Pathology and Progression of Injury

Hypoxic Ischemic Encephalopathy (HIE) is an acquired brain injury, around the time of birth, affecting 1 to 8 per 1000 infants born in developed countries, with a higher rate in underdeveloped countries.[1,2] Many infants who suffer HIE perinatally are born full-term but suffer asphyxia around the time of labor, birth, or shortly after birth.[2,3] The newborn infant then develops neonatal acidemia after a disruption in oxygen and glucose delivery to the brain occurs.[1] This hypoxic event causes a decrease in the infant's cardiac output, further lowering cerebral blood flow.[1] As the infant's body attempts to maintain perfusion to the brainstem, a natural decrease of arterial blood flow to the cerebral cortex occurs, causing "watershed damage" to both hemispheres.[1] Additionally, the disrupted cerebral blood flow then cause hypoxic damage to the basal ganglia and the thalami.[1]

The progression of injury to the brain can last hours, days, or weeks. There are distinct phases that take place during the injury:[1,2]

A. **Acute Phase**: 30-60min time frame generally -- ↓ cerebral blood flow = ↓ 02 and glucose to the brain = anaerobic metabolism
    I. Adenosine triphosphate ↓ & lactic acid ↑
    II. Intracellular accumulation of sodium, water, calcium occurs
    III. Cell membrane depolarizes and releases glutamate with calcium flowing into the cell, causing excitotoxicity = necrosis/cell death
B. **Latent Phase**: 1 to 6-hours after acute phase -- recovery of oxidative metabolism, inflammation occurs, apoptotic cascade in effect
C. **Secondary Phase**: 6 to 15-hours after acute phase – mitochondrial failure and cell death
    I. Clinical deterioration noted in moderate/severe cases
    II. Possible seizure activity starts
D. **Tertiary phase**: occurs in the months following the previous phases – late cell death, remodeling of the brain, and astrogliosis

Shortly after birth, clinical "hallmark" signs seen in the infant include altered consciousness, respiratory depression, atypical muscle tone, seizures, cranial nerve dysfunction, low Apgar scores, and decreased newborn arterial cord oxygen levels.[1] The infant may also show signs of

organ damage to the liver, kidneys, heart demonstrating metabolic dysfunction. Lastly, magnetic resonance imaging (MRI) can confirm HIE injury.[1,2] Infants with HIE can be classified on the Sarnat Scale, providing three different stages and severity of the injury. The scale takes into consideration the level of consciousness, neuromuscular control, reflexes, heart rate, and pupil responses, as well as gastrointestinal regulation and seizure activity.[4]

Impairments to Body Structure and Function

The infant's brain is the primary body structure affected with a range of damage from mild to severe, and at times death can occur. As severity increases, the number of body structures and functional impairments for the infant increases. The brain controls all aspects of the human body, from motor control and vision to muscle tone and breathing and swallowing (to name a few). At times, children are later diagnoses with Cerebral Palsy (CP), which is classically defined as a disorder of movements and atypical postural control. However, recent studies have shown than spastic quadriplegia and dyskinetic CP are the only types of CP associated with hypoxic "intrapartum events."[5] In contrast, unilateral brain lesions that are associated with hemiplegia and spastic diplegia have not demonstrated association with a hypoxic event.[5] Hankins et al. point out that 75% of children later diagnosed with CP have normal Apgar scores just after birth.5 In contrast, children with HIE tend to have low Apgar scores at 5-minutes.[5] Additionally, the infant may suffer organ damage due to the altered blood perfusion and then reperfusion during the first few days after birth.[1] This organ damage may affect the infant's respiration, cardiac output, and kidneys.[1] Muscle tone, visual perception, or blindness, and hearing may also be impacted for an infant who suffers HIE.[2,5]

