The Severity of Hypoxic-Ischemic Encephalopathy Correlates With Multiple Organ Dysfunction in the Hypothermia Era

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Objectives: The objectives are to 1) determine whether there is a positive correlation between the severity of hypoxic-ischemic encephalopathy and multiple organ dysfunction and 2) evaluate the organ dysfunction pattern in infants with hypoxic-ischemic encephalopathy in the hypothermia era.

Design: Retrospective observational study of prospective data collected between April 2009 and December 2012.

Setting: The study took place in the neonatal ICU of Hospital Sant Joan de Déu–Hospital Clínic of Barcelona.

Patients: Prospective consecutive newborns with greater than or equal to 36 weeks of gestation, greater than or equal to 1,800 g of weight at birth, and a diagnosis of hypoxic-ischemic encephalopathy was included.

Interventions: Severity of hypoxic-ischemic encephalopathy was established before starting controlled hypothermia. Six organ systems and 23 clinical and laboratory variables were studied by means of an asymmetrical grading scale. Data were recorded daily during the first 72 hours of life.

Measurements and Main Results: Seventy-nine patients were studied. All presented with multiple organ dysfunction on day 1. There were differences in the number of affected organs on day 1 according to hypoxic-ischemic encephalopathy stage ($p < 0.001$). Scale scores correlated positively with the severity of hypoxic-ischemic encephalopathy (area under the curve ranged from 0.77 to 0.87 on every day studied). There were significant differences in the severity of dysfunction of each organ system among the three hypoxic-ischemic encephalopathy stages ($p < 0.05$). Although the most frequently involved were hepatic and pH and electrolyte imbalance, the most severely affected were the respiratory and cardiovascular systems.

Conclusions: In the hypothermia era, multiple organ dysfunction continues to be almost universal in newborns with hypoxic-ischemic encephalopathy. There is a high correlation between the severity of hypoxic-ischemic encephalopathy and multiple organ dysfunction during the first 3 days of life. A high index of suspicion of relevant multiple organ dysfunction is required in infants admitted with a diagnosis of severe hypoxic-ischemic encephalopathy. Patients with moderate hypoxic-ischemic encephalopathy present wide variability in the severity of multiple organ dysfunction. In the absence of multiple organ dysfunction, a perinatal hypoxic-ischemic origin of acute severe neonatal encephalopathy should be carefully reconsidered. (*Pediatr Crit Care Med* 2017; 18:234–240)

Key Words: biomarker; hypothermia; hypoxic-ischemic encephalopathy; illness severity score; multiple organ dysfunction; perinatal asphyxia

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Perinatal asphyxia is a major cause of multiple organ dysfunction (MOD) in the newborn (1–4). The reported prevalence of MOD in asphyxiated newborns is uneven, in part, due to differences in inclusion criteria, organ systems studied, and terms used to define dysfunction in each organ system. However, the most recent studies indicate that a large majority of patients with hypoxic-ischemic encephalopathy (HIE) develop MOD, and most of them present with dysfunction in a large number of organ systems (1–4).

The introduction of therapeutic hypothermia in the last decade has led to the publication of safety studies that revealed minimal organ injury from hypothermia (5–8). A beneficial effect of this therapy over organ systems other than the CNS has been suggested (4), but the frequency, severity, and temporal course of MOD in newborns with HIE evaluated for inclusion in hypothermia therapy programs have not been examined. Furthermore, only scarce data about the correlation of extracerebral damage and the severity of HIE are available. This information might help to anticipate the evolution of MOD according to the severity of HIE and vice versa.

This study evaluates a thorough profile of MOD by means of an asymmetrical grading scale, in a large cohort of patients with the entire spectrum of HIE severity. The aims of the study were 1) to analyze the correlation between HIE and MOD and 2) to assess the severity and spectrum of MOD in infants with HIE.

