Hypoxic-Ischemic Neonatal Encephalopathy

Hamid Nemati .MD, Child Neurologist
Shiraz Neurosciences Research Center, SUMS

SCOPE OF THE PROBLEM

Neonatal encephalopathy (NE) is a clinical syndrome characterized by “a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes,” in the earliest days of life of a term newborn.

The clinical signs and symptoms of neonatal brain injury depend on the severity, timing, and duration of the insult, and the newborn’s maturity, even within ages considered “full term.”

Not all newborns with significant acquired brain injuries present with an easily recognizable encephalopathy or seizures. Some conditions, such as stroke and perinatal white-matter injury, may only have subtle manifestations that may not be recognized on clinical examination.

NE remains a major cause of neurodevelopmental disability, with a spectrum of outcomes that are not limited to cerebral palsy and also include cognitive and behavioral disabilities and epilepsy.

TABLE 19-1 Encephalopathy Score

Encephalopathy Sign	Score = 0	Score = 1
Feeding	Normal	Gavage feeds, gastrostomy tube or nothing by mouth
Alertness	Alert	Lethargy, irritable, poorly

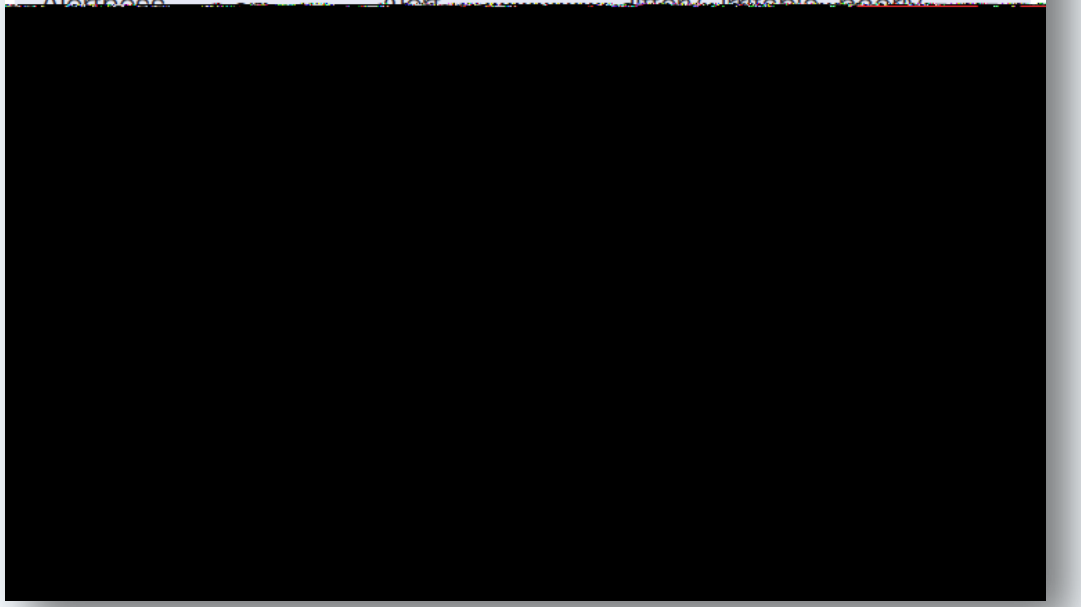


TABLE 19-2 Distinguishing Features of the Three Clinical Stages of Post-Anoxic Encephalopathy in the Full Term Infant

	Stage 1 (<24 hours)	Stage 2 (2–14 Days)	Stage 3 (Few Hours to Weeks)
Alertness	↑	↓/↓↓	↓↓↓
Tone	Normal	↓	⊘
Posture	Mild distal flexion	Strong distal flexion	±Decerebration
Muscle stretch reflexes	↑	↑	↓↓/⊘
Myoclonus	+	+	⊘
Primitive reflexes*	± Normal	↓	⊘
Autonomic functions**	Sympathetic ↑	Parasympathetic ↑	Both sympathetic and parasympathetic ↓ Symptoms variable
Seizures***	⊘	+	±

Modified with permission from Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696–705.

*Primitive reflexes include suck, Moro, oculovestibular, and tonic neck reflexes.

