Neurodevelopmental Outcome at Seven Years in Term, Acidotic Newborns

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The objective was to follow up a cohort of acidotic full-term infants with or without hypoxic ischemic encephalopathy (HIE) and determine if at 7 years they displayed any neurodevelopmental delays. Children (n=44) were divided according to those with mild (n=25), or severe (n=19) acidosis and were then further subdivided into those with or without HIE. Participants were assessed using the Wechsler Intelligence Scale for Children (WISC-IVUK) and Achenbach Child Behaviour Checklist (CBCL). No differences in WISC-IVUK scores in children without HIE irrespective of the cord pH value were found. Children with HIE grade I scored significantly higher in perceptual reasoning (p=0.04) and working memory (p=0.01). CBCL scores revealed no differences between groups. Findings suggest evidence of impairment at school age, with the degree of encephalopathy. Acidosis without the presence of clinical encephalopathy was associated with normal outcome.

Introduction
HIE occurs in 1-3/1000 live births and can result in significant neurologic morbidity and mortality in the term infant. There is a spectrum of severity ranging from Sarnat grade I to grade III. Grade I refers to mild HIE, grade II moderate HIE and grade III severe HIE. Research has traditionally focused on developmental outcomes at relatively young ages. There is also limited and variable information on neurodevelopmental outcomes in mild grade I HIE groups, moderate grade II HIE display increased hyperactivity and lower scores, whereas the severest grade III HIE group show profound cognitive attainment. There remains continued uncertainty about the relationship between acidosis at birth, the development of HIE following perinatal asphyxia and long-term outcomes. Studies suggest normal cognitive and behavioural development in mild grade I HIE groups, as well as reduced scores in IQ, but the impact of HIE on neurodevelopment in those with a pH value of <7.0 is not well understood. It is hypothesised that the more significant the level of acidosis at birth, the greater the implication for negative cognitive impact on development. It is also hypothesised that all children with HIE will have less positive cognitive outcomes, and that within the HIE group those with severe acidosis will do worse than with those mild acidosis.

Methods
A cohort of term infants (n=64; 37 weeks gestation) were recruited who met one of the following criteria: emergency section, instrumental delivery, presence of meconium stained liquor or low pH (<7.25) from fetal blood sampling taken during labour. Of these, 41 had arterial cord blood samples taken after birth, the remainder was excluded based on a pH value of <7.0. Infants with a cord pH value = 7.0 and all infants who had clinical signs of encephalopathy irrespective of cord pH values were recruited. All infants were examined clinically and were deemed to be either normal or have varying degrees of encephalopathy. The degree of encephalopathy was classified during the first week of life as mild, moderate or severe (stages I, II or III according to Sarnat and Sarnat (1976)). The remaining infants were then subdivided based on cord pH. Exposure to severe acidosis was quantified as a cord pH value = 7.0. The non-exposed were those infants with an arterial cord pH value of 7.0 - 7.25 (n=606). For each infant with a pH value = 7.0 and who had no signs of encephalopathy, the next three consecutive infants who met the study criteria, were clinically normal and had a pH value of 7.0-7.25 were taken as controls (n=32). As spontaneous vaginal delivery and elective Caesarean section were considered low risk deliveries, those infants were excluded. During the study period there were 5,800 term deliveries in the Dublin region with a cord pH value = 7.25. Of these 611 infants, 25 were severely acidotic with a cord pH value = 7.0 and 606 were mildly acidotic with a cord pH value at birth of 7.01 - 7.25. We prospectively recruited all infants with a cord pH value = 7.0 who met the study criteria and all infants who had clinical signs of encephalopathy irrespective of cord pH values. From this population, it was found that 61 children were eligible for follow-up. Of these, 44 completed the training and ensured the standard of assessments. The assessor was blinded to cord pH values. After all assessments were complete, children were divided according to those with HIE (n=13) and without HIE (n=31). These were then further subdivided after assessment into those with HIE with severe acidosis (n=8), or with mild acidosis (n=5), and those without HIE, with either severe (n=11) or mild (n=20) acidosis. In addition, HIE children irrespective of cord pH were compared based on Sarnat grading: HIE I (n=5), HIE II (n=5) and HIE III (n=3). All children were assessed in the hospital. Cognitive ability was measured using the Wechsler Intelligence Scale for Children-4th Edition (WISC-IV). This clinical instrument provides scores that represent intellectual functioning across a number of indices, including the verbal comprehension (VCI), working memory (WMI), perceptual reasoning (PRI) and processing speed (PSI) and the full scale IQ (FSIQ) with each index having a mean composite score of 100 and a standard deviation of 15.

