Long-Term Neurodevelopmental Outcome with Hypoxic-Ischemic Encephalopathy

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Objectives To determine the long-term neurodevelopmental outcome for children after hypoxic-ischemic encephalopathy (HIE) without major disability, and to examine neonatal injury patterns detected on cerebral magnetic resonance imaging (MRI) in relation to later deficits.

Study design Prospectively enrolled children with HIE and neonatal cerebral MRI data (n = 68) were examined at a mean age of 11.2 years (range, 8.2-15.7 years). Eleven children had a major disability (ie, cerebral palsy or mental retardation). Brain injury was scored according to the region and extent of injury.

Results Children without major disability (n = 57) had lower full-scale and performance IQ scores compared with norms (P = .02 and .01, respectively), and the proportion of children with an IQ <85 was higher than expected (P = .04). Motor performance on the Zurich Neuromotor Assessment was affected in the pure motor, adaptive fine motor, and gross motor domains, as well as in the movement quality domain (all P < .001). Watershed injury pattern on neonatal MRI correlated with full-scale and verbal IQ scores (P = .006 and <.001, respectively), but neonatal MRI pattern did not correlate with motor performance in children without major disability.

Conclusion Children who sustained neonatal HIE without major disability are at increased risk for long-term intellectual, verbal, and motor deficits. The severity of watershed injury is correlated with later intellectual performance. Long-term follow-up examinations are necessary for early detection of neurodevelopmental impairment and early initiation of adequate therapies. *(J Pediatr 2013;163:454-9)*.

Hypoxic-ischemic encephalopathy (HIE) occurs in 1-6 of 1000 live term births and is a major cause of neurodevelopmental disability.[1,2] Long-term neurodevelopmental outcome depends on the severity of HIE,[2] with adverse outcomes rare in children with mild HIE, more common in children with moderate HIE, and invariably present in children with severe HIE.[3] Numerous previous outcome studies of children with HIE have focused on major adverse outcomes, including death, cerebral palsy (CP), or severe cognitive impairment. However, deficits in the absence of CP or major disability may include intellectual impairments, specific memory and verbal problems, and difficulties in executive functions, behavior, and social competence.[4,5] Some studies also have reported motor problems in children with only mild HIE.[6,7] Whether these problems persist into adolescence and young adulthood is not clear. Some studies including neonates with biochemical markers of hypoxia found that problems with short-term memory and time perception, as well as difficulties in social interaction, persisted into young adulthood.[8,9]

Neonatal cerebral magnetic resonance imaging (MRI) has become the standard tool to determine the timing of brain injury and define injury patterns.[10] It has been widely accepted that the risk of an abnormal neurodevelopmental outcome increases with the severity of brain injury.[11,12] However, the pattern of injury may be more predictive than the severity of lesions identified on MRI. The basal ganglia/thalamus pattern has been associated with severely impaired motor and cognitive outcomes,[2,7] and the "watershed"-predominant pattern has been associated with cognitive impairments that often occur in the absence of functional motor deficits.[2,3] More recently, a correlation between a watershed-predominant pattern of injury and verbal IQ has been demonstrated in 4-year-old children.[13] Little is known about the association between neonatal MRI injury pattern and long-term neurodevelopmental outcomes in children without major disability. We examined the spectrum and severity of neurodevelopmental impairments in 11-year-old nondisabled survivors of HIE and evaluated the role of MRI-detected injury patterns on neurodevelopmental outcomes in these children.

Methods

Between 1989 and 1993, 94 term neonates born at ≥36 completed weeks of gestation who were at risk for hypoxic-ischemic brain injury due to perinatal

CP	Cerebral palsy
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
ZNA	Zurich Neuromotor Assessment

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asphyxia were included in this prospective cohort study. The study was approved by the local Ethics Committee. Informed consent was obtained from the parents. For enrollment into the study, 3 groups of diagnostic criteria were established (at least 1 criterion in 2 groups had to be fulfilled): (1) intrauterine asphyxia: bradycardia (heart rate <80 bpm), limited beat-to-beat variability, late decelerations, or meconium-stained amniotic fluid; (2) perinatal asphyxia: Apgar score <5 at 5 minutes or <6 at 10 minutes, umbilical cord blood pH <7.1, and base deficit <−10 mmol/l; and (3) postpartum encephalopathy during the first 48 hours of life: seizures, lethargy, or pathological spontaneous movements. Infants with a genetic syndrome or major malformations, a metabolic and/or endocrinologic disease, requiring surgery, cardiovascular resuscitation (attributable to a condition other than asphyxia), exchange transfusion owing to severe hyperbilirubinemia during the neonatal period, repetitive hypoglycemia <1 mmol/L, meningitis and/or encephalitis, or septic shock were excluded.

