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Early intervention after perinatal stroke: Opportunities and challenges

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Abstract

Perinatal stroke is the commonest cause of hemiplegic cerebral palsy. No standardised early intervention exists despite evidence for a critical time window for activity-dependent plasticity to mould corticospinal tract development in the first few years of life. Intervention during this unique period of plasticity could mitigate the consequences of perinatal stroke to an extent not possible with later intervention, by preserving the normal pattern of development of descending motor pathways. This article outlines the broad range of approaches currently under investigation. Improved early detection and outcome prediction remain important goals, despite significant progress in this area.

Background: scope of the problem

Perinatal stroke, defined as stroke occurring between the 20th week of foetal life and the 28th postnatal day¹, affects up to 1/2300 term² and 7/1000 preterm infants³. The majority of cases are due to ischaemic events. These may be arterial ischaemic strokes, or periventricular venous infarction, which is due to compression of the medullary veins following germinal matrix haemorrhage prior to 34 weeks gestation⁴. Smaller numbers of cases are due to intracerebral haemorrhage or venous sinus thrombosis. Up to 60% of perinatal strokes result in neurological deficits⁵, with hemiplegic cerebral palsy being a frequent adverse motor outcome. In fact, perinatal stroke is the commonest cause of hemiplegic cerebral palsy⁶. This lifelong condition has implications for performance in activities of daily living, quality of life and self-esteem⁷. Adults with hemiplegic cerebral palsy (HCP) are less likely than their peers to live independently or be in full-time employment⁸. Hemiplegia is not the only reported adverse outcome after perinatal stroke: others include seizures, cognitive, language and visual deficits and behavioural problems^{5,9}. Not surprisingly there is a substantial long-term financial burden from perinatal stroke¹⁰.

Why is perinatal stroke problematic to diagnose and manage?

In contrast to the significant progress that has been made with prevention, diagnosis and management in stroke in adults, management of perinatal stroke remains problematic at each step. The aetiology of perinatal stroke is multifactorial¹¹ and incompletely understood¹², limiting preventative options. Whereas stroke in adults is quickly detected, perinatal stroke often presents non-specifically in the first days of life with seizures¹³, lethargy and/or poor

feeding¹⁴. Moreover, around 40% of cases (“presumed perinatal strokes”) are first detected outside the neonatal period. For this group, presentation occurs on average 5 months after birth, often with asymmetrical movement difficulties¹⁵. Most patients with presumed perinatal stroke genuinely appear to have been asymptomatic during the neonatal period and early infancy, with only a minority representing “missed symptomatic perinatal strokes”¹⁶. However, there are often significant delays between onset of parental concern and final diagnosis of presumed perinatal stroke, the latter reported to occur at a mean age of 12.6 months¹⁵.

In contrast to adult stroke, there is no established immediate treatment for perinatal stroke except symptomatic measures (e.g. stabilisation and management of bleeding diathesis, thrombophilia, hydrocephalus etc.)¹⁷. What evidence-based recommendations there are have been summarised by Roach et al. in an article encompassing management of stroke in infants and children¹⁸.

To complicate things further, although most cases presenting as presumed perinatal stroke will become confirmed cases of hemiplegic cerebral palsy⁹, this is not true for symptomatic perinatal stroke. Of the patients presenting in the neonatal period with symptomatic stroke, around 50% develop cerebral palsy and around 35% may have normal outcome, with the rest having relatively minor motor abnormalities¹⁶. Some inroads have been made regarding outcome prediction¹⁹, though this remains problematic, as will be discussed below. Clearly, this is important when considering whom to target with early intervention. At present however, rehabilitative management for perinatal stroke, though variable, is largely structured around observation and referral to therapy services as and when emerging focal neurological signs are observed. Early identification and referral of at-risk infants for intervention, rather than referral of infants with established cerebral palsy, has been called for²⁰. However, this approach requires both more widespread use of appropriate tools for early diagnosis, and more evidence for effective early interventions.

There is a large and expanding literature on the established and experimental approaches to management of hemiplegic cerebral palsy. (For the upper limb, this has been recently reviewed and summarised by Sakzewski et al.²¹). “Late intervention” approaches for children with established hemiplegia, ranging from orthoses and botulinum toxin injections to orthopaedic surgery, will not be covered here as they are well-known. This article aims to explain the rationale for early intervention in perinatal stroke and provide an overview of current experimental approaches addressing this.

Why aim to intervene early after perinatal stroke?

