Survivors with bad outcome after hypoxic-ischaemic encephalopathy: full-term neonates compare unfavourably with children

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Summary

Hypoxic-ischaemic encephalopathy (HIE) is of major importance in neonatal and paediatric intensive care with regard to mortality and long-term morbidity. Our aim was to analyse our data in full-term neonates and children with special regard to withdrawal of life support and bad outcome.

Patients: All patients with HIE admitted to our unit from 1992–96 were analysed. Criteria for HIE were presence of a hypoxic insult followed by coma or altered consciousness with or without convulsions. Severity of HIE was assessed in neonates using Sarnat stages, and in children the duration of coma. In the majority of cases staging was completed with electrophysiological studies. Outcome was described using the Glasgow Outcome Scale. Bad outcome was defined as death, permanent vegetative state or severe disability, good outcome as moderate disability or good recovery.

Results: In the neonatal group (n = 38) outcome was significantly associated with Sarnat stages, presence of convulsions, severely abnormal EEG, cardiovascular failure, and multiple organ dysfunction (MOD). A bad outcome was observed in 27 cases with 14 deaths and 13 survivors. Supportive treatment was withdrawn in 14 cases with 9 subsequent deaths. In the older age group (n = 45) outcome was related to persistent coma of 24–48 h, severely abnormal EEG, cardiovascular failure, liver dysfunction and MOD. A bad outcome was found in 36 cases with 33 deaths and 3 survivors. Supportive treatment was withdrawn in 15 instances, all followed by death.

Conclusions: Overall, neonates and older patients did not differ with regard to good or bad outcome. However, in the neonatal group there were significantly more survivors with bad outcome, either overall or after withdrawal of support. Possible explanations for this difference include variability of hypoxic insult, maturational and metabolic differences, and the more compliant neonatal skull, which prevents brainstem herniation.

Keywords: hypoxic-ischaemic encephalopathy; full-term neonate; child; outcome; ethics; withdrawal of life support

Introduction

Hypoxic-ischaemic encephalopathy (HIE) is due to cerebral hypoxia of various cause and duration. Hypoxia may be limited to the brain (acute hydrocephalus with brain herniation and cerebral ischaemia etc.) or it may be global (cardiorespiratory arrest etc.). Pathophysiological global hypoxia is classified as hypoxaemic, stagnant, anaemic and cytotoxic. Criteria for the diagnosis of HIE are the presence of an acute event causing cerebral hypoxia followed by protean neurological signs of altered consciousness with or without convulsions. The outcome of HIE depends on the severity of hypoxia, but is usually grim. HIE is one of the leading causes of death and permanent disability in paediatric intensive care units, and poses major problems in ethical decision making [1–7]. It was our impression that in our unit we had more survivors with bad outcome after HIE in neonates than in children. The aim of the present study was therefore (1) to document the incidence and causes of HIE in full-term neonates and children, and (2) to report on outcome in these patients, with special regard to withdrawal of life support and bad outcome.

List of abbreviations:
CPR = cardiopulmonary resuscitation
CS = caesarean section
GCS = Glasgow coma scale
GOS = Glasgow outcome scale
HIE = hypoxic-ischaemic encephalopathy
MOD = multiple organ dysfunction
PICU = paediatric intensive care unit
Patients and methods

All patients with diagnosis of HIE (computerised database) admitted to our unit between 1.1.92 and 31.12.96 were reviewed. During this five year period, there were a total of 3363 admissions, comprising 1048 neonates (postnatal age less than 28 days) and 2315 infants and children. All neonates were outborn and had been transported to our hospital by a specialised team. 770 neonates had a birth weight \( \geq 2000 \) g. A total of 223 deaths was observed, 117 in neonates, and 106 in infants and children. 87 neonates with a fatal outcome had a birth weight \( \geq 2000 \) g.

Inclusion/exclusion criteria for neonates

Only full-term neonates \((\geq 38 \text{ weeks of gestational age}; \leq 28 \text{ days after birth})\) within 24 h after birth or hypoxic event, and classified as suffering from HIE were included. Patients suffering from septic shock (1), cardiac malformations (2), chromosomal anomalies (1), inborn errors of metabolism (1) and dysmorphic syndromes (1) were excluded [8].

Inclusion/exclusion criteria for children

This age group comprised patients from infancy \((>28 \text{ days postnatal age or } >44 \text{ weeks postconceptional age})\) to 16 years. Children with a diagnosis of traumatic brain injury, meningitis/encephalitis, acute hydrocephalus, or space occupying cerebral haemorrhage were excluded, although these underlying conditions may be complicated by hypoxic or ischaemic cerebral insults [9].

