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Perinatal stroke and overlapping clinical presentation with HIE; studying practical diagnostic and management challenges through observational analysis of a single tertiary centre stroke patients

Abstract

Background: While therapeutic hypothermia is accepted as a standard of care for improving neurological outcome for HIE patients, evidence of its benefits for neonatal stroke is lacking. Neurological presentations of HIE and neonatal stroke can be difficult to distinguish and indeed neonatal stroke can coexist with HIE. Our observational analysis of a single centre cohort of stroke infants with MRI diagnosis highlights the practical challenges for distinguishing between the two groups and reaching an early definitive diagnosis to inform appropriate treatment.

Methods: A retrospective cohort study of term neonates >37 weeks gestation born between May 2011 and April 2020 born at a specialised NICU network in the East of England with a principal diagnosis of neonatal stroke were obtained from Badgernet data.

Results: 81% of infants (13/16) had sentinel events around delivery. 50% (8/16) of infants were therapeutically cooled. Of the 8 cooled infants only 3 (37%) of cooled infants fulfilled both Toby A and B criteria. Infants who received therapeutic hypothermia were more likely to present with early onset seizures (5/8) than infants who were not cooled (1/8) (p=0.019) . 6 of the 8 non-cooled infants compared to 2of the 8 cooled infants (p=0.03) had a higher seizure burden requiring escalation of antiepileptic medication to second line or need for maintenance treatment.

Conclusion: Infants with neonatal stroke who present with early seizures are more likely to receive therapeutic hypothermia despite failure to fulfil both Toby A and B criteria. Early suspicion to inform management can be obtained more effectively from CFM while cranial ultrasound findings are generally non-specific. A normal CFM background, unilateral abnormal background and unilateral seizure activity are highly suggestive of neonatal stroke.

Keywords: perinatal stroke, cerebral vein, neuroimaging, gestational diabetes

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Gupta R, Nafees M, Chetcuti Ganado Claudia
Bedfordshire hospitals NHS trust, Luton & Dunstable University hospital, UK

Correspondence: Chetcuti Ganado Claudia, Bedfordshire hospitals NHS trust, Luton & Dunstable University hospital, UK, Tel 07582267084, Email Claudia.Chetcutiganad@ldh.nhs.uk

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Background

Perinatal stroke is a common neurological disorder often causing admission to the neonatal unit. It is often unrecognized in the neonatal period and diagnosis is often retrospective, when patients present with neurological symptoms correlating with stroke. This is partly due to lack of established diagnostic guidelines for perinatal stroke.

Neonatal stroke can be considered under the umbrella of perinatal stroke, although these terms are often used interchangeably. Perinatal stroke is an area of damaged cerebral tissue resulting from disruption to blood flow in a major cerebral artery resulting from thrombosis or embolism (Perinatal Arterial Ischaemic stroke; PAIS). Thrombosis in a major cerebral vein (cerebral sinus venous thrombosis (CVST) is also possible. By definition, these events occur between 20 weeks of foetal life and the 28th postnatal day, and are confirmed by neuroimaging or neuropathological studies.[1] PAIS can be further divided into 3 categories:

a. Foetal ischaemic stroke, diagnosed before birth using imaging or in stillbirths from neuropathological examination;

b. Neonatal ischaemic stroke, diagnosed from birth to 28th postnatal day (including preterm infants);

c. Presumed perinatal ischaemic stroke (PPIS), diagnosed after 28 postnatal days when it is presumed (but not certain) that the ischaemic event occurred in the perinatal period.[1]

The incidence of PAIS occurs in 1 per 2300 – 4000 deliveries and that of the much rarer neonatal CVST between 1 and 2.69 per 100 000 newborns. The incidence of both conditions is underestimated due to the non-specific clinical presentation and inadequate neuroimaging.[1]

Perinatal arterial ischaemic stroke (AIS) is the diagnosis in 10 -15 % of neonates with seizures and accounts for approximately 30% of childhood hemiplegia.[1]

Risk factors for the development of PAIS and CVST may be maternal and/or foetal and neonatal but both conditions are likely to result from a combination of predisposing factors. Prothrombotic factors such as increased lipoprotein A and factor V Leiden mutation have been found in infants with PAIS and CVST. Similarly, conditions like pre-eclampsia, gestational diabetes, sickle cell disease, primiparity, placental disorders, instrumental deliveries and foetal cardiac disorders increase the risk of stroke.[2] Unique inflammatory biomarkers are associated with specific perinatal strokes and it may be possible to identify at risk pregnancies by measuring certain biomarkers like cytokines.[3] Signs of foetal compromise during labour

are common in neonates with PAIS and arterial infarction has been reported in association with hypoxic ischaemic encephalopathy. Hypoglycemia can be associated with PAIS in preterm neonates. The most widely reported additional pathologies are sepsis and non-central nervous system sepsis.

