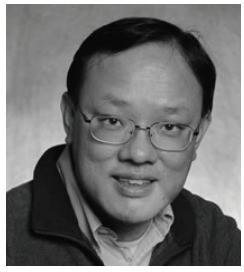
Neonatal ischemic stroke: a hypoxic–ischemic injury to the developing brain



Lauren L Jantzie, Kathryn G Todd & Po-Yin Cheung†

†Author for correspondence
Royal Alexandra Hospital, NICU, Rm 5027, 10240 Kingsway Avenue, Edmonton, AB T5H 3V9, Canada
Tel.: +1 780 735 4670; Fax: +1 780 735 4072; poyin@ualberta.ca

future medicine part of fsg

'...understanding when inflammation is beneficial and when it is detrimental is crucial to the success and clinical efficacy of anti-inflammatory therapies.'

Neonatal stroke is a major cause of neonatal death and pediatric disability. The type of stroke and the etiology depend on the age of the fetus and infant, but arterial ischemic stroke is the most common entity [1]. Despite being relatively small for the body's mass, the brain receives 15% of total cardiac output and 20% of the body's oxygen supply. As such, the brain is extraordinarily vulnerable to changes in blood flow and oxygen content. While arterial ischemic stroke and hypoxia–ischemia (HI) share some common pathogenetic features, the term HI is commonly used to reflect the alterations in blood flow and oxygen delivery to the brain and may offer greater specificity in designing management strategies.

Ischemic stroke in neonates has a wide range of presentations and manifestations and, thus, is very difficult to diagnose. Although HI injury is detrimental to almost every organ of the body, the brain is amongst the most vulnerable. HI injury to the brain may result in devastating consequences. Common diseases such as cerebral palsy, seizure disorders, hearing and vision loss, mental retardation, learning disabilities, schizophrenia, attention-deficit hyperactivity disorder, conduct disorders and developmental diseases, including neuronal migration disorders (lissencephaly and heterotopias), can all have some degree of cerebral HI linked to their etiologies. As the neonatal brain is constantly undergoing natural programmed cell death (apoptosis), it is inherently primed for cell death. Thus, cerebral HI itself may be viewed as a developmental disorder. The fetal brain develops in a stepwise, organized fashion, involving discrete and sequential processes including division, migration and differentiation of diverse cell types [2]. As this occurs and as neurotransmitter systems mature, behavioral patterns emerge that reflect the integration of complex cerebral networks [2]. Cerebral apoptosis is a required developmental process for axonal outgrowth, synaptic consolidation and to establish the appropriate number of neurons and eliminate cells with DNA damage. The fetus has twice as many neurons as required in a mature brain [2], and the developmental 'pruning' that occurs is vital and occurs in all cell types. By contrast with the other organs, which are fully formed by the 12th week of gestation, the CNS continues to develop throughout pregnancy and early childhood. After birth, the pruning of excess cells occurs as myelination, neuronal migration and synapse formation are part of postnatal brain development. As the window for potential insult is quite large, it is intuitive that dysregulation of the molecular and cellular events of apoptotic cell death results in detrimental developmental brain pathology.

'Ischemic stroke in neonates has a wide range of presentations and manifestations and, thus, is very difficult to diagnose.'

The primary objective in the treatment of neonatal ischemic stroke is re-establishing the obstructed blood flow and, thus, reduced oxygen supply. While the use of thrombolytic agents, such as tissue plasminogen activators, in adults has been shown to be effective [3], their use in neonates with stroke remains experimental. Nevertheless, heparin therapy has been suggested to be considered in neonatal stroke of cardioembolic origin [4]. The therapeutic potential of the clot-buster therapy is limited by the possibility and consequence of hemostatic derangement in the developing human, as well as the narrow therapeutic window. Thus, therapies for neonatal stroke should also involve neuroprotective and neurorescuing management stratagies.

Currently, there are no approved therapies for the brain damage associated with neonatal HI beyond the supportive therapies and interventions provided as part of intensive care.

However, there is lots of promising research being conducted to improve existing avenues for intervention and to discover new strategies in the wake of therapies that have failed when they were tested for clinical applications. Examples of failed therapies include supplemental glucose during resuscitation, hyperventilation, midazolam, barbiturates, dexamethasone and other glucocorticoids, calcium-channel blockers, magnesium sulfate, indomethacin, superoxide dismutase/catalase conjugated to polyethylene glycol, MK-801, detromethorphan and caspase inhibitors. The management of neonatal cerebral HI includes supportive care to provide adequate ventilation, meticulous fluid management, avoidance of hypotension and hypoglycemia, and treatment of seizures [5]. Indeed, it has been hypothesized that improving the manner in which infants are resuscitated post-HI may be a crucial first step to improving outcome and reducing disability. The concentration of oxygen used during resuscitation may affect brain damage after HI [6,7]. Hyperbaric oxygen has been tried in neonates with HI and in rodent models of focal ischemic stroke with some success [8,9]. Further studies are required to examine the role of oxygen in neonates with stroke, who are also at risk for 'oxygen free radical disease' [10].

