were nearly identical (mean full-scale IQ: 80.7 vs 81.2). Findings in the 21 children with a level of $\leq 2.5$ mmol/L on $\geq 4$ days, 7 children with a level this low on 5 days, and 11 children with a level of $<2.0$ mmol/L on 3 different days did not alter these conclusions.

CONCLUSIONS: This study found no evidence to support the belief that recurrent low blood glucose levels ($\leq 2.5$ mmol/L) in the first 10 days of life usually pose a hazard to preterm infants. Pediatrics 2012;130:e1497–e1503
An important and very influential article by Lucas et al. published in 1988 opened by commenting that “There has been considerable debate over what should be chosen as a safe lower limit for blood glucose concentration in the neonatal period.” This article provided data on 661 infants who weighed <1850 g at birth, and the authors concluded that “contrary to general belief, moderate hypoglycaemia may have serious neurodevelopmental consequences, and reappraisal of current management is urgently required.”

The authors had used statistical strategies to analyze the data to see if they could find some “threshold” value that reliably predicted an adverse outcome before concluding that glucose concentration of ≤2.5 mmol/L (45 mg/dL) offered the greatest predictive power. They reported that “The number of days on which moderate hypoglycaemia occurred was strongly related to reduced mental and motor development at 18 months corrected age, even after adjustment for a wide range of factors known to influence development.” Similar but less dramatic differences were found when the children were seen again, as part of a larger study when the children were 7 to 8 years old.

These findings have profoundly influenced the neonatal care of the preterm infant across the developed world ever since, but while accepting that symptomatic hypoglycemia can cause lasting damage, many have doubted whether low levels are ever damaging when there are no associated clinical signs. In their systematic review of all the available data in 2006, Boluyt et al. concluded that none of the 18 eligible studies they identified “provided a valid estimate of the effect of neonatal hypoglycaemia on neurodevelopment.”

Mindful of the need to confirm the findings of the study by Lucas et al., clinicians in the north of England initiated an observational study in 1990 designed, among other things, to replicate the earlier study. This article reports the outcome of that study now that it has been possible to assess the outcome for all but 2 of the teenage survivors.

METHODS

Patients
Every infant born before 32 weeks' gestation in 1990 and 1991 to a mother residing in the north of England was recruited into this prospective study of the child’s neonatal care and later development, and most also were recruited into 2 controlled trials “nested” into this study.

Ethics Approval
Approval for the study was obtained from all 16 district research ethics committees in 1989. The strategy for contacting these families and for reassessing the children when they were 15 years old was approved by the Newcastle and North Tyneside Health Authority research ethics committee in 2005.

Documentation of Early Care
Details of the early care given to these infants were collected prospectively, and every infant had a blood sample taken each morning at a fixed time in the first 10 days of life. Information on the blood glucose level (glucose oxidase assay) at this time was collected prospectively, and the results of additional glucose samples taken at other times for any clinical reason also were recorded.

Assessment at 2 Years
By using a combination of menstrual history cross-validated by early obstetric ultrasound assessment, a total of 781 infants were assessed as having been born before 32 weeks in 1990–1991. All 566 who were still alive were then seen for development assessment at 2 years’ corrected age by using the Griffiths scales for Mental Development by a single clinician. Forty-eight of the 566 children who had blood glucose levels of ≤2.5 mmol/L at the standard pre-set time for blood sample collection on ≥3 days during the first 10 days of life were identified as index children. Results from 1 child with severe myotonic dystrophy were excluded from analysis, but the findings from all the other children were individually matched with those found in control children who had never had a documented blood glucose level this low, prespecified or not. These controls were chosen from the same birth cohort and matched, for the hospital of early care, then for gestation at birth, and then for birth weight. No differences in developmental progress or in physical disability were detected but because a child’s cognitive and academic potential cannot be assessed reliably this early, it was agreed with the parents that all children would be assessed again as teenagers.