METHODS

Patients

The study population included infants consecutively born at greater than or equal to 36 weeks of gestational age and greater than or equal to 1,800 g, admitted to Hospital Sant Joan de Déu–Hospital Clinic of Barcelona, between April 2009 and December 2012. Infants qualified if they presented with HIE within the first 6 hours of life, defined by the two following conditions: 1) neonatal encephalopathy, defined as a syndrome of neurologic dysfunction manifested by a subnormal level of consciousness with or without seizures, or palmary hyperexcitability (tremor, overactive myotatic reflexes, hypersensitivity to stimulation, or startle responses), and 2) at least one of the following clinical surrogates of hypoxic-ischemic insult: altered fetal heart rate pattern, sentinel event, labor dystocia, Apgar les than or equal to 5 at 5 minutes, or acidosis at birth (pH ≤ 7.0 in arterial umbilical cord). Newborns were excluded if they presented with 1) congenital abnormalities, 2) other identifiable etiologies of neurologic dysfunction, or 3) if parents refused consent.

The severity of HIE was graded according to our previously reported score including the Amplitude-integrated electroencephalogram (aEEG) background (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A370) (9). Newborns with moderate or severe HIE underwent whole-body hypothermia. All patients were evaluated and treated according to a strict clinical protocol for the integrated management of HIE. Contraindications for hypothermia included a moribund state, refractory severe pulmonary hypertension, and refractory bleeding. Hospital Sant Joan de Déu research ethics board approved the study.

Evaluation of Multisystem Dysfunction

A scale to graduate the severity of MOD was designed (**Table 1**). Six organ systems with a total of 23 parameters were studied. For each organ system, three degrees of severity were established (1–8, 10–19). All variables were scored on an asymmetric scale, as described in the Pediatric Logistic Organ Dysfunction score (20). Laboratory tests were performed at admission and at 12,

TABLE 1. Multiple Organ Dysfunction Scale

	Score			
Organ System Variables	**0**	**1**	**10**	**20**
Cardiovascular				
Troponin T (μg/L)	< 0.1	0.1–0.243	≥ 0.244	≥ 2 drugs
	and	or	or	
Need for vasoactive drugs[a]	No	1 drug < 24 hr	1 drug ≥ 24 hr	
Renal				
Plasma creatinine (mg/dL)	< 1 and	1–1.25 or	1.26–1.5 or	> 1.5 or ↑≥ 0.3 in 24 hr
Diuresis (mL/kg/hr)	≥ 1 and	0.99–0.51	≤ 0.5	or
Need for replacement therapy	No			Yes
Respiratory				
Need for respiratory support due to other causes than central apnea or pharmacological effect[b]	No	Noninvasive ventilation or High-flow nasal cannulae or Mechanical ventilation < 24 hr or FIO_2 0.4 or ≥ 0.4 for < 24 hr	MV ≥ 24 hr or FIO_2 ≥ 0.4 and for ≥ 24 hr	Nitric oxide or High-frequency oscillatory ventilation

(*Continued*)

TABLE 1. (*Continued*). Multiple Organ Dysfunction Scale

Organ System Variables	Score			
	0	1	10	20
Hematological				
Leukocyte count (mm^3)				
Lower limit	≥ 4.5 and	< 4.5 or		
Upper limit	≤ 30 and	> 30 or		
Platelet count (mm^3)	≥ 150 and	149–51 or	50–21	≤ 20
Activated partial thromboplastin time (sec)	≤ 45 and	> 45 or	or	or
No. of platelet or fresh frozen plasma concentrate (units)	0	≤ 2 in 24 hr	> 2 in 24 hr	≥ 4 in 24 hr
Hepatic				
Glutamic oxaloacetic transaminase or glutamic pyruvic transaminase (UI/L)	< 100 and	≥ 100 or	≥ 500 and	≥ 1,000 and
Prothrombin activity (%)	> 60	≤ 60	< 40	≤ 20
pH and electrolytic imbalance[c]				
pH (≥ 12 hr of life)				
Upper limit	≤ 7.45 and	7.46–7.55 or	7.56–7.59 or	≥ 7.6 or
Lower limit	≥ 7.35 and	7.34–7.20 or	7.19–7.11 or	≤ 7.10
Na^+ (mmol/L)				
Upper limit	≤ 145 and	146–159 or	≥ 160 or	
Lower limit	≥ 135 and	134–121 or	≤ 120 or	
K^+ (mmol/L)				
Upper limit	≤ 5.5 and	5.6–6.4 or	≥ 6.5 or	
Lower limit	≥ 3.5 and	3.4–2.6 or	≤ 2.5 or	
Ionic Ca^+ (mmol/L)				
Upper limit	≤ 1.3 and	1.31–1.49 or	≥ 1.5 or	
Lower limit	≥ 1	0.99–0.71	≤ 0.7	

