Follow-up of the term infant after hypoxic-ischemic encephalopathy

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While the number of survivors of term hypoxic-ischemic encephalopathy (HIE) is lower than the number of survivors of extreme prematurity, the proportion of neonates with long-term sequelae is higher. All neonates with Sarnat stages 2 (moderate) and 3 (severe) should be enrolled in follow-up programs. The present paper discusses the clinical and imaging diagnostic criteria for HIE, which are essential to decisions about follow-up. Prognostic indicators are also summarized. The recommendations for follow-up and intervention are based on the clinical condition of the baby at the time of discharge from intensive care, including an assessment of feeding, vision, hearing and whether seizures continue to be present. Early assessments (at four to eight months) focus on head growth, general health and motor neurodevelopment. Assessments at 12 to 24 months focus on cognitive skills and language development. Preschool assessments are also strongly recommended to provide for the identification of children requiring early education programs. Knowledge of long-term outcome and its secular changes enhance prognostication, and the evaluation of new preventive and therapeutic approaches.

Key Words: *Asphyxia; Follow-up; Outcome; Term infant*

Le suivi du nourrisson à terme après une encéphalopathie hypoxique-ischémique

Le nombre de survivants d'une encéphalopathie hypoxique-ischémique (EHI) est plus faible que le nombre de grands prématurés survivants, mais la proportion de nouveau-nés ayant des séquelles à long terme est plus élevée. Tous les nouveau-nés au stade de Sarnat 2 (modéré) et 3 (grave) devraient être inscrits à un programme de suivi. Le présent article traite des critères diagnostiques cliniques et d'imagerie de l'EHI, essentiels pour prendre des décisions au sujet du suivi. Les indicateurs pronostiques sont également résumés. Les recommandations de suivi et d'interventions dépendent de l'état clinique du bébé au moment du congé des soins intensifs, y compris une évaluation de son alimentation, de sa vue, de son ouïe et de la présence ou de l'absence de convulsions. Les premières évaluations (entre quatre et huit mois) sont axées sur la circonférence crânienne, l'état de santé général et la neurologie du développement moteur. Les évaluations entre 12 et 24 mois portent sur les aptitudes cognitives et le développement du langage. De plus, les évaluations préscolaires sont fortement recommandées afin de dépister les enfants ayant besoin d'un programme d'éducation précoce. Le fait de connaître le sort et les changements à long terme améliore le pronostic ainsi que l'évaluation de nouvelles démarches préventives et thérapeutiques.

The goals of follow-up are to detect impairment or normality, keep parents informed, promote early intervention and detect changes in outcomes. The purposes of the present paper are to describe a follow-up regimen for newborn infants with hypoxic-ischemic encephalopathy (HIE) and to explain its basis. The basis depends on accurate diagnosis of neonatal HIE, which is needed to identify, categorize and select patients for follow-up. Therefore, we summarize the literature on prediction of outcome in the first days after birth, which is needed to provide information to families and to individualize follow-up. Based on the prognosis of appropriately categorized infants, a plan of follow-up and early intervention is suggested.

DEFINITION OF HIE

Neonatal HIE is an acute, nonstatic encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia. Persistent hypoxia implies 'asphyxia', usually associated with hypercarbia and causing metabolic acidosis. The latter – in effect, a cumulative oxygen debt – is quantified in blood by the base deficit value. The effects of hypoxia on the perfusion of individual organs or vascular territories depend on a number of variables. Ischemia (insufficient blood to supply needs) of the 'nonessential' organs occurs in early hypoxia; with prolongation, the essential organs (brain, heart and adrenal glands) also become ischemic. Brain 'hypoxia-ischemia' results in HIE with its clinical manifestations (1,2).

HIE severe enough to cause permanent brain injury is conventionally defined retrospectively by consensus-based criteria (3,4), together constituting a clinical syndrome that describes a causal pathway of HIE (5). The pathway includes evidence of fetal difficulty in the final hours before birth, depression at birth and the need for resuscitation, severe metabolic acidosis, neonatal clinical and imaging signs of acute neurological abnormalities, evidence of dysfunction of other systems and exclusion of other causes of neonatal encephalopathy (4).