Assessment at 15 Years
All but 2 of 47 families with index children and the families of 47 control children were traced and seen again once the child was at least 15 years old by a research psychologist (GB) who was unaware whether she was in contact with an index or a control family. Information concerning current health and school progress was collected. Thirty-eight of the index children and an equal number of control children also agreed to have a formal psychometric assessment. All of these children had their full-scale IQ determined by using the Short Weschler-III assessment tool, and nearly all also had their reading and...
RESULTS

Table 1 shows how well matched the psychometrically assessed 38 index and control children had been at birth and during the neonatal period, except in terms of their routinely timed blood glucose measurements. Table 2 summarizes the outcome of their assessment when they were 15 to 16 years old, and Fig 1 shows how very variable the individual IQ values were. The Achenbach scores are reassuring (a normal score is 50±10), whereas the low mean IQ score (85.3) for the 65 fully assessed children without sensorimotor disability (Fig 1) is not unexpected; similar low values have been seen in other long-term cohort studies of infants weighing <1.5 kg at birth.27 The 2 children whose outcome is not known at 15 years of age had been entirely healthy and making normal developmental progress when formally assessed at 2 years.

An identical analysis, limited to the 21 children with a blood glucose level this low at the pre-set time on at least 4 days and the 7 children with a level this low on 5 days, did not alter these conclusions. Neither did an analysis using all the blood glucose samples collected during the first 10 days of life, or an analysis limited to the 11 matched pairs in which the index child had had a level of <2.0 mmol/L on at least 3 different days. In children free from sensorimotor disability, there was no trend for IQ to be lower in children with a low blood glucose level on many different days. Neither is there anything to suggest, from what is known about school performance, that a full psychometric assessment of the remaining 9 index children would have changed these findings.

Factors Making Low Blood Glucose Levels More Likely

Infants recruited into this study received their early care in 13 different units in the north of England, where policies for early fluid management and calorie intake varied widely. Low blood glucose levels were most common on the second to sixth day of life, were rare in infants >9 days old, and were seen least often in units that aimed to give all infants at least 120 mL/kg of 10% dextrose per day intravenously (8.3 mg/kg/min of glucose) once they were 2 days old.

Clinical Signs

Two index children were reported to have had seizures in the first week of life and to have been treated with an anticonvulsant. In neither was the timing of the seizures related to any of the periods when the blood glucose level was low. Neither child ever had a recognizable cerebral ultrasound abnormality, and both had normal IQ scores at follow-up. No other child had any manifestation typically associated with hypoglycemia, such as tremor or stupor, but it has to be accepted that these signs could have been missed in the 20 children who were being ventilated at a time when the blood glucose level was later found to have been low.

Cerebral Palsy and Its Antecedents

Six index and 4 control children had cerebral palsy (Table 2), and all but 2 had an IQ score of <70 (Fig 1). Eight of these 10 children (4 index children and 4 controls) with cerebral palsy had had late (~6 week) cerebral ultrasound scans, all showing major abnormalities. Four children with cerebral palsy also had epilepsy (Table 2).

Self-sufficiency

What is going to matter to these teenagers is not so much whether they have some physical or intellectual disability, but the extent to which it seems likely to impact on their ability to care for themselves, an issue the Vineland Adaptive Behavior Score tries to address (Table 2). Six index and 8 control children had a Vineland score of <60. A combination of cerebral palsy and cognitive problems probably accounted for the low score in 4 index children, and cognitive problems accounted for the low score in the other 2 children.

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**TABLE 1** Characteristics at Birth and Experiences Before Discharge in the 38 Children Who Had a Blood Glucose Level of ≤2.5 mmol/L at a Pre-Set Time on at Least 3 of the First 10 d of Life