Diagnostic criteria of HIE

The main clinical findings required for the diagnosis of HIE were altered consciousness, with or without convulsions, following a hypoxic event documented in the history. Other causes of altered consciousness/convulsions had to have been excluded by appropriate clinical investigations (metabolic, traumatic, infectious, epilepsy etc.). In the neonatal group the hypoxic event was classified as pre-, intra- or postpartal. The occurrence of a hypoxic event was documented by abnormal cardiotocography, meconium amniotic fluid, low Apgar scores or umbilical cord pH or loss of fetal movements (2). Eight babies were thought to have suffered intrapartum hypoxia.

Management in PICU

The main emphasis was placed on securing adequate gas exchange (all patients with the exception of one neonate and one child were on mechanical ventilation), on adequate cardiac output and mean arterial pressure to assure sufficient cerebral perfusion, as well as anticonvulsive treatment and excellent basic intensive care. The neurological course was evaluated by observing recovery of consciousness or wakefulness, brainstem functions and reflexes. If necessary, we performed electrophysiological studies (EEG, somatosensory evoked potentials) and/or brain imaging techniques (ultrasound, computerized tomography or magnetic resonance imaging) [12]. Other organ/system dysfunctions (cardiovascular, respiratory, hepatic, gastrointestinal, renal and haematological) were classified according to slightly modified criteria of Wilkinson [13].

Criteria for withdrawal of supportive treatment

In those cases in which a bad outcome was highly likely, parents were advised to consent to withdrawal of life support. The presence of brain death, i.e. complete failure of brainstem functions was not considered to be a withdrawal situation, as the patient was pronounced dead.

Tools for predicting bad outcome included repeated neurological examination (persisting Sarnat stage 3 or duration of coma \( >24–48 \) h), persistence of abnormal brainstem reflexes \( >24–48 \) h, severely abnormal EEG (low-amplitude activity, alpha-coma, areactive delta- or theta-coma, burst-suppression activity, isoelectricity or uninterrupted seizure activity resistant to therapy) and in some cases severely abnormal somatosensory evoked potentials (bilateral absent N20 components) [12]. In case of withdrawal of life support liberal use of morphine was allowed for comfort care.

Classification of outcome

Outcome was classified using the Glasgow Outcome Scale (GOS) (GOS 1 = dead, GOS 2 = persistent vegetative state, GOS 3 = severely disabled, functionally independent, GOS 4 = moderately disabled, functionally independent, and GOS 5 = good recovery) [14]. GOS 1–GOS 3 were considered a bad outcome and GOS 4 and GOS 5 a good outcome. In surviving neonates outcome was assessed at between 15 and 18 months of age for psychomotor development, signs of cerebral palsy, hearing, vision, and epileptic seizures. Surviving infants were assessed at the same age, and children, 6 to 12 months after the hypoxic event. Statistical analysis was done using Fisher’s exact probability test, Chi-square test, Wilcoxon signed rank test or Mann-Whitney U test. P-values <0.05 were considered to be significant.

Results

During the period under review we identified 39 neonates and 46 infants and children who fulfilled inclusion criteria. One neonate and one child were lost to follow-up, resulting in final numbers of 38 and 45 respectively.

Neonates

The main clinical data are presented in table 1. In nine patients prepartal hypoxia was diagnosed by abnormal cardiotocography (7) or by decrease or loss of fetal movements (2). Eight babies were delivered by caesarean section (CS), and one was born by spontaneous vaginal delivery. 20 neonates were thought to have suffered intrapartum hypoxia.
caused by non-progressing delivery (11), umbilical cord problems (4), abruptio placentae (2), uterine rupture, maternal hypotension and unclear deterioration during delivery in one case each. Eight babies were delivered by emergency CS and six by operative vaginal delivery. In six cases the cause of HIE was not clearly attributable to pre- or intrapartal events (cigarette smoking, diabetes mellitus, maternal hypertension combined with breach presentation, shoulder dystocia, makrosomia etc.). Five babies were born by spontaneous vaginal delivery, one by elective CS. Three neonates suffered postpartal hypoxia, having developed unexpected apnoea and cardiac arrest 12 h, 24 h and 20 d after birth. Two were born by uneventful vaginal delivery, one by elective CS. The mother of this last baby had been treated with beta-blockers for hypertension during pregnancy. Overall, cardiac arrest or apnoea was thought to be present after birth or a hypoxic event in 17 and 25 instances respectively.

Statistical analyses revealed no significant association between the presence of apnoea or cardiac arrest, 5 min Apgar score (peripartal hypoxia group), first reliable pH, lactate or glucose value, and outcome. However, a highly significant relationship was found between Sarnat stages and outcome (p <0.001). The presence of dilated and areactive pupils (12 patients, all with bad outcome; p <0.01), presence of convulsions (28 patients, 23 with bad outcome; p <0.05) and a severely abnormal EEG (27 patients, 25 with bad outcome; p <0.001) correlated with bad outcome. Analysis of other organ/system dysfunctions revealed a correlation between cardiovascular failure and bad outcome (30 patients, 24 with bad outcome; p <0.05) and dysfunction of ≥3 organs/system (excluding CNS) (28 patients, 23 with bad outcome; p <0.05).