Certain caveats are necessary regarding the individual criteria for the neonatal diagnosis of HIE. Data are commonly

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missing, inaccurate and inconsistent, particularly for blood gases, Apgar scores, appropriate brain imaging and results of testing for organ dysfunction. The consensus criteria are probably restrictive, as evidenced by data from clinical trials of hypothermia to prevent brain injury in infants with HIE (eg, the 5 min Apgar score was greater than 3 in 27% of subjects in one trial and greater than 5 in 9% in another) (6,7). The consensus criteria changed significantly in the past decade, and more changes are anticipated as new research results are published. Further, hypoxic-ischemic insults in the recent antepartum period (measured in hours) may result in a similar obstetric and neonatal clinical picture, as well as identical brain injuries. With insults less proximal to birth, the clinical presentation is often delayed until well after birth and does not conform with the consensus-based criteria (8). Another caveat pertains to near-term infants (35 to 36 weeks), in whom the diagnosis of HIE may be confounded by hypotonia of prematurity. Despite these limitations, consensus criteria for HIE provide a useful framework.

The diagnosis of postasphyxial HIE may be difficult when conditions that cause or predispose to intrapartum asphyxia coexist with evidence of intrapartum asphyxia. Examples include chorioamnionitis, septic or hemorrhagic shock, cranial birth trauma, bilateral stroke involving two or more vascular territories, and neonatal hypoglycemia. HIE may also result from an asphyxial event occurring postnatally or from postnatal complications of prenatal disorders (eg, persistent pulmonary hypertension).

The three-stage categorization of HIE of Sarnat and Sarnat (1) is in common use; the most severe stage in serial examinations, between 1 h and seven days of life, is the stage most useful in prognosis and follow-up decisions (9). Other classifications of HIE are mentioned by Volpe (2), although long-term prognosis for neonates with stage 2 HIE is also not well clarified.

INVESTIGATION OF NEONATES AFTER ASPHYXIA AND WITH SIGNS OF ENCEPHALOPATHY

Neonatal investigations contribute to diagnostic and prognostic accuracy. Umbilical arterial and venous blood at birth, and samples from the newborn infant in the first hour or two after birth (although subject to various false-positive and false-negative results and difficulties of interpretation), are useful for the diagnosis of HIE (4). Pertinent brain imaging and electroencephalography have important diagnostic and prognostic roles in HIE. Other causes of neonatal encephalopathy should be excluded (4).

SUMMARY OF PROGNOSTIC INDICATORS IN THE FIRST DAYS AFTER BIRTH

Follow-up planning can wait until near discharge. As the neonatal illness progresses over the first few days, more information becomes available, and the accuracy of prediction of outcome of survivors improves. Reported useful predictors include fetal cardiotochography, administration of chest compressions at birth, severity of metabolic acidosis at birth, duration of apnea after birth, encephalopathy category, age of seizure onset, neonatal behavioural examination, electroencephalogram changes and brain imaging (10-15). Definition of the asphyxial time course and sites of brain pathology on imaging may contribute prognostic information (15). An understanding of the associations between time course of asphyxial insult, brain pathology, brain imaging findings and long-term disability, based on observations in animals and humans (16-18), is summarized in Table 1. Brain-damaging, acute, near-total asphyxial insults (eg, as caused by uterine rupture) are usually accompanied by continuous bradycardia that leads to emergency delivery and are associated with a central pattern of brain damage with relative cortical sparing. On the other hand, brain-damaging, prolonged, partial asphyxial insults (eg, as seen with functional placental insufficiency) are usually accompanied by intermittent fetal heart rate decelerations of longer duration, and are associated with cortical injury in the watershed zones and relative sparing of the central grey matter. Prolongation of either type of asphyxial insult results in more global damage.

TABLE 1
Relationships between time course of asphyxial insult, site(s) of brain injury and type of disability

Time course*		Typical site of brain injury	Disability
Acute, near-total	Moderate	Basal ganglia and thalami	Athetoid or dystonic CP, intact or mildly impaired cognitive development
	Severe or prolonged	Cerebral cortex added to basal ganglia and thalami	Severe, spastic quadriplegia, cortical visual impairment, microcephaly, cognitive deficit
Prolonged, partial	Moderate	Watershed regions	Moderate, spastic quadriplegia, variable cognitive deficit
	Severe	Extensive cortical pathology	Spastic quadriplegia, severe cognitive impairment, cortical visual impairment, microcephaly

**See references 16-18. CP Cerebral palsy*

RECOMMENDATIONS FOR FOLLOW-UP AND INTERVENTION

The timing and type of individual childhood follow-up after HIE are based on the detectability of impairments as follows: severe motor or sensory loss (first year), low developmental quotient (second year), fine and gross motor dysfunction (two to four years), abnormalities in cognitive function (four to seven years) and learning disabilities (seven to nine years) (19). Levene (20) commented that cognitive impairment, as measured by IQ, appears to represent a continuum of disability reflecting the severity of the asphyxial insult. This differs from the assertion that adverse outcomes of postasphyxial

HIE are restricted to cerebral palsy of the quadriplegic or dyskinetic types (4). Recommended standardized measurements and their times of administration for high-risk newborns are available (21).

