Multiple organ involvement in perinatal asphyxia

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Objectives: **(1) To evaluate the frequency and spectrum of severity of multisystem dysfunction after perinatal asphyxia and (2) to analyze the relationship between the clinical and biochemical markers of perinatal asphyxia and multiorgan involvement.**

Study design: **Seventy-two consecutive term newborn infants with perinatal asphyxia were studied prospectively. Systematic neurologic, renal, pulmonary, cardiac, and gastrointestinal evaluations were performed. Involvement of each organ was classified as moderate or severe.**

Results: **Involvement of one or more organs occurred in 82% of the infants; the central nervous system (CNS) was most frequently involved (72%). Severe CNS injury (7 infants) always occurred with involvement of other organs, although moderate CNS involvement was isolated in 14 infants. Renal involvement occurred in 42%, pulmonary in 26%, cardiac in 29%, and gastrointestinal in 29% of the infants; 15% neonates had renal failure and 19% had respiratory failure. The Apgar scores at 1 and 5 minutes were the only perinatal factors related to the number of organs involved and the severity of involvement; the Apgar score at 5 minutes had the stronger independent association. No relationship of organ dysfunction was found with the umbilical cord arterial blood pH, meconium-stained amniotic fluid, umbilical cord abnormalities, presentation, or type of delivery.**

Conclusions: **Our findings indicate that the Apgar score at 5 minutes, in infants who have other criteria for asphyxia, is the perinatal marker that may best identify infants at risk of organ dysfunction. (J PEDIATR 1995;127:786-93)**

Dysfunction of organs other than the central nervous system is often recognized after perinatal asphyxia, and organ-specific studies have evaluated the pathophysiologic and clinical manifestations of hypoxic-ischemic insults to the heart, lungs, kidneys, and bowel.[1-5] However, few studies have assessed multisystem involvement in the severely asphyxiated neonate,[6-9] and there has been no prospective evaluation of the frequency and spectrum of severity of multiple organ dysfunction in asphyxiated newborn infants, including infants with mild asphyxia who did not require intensive care. Moreover, little is known about the relationship between the traditional perinatal markers of asphyxia and multiple organ involvement.[6-9] However, early recognition of the infants at greatest risk of multisystem dysfunction after a perinatal asphyxial insult may affect the management of these infants.

HIE	Hypoxic-ischemic encephalopathy

This study is a prospective evaluation of term newborn infants with clinical and biochemical criteria for perinatal asphyxia, including infants with a broad clinical spectrum, from none to severe, of effects of the asphyxial event. Our objectives were (1) to evaluate the frequency and spectrum

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of severity of multisystem dysfunction in the neonatal period after a perinatal asphyxial insult and (2) to analyze the relationship between the traditional clinical and biochemical markers of perinatal asphyxia and multiple organ dysfunction to determine whether any of those early markers might help to identify promptly the asphyxiated neonates at risk of multisystem involvement.

METHODS

Patients. The study population comprised asphyxiated term neonates admitted consecutively to the neonatal unit at La Paz Children's Hospital, Autonoma University of Madrid, between January 1990 and February 1992. The infants were identified as having had perinatal asphyxia when at least three of the following criteria were present: (1) fetal scalp blood pH <7.20, (2) umbilical cord arterial pH <7.20, (3) Apgar scores <4 at 1 minute and/or <7 at 5 minutes, (4) requirement of more than 1 minute of positive pressure ventilation before sustained respiration occurred. The criteria for exclusion were congenital malformations, metabolic disorders, congenital infections, maternal drug addiction, and lack of parental consent.

Complete obstetric histories were obtained and examinations were performed at the time of admission. The neonatal clinical course was followed up prospectively, and data were recorded on standard protocol forms. Pathologic examinations were performed on each infant who died.

Informed written parental consent was obtained for all infants before entry in the study, which was approved by the Human Studies Committee of La Paz Children's Hospital.

Involvement of each organ evaluated was classified as moderate or severe, according to the definitions shown in Table I.