[a]Use of inotropic agents in our unit is aimed at maintaining a mean blood pressure above 40 mm Hg. Dobutamine and dopamine are drugs of first choice and rescue epinephrine and hydrocortisone are used.

[b]According to the protocol in force in the unit, the ventilation mode of onset is conventional pressure ventilation, whereas high-frequency ventilation would be the rescue mode.

[c]Values of pH were temperature corrected. According to the current protocol, initial intake volume is between 40 and 50 mL/kg/d for the first 24 hours, with routine administration of 10% calcium gluconate at 2 mEq/kg/d. Sodium and potassium are introduced in the subsequent days, depending on urine output and serum electrolyte values.

24, 48, and 72 hours of life. The score was measured daily during the first 3 days of life. For each variable, the most abnormal value measured on each day was chosen to contribute to that day's score (20). If one value of a variable was not available, it was estimated by the mean of the previous and the following values (15). Neither blood gas nor electrolyte values were extrapolated.

Statistical Analysis

Numerical variables were expressed as mean and SD or median and interquartile range and categorical variables as frequencies and percentages. HIE stages were compared by univariate analysis. Distribution of quantitative variables was compared with the Kruskal-Wallis test. Differences between qualitative variables were analyzed with chi-square or Fisher exact tests. Receiver operating characteristic curves were constructed to correlate MOD scale scores and HIE stages. Dichotomous variables were created for each organ-system: 1) no involvement/mild involvement versus moderate-to-severe involvement and 2) no involvement versus mild-to-severe involvement; positive predictive value (PPV) and negative predictive value (NPV) for significant HIE (moderate or severe) versus mild HIE were estimated. Statistical analyses

TABLE 2. Perinatal Data According to Hypoxic-Ischemic Encephalopathy Stage

Perinatal Data	Total 79	Mild HIE 23 (29)	Moderate HIE 25 (31)	Severe HIE 31 (39)	*p*
Gestational age, mean (SD), weeks	38.8 (1.8)	38.3 (2)	38.6 (2)	37.9 (2.6)	0.54
Birth weight, mean (SD), grams	3170 (570)	3282 (601)	2977 (498)	2994 (651)	0.10
Male, *n* (%)	55 (69)	15 (65)	18 (72)	22 (71)	0.86
Outborn birth, *n* (%)	54 (68)	8 (35)	20 (80)	26 (84)	< 0.001
Age at admission, mean (SD), hours	3.9 (3.3)	1.8 (2.4)	4 (2.5)	5 (3.6)	0.001
Growth restriction, *n* (%)	10 (13)	2 (9)	5 (20)	3 (10)	0.51
Sentinel event, *n* (%)	24 (30)	6 (26)	10 (40)	8 (26)	0.48
Labor dystocia, *n* (%)	73 (92)	19 (83)	23 (92)	31 (100)	0.03
Emergency cesarean section, *n* (%)	62 (66)	6 (26)	19 (76)	27 (87)	< 0.001
Meconium-stained liquor, *n* (%)	25 (31)	4 (17)	5 (20)	16 (51)	0.012
Altered heart rate pattern, *n* (%)	57 (72)	11 (48)	19 (76)	27 (87)	0.007
Apgar 1 min, median (IQR)	2 (1–4)	3 (2–4)	2 (1–3)	2 (0–3)	0.04
Apgar 5 min, median (IQR)	5 (3–7)	6 (5–7.8)	6 (3.3–7)	4 (1–5)	< 0.001
Apgar 10 min, median (IQR)	7 (6–8)	7 (7–8)	7 (6–8)	5 (3.8–7)	0.002
Artery pH at birth, mean (SD)	6.94 (0.19)	7.06 (0.16)	6.87 (0.17)	6.92 (0.19)	0.003
Advanced resuscitation[a], *n* (%)	53 (67)	13 (56)	15 (60)	25 (80)	0.11
Whole-body hypothermia, (72 hr) *n* (%)	58 (73)	0 (0)	25 (100)	28 (90)	< 0.001
Hospitalization, mean (SD), d	11 (10.5)	8.9 (9.4)	12.3 (5.3)	10.7 (13.6)	0.001
Neonatal death, *n* (%)	22 (28)	0 (0)	1 (4)	21 (67)	< 0.001

