ORIGINAL ARTICLE

Multiorgan dysfunction in infants with post-asphyxial hypoxic-ischaemic encephalopathy

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Background: Multiorgan dysfunction (MOD) is one of four consensus based criteria for the diagnosis of intrapartum asphyxia. The theoretical concept behind MOD is the diving reflex (conservation of blood flow to vital organs at the cost of non-vital organs).
Objectives: To assess the patterns of involvement of each major organ/system and combinations of involvement in infants with post-asphyxial hypoxic-ischaemic encephalopathy (HIE), and to describe this in relation to long term outcome.
Design: Retrospective cohort study.
Setting: Regional tertiary neonatal intensive care unit at the Hospital for Sick Children, Toronto, Canada.
Patients: Term neonates with post-intrapartal asphyxial HIE assessed for kidney, cardiovascular system, lung, and liver function.
Outcome: Death and presence or absence of severe neurodevelopmental disability.
Results: Out of 130 of 144 eligible infants with outcome data, 80 (62%) had severe adverse outcome and 50 (38%) had good outcome. All infants had evidence of MOD (at least one organ dysfunction in addition to HIE). Renal, cardiovascular, pulmonary, and hepatic dysfunction was present in 58–88% of infants with good outcome and 64–86% of infants with adverse outcome.
Conclusions: MOD was present in all the infants with severe post-asphyxial HIE. However, there was no association between MOD and outcome in these infants. No relation between individual or combinations of organ involvements and long term outcomes was observed.

There is consensus of opinion of representative obstetric and paediatric associations that multiorgan or multisystem dysfunction (MOD) is a constant feature of the neonatal post-asphyxial syndrome.[1 2] The MOD phenomenon is mechanistically related to the diving reflex. The reflex, activated by asphyxia, consists of shunting blood from the skin and splanchnic area to the heart, adrenals, and brain, ostensibly to protect these vital organs from hypoxic-ischaemic injury.[3 4–6] Thus, it is likely that each neonate with clinically detectable heart or brain dysfunction resulting from intrapartum asphyxia would have activated the diving reflex for long enough to cause dysfunction of one or more non-essential organs, particularly kidney and liver. This is expected especially in neonates who prove to have permanent brain injury.

The presence of MOD in every neonate with post-asphyxial hypoxic-ischaemic encephalopathy (HIE) has been questioned by some authors.[7 8] Inconsistencies in the involvement of the various organs would support the notion that the diving reflex is inconsistently activated in the human, as is the case in animal models of asphyxia.[6] If MOD is not consistently present in infants with severe HIE, then the dependability of the protection afforded by the diving reflex would be questionable. The patterns of MOD have not been studied in relation to the long term neurological outcome of human infants who sustained post-intrapartum asphyxial HIE of variable severity, and who had had at least four organs/systems tested in addition to the central nervous system.

The objective of the study was to assess the patterns of involvement of each major organ/system and combinations of organs/systems in infants with post-asphyxial HIE, and to describe the associations between the dysfunction of each organ/system and long term outcome.

PATIENTS AND METHODS

Infants

The infants were admitted between 1985 and 1995 to the regional neonatal intensive care unit at the Hospital for Sick Children, Toronto, Canada. All infants were born in peripheral hospitals in and around Toronto (total number of live births about 600 000 during the 11 year period) at full term.

Eligibility criteria

The following eligibility criteria were adapted from the statements of the American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynecologists of Canada[1 2 9] for ascertaining the presence of post-intrapartum asphyxial HIE:

(1) One or more of the following:

- (a) five minute Apgar score of < 5
- (b) metabolic acidosis (cord arterial blood or blood gas analysis within first hour after birth) indicated by a base deficit ≥ 16 mmol/l
- (c) delayed onset of respiration for five or more minutes

(2) Need for mechanical ventilation at birth

(3) Evidence of encephalopathy including altered state of consciousness and/or seizures (seizures were defined retrospectively from the description provided in the health records

Abbreviations: HIE, hypoxic-ischaemic encephalopathy; MOD, multiorgan dysfunction

using Volpe's criteria and were mostly subtle, tonic, and tonic clonic types)[10]

(4) Infants who had complete clinical and/or investigational assessments of the function of all four organs as outlined below

Infants with missing data for criterion 1 were included if they were born by emergency caesarean section and had features typical of criteria 2 and 3 and other causes of neonatal encephalopathy could be excluded with confidence.

Exclusion criteria

Infants were excluded if they were born preterm (< 37 weeks postmenstrual age), had congenital abnormalities including subtle dysmorphism of unknown significance or a major anomaly of a single organ, inborn errors of metabolism, congenital viral infections, haemorrhagic shock without evidence of intrapartum asphyxia, septic shock, cranial birth trauma, meconium aspiration syndrome, or evidence of antepartum asphyxia. The criteria for antepartum asphyxia were one or more of the following: a history of an antepartum episode of loss of fetal movements lasting for 24 hours or more, severe intrauterine growth retardation (birth weight below the mean for sex and gestational age minus 2 SD), oligohydramnios, or lack of fetal heart rate variability on admission of the mother to hospital.