In the absence of any obvious primary preventative strategies, the next best option is “damage control”. Neuroprotective strategies discussed below could help minimise tissue damage from the initial insult. However, there are also opportunities for intervention outside this immediate post-injury period. Major developmental changes are occurring in the nervous system in the first year of life, with long-term implications for function. One of the most striking of these, highly relevant to motor outcome after stroke, is the ongoing activity-dependent plasticity within descending motor pathways. The corticospinal tract is the major

descending pathway from the brain to the spinal cord controlling voluntary movement. At term, corticospinal fibres from each hemisphere project to each side of the spinal cord (bilateral system). Neurophysiological evidence indicates that in healthy infants, gradual progression to a predominantly crossed projection occurs, within the first 2 years of life, with the most marked changes concentrated within the first year²². Following unilateral perinatal stroke, corticospinal projections from the affected hemisphere are at a competitive disadvantage and, in patients with poor motor outcome, are gradually downregulated whilst uncrossed projections from the undamaged hemisphere are pathologically retained^{22,23}. Patients with the most favourable functional outcome retain crossed projections from the affected hemisphere²⁴. This is true for a variety of lesion types, though lesions acquired early in pregnancy (such as malformations of cortical development), typically lead to less severe motor dysfunction than those acquired later (e.g. middle cerebral artery territory infarctions) where both have led to pathologically retained uncrossed projections from the undamaged hemisphere. This may reflect a greater capacity for intrahemispheric reorganizational potential earlier in fetal development²⁵. Animal models demonstrate similar findings²⁶. Thus, interventions within this early time window after perinatal stroke might have the potential to steer the course of corticospinal tract development towards a more normal pattern, providing a unique opportunity to influence outcome.

Predictions that the course of corticospinal tract development can be altered during this critical time window have been confirmed in animal models by seminal studies by Martin et al.²⁷. Electrical stimulation of a unilaterally inactivated corticospinal tract re-established normal connectivity and partially restored motor function in a neonatal cat model²⁸. Constraint of the unaffected side, plus encouragement of use of the affected limb, improved motor outcome and restored corticospinal tract connections, spinal cord circuitry and the motor cortical map²⁹. Outcome was best when training began early, and training plus constraint was more effective than constraint alone. However, preventing normal limb use very early in development could adversely affect function of that limb long-term³⁰. Immediate and total immobilisation of the unimpaired forelimb, producing forced overuse of the impaired limb (whilst obviously an extreme example), also worsened the neuronal injury in adult rodent stroke models³¹. Thus the nature and risk-benefit ratios of potential intervention strategies must be very carefully explored.

Notwithstanding these dramatic developmental changes during infancy, when the greatest potential effects of intervention on outcome may be expected, there is also the option for later intervention which exploits ongoing neuronal plasticity. Neurophysiological approaches modulating cortical excitability, and therapy approaches such as constraint, have been shown to influence motor outcome after stroke even in elderly adults. However, in hemiplegic cerebral palsy, morbidity can increase over time – examples being developmental disregard of the affected side and contractures. The earlier the onset of an effective intervention, the more secondary morbidity could hopefully be prevented.

What types of approach are being explored?

Although as yet no standard early interventional approach exists for perinatal stroke, there is a very broad range of experimental approaches, which can only be highlighted within the scope of this review. The relative merits of each remain to be established.

Minimising damage from the initial insult: neuroprotective strategies

Therapeutic hypothermia reduces the risk of major neurodevelopmental disability and mortality by around 25% in term and late preterm neonates with hypoxic ischaemic encephalopathy³². Side effects include sinus bradycardia and thrombocytopenia. In a systematic review and metaanalysis of animal models of acute ischaemic stroke, hypothermia produced a 44% reduction in lesion size³³. The mechanism appears to be multifactorial but is broadly related to reduction in excitotoxicity and inflammation³³. Hypothermia has not been systematically investigated as an approach to perinatal stroke. However, in one study of neonatal encephalopathy, none of 5 patients with focal stroke receiving cooling developed neonatal seizures, in contrast to 7 of 10 similar patients who did not receive cooling³⁴.

It has been suggested that induced hypothermia is investigated as a therapeutic option in infants with arterial ischaemic perinatal stroke³⁵. The evidence from animal models suggests that treatment should begin within 6 hours of stroke in order to be effective³³. This poses a problem for patients with stroke who do not present with very early onset encephalopathy or seizures.