RECOMMENDATIONS FOR THE NEWBORN PERIOD, BEFORE HOSPITAL DISCHARGE

Intensive follow-up for those most likely to have severe disability

Surviving neonates with stage 3 HIE, as well as those with stage 2 HIE and feeding and swallowing difficulties, should be referred directly to a developmental therapist, and, if severe, to a feeding team. Referral before hospital discharge helps parents to learn how to use community resources, including respite. Acceptance of a shared-care concept for the severely disabled child greatly assists the parents in future years. Parents should also be aware of the risk of post-discharge death of the most severely affected infants.

Vision loss

Because of the possibility of damage of the posterior visual pathway, including the primary visual cortex, the indications for early referral to a paediatric ophthalmologist include the following: stage 3 HIE, stage 2 HIE with an abnormal neurological examination or reduced visual awareness at hospital discharge, and stroke associated with HIE. Although cortical visual impairment may improve with time, close monitoring and appropriate intervention by an ophthalmologist can avoid secondary amblyopia, with optimal preservation of vision. Ophthalmological examination may have other benefits, such as revealing optic atrophy or optic nerve hypoplasia.

Sensorineural hearing loss

The assessment of sensorineural hearing by testing brainstem evoked responses is indicated after intrapartum asphyxia and before discharge from hospital (22). Should persistent pulmonary hypertension of the newborn accompany the diagnosis of HIE, the child is at risk for late-onset sensorineural hearing loss (23), and repeated testing in early childhood is indicated.

Seizures

More than one-half of infants with HIE have neonatal seizures (24). Epilepsy develops by 3.5 years of age in 10% of subjects (9); few develop epilepsy after this age (25,26). Neonates with continuing, difficult-to-treat neonatal seizures should have postdischarge medical supervision by a physician with knowledge of epilepsy.

Head circumference and growth

The head circumference at birth is an important baseline parameter; measurements below the third percentile may indicate that brain pathology preceded the intrapartum asphyxia, whereas a normal baseline with subsequent decelerated growth suggests a peripartum cause. A decrease of head circumference growth in the early months, as determined by serial measurements, is associated an with adverse outcome (27-29).

Newborns with HIE who are feeding adequately on discharge

Newborns with HIE who are feeding adequately on discharge – the majority of cases of HIE – fall into two groups. Those with stage 1 encephalopathy, including hyperalertness and hyperexcitability and no hypotonia, should be discharged to regular care unless they have a secondary diagnosis requiring specialized follow-up; their parents should be assured of their good prognosis (26,30). We recommend that those with any degree of hypotonia for any duration or abnormalities on cranial imaging should attend a developmental follow-up clinic. Low shoulder girdle muscle tone implies a watershed lesion for which regular follow-up is indicated. In the authors' opinion, follow-up is indicated for all infants surviving stages 2 and 3 HIE, as well as those with encephalopathic signs persisting at discharge (21).

Later sequelae of neonatal HIE

Neonatal HIE in infants with a gestational age of 34 weeks or more was considered the likely cause of cerebral palsy in 23 of 152 cases (15%) born in western Sweden in 1995 to 1998 (numbers derived from Table 1), most commonly spastic quadriplegia and dyskinetic cerebral palsy (8). Prevalence of the latter has increased (8), which may be related to an increased rate of vaginal birth after previous cesarean section (31). Hemiplegic and diplegic spastic cerebral palsy and ataxia are uncommonly attributable to neonatal HIE (32). Severe cerebral palsy is usually detected by 12 months and less severe cerebral palsy by two years of age; dystonia and athetosis are occasionally detected later. Developmental delay without motor sequelae may result from neonatal HIE (20,33), and less severe cognitive deficits without motor sequelae may not be detected until school age (26,33).

RECOMMENDATION FOR THE FOUR- TO EIGHT-MONTH NEURODEVELOPMENTAL FOLLOW-UP VISIT

For the more severely involved neonates, several early assessments may be necessary to initiate early intervention. Key concerns are adequate feeding and nutrition, head growth, visual awareness and motor development. Oral-motor function, including facial and mouth muscle tone, salivary control, coordination of feeding and swallowing, and early vocalization, are evaluated. At six months, the opportunity exists to ensure that primitive reflexes have subsided, balance reactions are developing and muscle tone has normalized. For those infants without a chronic neurological diagnosis, assessment by a physical therapist with a standardized measure (34-36) to monitor progress and guide therapy is useful. Other standardized neurological or visual tests (37) may be similarly valuable.

