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Editorial

Editorial Note on Neonatal Stroke

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EDITORIAL

The incidence of perinatal stroke is high, similar to that in the elderly, and produces a significant morbidity and severe long-term neurologic and cognitive deficits, including cerebral palsy, epilepsy, neuropsychological impairments, and behavioural disorders. Emerging clinical data and data from experimental models of cerebral ischemia in neonatal rodents have shown that the pathophysiology of perinatal brain damage is multifactorial. These studies have revealed that, far from just being a smaller version of the adult brain, the neonatal brain is unique with a very particular and age-dependent responsiveness to hypoxia–ischemia and focal arterial stroke.

In this study, we discuss fundamental clinical aspects of perinatal stroke as well as some of the most recent and relevant findings regarding the susceptibility of specific brain cell populations to injury, the dynamics and the mechanisms of neuronal cell death in injured neonates, the responses of neonatal blood–brain barrier to stroke in relation to systemic and local inflammation, and the long-term effects of stroke on angiogenesis and neurogenesis. Finally, we address translational strategies currently being considered for neonatal stroke as well as treatments that might effectively enhance repair later after injury.

Perinatal arterial ischemic stroke is common and produces a significant morbidity and severe long-term neurologic and cognitive deficits, including cerebral palsy, epilepsy, neurodevelopmental disabilities, behavioural disorders, and impaired vision and language function. More than half of all children with cerebral palsy are born at term and in many instances the etiology is related to some form of cerebrovascular focal or global insult.

The pathophysiology of perinatal brain damage has proven to be multifactorial. With the availability and safe use of magnetic resonance imaging (MRI) in newborns, older infants, and children over the past two decades, much has been learned about how the stroke phenotype differs in these age groups compared with adults, as well as the underlying causes and pathophysiology.

From an experimental perspective, stroke models in neonatal animals are technically very challenging when one considers the surgical difficulties based on size (e.g., body weight of a postnatal day (P7) rat pup is <15 g and of a P9 mouse pup is <5 g). Therefore, the first and most commonly used model to mimic ischemic brain injury in term neonates is an hypoxia–ischemia (H–I) model in P7 to P12 rats and mice, which consists of ligation of the common carotid artery followed by systemic hypoxia.

The maturational stage of the brain at the time of injury is a key factor in the pattern of brain damage, including regional and cell type-specific susceptibility. In preterm newborns, brain injury associated with hypoxia–ischemia generally coincides with a time window of high susceptibility of oligodendrocyte progenitors (OLPs) to excitotoxicity, oxidative stress, and inflammation, adversely affecting OLP differentiation into mature, myelinating oligodendrocytes. The arrest in OLP differentiation in turn predisposes the brain to defective white-matter tract development, including periventricular white-matter injury and cerebral palsy. Subplate neurons, which exist transiently during human fetal brain development, are involved in the formation of visual thalamocortical projections, and are another cell population selectively vulnerable to H–I in preterm babies that leads to long-term deficits. Several reviews have discussed the unique features of fetal brain neuroinflammation and injury in humans and in corresponding injury models.

Recognition of the dynamic nature of changes during brain maturation and the integrative nature of brain injury, which evolves via communication between different cell types and between regions that may reprogram injured immature brain, is another conceptual advance. While much is to be learned about the underlying mechanisms, the knowledge gained is important for advancement to clinical trials.

Distinct age-related susceptibility of particular cell populations and mechanisms controlling local inflammation and immune cell infiltration may guide a time-dependent selection of therapeutic targets.

In view of new knowledge of the relative impermeability of the BBB after acute neonatal stroke, the distribution and bioavailability of therapies must be carefully considered to ensure that agents that are expected to produce effects locally in the brain do in fact reach the brain.

Short-lived protection of acutely administered therapies, paradoxical responses to antiinflammatory and antioxidant drugs, and the plasticity of the immature brain suggest that one

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of the critical features to improve outcomes should be a focus on rebuilding the injured neonatal brain by enhancing repair. It is also likely that combinatorial therapies may be superior to single therapies but future research should address the optimal timing for modulating effects of interventions and the role of genetic factors. Among other unanswered questions are why pediatric stroke is recurrent while perinatal stroke is rarely recurrent.