Therapeutic hypothermia treatment is now the standard of care for infants post hypoxic events perinatally.[6] Clinical trials have shown that neurological outcome is improved with this treatment.[6,7] The primary purpose of the treatment is to reduce inflammation and delay the onset of anoxic cell depolarization and decrease the injury that comes with reperfusion of the central nervous system.[6,7] Prior to the age of therapeutic hypothermia, disability rate for infants with moderate HIE was 21% and 100% for those with severe HIE.[7] And, children who suffer mild to moderate encephalopathy, but did not have physical disability, demonstrated lower IQ scores by 10-points compared to peers.[7] More recently, randomized controlled trials have compared

outcomes for children who received therapeutic hypothermia to those who did not.[7] The results of these studies demonstrated decreased rates of diagnoses of CP later in life, decreased rate of blindness and hearing impairments, decreased rate of IQ score <70 for children who had received hypothermia treatment.[7] This medical treatment can have an impact of the infant's body structure and function early in life, as well as later in childhood and beyond which will determine physical therapy assessment needs and interventions.[7]

In summary, the body structures involved for an infant or child with HIE can involve any of the following:[1,5-7]

- Brain structures
- Vision
- Hearing
- Muscle Tone and Muscle Function
- Heart, kidneys, and gastrointestinal structures
- Respiration
- Cognition/Executive Function

Activity and Participation

Cognitive tasks, executive functioning, memory, gross motor skill acquisition, fine motor tasks, self-feeding, and ability to independently mobilize are all activities affected by the infant who suffers HIE.[2,7] Physical therapy assessment of activity limitations has been researched to determine outcomes for children with HIE. Hayes et al., reported that when assessing survivors of HIE, without a later diagnosis of CP, impairment rates are similar to those in the general population in cognition, motor skills, and language.[2] But, this same group of children presented with lower scores on the adaptive behavior and *timed* motor test items.[2] The authors believe that the lower scores are not actual motor impairments. However, the lower scores may be related to executive functioning impairments (memory, attention, processing).[2] Prior to Hayes et al. studies found that 28.9% of infants with mild grade 1 HIE had deficits in attention, memory, and executive functioning.[2] As one would be expect an increase in activity limitations in the area of learning/classroom functioning was found.[2]

To understand the effects of therapeutic hypothermia and participation in schools and mobility activities, Lee-Kelland et al. found that school-aged children who underwent "cooling" still presented with lower scores on the Movement Assessment Battery-2 (MABC-2) than their peers.[8] These children scored lower in cognitive, behavioral, and motor skills on standardized tests, and one-third received school/classroom supports for these limitations.[8] The results of this study indicate that despite the positive outcomes and reduced disability since therapeutic hypothermia has become standard of care, children with HIE are still at risk for limitations in functional mobility and school performance.

Researchers in the Netherlands studied children who had a history a difficulty birth (at term) and mild HIE signs and symptoms, and they found that at age six, these children had more limited mobility and challenges with manual dexterity and balance.[8] In contrast, children who had a difficult birth but no hypoxic events did not demonstrate mobility/activity limitations.[9] Children with a difficult birth and hypoxic events present with more behavioral problems and utilized physical therapy intervention more often.[9] Additionally, children who suffered a difficult birth, a hypoxic event, and then later diagnosed with CP required more support at school than peers (10x more), demonstrating participation limitation in the educational setting, which demonstrates that both physical and academic support needs are present.[9] The authors conclude that the results of their study and previous studies support neuromotor monitoring, early detection of impairments by utilizing early intervention, and then ongoing assessment through childhood for both motor and cognitive deficits.[9] By providing routine assessments, physical therapists can pinpoint impairments, activity, and participation limitations and intervene with evidence-based interventions based on the results of the assessment.

The use of standardized assessment to pinpoint impairments and formulate their link to activity limitations for these children might include:[2]

1. Movement Assessment Battery for Children 2
2. Behavior Rating Inventory of Executive Function
3. Bayley Scales of Infant Development III
4. Pediatric Disability Inventory

ICF Table:

Health Condition	**Impairment**	**Activity Limitation**	**Participation Restriction**
Hypoxic Ischemic Encephalopathy – *(infant age 3-6-month)*	Muscle dystonia Irritability Muscle Weakness Decreased Head Control Decreased Postural Control Decreased visual awareness	Difficulty kicking and reaching/grasping Decreased ability to hold self - upright when held by a caregiver Inability to see self or object in a mirror Decreased floor play	Decreased self-exploration and play on the floor when in a group of peers Decreased ability to sit upright for oral feeds Decreased ability to bath in an upright position

The child's quality of life can be impacted in a wide variety of ways. Should the infant suffer from the impairments, activity limitations, and participation restrictions listed above, a negative impact on the child's quality of life could increase with reliance from equipment or family members to participate in daily life routines. Reliance on family members for mobility and access to community engagement could decrease overall self-satisfaction with life's pleasure.