Other neuroprotective factors are also being explored in the context of neonatal brain injury – this has been recently reviewed by Gonzalez and Ferriero³⁶. Some of these are surprisingly familiar from other clinical contexts, such as growth factors (for example erythropoietin³⁷), antioxidants (including melatonin), anti-inflammatory agents (including minocycline) and a range of agents aimed at reducing excitotoxic damage (including topiramate). Combinations of hypothermia and other neuroprotective agents are now being investigated through clinical trials for neonates with hypoxic ischaemic encephalopathy.

Cell replacement therapy: Stem cell transplantation

Stem cells are cells with the potential for both self-renewal and differentiation into a wide range of cell types. There is much interest in their potential to reduce the burden of morbidity following ischaemic insults to the developing brain³⁸. Investigations are being pursued with a range of stem cell types, which are likely to act in different ways. For example, neural precursor stem cells have been shown to migrate to the lesion site following unilateral hypoxic ischaemic injury in neonatal rats; some of the cells then differentiated into glial subtypes, with a small minority differentiating into neuronal subtypes³⁹. In contrast, mesenchymal stem cell transplants from human umbilical cord blood, whilst also migrating to the lesion site, showed little evidence of differentiation into either neural or glial subtypes in a neonatal rat ischaemic stroke model⁴⁰. The reduced infarct volume and improved functional outcome in the transplanted group were attributed to anti-inflammatory effects through release of trophic factors.

The potential risks from stem cell transplantation are high, including tumour development and transplant rejection, and there remain many unanswered questions regarding mode of delivery, mode of action, optimal use, timing etc. However, autologous umbilical cord blood-derived cells, which pose a number of obvious advantages from ethical and safety viewpoints, have reached the stage of phase one clinical trials following perinatal arterial ischaemic stroke ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01700166) reference NCT01700166) and acutely in neonatal hypoxic ischaemic encephalopathy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01506258) reference NCT01506258).

Modulating cortical excitability: neurophysiological approaches

There has been much recent interest in the possibility of modulating cortical excitability using noninvasive brain stimulation to improve outcome after stroke⁴¹. Cortical excitability is altered following stroke, in infants as well as adults⁴², although the precise pattern of alteration differs by lesion location⁴³. One of the observed effects in adults following stroke is a high level of interhemispheric inhibitory drive from the intact hemisphere to the affected hemisphere, correlating with poor motor performance of the paretic hand⁴⁴. This finding has driven studies aiming to increase excitability of the affected motor cortex and/or decrease excitability of the unaffected motor cortex. This has been done non-invasively using transcranial direct current stimulation⁴⁵ (with the anode being excitatory and the cathode being inhibitory), or using repetitive transcranial magnetic stimulation (rTMS, with low stimulation rates being inhibitory and high stimulation rates being excitatory)⁴⁶.

Low rate rTMS to the unaffected hemisphere has also been studied in older children with subcortical stroke, demonstrating safety and feasibility of the approach⁴⁷. There is an ongoing trial comparing the effect of rTMS and constraint-induced movement therapy in combination with each treatment separately (or neither) on motor outcomes in school-age children with hemiplegia due to perinatal ischaemic stroke ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01189058) identifier NCT01189058). It is at present unclear as to whether such non-invasive brain stimulation approaches are applicable earlier in life after perinatal stroke, when interhemispheric inhibition is still immature⁴⁸.

Therapy-based approaches with onset in infancy

The current emphasis on therapy-based interventions remains on children with established hemiplegic cerebral palsy, not on young infants. One approach is constraint-induced movement therapy (CIMT), in which use of the ipsilesional hand is prevented for a period of time for example using a restraining glove. During this time, intensive movement practice is achieved with the contralesional (more-affected) arm and hand. An alternative approach is intensive bimanual therapy. Whilst there remain a number of unanswered questions including the optimal duration and mode of delivery and the effect of the nature and severity of the underlying lesion, there is evidence for the effectiveness of both CIMT and bimanual therapy in this older age group⁴⁹.

In the first few years of life, the principle of activity-dependent competition shaping corticospinal tract development might suggest that constraint of the ipsilesional hand would be the more appropriate approach. However, along with increased potential for benefit in this age group comes increased risk from aberrant plasticity. For example, constraint of the

ipsilesional hand in infants at risk of hemiplegia may have adverse effects on development of movement control of that hand. The correct balance between promoting use of the contralesional arm and hand versus hindering development of the ipsilesional arm and hand must be struck if constraint is to be used⁵⁰. In a nonrandomised trial, constraint improved use of the hemiplegic hand in bimanual play compared with standard therapy approaches in children age 18 months to 4 years⁵¹. More commonly, infants undergoing constraint have been studied as part of a larger group with a broad age range⁵². There is increasing recognition that therapy interventions in an even earlier time window need to be explored⁵³. A randomised single blind trial comparing modified CIMT with baby massage for infants age 3-8 months with unilateral brain lesions and emerging motor asymmetries is currently recruiting ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01864811) identifier NCT1864811).

