

Neurodevelopmental Outcome at Seven Years in Term, Acidotic Newborns

Abstract:

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Abstract

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 values were found. Children with HIE grade I scored significantly higher in perceptual reasoning than those with grade III (p<0.01). CBCL scores revealed no differences between groups. Findings suggest evidence of impairment at school-age that correlates 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^{1,3}. 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 consequences at relatively young ages⁴. Studies suggest normal cognitive and behavioural development in mild grade I HIE groups⁸, moderate grade II HIE display increased hyperactivity and lower scores¹², whereas the severest grade III HIE group show poorest cognitive attainment¹³. There remains continued uncertainty about the relationship between acidosis at birth, the development of HIE following perinatal asphyxia and long-term outcomes¹⁴. One study found that once the umbilical cord pH is <7.2, it can lead to neurodevelopmental dysfunction at 1-2 years¹⁵ that can continue to school age, with deficits particularly seen in verbal functioning¹⁶. Contrary findings, however, found that lower cord pH (<7.0) did not result in any significant deficits in cognitive or behavioural functioning when compared with similar aged controls¹⁸. Given these inconsistencies, this study aimed to examine the effect of both acidosis and HIE on cognitive and behavioural outcomes. 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 those with 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. All infants who met the inclusion criteria had arterial cord pH values taken after delivery. 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 value. Exposure to severe acidosis was quantified as a cord pH value = 7.0 (n=25). 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, of which 631 were acidotic (arterial cord pH value = 7.25). Of these 631 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 as the cord pH dropped below 7.0 the rate of encephalopathy increased 16 fold (see Table 1). 61 children were eligible for follow-up; 22 with HIE and 42 controls. 44 completed follow up giving us a total follow up rate of 72%. There were 22 children with HIE, of which 3 had died and 3 were not contactable leaving an available 16. Of this, 3 declined consent, giving a follow-up rate of 13/16 (81%) in the available HIE group. There were 42 in the control group; 7 were not contactable and 4 refused, giving a follow-up rate of 31/35 (89%) in the available control group.

Follow-up cognitive and behavioural assessment was carried out on this group of infants at age 7 years 6 months (n = 44) by one psychologist (MD). Two highly experienced psychologists (CM and HR) supervised 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 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 6& 18 years (CBCL)¹⁹ 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 all children were obtained. Few differences were noted between the groups (Table 2).

WISC-IV Composite Scores

Mann-Whitney U tests were used to analyse composite score data on each of the five WISC-IV indices. Mean scores of the severe acidotic group (+/- HIE) were lower than the mildly acidotic group (+/- 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-IV 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

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 indexes. 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, with either severe or mild acidosis on any of the scales. There was also no differences noted in the severely acidotic 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 long-term cognitive or behavioural impairment at age 7.5 years, with both the mild and severe acidotic groups scoring within the average range on all indices. A similar finding has been reported by Wildschut et al²⁰, i.e. no correlation between cognitive outcomes and cord pH when assessing children at 4 years. Others also suggest that low cord pH does not lead to long-term neurological problems and that only very low pH scores have later undesirable effects^{21,22}. Yudkin et al¹⁰, also report that acidotic infants without encephalopathy had no significant cognitive 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, Toh²³ found, through retrospective assessment²⁴, that infants with HIE who were also acidotic at 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 is 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 acidotic 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 indicated no 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. Due to low numbers in these subgroups, however, it is difficult to accurately interpret the findings. Earlier research has, 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 impairment²⁵.

Overall the encephalopathic group also displayed a relative area of weakness in working memory scores when compared to verbal reasoning outcomes. Marlow et al¹ 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 children with HIE display attention and hyperactivity difficulties¹. 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