'...therapies for neonatal stroke should also involve neuroprotective and neurorescuing management stratagies.'

Beyond improving intensive care, many studies have been performed to identify new treatment options and potential interventions to ameliorate the process of ongoing brain injury. Brain injury after HI results from the combined effects of cellular energy failure, acidosis, glutamate release, intracellular calcium accumulation, lipid peroxidation, nitric oxide neurotoxicity, mitochondrial dysfunction and inflammation, which all serve to disrupt essential components of the cell, resulting in death [5]. As such, novel neuroprotective or neurorescuing compounds are usually designed to target one or more of the aforementioned events. The therapeutic effect of hypothermia has received much attention in the past decade. Despite many promising studies conducted in neonatal subjects that attest to the neuroprotective effects of hypothermia, controversies exist regarding the administration of hypothermia as well as the selected population of infants with cerebral HI in whom it is an effective clinical intervention [11]. Furthermore, although therapeutic hypothermia has been used in adults with ischemic stroke and the preliminary results are encouraging, its effectiveness in neonatal stroke remains experimental [12,13]. Nonetheless, temperature control with the avoidance of pyrexia appears to be important for the functional outcome.

'Brain injury after HI results from the combined effects of cellular energy failure, acidosis, glutamate release, intracellular calcium accumulation, lipid peroxidation, nitric oxide neurotoxicity, mitochondrial dysfunction and inflammation...'

In addition to hypothermia, a variety of anti-inflammatory compounds have been investigated. Neuroinflammation, which is an important component of delayed or secondary cell death post-HI, occurs hours to days following the injury, thus potentially leaving a large window for therapeutic intervention. Due to high lipophilicity, the second-generation tetracycline derivatives (minocycline and doxycycline) can cross the BBB, which is a common problem with some experimental neuroprotective agents. These compounds have been studied extensively *in vitro* and *in vivo* and were shown to effectively inhibit microglial activation whilst improving neuronal survival in newborn rat pups with HI [14,15]. However, inflammation is also an important component of repair. Therefore, understanding when inflammation is beneficial and when it is detrimental is crucial to the success and clinical efficacy of anti-inflammatory therapies. A similar dichotomy exists with glutamate and may pose a problem for putative treatments. Glutamate is a major excitatory neurotransmitter and is required for synapse development and maturation of neuronal circuitry in the developing brain [16]. However, after an event such as HI, brain glutamate levels can increase, causing excitotoxicity and massive cell death. Inhibiting the actions of glutamate as a putative treatment for HI has long-term developmental consequences in addition to serious side effects. Additionally, drugs that inhibit glutamate receptors typically do not cross the BBB and have been criticized for targeting an event that occurs early in the cell death cascade, such that the therapeutic window is too narrow to be clinically relevant.

Several interventions, such as allopurinol/oxypurinol, desferoxamine and melatonin, attempt to reduce HI-induced cerebral damage resulting from free radicals and have failed to generate clinical interest based on their side-effect profiles and some failed trials. Recent promising therapies include erythropoietin and *N*-acetylcysteine. Erythropoietin is an antioxidant that possesses antiapoptotic, antinitrosative and angiogenic properties [17]. Erythropoietin has also been reported to promote neuroprotection and neurogenesis through the alteration of cell-fate decisions, and to improve functional outcome after stroke in immature rats [18,19]. *N*-acetylcysteine, a well-known antioxidant and free radical-scavenging agent, can cross the placenta and the BBB and has a good safety profile during pregnancy. *N*-acetylcysteine has been shown to reduce oxidative stress, restore intracellular glutathione levels, scavenge oxygen free radicals, improve cellular redox potential and reduce apoptosis and inflammation of the neonatal brain [20,21], in addition to the improved cardio–renal recovery observed after asphyxia [22].

In the face of challenging acute diagnosis, there is a well established temporal and spatial profile of pathophysiology that provides clues to the chronology of brain lesions post-HI. Thus, a series of strategies and/or cocktail therapies could be the effective treatment of cerebral HI and neonatal stroke. Furthermore, the continued development of clinically relevant animal models is essential to drug development. In the interest of being aware of the risk of exchanging one developmental disorder for another, potential treatments need to be carefully examined to elucidate cellular processes crucial to normal development and novel therapeutic approaches need to be tested in well-designed clinical trials.