HIE = hypoxic-ischemic encephalopathy, IQR = interquartile range.
[a]Included intubation for ventilation, chest compressions, or use of medications (epinephrine, sodium bicarbonate, and volume expansion).

were performed using SPSS version 20 (SPSS, Chicago, IL).

RESULTS

Eighty-six patients were enrolled; seven patients were excluded (one with cerebral stroke, two with cerebral vascular malformations, and four with sepsis-meningitis proven by cultures). Perinatal data are shown in **Table 2**. Differences between the three HIE stages were found with regard to: labor dystocia, emergency caesarean section, presence of meconium-stained liquor, umbilical cord artery pH at birth, Apgar scores at 1, 5, and 10 minutes, outborn birth, and age

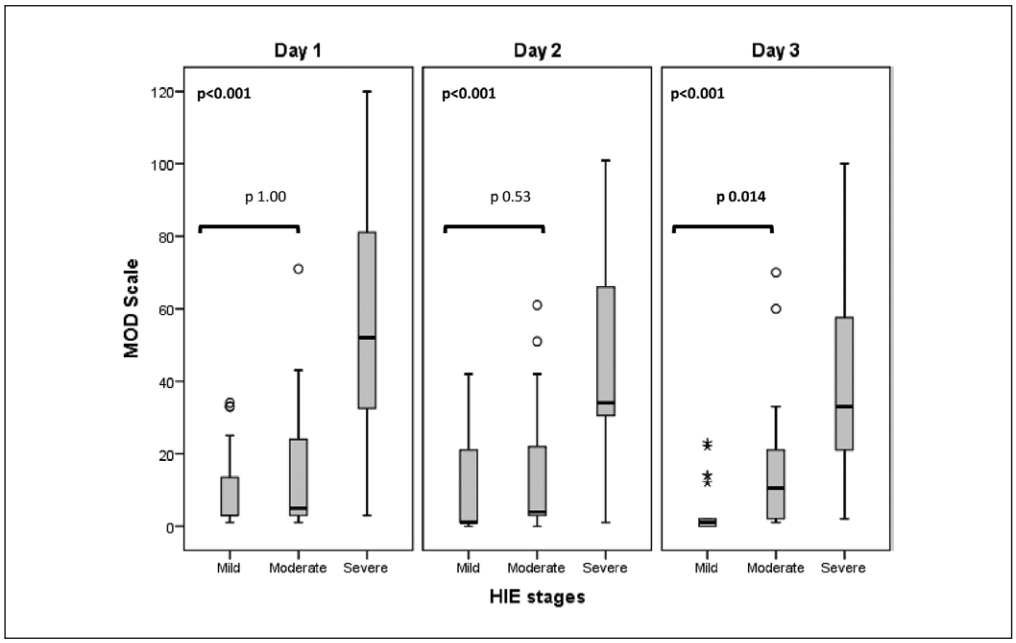

Figure 1. Multiple organ dysfunction scale scores according to hypoxic-ischemic encephalopathy stage. *Open circle* exceeds > 1.5 times interquartile range (IQR); *asterisk* exceeds > 3 times IQR. HIE = hypoxic-ischemic encephalopathy.