1. Shevell MI, Bodensteiner JB. Cerebral palsy: defining the problem. *Semin Pediatr Neurol*. 2004; 11:2-4.
2. Finer NN, Robertson CM, Richards RT, Pinnell, LE, Peters, KL. Hypoxic-ischemic encephalopathy in term neonates: perinatal factors and outcome. *J Pediatr*. 1981; 98:112-117
3. Smith J, Wells L, Dodd K. The continuing fall in incidence of hypoxic-ischaemic encephalopathy in term infants. *Br J Obstet Gynaecol*. 2000; 107:461-466.
4. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol*. 1976; 33:696-705.
5. Perlman JM. Brain injury in the term infant. *Semin Perinatol*. 2004; 28:415-424.
6. Carli G, Reiger I, Evans N. One-year neurodevelopmental outcome after moderate newborn hypoxic ischaemic encephalopathy. *J Paediatr Child Health*. 2004; 40:217-220.
7. Van Handel M, Swaab H, de Vries LS, Jongmans MJ. Long-term cognitive and behavioural consequences of neonatal encephalopathy following perinatal asphyxia: a review. *Eur J Pediatr*. 2007; 166:645-654
8. Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Pediatr*. 1989; 114:753-760.
9. Marlow N, Rose AS, Rands CE, Draper ES. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 2005; 90:F380-F387.
10. Yudkin P, Johnson A, Clover L, Murphy K. Clustering of perinatal markers of birth asphyxia and outcome at age five years. *Br J Obstet Gynaecol*. 1994; 101:774-781.
11. Moster D, Lie RT, Markestad T. Joint association of Apgar scores and early neonatal symptoms with minor disabilities at school age. *Arch Dis Child Fetal Neonatal Ed*. 2002; 86:F16-21.

12. Zappitelli M, Pinto T, Grizenko N. Pre-, peri-, and postnatal trauma in subjects with attention-deficit hyperactivity disorder. *Can J Psychiatry*. 2001; 46:542â548.
13. Pin TW, Eldridge B, Galea MP. A review of developmental outcomes of term infants with post-asphyxia neonatal encephalopathy. *Eur J Paediatr Neurol*. 2009; 13:224â234.
14. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. *Br Med J*. 2010; 340:c1471.
15. Gjerris AC, Staer-Jensen J, J[^]rgensen JS, Bergholt T, Nickelsen C. Umbilical cord blood lactate: a valuable tool in the assessment of fetal metabolic acidosis. *Eur J Obstet Gynecol Reprod Biol*. 2008; 139:16-20.
16. Gaudier FL, Goldenberg RL, Nelson KG, Peralta-Carcelen M, Johnsini SE, DuBard MB, Roth TY, Hauth JC. Acid-base status at birth and subsequent neurosensory impairment in surviving 500 to 1000 gm infants. *Am J Obstet Gynecol*. 1994;170:48-53.
17. Ingemarsson I, Herbst A, Thorngren-Jerneck K. Long term outcome after umbilical artery acidaemia at term birth: influence of gender and duration of fetal heart rate abnormalities. *Br J Obstet Gynaecol*. 1997; 104:1123-1127.
18. Svirko E, Mellanby J, Impey L. The association between cord pH at birth and intellectual function in childhood. *Early Hum Dev*. 2008; 84:37-41.
19. Achenbach TM, Rescorla, LA. Manual for the ASEBA School-Age Forms and Profiles. Burlington, VT: University of Vermont 2001.
20. Wildschut J, Feron F, Hendriksen J, van Halla M, Gavilanes-Jiminez DWD , Hadders-Algrae M, Vlesa JSH. Acid-base status at birth, spontaneous motor behaviour at term and 3 months and neurodevelopmental outcome at age 4 years in full-term infants. *Early Hum Dev*. 2005; 81:535-544.
21. Dennis J, Johnson A, Mutch L, Yudkin P, Johnson P. Acid-base status at birth and neurodevelopmental outcome at four and one-half years. *Am J Obstet Gynecol*. 1989; 161:213-220.
22. Ingemarsson I, Herbst A, Thorngren-Jerneck K. Long term outcome after umbilical artery acidaemia at term birth: influence of gender and duration of fetal heart rate abnormalities. *Br J Obstet Gynaecol*. 1997; 104:1123-1127.
23. Toh VC. Early predictors of adverse outcome in term infants with post-asphyxial hypoxic ischaemic encephalopathy. *Acta Paediatr*. 2000; 89:343â347.
24. Takenouchi T, Cuaycong M, Ross G, Engel M, Perlman JM. Chain of brain preservationâ A concept to facilitate early identification and initiation of hypothermia to infants at high risk for brain injury. *Resuscitation*. 2010; 81:1637-1641.
25. Cowan F. Outcome after intrapartum asphyxia in term infants. *Semin Neonatol*. 2000; 5:127-140.