Neonatal Hypoxic-Ischemic Encephalopathy Diagnosis and Treatment: A National Survey in China

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Abstract

Background: Neonatal hypoxic-ischemic encephalopathy (HIE) affects as many as 100,000 infants each year in China. Therapeutic hypothermia reduces HIE related mortality and long-term neurodevelopmental disabilities. National guidelines for HIE management were published a decade ago. This study aimed to investigate the current status of HIE diagnosis and treatment in China.

Method: This prospective cross-sectional national survey used a questionnaire evaluating practices related to HIE management. Descriptive statistics and Chi-square or Fisher's exact test were used, and a p-value of <0.05 was considered significant.

Results: The 273 hospitals that completed the survey were located in 31 of the 34 provincial districts in China. Eighty-eight percent of the hospitals were Level III hospitals, and 74% treated ten or more HIE cases annually. Awareness rates of the national guidelines for HIE diagnosis, HIE treatment, and therapeutic hypothermia protocol were 85%, 63%, and 78%, respectively. Neurological manifestations and blood gas were used as HIE diagnostic criteria by 96% (263/273) and 68% (186/273) of the hospitals, respectively. Therapeutic hypothermia was used in 54% (147/273) of hospitals. The percentage of general hospitals that implemented therapeutic hypothermia (43%, 71/165) was significantly lower than that in maternity and infant hospitals (67%, 49/73) ($\chi^2=11.752$, $p=0.001$) and children's hospitals (77%, 27/35) ($\chi^2=13.446$, $p<0.001$). Reasons for not providing therapeutic hypothermia included reduction of HIE cases in recent years (39%), high cost of cooling devices and treatment (31%), lack of training (26%), and safety concerns (4%). Among the hospitals that provided therapeutic hypothermia, 27% (39/147) were in full compliance with the recommended protocol. Eighty-one percent (222/273) of the hospitals treated HIE infants with putative neuroprotective agents alone or in combination with cooling. Ninety-one percent of the hospitals had long-term neurodevelopmental follow-up programs for infants with HIE.

Conclusions: There is significant heterogeneity in HIE diagnosis and treatment in China. Therapeutic hypothermia has not become a standard of care for neonatal HIE nationwide. Unproven agents are widely used for HIE treatment. Nationwide standardization of HIE management and dissemination of therapeutic hypothermia represent the opportunities to reduce mortality and improve long-term neurodevelopmental outcomes of children affected by HIE.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the latest manuscript can be downloaded and [accessed as a PDF](#).

Tables

Table 1. Characteristics of the survey respondents

Survey Variables	N=273	
Profession, No. (%)		
Neonatologist	196	(72)
Pediatrician	77	(28)
Professional title, No. (%)		
Senior	203	(74)
Intermediate	60	(22)
Junior	10	(4)
Type of hospital, No. (%)		
General hospital	165	(60)
Maternity and infant hospital	73	(27)
Children's hospital	35	(13)
Level of hospital, No. (%)		
III	239	(88)
II	33	(12)
I	1	(0.4)
NICU beds, No. (%)		
≥200	9	(3)
151-200	15	(5)
101-150	26	(10)
61-100	60	(22)
30-60	100	(37)
≤30	63	(23)
HIE cases treated annually, No. (%)		
≥50	47	(17)
40-50	10	(4)
30-40	26	(10)
20-30	53	(19)
10-20	66	(24)

Abbreviation: NICU: neonatal intensive care unit; HIE hypoxic-ischemic encephalopathy.

Table 2. HIE Diagnosis, Treatments and Follow-up

Survey Variables, <i>n</i> (%)	Total hospital <i>n</i> = 273	General hospital <i>n</i> = 165	Maternity and infant hospital <i>n</i> = 73	Children's hospital <i>n</i> = 35	<i>P</i> -value
Which indicator will you select to diagnose HIE?					0.516
Neurological manifestations	263 (96.3)	157 (95.2)	71 (97.3)	35 (100.0)	
Arterial blood gas	186 (68.1)	110 (66.7)	49 (67.1)	27 (77.1)	
Abnormal EEG/aEEG	152 (55.7)	79 (47.9)	44 (60.3)	29 (82.9)	
Abnormal MRI	200 (73.3)	126 (76.4)	43 (58.9)	31 (88.6)	
CT low density shadow	79 (28.9)	44 (26.7)	25 (34.2)	10 (28.6)	
Blood neuroenzymatic changes	86 (31.5)	52 (31.5)	18 (24.7)	16 (45.7)	
Does the unit you work provide TH?					<0.001
Yes	147 (53.8)	71 (43.0)	49 (67.1)	27 (77.1)	
Do you use any of the following agents to treat HIE?					0.462
Cytidine diphosphate choline	57 (20.9)	41 (24.8)	8 (11.0)	8 (22.9)	
Rat nerve growth factor	70 (25.6)	46 (27.9)	11 (15.1)	13 (37.1)	
Ganglioside	179 (65.6)	111 (67.3)	45 (61.6)	23 (65.7)	
Erythropoietin	37 (13.6)	21 (12.7)	11 (15.1)	5 (14.3)	
Cerebrolysin	24 (8.8)	17 (10.3)	5 (6.8)	2 (5.7)	
Does the unit you work have a long-term					0.69