RECOMMENDATIONS FOR 12- TO 24-MONTH NEURODEVELOPMENTAL FOLLOW-UP VISITS

For most survivors not referred to paediatric rehabilitation programs, follow-up is recommended between 12 and 24 months, ensuring ongoing multidisciplinary team monitoring. By 18 to 24 months, motor impairment, including oral-motor dyspraxia, can be confirmed. We recommend that the Bayley III cognitive, language, motor and adaptive behavioural scales (35) be conducted at this time, if not precluded by severe motor, mental or visual impairment. Enrolment in early learning programs is encouraged. Language scores lower than mental scores are not uncommon after bilateral asphyxial watershed injury at term; referral to a speech-language pathologist is helpful. If hearing loss of late onset is suspected for any reason, audiological examination is repeated.

RECOMMENDATIONS FOR THE THREE- TO FIVE-YEAR ASSESSMENT

A three-year assessment provides the child with the opportunity of referral to an early educational program. A speech and language assessment rules out oral-motor dyspraxia or language disorders. Isolated cognitive deficit occurs more commonly than in the general population (33,38), and school-readiness delay is found in almost one-half of the nondisabled survivors (25). A number of measures may be used to evaluate cognitive and adaptive behavioural function (21). Examination of gross motor skills, especially those requiring balance, and fine motor skills, especially motor speed and visual attention, are important (33).

RECOMMENDATIONS FOR THE EIGHT- TO 10-YEAR ASSESSMENT

Most children requiring specialized educational assistance are identified by school age. For those remaining with school difficulties, assessments to be offered include the Wechsler Intelligence Scale for Children – IV (39), a school achievement test (40,41), and measures of language and auditory processing (33). An adaptive behavioural measure (42) is recommended to support findings of the cognitive assessment. In some cases, a neuropsychological screen (43) or referral to a neuropsychologist may be indicated.

THE FUTURE

Follow-up is based on prognostication. Outcome predictions are improving, qualitatively and quantitatively, based on developing epidemiological and statistical methods, as well as better definition of neuropathology and neuropathophysiology by brain imaging and electrophysiology. Better predictive data from prospective, geographically based clinical research with interdisciplinary participation will contribute to improved prognostication. A culture of multicentre collaboration through the implementation of large clinical trials and disease registries will contribute to progress. Follow-up challenges will continue as long as the prevention or cure of postasphyxial HIE is beyond our reach.

REFERENCES

1. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
2. Volpe JJ. Hypoxic-ischemic encephalopathy: Clinical aspects. In: Neurology of the Newborn, 4th edn. Philadelphia: WB Saunders Co, 2000:331-96.
3. Policy Statement of the Society of Obstetricians and Gynaecologists of Canada. Task Force on Cerebral Palsy and Neonatal Asphyxia (Part I). J Soc Obstet Gynaecol Can 1996;18:1267-79.
4. American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy and Cerebral Palsy and the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology. Washington: American College of Obstetricians and Gynecologists, 2003.
5. Blair E, Stanley F. Aetiological pathways to spastic cerebral palsy. Paediatr Perinat Epidemiol 1993;7:302-17.
6. Gluckman PD, Wyatt JS, Azzopardi D, et al; Cool Cap Study Group. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomized trial. Lancet 2005;365:1319-27.
7. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84.
8. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. XI. Prevalence and origin in the birth-year period 1995-98. Acta Paediatr 2005;94:287-94.
9. Robertson CMT, Finer NN. Term infants with hypoxic-ischemic encephalopathy: Outcome at 3.5 years. Dev Med Child Neurol 1985;27:473-84.
10. Schifrin BS. The CTG and the timing and mechanism of fetal neurological injuries. Best Pract Res Clin Obstet Gynaecol 2004;18:437-56.
11. Peliowski A, Finer NN. Birth asphyxia in the term infant. In: Sinclair JB, Bracken MB, eds. Effective Care of the Newborn Infant. Oxford: Oxford University Press, 1992:249-79.
12. Ekert PG, Perlman M, Steinlin M, Hao Y. Predicting outcome of severe perinatal asphyxia in term infants in the first 4 hours of life. J Pediatr 1997;131:613-7.
13. Shah PS, Beyene J, To T, Ohlsson A, Perlman M. Post-asphyxial hypoxic ischemic encephalopathy in neonates: Outcome prediction rule within four hours of birth. Arch Pediatr Adolesc Med 2006. (In press)
14. Thompson CM, Puterman AS, Linley LL, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr 1997;86:757-61.
15. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr 2005;146:453-60.
16. Myers RE, Adamsons K. Obstetric considerations of perinatal brain injury. In: Scarpelli EM, Cosmi EV, eds. Reviews in Perinatal Medicine, vol 4. New York: Raven Press, 1981:221-45.
17. Pasternak JF, Gorey MT. The syndrome of acute near-total intrauterine asphyxia in the term infant. Pediatr Neurol 1998;18:391-8.
18. Roland EH, Poskitt K, Rodriguez E, Lupton BA, Hill A. Perinatal hypoxic-ischemic thalamic injury: Clinical features and neuroimaging. Ann Neurol 1998;44:161-6.
19. Amiel-Tison C, Ellison P. Birth asphyxia in the full term newborn: Early assessment and outcome. Dev Med Child Neurol 1986;28:617-82.
20. Levene MI. Management and outcome of birth asphyxia. In: Levene MI, Lilford RJ, Bennett MJ, Punt J, eds. Fetal and Neonatal Neurology and Neurosurgery. London: Churchill Livingstone, 1995:427-42.
21. Vohr B, Wright LL, Hack M, Aylward G, Hirtz D. Follow-up care of high-risk infants. Pediatrics 2004;114(Suppl 1):1377-97.
22. Joint Committee on Infant Hearing 1990 Position Statement. ASHA Suppl 1991;5:3-6.
23. Inhaled nitric oxide in term and near-term infants: Neurodevelopmental follow-up of the neonatal inhaled nitric oxide study group (NINOS). J Pediatr 2000;136:611-7.
24. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology 1987;37:1837-44.