Financial & competing interests disclosure

Po-Yin Cheung is a Clinical Investigator of the Canadian Institutes of Health Research and the Alberta Heritage Foundation for Medical Research (AHFMR). Kathryn Todd is a Heart and Stroke Foundation of Canada/Canadian Institutes of Health Research and Canadian Stroke Network Investigator. Lauren L Jantzie is a recipient of a Canada Graduate Scholarship from the Natural Science and Engineering Research Council of Canada and a Doctoral Research Award from AHFMR. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Andrew ME, Monagle P, deVeber G, Chan AK: Thromboembolic disease and antithrombotic therapy in newborns. *Hematology (Am. Soc. Hematol. Educ. Program)* 358–374 (2001).
2. Badr L, Purdy I: Brain injury in the infant: the old, the new, and the uncertain. *J. Perinat. Neonat. Nurs.* 20, 163–175 (2006).
3. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P: Antithrombotic and thrombolytic therapy for ischemic stroke: the *Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest* 126(Suppl. 3), S483–S512 (2004).
4. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD: Antithrombotic therapy in children: the *Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest* 126(Suppl. 3), S645–S687 (2004).
5. Perlman JM: Intervention strategies for neonatal hypoxic–ischemic cerebral injury. *Clin. Therapeutics* 28, 1353–1365 (2006).
6. Presti AL, Kishkurno SV, Slinko SK *et al.*: Reoxygenation with 100% oxygen versus room air: late neuroanatomical and neurofunctional outcome in neonatal mice with hypoxic–ischemic brain injury. *Pediatr. Res.* 60, 55–59 (2006).
7. Jantzie LL, Cheung PY, Obaid L *et al.*: Persistent neurochemical changes in neonatal piglets after hypoxia–ischemia and resuscitation with 100%, 21% or 18% oxygen. *Resuscitation* (Epub ahead of print) (2007).
8. Liu Z, Xiong T, Meads C: Clinical effectiveness of treatment with hyperbaric oxygen for neonatal hypoxic–ischaemic encephalopathy: systematic review of Chinese literature. *BMJ* 333, 374 (2006).
9. Henninger N, Küppers-Tiedt L, Sicard KM, Günther A, Schneider D, Schwab S: Neuroprotective effect of hyperbaric oxygen therapy monitored by MR-imaging after embolic stroke in rats. *Exp. Neurol.* 201, 316–323 (2006).
10. Saugstad OD: Oxidative stress in the newborn – a 30-year perspective. *Biol. Neonate* 88, 228–236 (2005).
11. Wyatt JS, Gluckman PD, Liu PY *et al.*; for the CoolCap Study Group: Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics* 119, 912–921 (2007).
12. den Hertog H, van der Worp B, van Gemert M, Dippel D: Therapeutic hypothermia in acute ischemic stroke. *Expert Rev. Neurother.* 7, 155–164 (2007).
13. Pabello NG, Tracy SJ, Keller RW Jr: Protective effects of brief intra- and delayed postischemic hypothermia in a transient focal ischemia model in the neonatal rat. *Brain Res.* 995, 29–38 (2004).
14. Arvin KL, Han BH, Du Y, Lin SZ, Paul SM, Holtzman DM: Minocycline markedly protects the neonatal brain against hypoxic–ischemic injury. *Ann. Neurol.* 52, 54–61 (2002).
15. Jantzie LL, Cheung PY, Todd KG: Doxycycline reduces cleaved caspase-3 and microglial activation in an animal model of neonatal hypoxia–ischemia. *J. Cereb. Blood Flow Metab.* 25, 314–325 (2005).

16. Jensen F: Developmental factors regulating susceptibility to perinatal brain injury and seizures. *Curr. Opin. Pediatr.* 18, 628–633 (2006).
17. Sola A, Wen TC, Hamrick SE, Ferriero DM: Potential for protection and repair following injury to the developing brain: a role for erythropoietin. *Pediatr. Res.* 57, R110–R117 (2005).
18. Chang YS, Mu D, Wendland M *et al.*: Erythropoietin improves functional and histological outcome in neonatal stroke. *Pediatr. Res.* 58, 106–111 (2005).
19. Gonzalez FF, McQuillen P, Mu D *et al.*: Erythropoietin enhances long-term neuroprotection and neurogenesis in neonatal stroke. *Dev. Neurosci.* 29, 321–330 (2007).
20. Jatana M, Singh I, Singh AK, Jenkins D: Combination of systemic hypothermia and *N*-acetylcysteine attenuates hypoxic–ischemic brain injury in neonatal rats. *Pediatr. Res.* 59, 684–689 (2006).
21. Lee T-F, Jantzie LL, Todd KG, Cheung P-Y: Postresuscitation *N*-acetylcysteine treatment reduces cerebral hydrogen peroxide in the hypoxic piglet brain. *Inten. Care Med.* 34, 190–197 (2008).
22. Johnson ST, Bigam DL, Emara M: *N*-acetylcysteine improves the hemodynamics and oxidative stress in hypoxic newborn pigs reoxygenated with 100% oxygen. *Shock* 28, 484–490 (2007).

Affiliations

- *Lauren L Jantzie*
University of Alberta, Neurochemical Research Unit, Department of Psychiatry, Edmonton, AB T6G 2R7, Canada
Tel.: +1 780 492 6589;
Fax: +1 780 492 6841
- *Kathryn G Todd, PhD*
University of Alberta, Neurochemical Research Unit, Department of Psychiatry, Edmonton, AB T6G 2R7, Canada
Tel.: +1 780 492 6589;
Fax: +1 780 492 6841;
kgtodd@ualberta.ca
- *Po-Yin Cheung, MBBS, PhD*
Royal Alexandra Hospital, NICU, Rm 5027, 10240 Kingsway Avenue, Edmonton, AB T5H 3V9, Canada
Tel.: +1 780 735 4670;
Fax: +1 780 735 4072;
poyin@ualberta.ca