at admission. Therapeutic hypothermia was not undertaken in four of 56 patients with moderate and severe encephalopathy, due to the contraindications for this treatment. Two outborn patients with mild HIE produced serious doubts about the severity of the encephalopathy at 6 hours of life because of sedation at admission. Therefore, the physician in charge decided to start controlled hypothermia; the two patients were evaluated some hours later without sedation, and hypothermia was discontinued. Twenty-two patients (28%) died: one on day 1, four on day 2, four on day 3, and 13 after day 3. Nineteen patients with severe HIE died because of withdrawal of cardiorespiratory support. This decision was made after having the most accurate prognosis in those patients who had clinical findings consistent with persistent severe encephalopathy (coma) in combination with severe altered aEEG and severe neuroimaging findings (brain ultrasound scans and/or MRI) and after discussing the prognosis with the entire team involved (physicians, nurses, and other therapists) and the parents. One patient with severe HIE died because of refractory shock. In two patients (including the only patient with moderate HIE who died), death was due to refractory bleeding.

MOD scale was performed daily in 79 patients until day 3 or death. A total of 231 measurements were recorded: 79 on day 1, 78 on day 2, and 74 on day 3.

Correlation Between MOD Scale Scores and HIE Stage

Differences in MOD scores between the 3 HIE stages were found every day, from day 1 to 3 ($p < 0.001$). Post hoc analysis showed significant differences between severe HIE and the other HIE stages. No differences in the scores between moderate and mild HIE on days 1 and 2 were found, but there was a significant difference on day 3 (**Fig. 1**).

The ability of MOD scale to discriminate between patients with moderate-to-severe HIE and patients with mild HIE, evaluated by ROC analysis, comprised an area under the curve higher than 0.76 for every day assessed (**Supplementary material content 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A371).