In 14 cases withdrawal or limitation of supportive treatment was implemented 0.9 to 8.2 d after birth or hypoxic event (median 2.9 d). All these patients showed persistent signs of severe en-

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<tr>
<th>Table 1</th>
<th>Full-term neonates with hypoxic-ischaemic encephalopathy (n = 38).</th>
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<tbody>
<tr>
<td>Gender (f : m ratio)</td>
<td>prepartal hypoxia (n = 9)</td>
</tr>
<tr>
<td>6:3</td>
<td>12:8</td>
</tr>
<tr>
<td>Median birth weight (g) (range)</td>
<td>3200 (2220–3850)</td>
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<tr>
<td>Median 5' Apgar score (range)</td>
<td>3.5 (0–7)</td>
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<tr>
<td>Sarnat stage</td>
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GOS = Glasgow Outcome Scale

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<th>Table 2</th>
<th>Infants and children with hypoxic-ischaemic encephalopathy (n = 45).</th>
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<tr>
<td>Underlying disease</td>
<td>hypoxaemic hypoxia (n = 22)</td>
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<tr>
<td>near drowning, 14 infectious upper airway obstruction, 5 strangulation, 2 bolus aspiration, 1 myocarditis, 1</td>
<td>2.75 (0.8–14)</td>
</tr>
<tr>
<td>complex cardiac surgery, 7 gastroenteritis, 4 burns, 1 intraoperative haemorrhage, 1 transfusion, 1</td>
<td>10 (0.2–15.5)</td>
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<tr>
<td>sudden infant death syndrome, 5 anaesthetic mishaps, 2 diabetic ketoacidosis with cardio-respiratory arrest, 1</td>
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<td>GOS</td>
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GOS = Glasgow Outcome Scale
cephalopathy (Sarnat stage 3). After withdrawal, nine patients died and five survived in a persistent vegetative state. In the complete sample of 38 newborns 14 died, 9 due to respiratory failure after extubation, 3 due to irreversible shock despite ongoing therapy and 2 suffered brain death. Time of death was 0.3 to 8.3 d after birth / hypoxic event (median 1.8 d). Autopsies were performed in 11 cases and confirmed the clinical diagnosis of severe HIE, in one case (unsuccessful operative vaginal delivery) an unexpected rupture of cranial sutures was also found.

**Infants and children**

Main clinical data are presented in table 2. 22 children were classified as having suffered hypoxic-aemic hypoxia. Near-drowning was the main cause, followed by infectious upper airway obstruction (single cases in association with spinal muscular atrophy, trisomy 21, atrial septal defect, pulmonary hypertension, Franceschetti syndrome, and epiglottitis), strangulation, and bolus aspiration. In 15 children stagnant hypoxia was thought to play a decisive role with complex cardiac surgery on cardio-pulmonary bypass together with postoperative low-output syndrome as the main cause (Fallot tetralogy, 1; complex transposition of great arteries, 1; hypoplastic right heart, 2; aortic valve replacement, 1; atrial septal defect with pulmonary hypertension, 1; complex single ventricle, 1), gastroenteritis with severe dehydration and shock. In the group with failure of the respiratory neuromuscular apparatus, sudden infant death syndrome was diagnosed in five cases, followed by critical incidents during and after anaesthesia, and diabetic keto-acidosis. Overall cardiac arrest was thought to be present in 30 and apnoea in 4 cases, respectively.

24–48 h after the critical incident, 8 patients had regained consciousness (6 with good outcome, 2 with bad outcome) and 37 remained in coma (4 with good outcome, 33 with bad outcome; p < 0.05). The two patients with fatal outcome who had regained consciousness died of irreversible dysrhythmia and multiple organ/system failure, whereas all four with prolonged coma and good outcome had undergone anaesthesia and major operations. Furthermore the presence of a severely abnormal EEG (28 patients, 26 with bad outcome; p < 0.001), cardiovascular failure (36 patients, 31 with bad outcome; p < 0.05), liver dysfunction (31 patients, 28 with bad outcome; p < 0.05), or dysfunction of ≥ 3 organs/systems (excluding CNS) (37 patients, 33 with bad outcome; p < 0.05) was associated with bad outcome.