Criteria for organ/system dysfunctions

The criteria for involvement of each organ/system were as follows:

- Renal: anuria or oliguria (< 1 ml/kg/h) for 24 hours or more, and a serum creatinine concentration > 100 mmol/l; or anuria/oliguria for > 36 hours; or any serum creatinine > 125 mmol/l; or serial serum creatinine values that increased postnatally
- Cardiovascular: hypotension treated with an inotrope for more than 24 hours to maintain blood pressure within the normal range, or electrocardiographic evidence of transient myocardial ischaemia
- Pulmonary: need for ventilator support with oxygen requirement > 40% for at least the first four hours after birth
- Hepatic: aspartate aminotransferase > 100 IU/l or alanine aminotransferase > 100 IU/l at any time during the first week after birth

Adverse outcome

Patients were considered to have severe adverse outcome if any of the following occurred:

(1) Death attributable to post-asphyxial HIE

(2) Severe cerebral palsy diagnosed by 12 months of age

(3) Mild or moderate cerebral palsy with blindness or deafness diagnosed by 12 months of age

(4) Moderate cerebral palsy with suspected developmental delay at 12 months of age, confirmed by a Bayley score lower than 2 SD below the mean at 21–24 months of age.

Ascertainment of outcomes

Outcome data were determined from the records of neonatal follow up and neurology clinics and from re-admissions. The clinicians conducting follow up examinations and authors reviewing health records for multiorgan data respectively were not blinded to the extent of MOD and the outcome of each subject. These potential sources of bias were minimised by our relatively objective outcome criteria. Where follow up was incomplete, a letter requesting a telephone interview was mailed to the family after the family doctor or paediatrician had been asked if this would be appropriate. Outcome data were obtained from the family doctor or paediatrician in seven such cases. The research ethics board of the Hospital for Sick Children approved the study.

Statistical analysis

For analyses, infants were grouped by long term outcome (adverse versus good outcome). Continuous variables were compared between the two outcome groups using the two tailed Student's *t* test. The incidence of the various organ involvements was calculated for both outcome groups.

RESULTS

From January 1985 through December 1995, 244 subjects met the eligibility criteria for post-intrapartum asphyxial HIE. Data enabling the evaluation of all four organs/systems additional to the central nervous system were available for 144 of these infants (59%). Four infants lacked data on eligibility criterion 1; all four had intrapartal as well as neonatal courses indicative of severe intrapartum asphyxia. Contact could not be established in 14 cases.

Table 1 gives the basic characteristics for both outcome groups of infants. The five minute Apgar score was less than 5 in 89/141 infants with data. Spontaneous regular respiration was established after five minutes in 110/123 infants with data. Chest compression was performed for more than one minute in 51 infants. Seizures or coma were documented in 125 (87%) infants (median age of onset four hours; interquartile range 2–8.5 hours; 119 infants had seizures before 24 hours of age). Another 15 infants were obtunded or lethargic (Sarnat stage 2), and four infants were irritable (Sarnat stage 1).

By the minimum age of 24 months, 80 of the 144 infants (55%) had severe adverse outcomes, 50 (35%) infants were free of severe adverse outcome, and 14 (10%) infants had missing outcome data (of the remaining 100 infants not included for lack of organ/system assessment in this study, 47 (47%) had adverse outcome, 41 (41%) had good outcome, and 12 (12%) had unknown outcome). Figure 1 shows the details of the outcomes.

All of the 130 infants with known outcomes showed evidence of at least one organ dysfunction in addition to brain. Renal, cardiovascular, pulmonary, and hepatic dysfunction was present in 91 (70%), 80 (62%), 112 (86%), and 110 (85%) infants respectively (table 2). No differences were observed in the rates of involvement of each organ according to outcome. Table 3 shows the relation between the number of additional organs involved and outcome. The rates of adverse outcomes increased as the number of additional organs involved increased from one to three, but decreased when an additional four organs were involved.

Table 1 Basic characteristics of the outcome groups

Variable	Good outcome (n = 50)	Adverse outcome (n = 80)	p Value
Gestational age (weeks)	40.2 (1.6)	39.9 (1.6)	0.34
Birth weight (g)	3488 (509)	3420 (500)	0.41
Maternal age (years)	29.1 (6.4)	29.3 (5.8)	0.82
Gravida (median)	2	2	–
Para (median)	0	0	–
Five minute Apgar score (median)	4	3	–

Where applicable, values are mean (SD).