Exploitation of the “mirror neuron system” is also under investigation as a method of improving motor outcome in children with hemiplegic cerebral palsy. Mirror neurons were first identified in animal studies and were so named because they fired when the animal either performed a motor task or observed the same task being performed⁵⁴. Indirect evidence for a human mirror neuron system has subsequently been presented⁵⁵. Cortical responses to action observation resembling those to action performance have been demonstrated in infants and young children as well as adults⁵⁶⁻⁵⁸. There is increasingly strong evidence that the mirror neuron system is an important component of motor learning. For example, movement practice combined with observation of the same movements increases motor learning compared with movement practice alone⁵⁹. Therapy based on action observation and imitation was shown to improve motor recovery following stroke in adults⁶⁰. A recently published randomised controlled trial indicated short-term improvements in use of the affected hand in bimanual tasks with therapy involving repeated action observation and execution compared with repeated practice alone in 24 children age 5-15 years with hemiplegia⁶¹. Researchers from the same group have taken on the significant challenge of applying similar approaches to infants with predominantly unilateral brain lesions from the age of 9 weeks⁶².

Predicting the development of hemiplegic cerebral palsy

One of the difficulties with very early interventions following perinatal stroke is the need for early identification of affected infants and early, accurate prediction of outcome so that interventions can be targeted to those at significant risk of developing hemiplegia. For neonates presenting with seizures (for which stroke is the second commonest cause) or encephalopathy, early cranial imaging is needed to make the diagnosis. For those infants presenting later with pathological hand preference or motor delay, swifter referral for investigation is an important aim. The two most effective early predictors of motor outcome following symptomatic perinatal stroke are the pattern of MRI abnormalities and the presence of abnormal “general movements” – however, neither of these assessments is infallible.

Cranial imaging

Following symptomatic neonatal unilateral arterial ischaemic stroke at term, early MRI evidence of involvement of both deep (basal ganglia, posterior limb of internal capsule) and

superficial (distal, cortical) middle cerebral artery territory structures is associated with a high probability of development of hemiplegia⁶³⁻⁶⁶. Conversely, involvement of only superficial cortical areas in the infarct is associated with a low probability of developing hemiplegia, as is pure basal ganglia involvement⁶³⁻⁶⁶. Extensive corticospinal tract involvement (more precisely, involvement of the posterior limb of the internal capsule and cerebral peduncle) on diffusion-weighted imaging at around age 1 week also has a high risk of hemiplegia^{63,67}; diffusion tensor imaging to study the corticospinal tract at age 3 months is similarly predictive⁶⁸. For infants who have sustained a haemorrhagic parenchymal infarct either antenatally or following preterm delivery, asymmetrical myelination of the posterior limb of the internal capsule detected on MRI at term equivalent age is also predictive of hemiplegia⁶⁹.

General movements

A trained observer of spontaneous infant movements, using Prechtl's method⁷⁰, can discern a number of patterns. These include complex and variable writhing "general movements" in the first few months of life, and elegant, small, circular "fidgety movements" peaking between 9 and 13 weeks. Absent fidgety movements, or movements of abnormal quality, are associated with the emergence of subsequent neurological deficits. In a study of 11 term neonates with predominantly unilateral cerebral infarction, the absence of fidgety movements predicted the development of hemiplegia⁷¹. Similar findings were observed in a group of preterm infants with unilateral periventricular lesions⁷². Minor early movement asymmetries could also be detected with video analysis⁷³. Algorithms for automated assessment of general movements are under investigation.

Conclusion

There is active interest in developing early intervention approaches for infants with unilateral perinatal stroke. Improved early detection rates and optimised outcome prediction will be needed in order to implement all but the most low-risk strategies. The degree to which outcome can be changed remains to be seen, especially as early imaging-based findings of corticospinal tract asymmetry currently predict later function⁷⁴, but early intervention is a challenge we must take on.

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What this paper adds

Experimental approaches targeting early therapeutic time windows after perinatal stroke have the potential for significant reduction of morbidity. Improved early detection rates and optimised outcome prediction will be needed in order to implement all but the most low-risk interventional strategies.