In 15 cases supportive treatment was withdrawn 0.3 to 11.5 d after the critical event (median 2 d), all these patients died. In summary, 33 of 45 patients died, 15 after withdrawal of support, in 12 patients brain death was diagnosed, and 6 died due to refractory cardiovascular failure. Time of death was 0.3 to 12.4 d after the hypoxic event (median 1.2 d). Autopsies were performed in 18 cases and were in agreement with severe HIE. In a five month old baby with sudden infant death syndrome a small capillary haemangioma was detected between the brainstem and cerebellum, in addition to severe brain swelling with brainstem herniation. 13 patients survived, 10 with good outcome, 2 severely disabled, and 1 in a permanent vegetative state. All 3 patients with bad outcome started to breathe adequately within hours after initial stabilisation.

**Comparison of the two groups**

Overall there was no difference in respect to good (neonates, 11; children, 9) and bad outcome (neonates, 27; children, 36). However, there were significantly more survivors with bad outcome (i.e. GOS 2 and 3), either overall (table 3) or after withdrawal of support (table 4) in the neonatal group. Both groups are comparable in incidence of MOD (neonates, 28; children, 37; n.s.), but the incidence of brain death was significantly higher in children (neonates, 2; children, 12; p = 0.008).

**Discussion**

To our knowledge this is the first outcome report to compare full-term neonates and children with HIE managed in the same unit over the same period of time. The two groups do not differ with regard to outcome: 27 (71%) neonates and 36 (80%) children showed a bad outcome, defined as death, survival in permanent vegetative state or survival with severe disability. However, more importantly and in contrast to the criterion of good and bad outcome, there were significantly more survivors with bad outcome (i.e. GOS 2 and 3) in the neonatal group, or vice versa significantly more deaths (GOS 1) in the older age group. Overall, 14 neonates and 33 children died in our series, ac-
Secondly, neonates might suffer not only one major hypoxic insult, but also repeated episodes of hypoxia. As we have shown in table 1, in at least 15 neonates, hypoxia was thought to be prepartal, i.e. probably prolonged and repetitive, or unclear. This situation is equivalent to that in the group of seven infants and children following complex cardiac surgery on cardiopulmonary bypass with post-operative low-output syndrome, where the exact time of hypoxia is also difficult to determine. Thirdly, the tolerance of the neonatal brain to hypoxia might differ from older subjects due to maturation, metabolic differences [23]. And fourthly, owing to the open fontanel and sutures, the neonatal brain is not contained in a box of similar rigidity as in older subjects. In case of severe brain swelling the compliant neonatal skull helps to avoid brain stem compression, which is eventually manifested by brain death. The higher incidence of brain death in infants and children compared to neonates who died supports this hypothesis.

A major issue emerging from this present study concerns ethical decisions, i.e. the withdrawal of life support and terminal care in hopeless situations. The guidelines of the Swiss Academy of Medical Sciences allow withdrawal of supportive treatment, if the expected outcome is poor, and if the parents or guardians of the child agree with the medical decision [24]. In this case, terminal care with liberal use of drugs (usually morphine) to minimize suffering has priority, even if the life span might be shortened. In the present series, life support was withdrawn in 29 (35%) instances. In comparison, Vernon et al. reported life support withdrawal as mode of death in 45 (37%) of 121 cases with central nervous system failure [15]. Ethical decisions are always a question of judgement and thus remain in some aspects subjective. In retrospect, our decisions seem to have been correct in the sense that all patients in whom treatment was withdrawn, either died (i.e. all infants and children and nine neonates) or survived in permanent vegetative state (five neonates). On the other hand, one might argue that hypoxia after withdrawal of life support had aggravated HIE and was the main cause of bad outcome. We do not think that this was the case. However, the results of terminal care in the neonatal group are disturbing. Five patients continued to breathe sufficiently and if the parents or guardians of the child agree with the medical decision [24]. In this case, terminal care with liberal use of drugs (usually morphine) to minimize suffering has priority, even if the life span might be shortened. In the present series, life support was withdrawn in 29 (35%) instances. In comparison, Vernon et al. reported life support withdrawal as mode of death in 45 (37%) of 121 cases with central nervous system failure [15]. Ethical decisions are always a question of judgement and thus remain in some aspects subjective. In retrospect, our decisions seem to have been correct in the sense that all patients in whom treatment was withdrawn, either died (i.e. all infants and children and nine neonates) or survived in permanent vegetative state (five neonates). On the other hand, one might argue that hypoxia after withdrawal of life support had aggravated HIE and was the main cause of bad outcome. We do not think that this was the case. However, the results of terminal care in the neonatal group are disturbing. Five patients continued to breathe sufficiently after extubation and survived in a permanent vegetative state, thus causing a heavy burden to their family and to society. For this reason we believe that the issue of terminal care and the use of potentially life shortening drugs [25, 26], requires further discussion in order to avoid such disastrous outcomes.

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