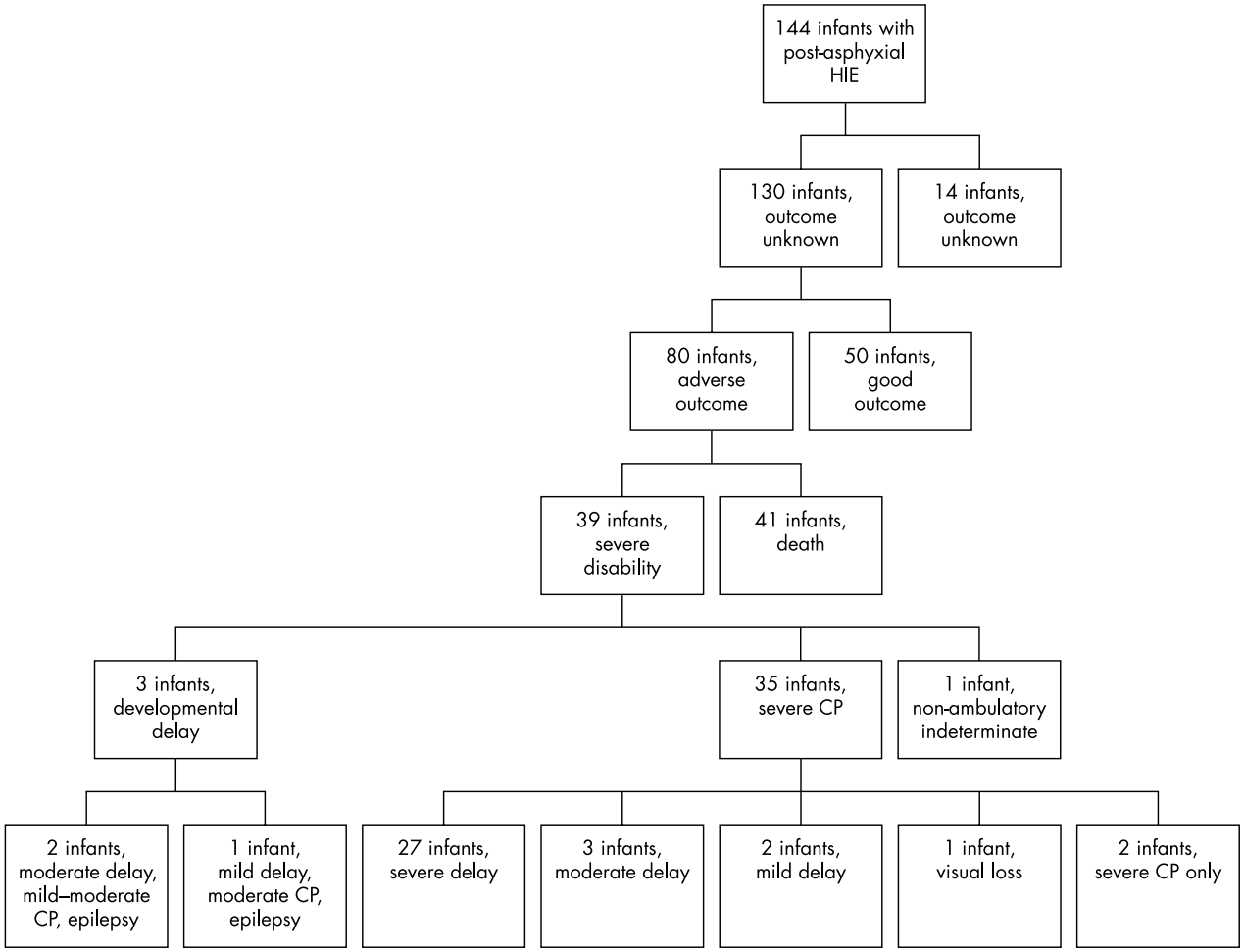

Figure 1 Outcome data of the study cohort. CP, Cerebral palsy.

DISCUSSION

All infants with severe post-asphyxial HIE had evidence of dysfunction of at least one organ/system in addition to the central nervous system. This conforms with the criteria of the American College of Obstetricians and Gynecologists[2] and Society of Obstetricians and Gynaecologists of Canada,[1] but not with some published reports of organ/system dysfunction in neonates with asphyxia of variable severity.[7 8 11 12] The variability in the reported incidence of MOD may be explained by (*a*) the selection criteria for studies of MOD—at the mild end of the spectrum are cases of "intrapartum asphyxia" with or without HIE during the neonatal period,[7 11 12] whereas at the severe end of the spectrum are known cases of cerebral palsy attributed to intrapartum asphyxia[8]—and (*b*) the differences in the definition of MOD with respect to the number of organs included in its definition, the definition of "organ/system" (for example, kidneys, hypocalcaemia), and the definition of dysfunction of each organ/system.