Neurologic assessment. A detailed structured neurologic examination[10] was performed at approximately 12, 36, and 72 hours and at 7 days of age by a single investigator (A. G.-A.). The stage of encephalopathy was assessed according to a simplified Amiel-Tison and Ellison staging system.[11] Briefly, stage 1 was diagnosed when hyperexcitability or hypotonia persisted for at least 72 hours after birth. Stage 2 was diagnosed in the presence of lethargy, hypotonia, and weak or partially absent primitive reflexes with or without seizures. Finally, stage 3 was identified when, in addition to severe tonus abnormality and frequent seizures, there was coma or stupor. Cranial sonographic evaluations were performed after each of the neurologic examinations. Computed tomographic scans were performed within the first week of life on all infants who had abnormal cranial ultrasonographic findings and survived more than 3 days. Electroencephalograms were obtained when there were clinical seizures and in every comatose infant at 16 to 48 hours after birth; these were repeated when necessary. Data regarding the neonatal neurologic status and outcome of 69 of these infants have been published elsewhere.[12]

Table I. Classification of the severity of involvement for each of the organs evaluated

	Moderate involvement	Severe involvement
CNS	HIE stage 1 and 2	HIE stage 3
Renal	Oliguria with azotemia and/or proteinuria	Serum creatinine >110 μmol/L (1.2 mg/dl) for two or more consecutive days
Pulmonary	Need of FiO_2 >0.4 for at least 4 hours	Mechanical ventilation not required for apnea or heart failure
Heart	Heart murmur and/or ECG abnormalities characteristic of myocardial ischemia	Signs of heart failure (tachycardia, tachypnea, and hepatomegaly)
GI	Repeated bloody gastric residuals and/or repeated vomiting	Necrotizing enterocolitis and/or massive bleeding (hemoglobin decrease >2 gm/100 ml)

GI, Gastrointestinal.

Renal evaluation. Urine output was monitored in each case. The time of the first micturition was recorded. Oliguria was defined as a urine flow rate of <1 ml/kg per hour that persisted for 24 hours or more after a volume challenge test and in the absence of urinary tract obstruction.[13] Qualitative urine protein concentrations were determined by means of a dipstick (Multistix, Bauer Diagnostics) at least twice during the first 72 hours of life in every infant; proteinuria was defined as 2+ or greater.[14] Blood samples from all infants were obtained at approximately 12 hours of age and repeated when necessary. Azotemia was defined by a blood urea nitrogen >7 mmol/L (20 mg/dl).[13] Parenteral fluid administration, when needed, consisted of 65 ml/kg per day during the first 24 hours after birth and 80 to 100 ml/kg per day afterward; fluid restriction was instituted when renal failure was diagnosed, in accordance with the infant's course.

Pulmonary evaluation. The respiratory status of each infant was assessed on the basis of the Silverman score, the need for oxygen supplementation, and the need for mechanical ventilation. Serial blood gas measurements and chest radiographs were performed in all infants who required oxygen supplementation. A two-dimensional echocardiographic study with Doppler examination was performed in every infant in whom persistent pulmonary hypertension was suspected (persistent partial pressure of oxygen <60 mm Hg with no evidence of pulmonary or cardiac pathologic disorder).

Cardiac assessment. Every infant was examined for the presence of heart murmurs, dysrhythmias, cyanosis, respira-

tory distress, hepatomegaly, and abnormal peripheral pulses. Blood pressure determinations were made at least every 8 hours by oscillometry (Dinamap, Critikon, Inc., Tampa, Fla.) or directly through the umbilical artery catheter; hypotension was defined as systolic and/or diastolic blood pressure equal to lower than the 5th percentile for age and sex.[15, 16] A 12-lead electrocardiogram was recorded within 24 hours after birth in 60 infants and was repeated as needed; electrocardiograms were interpreted by a single investigator (M. B.), who was unaware of the perinatal history and clinical status of the infants.[17] Chest radiographs were performed in the presence of any abnormal clinical finding, hypotension, or electrocardiographic abnormality. An M-mode echocardiogram and a two-dimensional echocardiogram with Doppler examination were made in infants with heart murmurs, cyanosis, heart failure, abnormal pulses, hypotension, increased cardiothoracic ratio (≥0.60), or electrocardiographic abnormalities.

Gastrointestinal evaluation. Every infant was examined for the presence of gastric residuals, vomiting, abdominal distention or tenderness, and gastrointestinal bleeding. Abdominal radiographs were made of infants with abnormal findings. Enteral feedings were not started until at least 8 to 12 hours after delivery in all infants; severely asphyxiated infants were not fed for 5 to 7 days.

Statistical analysis. Data are expressed as mean ± SD for descriptive purposes unless otherwise stated. The Mann-Whitney, Kruskal-Wallis, and chi-square tests were used as deemed appropriate. The relationship between Apgar scores and organ involvement was analyzed both by the Kruskal-Wallis test and by the chi-square test; for this analysis, the Apgar scores were divided into three groups (≤3, 4 to 6, ≥7). A stepwise logistic regression model was used to examine the relationship between perinatal data and organ involvement.

