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The investigation and management of neonatal hypoglycaemia

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Summary Assessment of neonatal glycaemic status requires accurate and reliable measurement of blood glucose concentrations. Most point-of-care technologies are, however, unsuitable for use in neonates. Although the definition of hypoglycaemia remains elusive, current knowledge allows adoption of pragmatic threshold blood glucose concentrations when clinical intervention should be considered. The vast majority of instances of neonatal hypoglycaemia are due to problems with the normal processes of metabolic adaptation after birth, and strategies to enhance the normal adaptive processes should help prevent such episodes. Further investigations and specific interventions should be considered when hypoglycaemia is of unusual severity or occurs in an otherwise low-risk infant.

Introduction

It is now nearly 40 years since Cornblath and Reisner established hypoglycaemia as a significant cause of neonatal mortality and morbidity,[1] yet the definition, significance and management of neonatal hypoglycaemia have remained controversial. This paper reviews the definition, screening, prevention and treatment of neonatal hypoglycaemia, and attempts to provide pragmatic recommendations for its overall management.

Definition of neonatal hypoglycaemia

Agreement on the definition of neonatal hypoglycaemia has remained elusive amongst the text books, paediatricians and experts in this field.[2—6] Attempts have been made to identify a threshold blood glucose concentration below

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which there is a substantial likelihood of functional impairment, particularly of the brain. These attempts can be broadly categorized into five main approaches: epidemiological, clinical, metabolic-endocrine, neurophysiological and neurodevelopmental.

Epidemiological approach

This approach is based on defining the range of blood glucose concentrations in a cohort of healthy infants, and then using an empirical cut-off such as that lower than two standard deviations below the mean.[1] However, blood glucose concentrations in the normal population represent a continuum, and any single value is unlikely to represent a threshold of abnormality. Moreover, statistical abnormality does not necessarily imply a biological impairment. The blood glucose values of normal infants are influenced by the pattern of feeding,[7] and at best represent a description of the glycaemic status in relation to a particular feeding regimen.

Clinical approach

In the early years, the blood glucose concentrations at which clinical signs occurred were used to define hypoglycaemia.[8,9] These signs—such as changes in level of alertness and tone, apnoeas, tremors or seizures—are non-specific. In particular, jitteriness occurs just as frequently among normoglycaemic babies as in those with a variety of other neonatal problems.[10] Moreover, equally low blood glucose levels are often found in infants who demonstrate none of the above signs ('asymptomatic hypoglycaemia'), making such an approach of limited value. This is strikingly seen in the first few hours after birth when fuels other than glucose are important in providing neural energy. The presence or absence of such signs cannot therefore be used to discriminate between normal and abnormal blood glucose levels, although clinical signs such as decreased level of consciousness or seizures should always suggest the possibility of cerebral fuel deficiency.

Metabolic-endocrine approach

The concentration of blood glucose at which metabolic counter-regulation occurs can be used to define a 'safe' lower limit of blood glucose concentrations. Hierarchical glycaemic thresholds for counter-regulatory hormonal stress response, autonomic and neuroglycopenic signs, as well as impaired cognitive function have been defined in adults,[11] but very little information exists for the neonatal population. All that is known is the inability of preterm infants to mount a mature counter-regulatory response to low blood glucose concentrations compared to their term counterparts, emphasizing their additional vulnerability during periods of fuel crisis.[12]

Neurophysiological approach

Few studies have attempted to measure neurophysiological changes in relation to blood glucose concentrations. In a study of 17 children, Koh et al. identified abnormalities of brain-stem auditory or somatosensory evoked potentials among some children when their blood glucose concentrations fell below 2.6 mmol/L.[13] Such abnormalities were not seen in any of the children with blood glucose concentrations of 2.6 mmol/L or higher. The authors suggested a blood glucose concentration of 2.6 mmol/L as a pragmatic safe threshold in neonates and children. It should be noted that this study included only five term neonates, and the concentrations of alternative fuels were not consistently measured. Others have failed to demonstrate such effects of hypoglycaemia on evoked responses.[14] Changes in cerebral blood flow have been described in relation to blood glucose concentrations <1.7 mmol/L among preterm infants.[15] However, the significance of such changes to define hypoglycaemia remains unknown.

Neurodevelopmental approach

In a follow-up study of 661 infants weighing less than 1750 g at birth enrolled in a randomized controlled trial of feeding regimens, Lucas et al. reported a strong association between the number of days (exceeding 5) on which blood glucose concentrations of <2.6 mmol/L were found and lower Bayley developmental scores at 18 months of age.[10] However, the monitoring of blood glucose was not standardized; sicker infants possibly had more frequent blood glucose determinations. Furthermore, this association was not sustained at a later assessment at 7.5—8 years of age,[16] which either casts doubt on their importance as markers of neuroglycopenia or indicates that early adversity may often be attenuated by later environmental factors.

Despite these caveats, the results of above studies are frequently misinterpreted as providing