Although we confirmed evidence of MOD in all infants with severe intrapartum asphyxia, we did not find any relation between MOD and long term outcome. The recent consensus statement[9] also suggested that MOD is a criterion to suggest intrapartum timing but is not a specific parameter. According to the concept of the diving reflex, dissonance would be expected between non-essential and essential organ/system dysfunction, particularly in the good outcome subgroup. Comparing the good and adverse outcomes groups, we found marginal differences in the incidences of kidney and cardiovascular system dysfunction but notably no differences in pulmonary and hepatic dysfunction. The rates of individual organ dysfunction varied from 64% to 86% for

Table 2 Organ involvement in relation to long term outcome

Organ	Good outcome	Adverse outcome	Total
Renal	30/50 (60)	61/80 (76)	91/130 (70)
Cardiovascular	29/50 (58)	51/80 (64)	80/130 (62)
Pulmonary	43/50 (86)	69/80 (86)	112/130 (86)
Liver	44/50 (88)	66/80 (82)	110/130 (85)

Values in parentheses are percentages.

Table 3 Number of additional organs/systems involved and outcome

Number of additional organs involved	Good outcome (n = 50)	Adverse outcome (n = 80)
1	5 (10)	1 (1)
2	15 (30)	18 (22)
3	9 (18)	34 (43)
4	21 (42)	27 (34)

Values in parentheses are percentages.

infants with severe adverse outcome, and from 58% to 86% for infants with good outcome. Thus, the proportion of infants with each individual organ/system involved does not distinguish infants in relation to long term outcome, suggesting that activation of the diving reflex was inconsistent.

Inconsistencies in organ involvement were also observed in animal experiments under controlled conditions.[6] In a review Jensen *et al*[6] reported that, in experimental animals, different causes of asphyxia have different effects on blood flow to various organs. For example, maternal hypoxaemia, graded reduction of umbilical blood flow, and graded/repeated reduction of uterine blood flow were associated with activation of the diving reflex, whereas arrest of uterine blood flow reduced the blood flow to the brain. Our study included patients with all causes of asphyxia, which may explain the inconsistency in the activation of the diving reflex that we observed. Variation in individual vulnerability may also explain this variation. There was a stepwise increase in the rates of adverse outcomes with increase in the number of additional organs involved up to three organs, but the trend did not extend to four organs involved. This again suggests variable activation of the diving reflex.

The involvement of kidneys in 70% of cases in this cohort was comparable to the reported incidence in representative studies reflecting the spectrum of severity of asphyxia referred to above, although we chose the middle of the spectrum of published definitions.[8 12–14] The rate of cardiovascular system involvement in the present study (62%) compares with the 50% rate reported by Shankaran *et al*[12] and the 78% rate reported by Hankins *et al*.[14] Despite different criteria for lung dysfunction, our result of 86% incidence of lung involvement concurs with the incidence reported by Shankaran *et al*[12] in a similar group of patients. Finally, using similar criteria to those of Phelan *et al*[8] for liver involvement, we found an 84% rate compared with 23%, whereas Hankins *et al*,[14] using plus 2SD to define abnormal values, reported a rate of 80%. These differences in liver involvement may be explained by differences in timing of the measurements, as values return to normal within a few days of the asphyxial event in most infants. Many missing data and the use of whole case series as the denominator, as discussed by Hankins *et al*,[14] may explain the discordance of the results of Phelan *et al*.

The criteria for determining the appropriate timing for evaluation of infants for MOD have not been fully studied. Data from the studies of normal and asphyxiated infants indicate that 24–72 hours after birth is most likely to capture biochemical and electrocardiographic abnormalities associated with asphyxia.[16–21] Simultaneous monitoring of infants by cerebral function monitor (amplitude integrated electroencephalography) can provide useful information about the changes in the neurological status of these infants.[22]

The strengths of our study are the large sample size, the variability of outcomes, the high proportion of infants with known long term outcomes, the selection of study subjects for completeness of data on involvement of organs/systems, and the consistency of our results with those reported in the literature. As indicated above, Hankins *et al*[14] reported similar rates of MOD in their 46 infants with neonatal encephalopathy; however, there were missing data in their study, and no correlations with long term outcomes were performed. Our study has the known limitations of retrospective studies.[23]

In conclusion, we found evidence in support of the MOD criterion in the definition of asphyxia, but not for identification of infants at risk of long term adverse outcome injury following severe intrapartum asphyxia. However, if MOD is to remain an essential criterion for intrapartum asphyxia, multiple organs/systems including the four in this study should be evaluated in each individual patient. In addition, the evaluation should be carried out at the most appropriate time for each criterion. For future prospective multicentre studies, there is clearly a need to develop a consensus of opinion about the definitions of organ dysfunction and the criteria for MOD.

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