25. Robertson CMT, Finer NN. Educational readiness of survivors of neonatal encephalopathy associated with birth asphyxia at term. J Dev Behav Pediatr 1988;9:298-306.
26. Robertson CMT, Finer NN, Grace MGA. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. J Pediatr 1989;114:753-60.
27. Cordes I, Roland EH, Lupton BA, Hill A. Early prediction of the development of microcephaly after hypoxic-ischemic encephalopathy in the full-term newborn. Pediatrics 1994;93:703-7.
28. Mercuri E, Ricci D, Cowan FM, et al. Head growth in infants with hypoxic-ischemic encephalopathy: Correlation with neonatal magnetic resonance imaging. Pediatrics 2000;106:235-43.
29. Badawi N, Kurinczuk JJ, Blair EE. Early prediction of the development of microcephaly after hypoxic-ischemic encephalopathy in the full-term newborn. Pediatrics 1994;93:703-7.
30. Handley-Derry M, Low JA, Burke SO, Waurick M, Killen H, Derrick EJ. Intrapartum fetal asphyxia and the occurrence of minor deficits in 4- to 8-year-old children. Dev Med Child Neurol 1997;39:508-14.
31. Landon MB, Hauth JC, Leveno KJ, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. N Engl J Med 2004;351:2581-9.
32. Nelson KB, Grether JK. Potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight. Am J Obstet Gynecol 1998;179:507-13.
33. Robertson C. Long-term follow-up of term infants with perinatal asphyxia. In: Stevenson KD, Sunshine P, eds. Fetal and Neonatal Brain Injury. Cambridge: Cambridge University Press 2002:829-58.
34. Piper MC, Darrah J. Motor Assessment of the Developing Infant. Philadelphia: WB Saunders Co, 1994.
35. Bayley Scales of Infant and Toddler Development – 3rd edn. San Antonio: The Psychological Corporation, 2006.
36. Amiel-Tison C. Neuromotor Status. Boston: Little, Brown & Company, 1987.
37. Atkinson JJ, van Hof-van Duin J. Assessment of normal and abnormal vision during the first year of life. In: Fielder A, Bax M, eds. Management of Visual Handicap in Childhood. London: Mac Keith Press, 1993:9-39.
38. Cowan F. Outcome after intrapartum asphyxia in term infants. Semin Neonatol 2000;5:127-40.
39. Wechsler D. The Wechsler Intelligence Scale for Children – IV. San Antonio: The Psychological Corporation, 2003.
40. Wechsler D. Wechsler Individual Achievement Test – II. San Antonio: The Psychological Corporation, 2004.
41. Sheslow D, Adams W. Wide Range Assessment of Memory and Learning Administration Manual. Wilmington: Jastek Associates, 1990.
42. Harrum PL, Oakland T. Manual for the Adaptive Behaviour Assessment System II (5 years). San Antonio: The Psychological Corporation, 2003.
43. Korkman M, Kirk U, Kemp S. Neuropsychological Test. San Antonio: The Psychological Corporation, 1997.