**Sympathetic functions include: mydriasis, tachycardia, sparse bronchial and salivary secretions, and decreased intestinal motility. Parasympathetic functions include: myosis, bradycardia, increased bronchial and salivary secretions, and increased intestinal motility.

***Seizures can be focal or multifocal.

↑ Mildly increased; ↑↑ Moderately increased; ↑↑↑ Markedly increased; ↓ Decreased; ⊘ Absent; + Present; ± May be present.

seizures in the term neonate with HIE can be difficult to diagnose based on clinical features alone and that **electrographic seizures** are common in these neonates, particularly in those with an **abnormal EEG background.**

Rigorous EEG monitoring of neonates with HIE, even those receiving therapeutic hypothermia.

The severity of brain injury in term asphyxiated newborns is not reliably predicted by commonly used clinical indicators during the first days of life, such as **umbilical cord pH and Apgar scores**. On the other hand, the severity of **clinical encephalopathy is a strong predictor of neurodevelopmental outcome.**

Patterns of Brain Injury

- The **basal-ganglia-predominant Pattern** involves the basal ganglia, thalamus, and perirolandic cortex.
- The ***watershed*** **pattern predominantly** involves the vascular watershed, from the white matter and extending to the cerebral cortex. Maximal injury in both the watershed region and basal ganglia results in **the total pattern** of brain injury.

- Identifying the predominant pattern of brain injury is helpful to the clinician caring for a term newborn with encephalopathy, because the predominant pattern is even more strongly associated with neurodevelopmental outcome than the severity of injury in any given region