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Index Child</th>
<th>Control Child</th>
<th>Mean Paired Difference&lt;sup&gt;b&lt;/sup&gt; (80% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation, d, mean ± SD</td>
<td>207 ± 13</td>
<td>205 ± 15</td>
<td>+2.6 (0.6 to 4.6)</td>
</tr>
<tr>
<td>Birth wt, g, mean ± SD</td>
<td>1330 ± 293</td>
<td>1287 ± 434</td>
<td>+63 (−71 to 196)</td>
</tr>
<tr>
<td>Birth wt below the 10th percentile, n (%)</td>
<td>8 (21)</td>
<td>4 (10.5)</td>
<td>—</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>21 (55)</td>
<td>24 (63)</td>
<td>—</td>
</tr>
<tr>
<td>Twin or triplet pregnancy, n (%)</td>
<td>6 (16)</td>
<td>8 (21)</td>
<td>—</td>
</tr>
<tr>
<td>Offered ventilator support, n (%)</td>
<td>22 (58)</td>
<td>19 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Days’ support if ventilated, mean</td>
<td>24.8</td>
<td>17.5</td>
<td>+7.3 (−1.9 to 16.5)</td>
</tr>
<tr>
<td>Proven sepsis, n (%)</td>
<td>8 (21)</td>
<td>6 (16)</td>
<td>—</td>
</tr>
<tr>
<td>Surgery for retinopathy of prematurity, n (%)</td>
<td>4 (10.5)</td>
<td>2 (5.3)</td>
<td>—</td>
</tr>
<tr>
<td>Surgery for necrotizing enterocolitis, n (%)</td>
<td>1 (2.6%)</td>
<td>2 (5.3%)</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>Table includes children for whom a full psychometric assessment was possible 15 y later and in their matched controls (who never had a documented low level).

<sup>b</sup>Controls who never had a blood glucose level of ≤2.5 mmol/L were matched, first for the unit where the index child received care in the first 2 wk of life, then for gestation, and then for birth wt.

<sup>c</sup>Paired t test was used to compare the 2 groups.

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Cognitive problems seemed to account for the low score in 5 of 8 control children, and 2 of the other 3 children with a low score had had serious behavior problems.

Outcome in Which Levels Were <2.0 mmol/L

Eighteen of the 47 index children were found to have had whole blood glucose levels of <2.0 mmol/L on at least 3 separate days in the first 10 days of life. Full assessment was possible in 14 children, and progress is known to have been within normal limits in the other 4 children. The mean (SD) IQ in the 14 who were fully assessed was 81.6 (20.1), and in the matched controls it was 82.2 (20.7). Excluding the 3 index and 3 control children with sensorimotor disability, the results were 88.9 (14.5) and 87.9 (18.9).

**DISCUSSION**

The study by Lucas et al in 1988 from Cambridge still remains, according to the authors of the systematic review published in 2006, the only high-quality study to document the subsequent developmental progress of preterm infants known to have been “hypoglycemic” in the neonatal period, although another study by Duvanel et al in 1999, in small-for-gestational-age preterm infants, showed similar findings. The only other high-quality study currently available, according to the authors of this review, was a study that focused on the later progress made by 75 full-term, large-for-date infants who had transient hypoglycemia on the first day of life, and this study found that the later progress of index and control children was virtually identical 4 years later. All of which, not surprisingly, led the authors of that review to conclude that “recommendations for clinical practice cannot be based on evidence because of a lack of valid empirical research.” We have known, for 50 years, that a low blood glucose level can cause neonatal seizures, and for 40 years, that it can also cause permanent brain damage. Recent neuroradiologic studies also have started to improve our understanding of how variable this damage may well be, but we still do not know whether low levels unassociated with any clinical signs can be damaging, particularly in the preterm infant who may not display the same immediate behavioral response to neuronal injury as the term infant.

The current study was a close replication of the study from Cambridge. It used gestation rather than birth weight for eligibility but collected a nonselective cohort of infants of similar size. Both studies only made use of laboratory estimates by using a glucose oxidase method; however, the present Northern study only used laboratory samples taken at a pre-set time once a day for its primary analysis, rather than samples taken whenever the clinician judged appropriate. This method avoided the possibility that more samples might be available for analysis in infants who seemed ill and more immature and might be at risk for a suboptimal outcome for other reasons, a potential weakness in the design of the Cambridge study that the authors acknowledged at the time. Blood sample collection continued for as long as seemed clinically justified in the Cambridge study, but routine sample collection stopped after 10 days in the current study.

Ninety-two percent of the surviving infants in the Cambridge study were reassessed when 18 months old, and all the infants in the Northern study were seen when they were 24 months old. Most of the children in the Cambridge study were seen again when they were 7 to 8 years old, by which time their IQ scores did not seem to differ, although the scores for reading and arithmetic using the British Ability Scales did still differ. In the Northern study, some information was available
Most clinicians have not noticed that subsequent studies using the same approach failed to find evidence for any such specific threshold. Despite this, it was not long before clinicians were extrapolating from this single observational study on preterm infants and assuming that the healthy term infant could be equally at risk from similar blood glucose levels even when the child seemed normal on clinical examination, which soon had an adverse impact on the care being given to the mothers of healthy infants trying to initiate lactation. Agree with the late Marvin Cornblath, who believed that the "adaptive fluctuations occurring in the first days after birth... should not be designated as 'hypoglycemia,' with its connotation of disease," and we have not used this word to describe the low levels seen in this study.