Intervention

The prognosis of a child who suffers HIE is far and wide. Interventions will vary based on the number of body structures involved and the overall degree of injury to the brain. A broad intervention choice for physical therapists could include annual pediatric physical therapy checkup. Annual PT checkups are not standard of care at this time, yet early intervention referral and enrollment are typical for children with this diagnosis. HIE is an *established condition* that ensures automatic enrollment in the Infant-Toddler Program in NC. Therefore, these children will likely have access to services with evidenced-based intervention approaches in early intervention. However, as the child ages out of the program at three years of age, children with mild HIE or those who present with executive functioning impairments may get lost to follow up.

For this paper, I will focus my unique intervention choice on the proposal of an annual physical therapy checkup for this population yearly throughout childhood. The APTA endorses a pediatric PT evaluation/checkup and has provided a format to organize the process.[9] The checkup form can be found here: http://www.apta.org/AnnualCheckup/Form/. This form is entirely complete with components that include the ICF model. There are two sections that are particularly well thought out, one labeled "Environmental Factors" and another labeled "Child and Family Goals/QOL." The focus of these sections is access to activities in the community, transportation, and questions about life goals or wishes for the child. Here are some examples of questions in the check-up:

- Do you have transportation access, and is it safe?
- Does the child need support in daily activities?
- Is the child active in the community or recreational activities?
- What does the child enjoy doing and do best?
- What are the child's strengthens?
- What dreams do you have for the child?

I believe that if this type of annual PT checklist/evaluation were standard of care for this population of children, we would see increased attention and problem-solve around activity limitations, participation limitations, environmental, and personal factors. I was unable to locate any quality research articles in physical therapy, utilizing an annual physical therapy assessment model. However, the APTA website provides two continuing education courses on the matter.[9] While there is little or no research on this topic, this type of evaluation would address the lower scores school-aged children are presenting with in comparison to peers, and allow for these problems to be addressed.

Bibliography

1. Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. *JAMA Pediatr.* 2015;169(4):397-403. doi:10.1001/jamapediatrics.2014.3269.
2. Hayes BC, Doherty E, Grehan A, et al. Neurodevelopmental outcome in survivors of hypoxic ischemic encephalopathy without cerebral palsy. *Eur. J. Pediatr.* 2018;177(1):19-32. doi:10.1007/s00431-017-3028-3.
3. Parker S-J, Kuzniewicz M, Niki H, Wu YW. Antenatal and Intrapartum Risk Factors for Hypoxic-Ischemic Encephalopathy in a US Birth Cohort. *J. Pediatr.* 2018;203:163-169. doi:10.1016/j.jpeds.2018.08.028.
4. What is HIE - Hope for HIE (Hypoxic Ischemic Encephalopathy). Available at: https://www.hopeforhie.org/whatishie. Accessed March 27, 2020.
5. Hankins GDV, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstet. Gynecol.* 2003;102(3):628-636. doi:10.1016/s0029-7844(03)00574-x.
6. Silveira RC, Procianoy RS. Hypothermia therapy for newborns with hypoxic ischemic encephalopathy. *J Pediatr (Rio J)* 2015;91(6 Suppl 1):S78-83. doi:10.1016/j.jped.2015.07.004.
7. Natarajan G, Pappas A, Shankaran S. Outcomes in childhood following therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy (HIE). *Semin Perinatol* 2016;40(8):549-555. doi:10.1053/j.semperi.2016.09.007.
8. van Iersel PAM, Algra AM, Bakker SCM, Jonker AJH, Hadders-Algra M. Limitations in the activity of mobility at age 6 years after difficult birth at term: prospective cohort study. *Phys. Ther.* 2016;96(8):1225-1233. doi:10.2522/ptj.20150201.
9. Annual Checkup by a Physical Therapist. Available at: https://www.apta.org/AnnualCheckup/. Accessed March 31, 2020.