Brain Imaging in NE

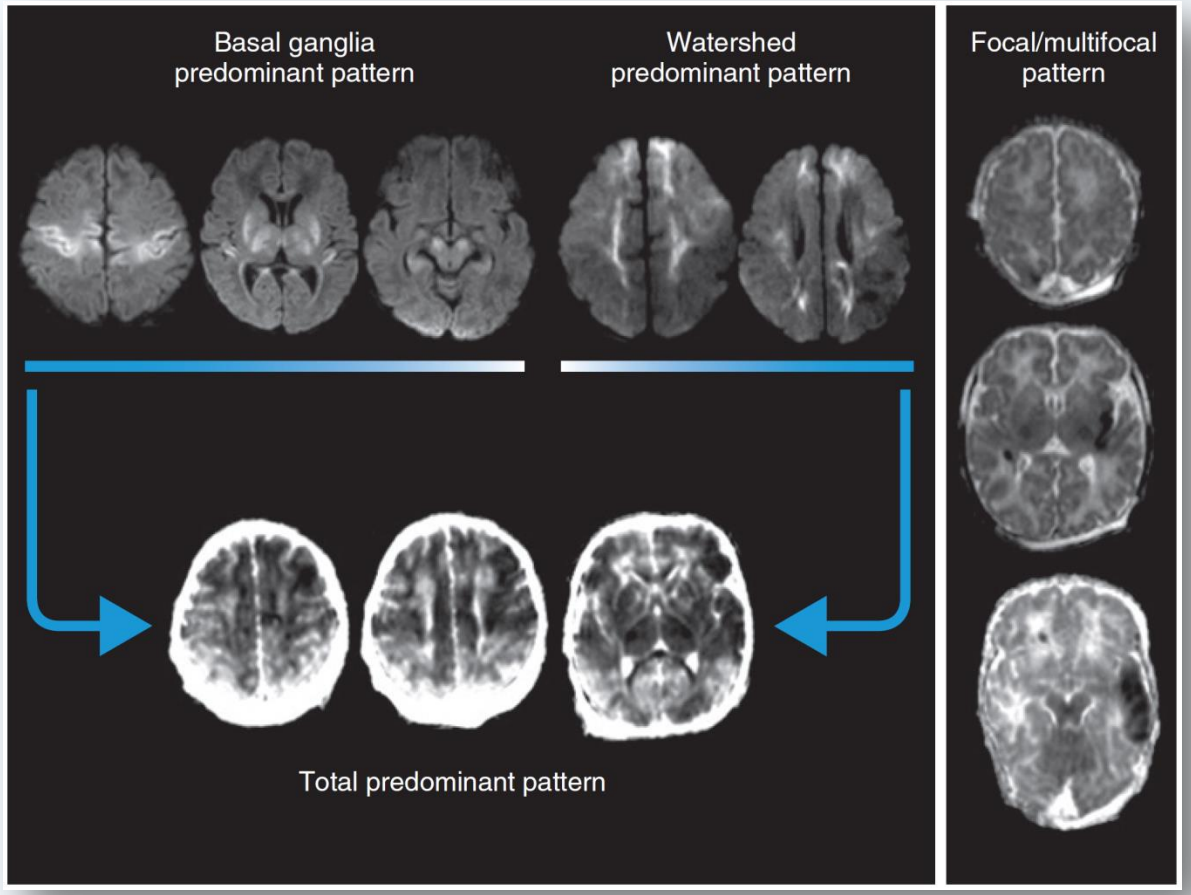
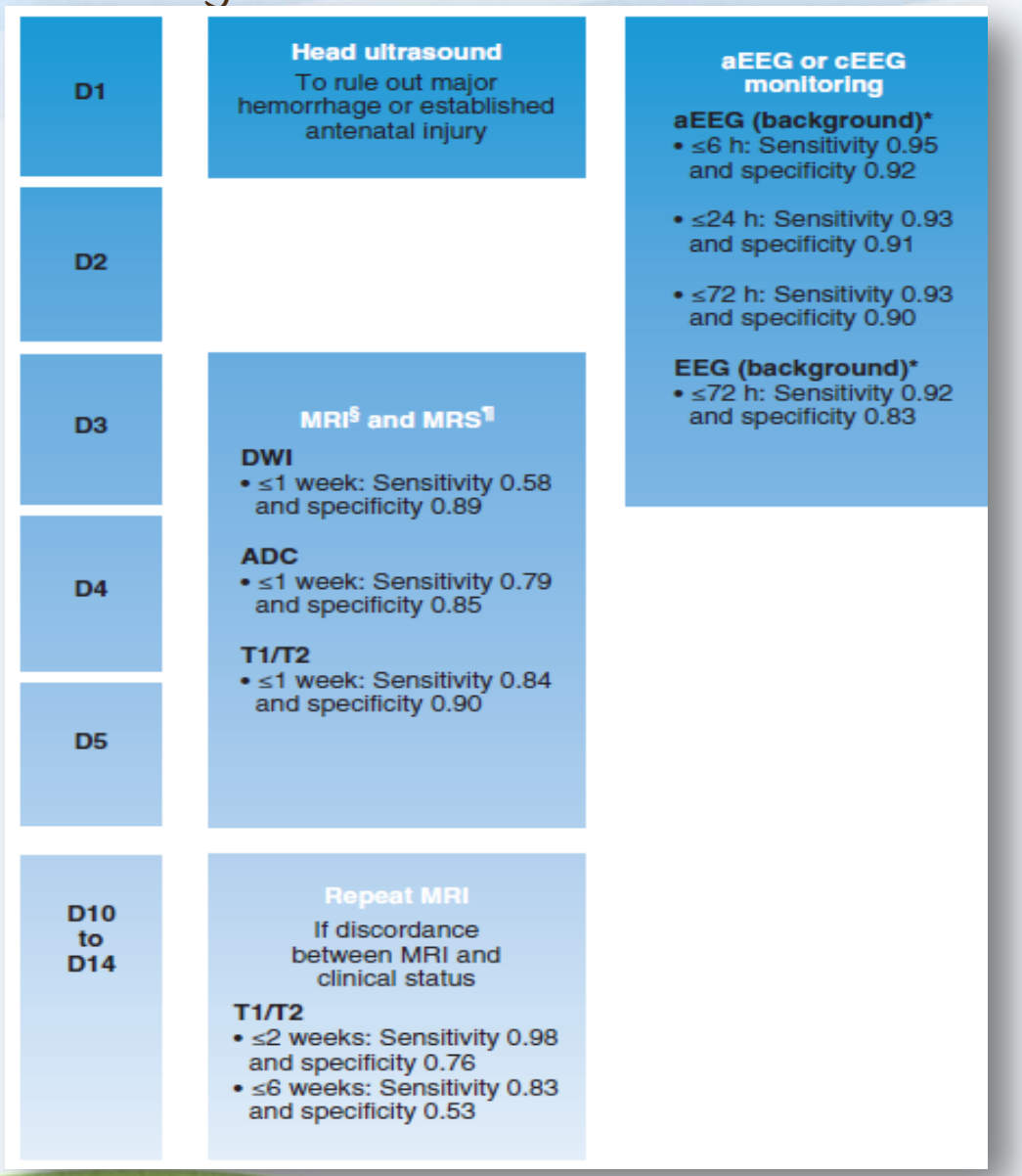


Figure 19-2. Suggested diagnostic tests for newborns with suspected HIE



- MRI with DWI appears to be the most sensitive imaging method to detect abnormalities associated with other causes of neonatal encephalopathy, such as cerebral dysgenesis, infections, stroke, and metabolic disorders.