It would be unwise to assume that low blood glucose levels cannot be damaging in the preterm infant even in the absence of overt recognizable signs, simply because this study has failed to replicate the earlier study from Cambridge. All that the current study can do is show that the danger threshold must be lower than many had come to think it was. Nevertheless, future studies will need to be large because detectable damage was not seen in the present region-wide study in which most infants were getting at least 6 mL/kg of intravenous 10% dextrose per hour by the time they were 4 days old, and only 2% had a documented level of <2 mmol/L on at least 3 different days in the first 10 days of life. The long-term outcome of the 389 infants in the recent European NURTURE trial designed to investigate whether an early fixed-dose insulin infusion combined with variable glucose support to maintain normoglycemia would reduce mortality will go some way to show just how large such a study would need to be.

The authors of the initial report from Cambridge concluded that frequent low blood glucose levels in the period shortly after birth might be linked to later motor delay (and/or cerebral palsy) and cognitive delay, but the subsequent brief report said nothing about sensorimotor disability. Overt documented structural damage to the brain of a type common after preterm birth seems to provide an adequate explanation as to why at least 4 of the 6 index children in the current study and all 4 of the control children developed severe cerebral palsy. The only reason the same cannot be said for the other 2 index children is simply because no late cerebral ultrasound scan was ever done.

There was an eightfold variation in the incidence of recurrent "hypoglycemia" in the 5 centers that contributed to the Cambridge study, and the authors thought that this finding was probably due to the fact that staff held differing views as to the significance of the levels found. A fivefold difference was also found in the present 13-center study; however, in this study, attitudes toward low values did not differ so widely, and staff often got to know about the existence of a low value only after 6 to 8 hours, by which time the blood glucose level had often risen again already. There is good evidence to suggest that most of the observed intercenter difference can be explained by differences in early fluid management. It is a finding that also points to a strategy that could easily and safely (by increasing the early intake of dextrose and milk) reduce the number of infants with low blood glucose levels in the first few days of life.

One reason the article from Cambridge made such an impact was because it was followed within months by the publication of an article reporting that auditory and somatosensory-evoked brainstem potentials in 5 infants were delayed or blocked when the blood glucose level fell below the very same "threshold" value (≤2.5 mmol/L).
be, because this trial used continuous subcutaneous glucose monitoring and highlighted a serious underestimate of occurrence of blood glucose level of \(\leq 2.5 \text{ mmol/L} \) by current routine monitoring practices, compared with continuous monitoring (5% vs 23%) in infants with birth weights \(<1500 \text{ g} \) during the first week of life.\(^2\)

**CONCLUSIONS**

Lucas et al wrote in their original article that “the association between modest hypoglycaemia and poor neurodevelopment reported here might not be causal and might reflect our failure to adjust adequately for confounding factors.”\(^1\) They also stressed in a later letter “the difficulty of proving causation when an observational approach is used,” saying that “when such observations generate hypotheses or legitimate clinical concerns, this should stimulate future studies.”\(^3\) We have now performed such a study and found no evidence to support that recurrent low blood glucose levels of \(\leq 2.5 \text{ mmol/L} (45 \text{ mg/dL}) \) pose a hazard to preterm infants.

**ACKNOWLEDGMENTS**

It was the neonatal nurses in every maternity unit in the north of England who, with the support of their medical colleagues, made the launch of this prospective, region-wide project possible. We are equally grateful for the encouragement and support of all of our pediatric colleagues for the past 20 years. All authors share responsibility for the reported research and for this report. The psychometric assessment of the 15-year-olds was organized by Dr Kelly and undertaken by Ms Brunskill. Dr Tin is the guarantor. The authors also wish to acknowledge the huge debit they owe to the late Dr Edmund Hey, who made the financing of the follow-up study possible and also helped with the initial drafting of this article.

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