Neonates with AIS have usually had complicated labour or delivery. Presentation is within 3 days of delivery in 90 % of cases and the most common presentations are seizures or apnoeas, hypotonia, episodes of duskiness, irritability or poor feeding.[4] The diagnosis is very commonly missed because of overlapping presenting symptoms with HIE and meningitis. To complicate things further, there is no consensus on diagnostic modalities and timing of imaging to diagnose the condition early, hence the critical period to intervene is frequently missed.Perinatal strokes have a high morbidity index hence early diagnosis is key to manage these patients. There should be a high index of suspicion to diagnose a perinatal stroke. Common diagnostic modalities are usually not ideal to diagnose perinatal strokes. Cranial ultrasound can detect abnormalities but miss out superficial infarcts. CT scans are good for hemorrhagic strokes but MRI with diffusion weighted imaging can provide a more detailed picture and can pick up almost all types of strokes. MRA and MRV are other useful imaging but clinically stable patients are required to carry out such detailed studies and are generally done after 1 week of birth.[1]

The preventive strategies for perinatal strokes are not well established and require further research before these can be used in neonates. Presently, stabilization and supportive treatment are the only management goals. However, mesenchymal stromal cells and erythropoietin have demonstrated short-term neuro-behavioral benefits.[5]

Neuroprotective strategies like therapeutic cooling is well established in HIE but is still under trial for strokes. With insufficient evidence on the benefits of cooling in patients with stroke, it should be discouraged for managing perinatal strokes. However, because of overlapping clinical presentations and late imaging, these babies are frequently cooled. The diagnosis is made retrospectively. Cerebral function monitoring (CFM) is a commonly used bedside tool to monitor the brain activity of patients with neurological concerns. It is a well-established monitoring tool for patients with encephalopathy, HIE and seizures. CFM continuously monitors the background electrical activity of brain and can detect seizures and abnormal background discharges. Our study aims to understand whether CFM can be useful to provide the first clues to PAIS.

Methods

A comparative analysis was done for neonates with a principal diagnosis of neonatal stroke. A Badgernet search of infants born at >37 weeks, between May 2011 and April 2020, with a principal diagnosis of neonatal stroke were recruited to the retrospective cohort study. These neonates were cared for in a level 3 NICU in the East of England. A total of 16 patients were identified of which 8 had an initial clinical diagnosis of HIE, and a retrospective MRI diagnosis of PAIS. The presence of antenatal sentinel events, APGAR scores and gas analysis (cord or gas at <1 hour), postnatal presentation and whether the infant was therapeutically cooled were identified retrospectively from the notes or the Badgernet summaries. Cranial ultrasound images and CFM traces were reviewed retrospectively by a neonatal consultant. All MRI images undertaken between days 7-10 were reported by a specialist neuroradiologist and brain injury scores (1a to 3) were based on the National Institute of Child Health and Human Development Neonatal Research Network classification. EEG reports were undertaken by the hospital's neurophysiologist. Babies were classed as having a high seizure burden on the basis of clinical need to escalate to second line treatment, the presence of status epilepticus or need for maintenance antiepileptic drugs.

Analysis

Data was collected in excel spreadsheets with P value calculator obtained using the T test and absolute difference

Ethical considerations

No ethical approval was required as this data was collected as part of a service evaluation. Consent was obtained from the Clinical Audit and Effectiveness committee.

Results

81% of infants (13/16) had sentinel events around delivery. 50% (8/16) of infants were therapeutically cooled. Of the 8 cooled infants only 3 (37%) of cooled infants fulfilled both Toby A and B criteria. Infants who received therapeutic hypothermia were more likely to present with early onset seizures (5/8) than infants who were not cooled (1/8) (p=0.019). 6 of the 8 non-cooled infants compared to 2of the 8 cooled infants (p=0.03) had a higher seizure burden requiring escalation of antiepileptic medication to second line or need for maintenance treatment.

	Cooled n =8	Non cooled n=8	P value
Early onset seizures	5	1	0.019
High seizure burden	2	6	0.03
MRI injury score =>2	5	6	0.29

Cooled infants were more likely to present with abnormal neurology at birth (p=0.15) and had a lower MRI injury score than non-cooled infants (p=0.29), although these findings did not reach statistical significance.

Cranial ultrasound findings were normal or non-specific in all infants.