Magnetic Resonance Spectroscopy (MRS)

- **N-acetylaspartate (NAA)** levels increase with advancing cerebral maturity. NAA levels decrease with cerebral injury or impaired cerebral metabolism.
- **Lactate** (produced by astrocytes and used as fuel by neurons). Lactate levels are elevated with hypoxia-ischemia.
- **Elevated lactate and reduced NAA** levels are highly predictive of neurodevelopmental outcome following neonatal brain injury.

OUTCOME PREDICTION

evoked potentials, mainly ABNL **VEPs** and **SSEPs**, associated with adverse outcomes. Later, the background of **EEG** and **aEEG** was also found to be associated with long-term outcomes. Abnormal backgrounds (flat trace, continuous low-voltage and burst-suppression patterns) that persist beyond the frst 24 hours of life seem to correlate best with outcomes.

The pattern of brain injury on neuroimaging

- **The basal ganglia pattern and the posterior limb of the internal capsule: severely impaired motor and cognitive outcomes (also The cerebral cortex and cerebellum).**
- **In contrast, the watershed pattern is associated with cognitive impairments that are not necessarily accompanied by major motor defcits. Importantly, the cognitive defcits following the watershed pattern may only be evident after 2 years of age. In survivors of neonatal encephalopathy without functional motor defcits assessed at 4 years of age, the severity of watershed-distribution injury was most strongly associated with impaired language skills.**

OUTCOMES

Motor Function

In term survivors of HIE (severe), the risk of cerebral palsy or severe disability may involve **> 1/3**

Spastic quadriparesis is the most common type of cerebral palsy, although athetoid or spastic hemiparesis may also occur.

Minor motor impairments that do not meet diagnostic criteria for CP are diagnosed in >1/3 with moderate encephalopathy, and in >1/4 of those with mild encephalopathy.

Vision and Hearing

- Severe visual impairment occurs in up to 1/4 of HIE, especially in the setting of hypoglycemia. Visual dysfunction may result: primary visual cortex.
- The pattern of brain injury involving the basal ganglia and thalamus is associated with deficits of visual acuity, visual field deficits, and stereopsis.
- Sensorineural hearing loss, likely secondary to brainstem injury, is also seen, even affecting up 18% of survivors of moderate encephalopathy without cerebral palsy.

Cognition

- Overall, cognitive deficits are seen in 30% to 50% of childhood survivors of moderate HIE.

- Intellectual performance in children with severe HIE *without* CP is also affected.

- School-age survivors of moderate neonatal encephalopathy are more likely to have difficulties with reading, spelling, and arithmetic, and require additional school resources.

- Cognitive deficits such as those in language and memory may be seen even when IQ scores are “normal.” Behavioral difficulties such as hyperactivity and emotional problems should also be considered even in those children without motor disability.

Outcome and Therapeutic Hypothermia

Therapeutic hypothermia, using selective head cooling or whole-body cooling, is now considered the standard of care for infants born at 35 weeks of gestation or greater with moderate to severe HIE who meet inclusion criteria used in clinical trials. Therapeutic hypothermia should be continued for 72 hours, with a target rectal (or esophageal) temperature of 33°C to 34°C for whole-body cooling or 34°C to 35°C for selective head cooling. Rewarming should occur over 6 to 12 hours (0.5°C every 1–2 hours).

- An initial meta-analysis done by Edwards and colleagues with an overall sample size of 767 participants from three randomized controlled trials clearly demonstrated that hypothermia is **neuroprotective**. Both mortality and disability were reduced at 18 months of age, and survival without disability was increased.
- However, infants with severe HIE do not seem to benefit from hypothermia.