Behavioural development was measured using the Achenbach Child Behaviour Checklist 618 years (CBCL) which was completed by the parent on the day of the assessment. All scores were categorised into competence, internalising and externalising behaviours and the T-scores for each of these areas were computed. Statistical analysis of the data was carried out using SPSS (v17). Due to a violation of the assumption of normality in the study sample, non-parametric tests including Mann-Whitney U tests and Kruskal Wallis were used. Statistical significance was reached when p < 0.05. Ethical approval was obtained from the Children's University Hospital, Temple Street ethics committee and full consent obtained from all parents.

Results
Demographic Information
Demographic details of the participants were obtained. Few differences were noted between the groups (Table 2).

WISC-IV Composite Scores
Mann-Whitney U tests were used to analyze composite score data on each of the five WISC-IVUK indices. Mean scores of the severe acidotic group with HIE revealed an overall pattern of lower scores across all five WISC-IVUK indexes when compared to severely acidotic children without HIE. However, this was not statistically significant (p values>0.05; Table 3). Examination of the mean scores of the severe acidotic group with HIE revealed an overall pattern of lower scores across all five WISC-IVUK indexes when compared to severely acidotic children without HIE. However, this was not statistically significant (p values>0.05; Table 3).

Comparison between children with or without HIE
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The effect of HIE alone, irrespective of cord pH, revealed no statistical significance in any of the WISC-IV composite scores (p>0.05; see Table 3).

HIE Sarnat Score Comparisons

WISC-IV composite scores were assessed within the HIE group; this revealed a pattern of lower scores only for the HIE III group on all indices. Significant differences between the groups were only revealed in the perceptual reasoning index, with HIE grade III children (Mean: 76.33 SD: 15.7) scoring significantly lower than those with HIE grade I (Mean: 112.75 SD: 5.5, p<0.01).

Achenbach Child Behaviour Checklist Scores

Behavioural problems were assessed using the CBCL. Mann-Whitney U tests comparing T-scores on the competence, internalising and externalising scales revealed no significant differences between the children with or without clinical HIE. Differences for mild or moderate acidosis on any of the scales was also there were no differences noted in the severely acidic children with or without HIE (p values>0.05; Table 4).

Comparison between children with or without HIE

CBCL behavioural comparisons were made between children based on the presence or absence of HIE. Significant differences between the groups on the internalising T-score only were found (p=0.014), however neither groups score reached clinical significance.

HIE Sarnat Score Comparisons

CBCL scores were further assessed to determine if the grade of encephalopathy lead to any long term behavioural problems. For this, each of the HIE Sarnat groups (I-III) T-scores were assessed. Results revealed no differences between groups in any score.

Discussion

Acidotic infants, irrespective of the severity of acidosis, without any clinical signs of encephalopathy did not display any significant delays when compared to normal controls at 5 years. Acidotic infants with encephalopathy at birth were also assessed for follow-up. In this group, infants with severe acidosis had consistently lower scores on all WISC-IV indexes in comparison to the mild acidotic group; however, these differences did not reach statistical significance. This could be due to the low numbers observed in each group, as a similar significant pattern of lower scores were reported by Toh23, who had a study population of 35. Specifically, Toh found, through retrospective assessment, that infants with HIE who were also acidotic in birth were more likely to have disability at 18 months. Takenouchi24 also found that the parallel occurrence of HIE and acidosis led to later abnormal developmental outcomes during infancy, suggesting that acidosis acts as a critical factor to consider when looking at the long-term outcome of infants, particularly when it is coupled with the presence of HIE.

Interestingly, descriptive statistics initially indicate higher mean scores on the WISC-IV for children with HIE who had mild acidosis in comparison to mildly acidic children without HIE. Further analyses, however, indicate no significant differences between these groups (data not shown). Further comparisons made between children with or without HIE did not reveal differences on cognitive or behavioural scores. Further subgroup analysis of encephalopathic children revealed cognitive impairments in the most severe HIE group in the area of perceptual reasoning. This finding may signify a spectrum of cognitive impairment at school-age which correlates with the degree of encephalopathy at birth. More to acidotic infants were more likely to have disability at 18 months. Overall, our findings have, however, provided evidence of a similar spectrum of difficulty with normal cognitive development evident in mild and moderately encephalopathic groups at school age 8-9, whereas those severely affected displaying most significant impairment.

Overall the encephalopathic group also displayed a relative area of weakness in working memory scores when compared to verbal reasoning outcomes. Marlow et al similarly noted a lower score in the area of memory in children with HIE. This discrepancy may also be due to attentional deficits; an area often compromised in neurologically damaged patients. While behavioural assessment with the CBCL did not reveal attentional disorders within this group, it has been previously reported that HIE display attention and hyperactivity difficulties. Overall, our findings suggest evidence of cognitive impairment at school-age that correlates with the degree of encephalopathy. Acidosis without the presence of clinical encephalopathy was associated with normal outcome.

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References