The severity of HIE was assessed clinically using the Sarnat staging system during the first days of life.[11] Of the 94 infants enrolled, 68 were eligible for follow-up examination at age 11 years (**Figure 1**; available at www.jpeds.com). Complete neurodevelopmental assessment could be obtained in 57 of these 68 children (84%). Among the other 11 children (16%), 9 had severe CP (Palisano grade 4 or 5) and 2 had mild CP (Palisano 1) with severe mental retardation (IQ <55). These 11 children were classified as having a major disability. Outcome information for the 11 children with a major disability was obtained from parental telephone interviews in 9 children and examination at the Child Development Center Zurich in 2 children.

Neuroimaging

Cerebral MRI was performed in all infants between day 1 and day 30 of life. In 56 of the 68 eligible infants (82.4%), MRI was performed within the first week of life, on day 1 in 4 (6%). Three of the latter 4 infants who were eligible for follow-up underwent repeat MRI at 6 days, 1 month, and 3 months, respectively. Sixty-three of the 68 infants (86.8%) underwent MRI within the first 10 days of life. Axial T1-weighted images (repetition time, 500 ms; echo time, 30 ms) and T2-weighted images (repetition time, 3000 ms; echo time, 120 ms) were obtained using a 256 × 256 imaging matrix, on a 2.35-T, 40-cm bore system. When axial MRI revealed suspected parasagittal lesions in very cephalad regions, additional coronal images were obtained.[14] A neuroradiologist (E.M.), blinded to the infants' clinical conditions and neurodevelopmental outcomes, scored each neonatal MRI on 3 scales, rating the degree of injury from 0 to 3 (normal to severe injury) for 3 injury patterns—watershed, basal ganglia/thalamus, and perirolandic region—as described previously.[14,15] Basically, each region was graded according to the degree of HIE (0, no injury; 1, mild; 2, moderate; 3, severe) in that specific injury site. Patterns of injury on MRI were then defined on the basis of the predominant site of injury: watershed-predominant, basal ganglia/thalamus-predominant, perirolandic region-predominant, or normal (**Table I**).

Neurodevelopmental Outcome

The children were examined at the Child Development Center of Zurich University Children's Hospital by an experienced developmental pediatrician (S.R) who was aware of their clinical courses. Socioeconomic status score was based on a 12-point scale based on paternal occupation and maternal education (each with a score of 1-6; total score, 2-12).[16] Children were examined with the German version of the *Wechsler Intelligence Scale for Children–Revised*.[17] This test consists of verbal IQ and performance IQ scales, which together compose the full-scale IQ. The German version of the *Kaufman-Assessment Battery for Children*[18] was administered to 2 children who were not able to complete the *Wechsler Intelligence Scale for Children–Revised*.

Neuromotor Assessment

CP was classified according to European guidelines,[19] and CP severity was graded according to the scale of Palisano et al.[20]

Table I. MRI injury pattern stratified for major disability status

Score	Children with a major disability (n = 11)*	Children without a major disability (n = 57)	*P* value†
Basal ganglia/thalamus, median (range)	2 (0-3)	0 (0-3)	<.001
0	2 (18.2)	39 (68.4)	<.001
1	2 (18.2)	9 (15.8)	
2	2 (18.2)	8 (14.0)	
3	5 (45.5)	1 (1.8)	
Perirolandic region, median (range)	3 (0-3)	0 (0-3)	<.001
0	3 (27.3)	40 (70.2)	<.001
1	0 (0)	13 (22.8)	
2	2 (18.2)	3 (5.3)	
3	6 (54.5)	1 (1.8)	
Watershed injury, median (range)	3 (0-3)	1 (0-3)	.006
0	2 (18.2)	17 (29.8)	.001
1	1 (9.1)	19 (33.3)	
2	2 (18.2)	19 (33.3)	
3	6 (54.5)	2 (3.5)	

Values are n (%) unless indicated otherwise.
*Major disability: severe CP or severe mental retardation (IQ <55).
†Mann-Whitney *U* test for comparison of median scores; χ^2 test for comparison of overall distribution of scores.