follow-up service for HIE infants?				
Yes	248 (90.8)	149 (90.3)	68 (93.2)	31 (88.6)
How long is the best time of follow-up for HIE infants?				0.715
1 year old	41 (15.0)	28 (17.0)	9 (12.3)	4 (11.4)
2 years old	86 (31.5)	48 (29.1)	26 (35.6)	10 (28.6)
Preschool age	148 (54.2)	89 (53.9)	38 (52.1)	21 (60.0)
Which scale do you select to HIE infants?				0.106
Bayley	140 (51.3)	76 (46.1)	45 (61.6)	19 (54.3)
CDCC	69 (25.3)	45 (27.3)	18 (24.7)	6 (17.1)
Other standardized tests ^a	30 (11.0)	22 (13.3)	2 (2.7)	6 (17.1)
None of above	34 (12.5)	22 (13.3)	8 (11.0)	4 (11.4)

Abbreviation: HIE hypoxic-ischemic encephalopathy; TH therapeutic hypothermia, EEG electroencephalography, aEEG amplitude-integrated electroencephalography, MRI Magnetic resonance imaging, CT computerized tomography, GMs general movements, NBNA neonatal behavioral neurological assessment, DDST Denver developmental screening test.

^a Include Gesell, GMs, NBNA, Wechsler intelligence scale, and DDST.

Table 3. Reasons for Not Providing Therapeutic Hypothermia

reasons, <i>n</i> (%)	Total hospital <i>n</i> = 126	General hospital <i>n</i> = 94	Maternity and infant hospital <i>n</i> = 24	Children's hospital <i>n</i> = 8
reduction of HIE cases	49 (38.9)	34 (36.2)	12 (50.0)	3 (37.5)
high cost of cooling devices	39 (31.0)	29 (30.9)	7 (29.2)	3 (37.5)
lack of training in TH	33 (26.2)	26 (27.7)	5 (20.8)	2 (25.0)
concerns about the safety of TH	5 (4.0)	5 (5.3)	0 (0.0)	0 (0.0)

Abbreviation: HIE hypoxic-ischemic encephalopathy; TH therapeutic hypothermia

Table 4 Impact of Awareness of HIE Diagnosis and Treatment Guidelines

	HIE diagnosis		<i>P</i> -value
HIE diagnostic indicators, <i>n</i> (%)	Aware <i>n</i> = 232 (85)	Unaware <i>n</i> = 41	
Neurological manifestations	222 (95.7)	41 (100.0)	0.366
Arterial Blood gas	167 (72.0)	19 (46.3)	0.001
Abnormal EEG/aEEG	136 (58.6)	16 (39.0)	0.02
Abnormal MRI	174 (75.0)	26 (63.4)	0.122
CT low density shadow	66 (28.4)	13 (31.7)	0.671
Blood neuroenzymatic changes	75 (32.3)	11 (26.8)	0.485
	HIE Treatment		
	Aware <i>n</i> = 171 (63)	Unaware <i>n</i> = 102	
Rate of TH, <i>n</i> (%)	98 (57.3)	49 (48.0)	0.137
Neuroprotection agents, <i>n</i> (%)	133 (77.8)	89 (87.3)	0.052
	TH Protocol		
	Aware <i>n</i> = 129 (88)	Unaware <i>n</i> = 18	
Rate of TH compliance, <i>n</i> (%)	37 (28.7)	2 (11.1)	0.195

Abbreviation: HIE hypoxic-ischemic encephalopathy; EEG electroencephalography, aEEG amplitude-integrated electroencephalography, MRI Magnetic resonance imaging, CT computerized tomography, TH

therapeutic hypothermia.

Figures

Figure 1

Geographic distribution of survey respondents. A grayscale map of China was divided into five levels depends on population density. The fractions represented the number of hospitals that participated in the survey (denominator) and the number of surveyed hospitals that performed hypothermia treatment (numerator) in each province. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.