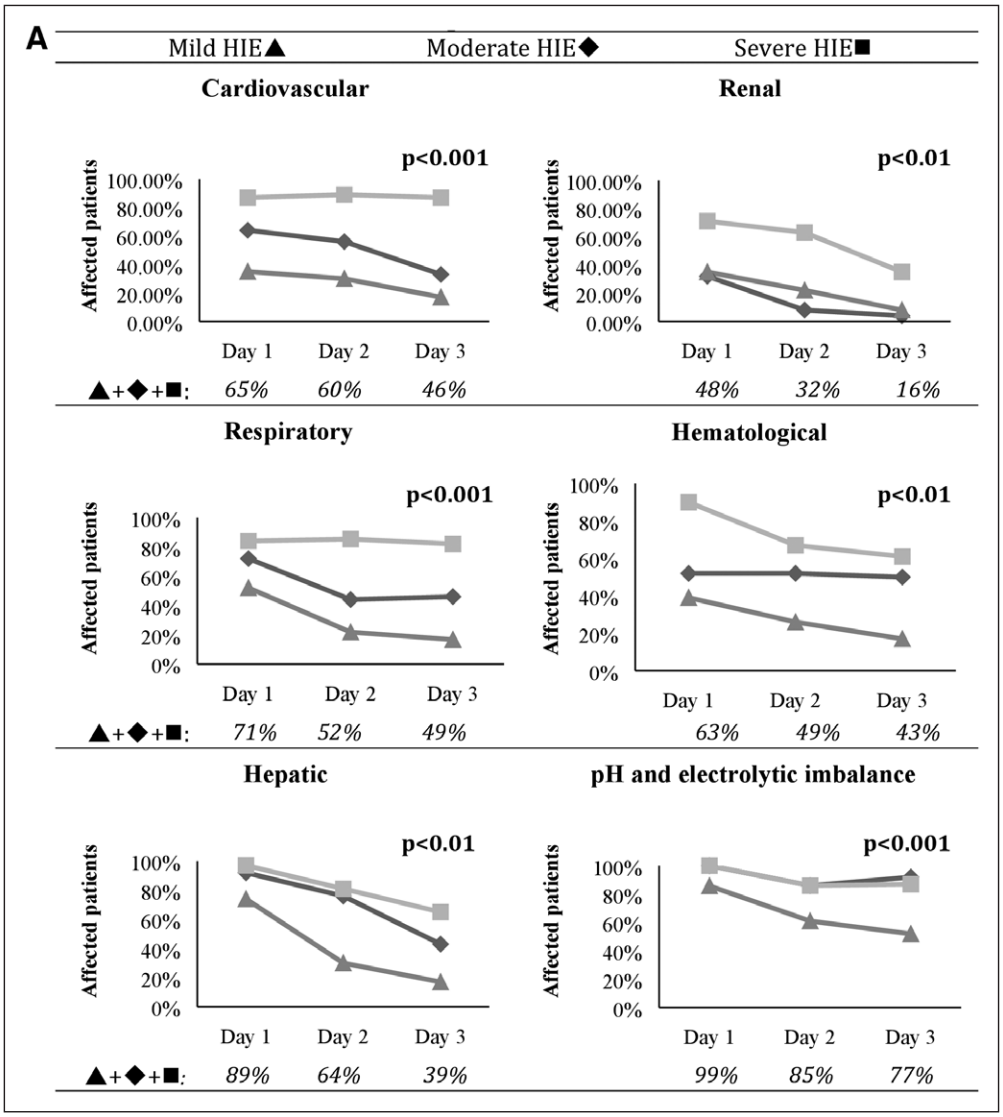

Figure 2. Specific organ involvement according to hypoxic-ischemic encephalopathy stage. **A**, Total organ involvement (mild to severe). (*Continued*)

Number of Affected Organs According to HIE Stage on the First Day of Life

In addition to CNS involvement, all patients had dysfunction of at least one organ system on the first day of life, and 56% presented dysfunction of five or six organ systems; the greater the severity of HIE, the higher the number of affected organs ($p < 0.001$). Moderate-to-severe involvement of at least one extracerebral organ was observed in 63% of patients: 43% of infants with mild HIE, 40% of those with moderate HIE, and 97% of those with severe HIE ($p < 0.001$). No patient with mild HIE had moderate or severe involvement of more than two organ systems, but in the case moderate and severe HIE, the figures were 12% and 74%, respectively.

Frequencies of Specific Organ Involvement

The organ systems most often affected were pH and electrolyte imbalance, and the hepatic system, while