The CFM showed unilateral seizure activity in 14 of the 16 (87.5%) infants. The background half (50%)of babies was continuous normal and discontinuous in the other half (50%). There was no correlation of the background trace to the seizure burden. All babies had unilateral seizures. Only 1 baby with high seizure burden had seizures starting unilaterally that evolved into bilateral. The majority of infants had the largest seizure burden between 24-48 hours. In 15 babies the seizures settled by 48 hours.

MRI findings showed 15 infants had middle cerebral artery infarction, and one infant had cerebral sinus thrombosis. MRI injury score =>2 was observed in 5/8 infants who received therapeutic cooling and 6/8 in non-cooled infants (p= 0.29).

Discussion

Neonates with PAIS present within 3 days of delivery in 90 % of cases and the most common presentations are seizures or apnoeas, hypotonia, episodes of duskiness, irritability or poor feeding. In our cohort, the median time of presentation was 7.5 hours (range 0-48 hours). Presenting findings often overlap with those of HIE. In our group, 6 infants presented with abnormal neurology and we noted that infants with abnormal neurology were more likely to be therapeutically cooled. Perinatal strokes have a high morbidity index hence early diagnosis is key to managing these patients. There is no consensus on diagnostic modalities and timing of imaging to

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diagnose the condition early, hence the critical period to intervene is frequently missed and diagnosis continues to depend on a high index of suspicion. Early diagnostic modalities for stroke in adults are also not well established. Acute ischaemic stroke in adults can be treated chemically using recombinant tissue plasminogen activator (rt PA) or mechanically.[6] However, even in adults, the therapeutic window from onset of stroke is very short. Hence much research is focused on effective early diagnostic modalities for strokes in adults. Certain inflammatory biomarkers like matrix metalloproteinase, thioredoxin, neuronal glial markers, and miRNA have shown promising results in animal experiments but further research is warranted before these can be successfully used in humans.[7]

In contrast, there are no chemical treatment options for neonatal strokes. Presently, the recommended treatment is mostly supportive. Evidence of benefits in the use of anticoagulants is mostly limited to central venous sinus thrombosis. Due to overlapping clinical features and lack of early diagnostic modalities, babies with perinatal stroke may be therapeutically cooled with a presumptive diagnosis of HIE. However, direct evidence for the role of therapeutic hypothermia in PAIS is still lacking.

The challenges for research on neuroprotective strategies includes the short therapeutic window and often a delayed or retrospective diagnosis. For neuroprotective strategies to be effective early diagnosis will be paramount. Common diagnostic modalities are usually not ideal for early diagnosis of perinatal strokes. Cranial ultrasound changes in the presence of infarction can take days to evolve and is therefore not effective for early diagnosis and can miss superficial infarcts. Neuroimaging with computed tomography although used in some centers uses large doses of ionizing radiation. The MRI is considered a gold standard but despite its accurate predictability the logistics of undertaking an MRI may pose significant logistic challenges.

Cerebral function monitoring is a well-established monitoring tool for patients with encephalopathy, HIE and seizures. It is easily available at the bedside and its ease of use makes it useful as a first line investigation in cases of suspected stroke. In our cohort, we have noted almost universal laterality in the background pattern and this coupled with the almost universal unilaterality of seizures suggests that this may be very useful in the early suspicion of neonatal stroke. Unlike in HIE where a high seizure burden is likely to be associated with significantly abnormal background the presence of unilateral seizures in the setting of a normal background further raises the suspicion of neonatal stroke.

Early CFM can help raise the suspicion of neonatal stroke soon after presentation and coupled with early MRI can potentially prevent infants from undergoing therapeutic hypothermia until evidence of its effectiveness in this setting is available. Although therapeutic hypothermia treatment is safe it is associated with invasive interventions, maternal infant separation and anxiety in the parents. Better recognition of the difference can prove beneficial.

Conclusion

Infants with neonatal stroke who present with early seizures are more likely to receive therapeutic hypothermia despite failure to fulfil both Toby A and B criteria. Early suspicion to inform management can be obtained more effectively from CFM while cranial ultrasound findings are generally non-specific. A normal CFM background or unilateral abnormal background with unilateral seizure activity are highly suggestive of neonatal stroke. Evidence of the effectiveness and indication of therapeutic hypothermia in this setting is still lacking. The new BAPM framework for HIE with the inclusion of the CFM in the selection of infants who undergo therapeutic cooling will likely decrease the incidence of infants with neonatal stroke receiving therapeutic hypothermia.[8] Future research in understanding the effectiveness of therapeutic hypothermia on neurological outcomes in neonatal stroke are needed.

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None.

Conflicts of interest

No conflicts of interest.

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