RESULTS

Seventy-two asphyxiated term infants were studied. During the study period, 85 consecutive patients met the entry criteria. Thirteen of these infants were excluded: seven because of congenital malformations, two because of maternal heroin addiction, and four because parental consent was not given. Seventy infants were born at our institution; two infants born elsewhere were admitted on the first day of life.

General data. Breech or transverse presentation occurred in 4 (5%) of the 72 infants. Meconium-stained amniotic fluid was present in 30 (42%) infants. Umbilical cord abnormalities were present in 16 (22%) infants. Labor was complicated by an abnormal fetal heart rate pattern in 26 of the 41 infants whose tracings were available. Twenty-three (32%) of the deliveries were vaginal, 16 (22%) involved forceps extraction, and 33 (46%) deliveries were by cesarean section.

Of the 72 infants, 38 were boys. The mean birth weight was 3215 ± 490 gm. Fetal scalp blood pH was <7.20 in 20 of the 41 infants in whom it was measured. The mean umbilical cord arterial pH was 7.04 ± 0.13 (range 6.75 to 7.32); it was <7.20 in 61 infants (85%). The Apgar score at 1 minute was <4 in 50 (70%) infants; the Apgar score at 5 minutes was ≥7 in 33 (46%) infants, 4 to 6 in 27 (37%), and ≤3 in 10 (14%) infants. Apgar scores were not available for the two outborn neonates. Cardiopulmonary resuscitation was performed in 66 (92%) patients, intubation in 32, and biochemical resuscitation in 20. Twenty-six infants (36%) were admitted to the newborn nursery, 21 (29%) to the neonatal ward, and 25 (35%) to the neonatal intensive care unit. Four infants died within the first week of life.

Characteristics of organ involvement. *Central nervous system* involvement occurred in 52 (72%) of the infants. According to the hypoxic-ischemic encephalopathy staging, 30 (41%) infants had stage 1, 15 (21%) had stage 2, and 7 (10%) had stage 3. Clinical seizures were present in 14 (19%) infants. Central apnea requiring ventilatory support occurred in 4 infants; 3 of them also had pulmonary hemorrhage or meconium aspiration syndrome. Sonographic evaluation revealed homogeneous or heterogeneous diffusely increased echogenicity of the brain parenchyma with obliteration of the ventricles in 6 infants. On computed tomographic scans these findings corresponded with generalized or patchy decreased brain density, respectively. One infant had a parietooccipital hemorrhagic infarction that evolved to a porencephalic cyst. The 4 infants who died had HIE stage 3.

Moderate or severe *renal* involvement was found in 30 (42%) infants. Oliguria was present in 38 (53%) neonates during the first 24 hours of life and persisted in 3 (4%) for the first 48 hours. Proteinuria was noted in 22 (31%) infants. Oliguria and proteinuria were associated in 16 infants ($p < 0.05$). Azotemia occurred in 18 (25%). Creatinine levels higher than 110 μmol/L (1.2 mg/dl) for at least 2 consecutive days were found in 11 (15%); in each case, oliguria was present.

Pulmonary involvement was noted in 19 (26%) infants. Five (7%) required supplementation with FiO2 >0.4 for more than 4 hours, the mean duration being 45 hours. Fourteen (19%) infants required mechanical ventilation for pulmonary disease. Four were extubated by 24 hours of life and another 4 by 48 hours of life; 3 required mechanical ventilation for more than 72 hours; 3 infants died during mechanical ventilation. Meconium aspiration syndrome was diagnosed in 6 of the 30 neonates with meconium-stained amniotic fluid, persistent pulmonary hypertension was present in 3 infants (2 of them with meconium aspiration), pulmonary hemorrhage occurred in 4, and a milder respiratory distress

Table II. Frequency of total and severe involvement for each of the organs in group 1 (infants with involvement confined to only one organ) and group 2 (infants with two or more organs involved)

	Group 1		Group 2	
	Total 19 (26%)	Severe 11 (15%)	Total 40 (56%)	Severe 9 (13%)
CNS	14	2	38	5
Renal	3	3	27	8
Pulmonary	1	6	18	8
Heart	0	0	21	0
Gastrointestinal	1	0	20	1

syndrome consistent with transient pulmonary hypertension occurred in 3 infants.