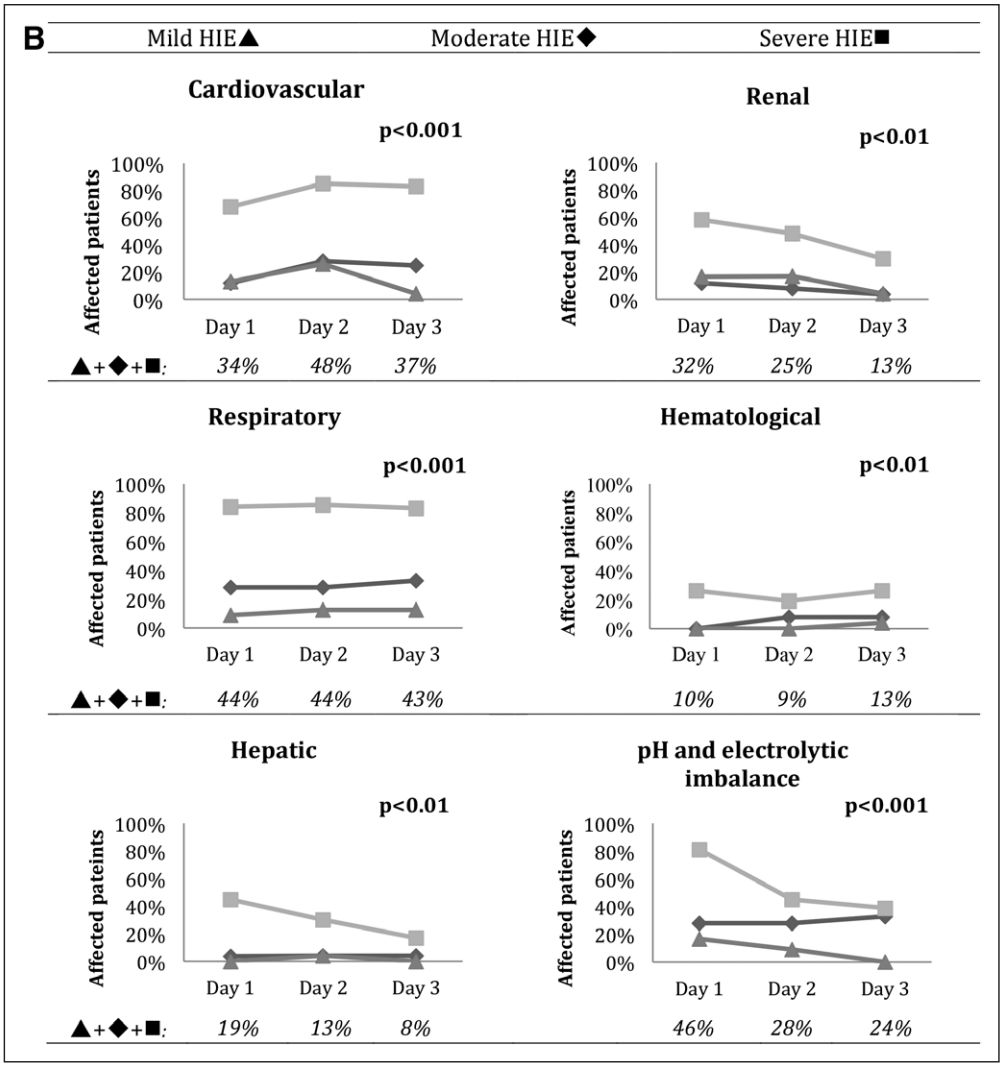

Figure 2 (*Continued*). B, Moderate and severe organ involvement. HIE = hypoxic-ischemic encephalopathy.

the least affected were the renal and hematological systems. Nevertheless, the organ systems most often affected in moderate-to-severe HIE were the respiratory system, pH and electrolyte imbalance on day 1, and cardiovascular system on day 2 (**Fig. 2**).

Specific Organ Involvement According to the Severity of HIE

Frequency and severity of involvement of the six organ systems evaluated were different between every HIE stage, from day 1 to 3 (**Fig. 2**). The distribution of each organ variable studied among HIE stages, from day 1 to 3, is shown in the **Supplementary Table 2** (Supplemental Digital Content 3, http://links.lww.com/PCC/A372).

On day 1, involvement of each organ system was compared in patients with significant HIE (moderate and severe) with those in mild HIE. Mild-to-severe involvement for each organ system had a PPV regarding significant HIE that ranged from 72% to 84%. When only moderate-to-severe organ involvement was considered, the PPV was greater than or equal to 89%, except for the renal system, which was 84%.

DISCUSSION

This is the first study to evaluate the correlation of MOD with the severity of HIE. In addition, it evaluates the profile of extracerebral damage within the first 3 days of life in a large cohort of asphyxiated newborns in the hypothermia era.

Extracerebral damage in infants with HIE that require admission to the neonatal ward remains almost universal: in our study, all patients had involvement of at least one extracerebral organ system on the first day of life, and nearly 90% had involvement of three to six organ systems.

The present study shows that the severity of MOD correlates with the severity of HIE. We found a positive correlation between the number of affected organ systems and the severity of HIE. By contrast, one previous retrospective study did not find a correlation between the number of affected organ systems and poor outcome (death or neurodevelopmental delay) (3); however, the high proportion of patients with missing data (59%) suggests caution be used in interpreting these results. In addition, our study found a stronger correlation between the severity of MOD and HIE when only moderate-severe degrees of organ involvement were considered: 12% and 74% of patients with moderate and severe HIE, respectively, presented with moderate to severe dysfunction of more than two organ systems, which did not occur in any case of mild HIE.

The use of our MOD scale allowed comparison of organ dysfunction across HIE stages. Therefore, the group of patients with significant MOD (moderate or severe) coincided closely with those with severe HIE. It is of interest to note that patients with moderate HIE presented a wide variability in MOD severity; some patients with moderate HIE presented with significant MOD, but the main difference between patients with moderate and mild HIE was that those with mild HIE had a faster resolution of organ damage.

Each of the six organ systems evaluated was more frequently and severely affected as the severity of HIE increased. The presence of moderate-severe involvement of each organ-system had a high PPV for moderate or severe HIE.

The profile of MOD in HIE infants in the era preceding hypothermia programs has been partially studied (1, 2). In last decades, several studies have yielded new data about the safety profile of hypothermia and the behavior of organ injury biomarkers in perinatal asphyxia (1, 3–8, 10–12, 16, 17, 21), and some of them have been shown to be either positively or negatively affected by hypothermia (7, 8), suggesting that the profile of MOD in asphyxiated newborns might have changed. The present study provides a complete spectrum of each organ system dysfunction, with which we may establish the profile of MOD in the hypothermia era. The ability to correct and maintain the acid-base imbalance and the presence of electrolytic disorders has been evaluated as part of MOD for the first time; it was the organ system most frequently affected, followed by the hepatic system, which was reported as the most frequently affected in previous studies (2). However, the organ systems most often affected in a moderate-severe degree were the cardiovascular and respiratory systems. A trend toward improvement of all organ systems with time was observed. Frequencies of involvement of the respiratory, cardiovascular, and hepatic systems were consistent with previously reported data (1–3). However, the renal system, which was the least affected, had less involvement than what was described in studies preceding hypothermia (1–3). This could be explained by the use of different criteria to define organ dysfunction, but it may also in part be due to the direct effect of hypothermia, as previously suggested (4). On the other hand, hematological involvement seems to be somewhat higher than in studies preceding the hypothermia era (1–3), which is probably due to the effect of this therapy on the platelet count (8).

Our study has several limitations. 1) Our scale is based on previous studies of MOD in perinatal asphyxia, safety studies of hypothermia, and studies of specific organ-damage biomarkers in asphyxiated newborns, but it has not been validated. However, the purpose of the present study was not to determine the prognostic value of the scale, but rather to use it as a mean to analyze the data. 2) Consistent and accepted surrogates of organ damage for each organ system were chosen. Although other biomarkers with greater specificity have been reported (e.g., ejection fraction to assess cardiovascular system function [12]), the biomarkers used in the study were those readily available in most hospitals in order to make our results maximally applicable in the clinical setting. 3) Our study was conducted at a single center, where the same encephalopathy grading scale is used and where there is homogeneous training in the evaluation of hypoxic-ischemic infants. Although this is a strength of the study, it needs to be considered when generalizing the results.

In summary, this study depicts the correlation of MOD in the first days of life with HIE severity and provides useful information for anticipating clinical problems. All patients with HIE admitted to the neonatal ward have MOD, and those with severe HIE suffer moderate or severe extracerebral organ dysfunction. Therefore, patients with moderate to severe dysfunction of more than two organ systems in the first hours of life are highly likely to have at least moderate, if not severe, HIE. On the other hand, when infants present with severe HIE in the first hours of life, it is possible to expect relevant MOD in the next hours, while those with moderate HIE can present wide variability in the severity of MOD. Finally, in the absence of MOD, the perinatal hypoxic-ischemic origin of a severe neonatal encephalopathy should be reconsidered.

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