Heart involvement was observed in 21 (29%) neonates. A transient systolic murmur was noted in 15 (21%) infants, and the electrocardiogram showed signs of myocardial ischemia in 14 (19%). Systolic murmur and electrocardiographic abnormalities were associated in 8 neonates ($p < 0.01$). Hypotension requiring sympathomimetic amines occurred only in the 3 infants with persistent pulmonary hypertension; electrocardiographic and echocardiographic evaluations of these infants ruled out anatomic and functional heart disease. Sustained sinus bradycardia, not associated with other signs of heart involvement, was present in 5 neonates. No infant had signs of heart failure.

Gastrointestinal involvement occurred in 21 (29%) infants. Sixteen had repeated bloody gastric residuals, and 5 had recurrent vomiting. One infant had profuse, bloody diarrhea. No infant had clinical and radiographic signs consistent with necrotizing enterocolitis.

Multiple organ involvement. The asphyxiated neonates were divided into three groups according to the total number of organs involved: 13 infants (18%) had no signs of organ dysfunction (group 0), 19 had involvement of one organ (group 1), and 40 had involvement of two or more organs (group 2). No differences were found among the three groups with regard to gender, gestational age, or birth weight. The frequency of organ involvement for groups 1 and 2 is shown in Table II. CNS involvement occurred in 74% of the infants with only one organ affected (group 1) and was moderate in all cases (HIE stage 1 or 2). No specific organ association was found to be significantly more frequent. Multiple organ involvement, not including CNS, was present in only two infants whose main problem was severe respiratory failure.

Twenty infants (28%) had signs of severe involvement of one or more of the organs (Table II). All 11 infants in group 1 had moderate involvement of at least another organ; the CNS was affected in only two infants with severe involvement confined to one organ. Severe organ involvement tended to be present in the same infants. Of the 11 infants with renal failure, 4 had HIE stage 3 ($p < 0.01$) and 6 had moderate CNS involvement; respiratory failure was also significantly associated with renal failure in 7 of the 11 infants ($p < 0.001$); in addition, severe CNS involvement was associated with respiratory failure in 4 of the 14 infants ($p < 0.05$).

Relationship between perinatal data and organ involvement. The Apgar score at both 1 and 5 minutes was the only perinatal marker of distress associated with the total number of organs affected in each infant. No relationship was found between meconium-stained amniotic fluid, umbilical cord abnormalities, umbilical cord arterial pH, the presentation or type of delivery, and the number of organs involved (Table III). The Apgar scores at 1 and 5 minutes were again the only perinatal markers associated with the number of organs severely affected (Table III). In addition, a stepwise logistic regression analysis showed that the Apgar score at 5 minutes (≤ 5 vs >5) had a strong independent association with the number of organs severely involved (odds ratio 17.5, 95% confidence interval, 4.58 to 66.9). When the infants were further categorized with regard to the presence or absence of severe organ involvement, all infants who had an Apgar score at 5 minutes <5 had severe involvement of at least one organ, whereas 90% of the infants with an Apgar score ≥ 5 at 5 minutes did not have severe involvement of any organ ($p < 0.001$). Our findings suggest a relationship between abnormal fetal heart rate pattern and organ involvement (Table III); however, as tracings were available in only 41 of the 72 infants, these data were not analyzed.

The spectrum of each organ's involvement (normal, moderate, or severe) was analyzed with regard to perinatal data. The Apgar score at both 1 and 5 minutes was again the only perinatal marker of asphyxia significantly related to the severity of each organ involvement ($p < 0.05$).

DISCUSSION

These results indicate that perinatal asphyxia, defined by the presence of at least three traditional criteria, is frequently followed by dysfunction of one or more organs during the neonatal period. Involvement of at least one organ was found in 82% of the infants (95% confidence interval, 72% to 91%)

Table III. Perinatal data in group 0 (infants with no organ involvement), group 1 (infants with involvement confined to only one organ), and group 2 (infants with two or more organs involved), according to both the total number of organs involved and the number of organs severely involved

		Group 0		Group 1		Group 2		*p*	
	n	Total	Severe	Total	Severe	Total	Severe	Total	Severe
MSAF	72	31%	42%	37%	18%	47%	67%	NS	NS
Abnormal FHR	41	44%	55%	45%	80%	81%	100%	NE	NE
Umbilical a pH	72	7.05 ± 0.08	7.06 ± 0.10	7.06 ± 0.01	7.01 ± 0.19	7.05 ± 0.13	7.00 ± 0.21	NS	NS
Apgar, 1 min	70	3 (1-6)	3 (0-7)	3 (1-7)	2 (0-4)	2 (0-6)	1 (0-4)	<0.05	<0.001
Apgar, 5 min	70	7 (5-9)	7 (5-9)	7 (5-9)	4 (1-7)	5.5 (0-8)	2.5 (0-6)	<0.001	<0.001

MSAF, Meconium stained amniotic fluid; *Abnormal FHR*, abnormal fetal heart rate pattern; *umbilical a pH*, umbilical cord arterial pH; *NS*, not significant; *NE*, not evaluated. Apgar scores are expressed as median (range).

and severe involvement of one or more organs in 28% (95% confidence interval, 17% to 39%). In addition, our findings indicate that the Apgar score at 5 minutes in infants with other putative markers of perinatal asphyxia may help to identify neonates at risk of organ dysfunction after perinatal asphyxia.

Our study differs from those previously reported[6-9] in two main ways: the criteria for inclusion of the infants in the study and the basis for defining dysfunction for each organ. Previous prospective reports included only asphyxiated infants who required admission to the neonatal intensive care unit. In contrast, our study included all the infants who met biochemical and clinical criteria for perinatal asphyxia; thus a broad spectrum of clinical effects, from none to severe, was found in our population (only 35% required admission to the neonatal intensive care unit). Second, in previous prospective studies, the definition of dysfunction for each organ evaluated either was not clearly provided or was based on very different criteria for each organ in the same study (i.e., mild biochemical involvement without clinical repercussion was defined as involvement in some organs, but severe failure was the criterion in others). Therefore the relative frequency of organ involvement was probably skewed toward those organs evaluated with the most sensitive definition of dysfunction. Although finding a balanced definition of involvement for different organs is difficult, our distinction between normal, moderate, and severe involvement for each organ was an attempt to enhance comparability among the organs evaluated.

According to the presence of primary signs of acute neonatal encephalopathy, the CNS was the organ most frequently involved in this study. However, most infants had only transient neurologic abnormalities (data previously reported[12]); of the 45 infants with moderate CNS involvement, none died or had cerebral palsy at 1 year of age, although 9 had mild motor impairment. In contrast, the 7 neonates who had severe HIE (stage 3) had brain damage documented by imaging techniques, postmortem studies, or both, and the 4 infants who survived had cerebral palsy at 1 year of age. On the other hand, moderate CNS involvement was found alone in 14 neonates, but brain damage (severe CNS involvement) always was associated with moderate or severe involvement of other organs, mainly the lungs and kidneys. These facts support the suggestion that infants with neonatal brain damage but without multisystem involvement are unlikely to have encephalopathy because of perinatal asphyxia,[18] although moderate CNS involvement (HIE stage 1 or 2) may occur in the absence of other organ involvement.

The redistribution of cardiac output away from the kidney in response to an asphyxial insult may in part account for renal involvement.[19-21] Tubular dysfunction in the asphyxiated newborn infant has been identified by means of markers such as β2-microglobulin,[22] retinol binding protein, myoglobin, and N-acetyl-β-D-glucosaminidase.[23] However, these studies found no significant differences in the concentrations of plasma electrolytes between infants with normal and abnormal tubular function. Therefore, although measurements of urinary levels of these proteins provide a sensitive indicator of proximal tubular function, we have considered renal involvement only in the presence of clinically significant dysfunction; renal function was evaluated by means of criteria comparable to those used for the other organs. Although the presence of oliguria was not required in our definition of severe renal involvement so that nonoliguric acute renal failure was not overlooked, all the infants with renal failure had oliguria on the first day of life. A significant association between clinical signs of HIE and long-term neurologic deficits with persistent oliguria has been reported.[24] In our study, renal failure was significantly associated with the presence of HIE stage 3. In addition, a significant association was found between renal failure and respiratory failure, which was also significantly associated with severe CNS involvement. Moreover, all the infants who had severe involvement of any organ also had either moderate or severe involvement of at least one other organ. Thus an asphyxial insult sufficient

to damage one organ severely usually also affects other organs.[18]

As previously reported,[7, 25] meconium aspiration syndrome, pulmonary hemorrhage, and pulmonary hypertension were the most frequent pulmonary abnormalities. The specific mechanisms causing respiratory failure in asphyxiated neonates are difficult to isolate, and multiple factors probably are mutually reinforcing in each infant: fetal hypoxemia, ischemia, meconium aspiration, left ventricular dysfunction, coagulation defects, oxygen administration, and the use of mechanical ventilation[2, 26-30] probably play interrelated roles in the clinical course of these infants.

Although the fetal and neonatal myocardium seems to be resistant to hypoxia,[31] heart failure was the main recognized manifestation of myocardial dysfunction after perinatal asphyxia in early studies.[32-34] No infant in our study had heart failure; nor did any infant in previous studies that analyzed multiorgan dysfunction after perinatal asphyxia. Thus the incidence of severe heart damage is low, although less severe manifestations of heart involvement may be frequent.[7-9] A murmur suggestive of atrioventricular valve insufficiency, electrocardiographic abnormalities characteristic of myocardial ischemia, or both were found in 29% of our subjects. However, the incidence of histologically proven myocardial ischemic damage after perinatal asphyxia seems to be greater than could be anticipated on clinical grounds;[1, 35, 36] the true incidence of mild myocardial ischemia might be underestimated if pathologic studies are not performed. Echocardiographic studies were performed in our patients only when heart disease or persistent pulmonary hypertension was suspected; mild ventricular dysfunction might have been overlooked. Although serum creatine phosphokinase MB isoenzyme has been proposed as a biochemical marker of myocardial ischemia in asphyxiated infants,[37] a normal value does not reliably exclude myocardial damage and the enzyme lacks cardiac specificity in the neonate.[1]

Reports of necrotizing enterocolitis have suggested an association with perinatal asphyxia.[38, 39] Platelet-activating factor triggered by local hypoxia[40] and oxygen radicals resulting from local ischemia-reperfusion injury[41] have been implicated as putative mechanisms of intestinal injury. Necrotizing enterocolitis was not found in any of our 72 infants or in any infant in other studies that have evaluated systemic manifestations of asphyxia.[7-9, 25] Moreover, only one neonate had severe gastrointestinal involvement. Whether these findings depend on the delay in starting enteral feeding is unclear from available data[42]. On the other hand, feeding intolerance[43] and subtle alterations of intestinal motor activity[5] and gastrointestinal peptides[44] have been reported in association with perinatal asphyxia.

We found no relationship between umbilical cord arterial pH, meconium-stained amniotic fluid, umbilical cord abnormalities, presentation or type of delivery, and the frequency or severity of organ involvement. Although acidosis has been considered the best evidence of perinatal asphyxia,[45, 46] the pH of umbilical cord arterial blood was not related to the frequency or severity of organ involvement. Other studies have not found any relationship between acidosis and either neonatal encephalopathy[47, 48] or multisystem involvement.[7] Although the relationship of acidosis to neonatal morbidity does not appear to be strong,[49, 50] extremely severe acidosis may be related to multiorgan dysfunction.[9, 51-54] The fact that the umbilical cord arterial pH provides limited information about the duration of the insult and the fetal adaptive mechanisms in response may in part account for these findings.

The Apgar score was the only perinatal factor related to the number of organs affected and to the severity of organ involvement. Moreover, the Apgar score at 5 minutes best defined the subgroup of infants at risk of organ dysfunction. Other studies also have found a relationship between the Apgar score and short-term morbidity after perinatal asphyxia,[8, 48] although this is an unreliable predictor of permanent neurologic deficit.[46] Low Apgar scores may be the result of factors other than perinatal asphyxia, and caution is needed in the interpretation of an individual Apgar score; other data are necessary to establish the diagnosis of perinatal asphyxia.

Our data must be interpreted with the following limitations in mind: A generally accepted definition of asphyxia is lacking, and many different clinical markers have been used to suggest that asphyxia has occurred.[46] The entry criteria in this study were based on the presence of at least three traditional markers, and it is possible that infants with mild asphyxia were missed. No control population was studied, and dysfunction of organs such as the liver or coagulation disorders were not evaluated systematically. Finally, our definition of involvement for each organ was arbitrary, although based on data from previous studies.

The results of this study further delineate the clinical picture of multiple organ involvement in the asphyxiated term newborn infant and indicate the need for global management of these infants. The Apgar score at 5 minutes in infants who meet other criteria of asphyxia is probably the single perinatal marker that best identifies infants at risk of organ dysfunction. It is important to study the involvement of other organs because new therapies for severe CNS damage are under investigation. Future clinical trials of treatments for hypoxic-ischemic encephalopathy must carefully evaluate possible adverse side effects on other organs potentially affected, as well as changes in the pharmacokinetics of drugs secondary to dysfunction of one or more organs, which may not be clinically evident until several hours after the treatment has been instituted.

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