

Commentary: “What Do We Know About Perinatal Stroke? A review of current practices, outcomes, and future directions”

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The review by Mailo, *et al.* provides an excellent contemporary summary of each of the perinatal stroke entities as well as a useful algorithm to diagnose and investigate underlying stroke etiologies. This review adds new insights by highlighting the definitive imaging modalities for the diagnosis of each stroke type, discussing the often-overlooked diagnosis of periventricular venous infarction, providing a thorough explanation of outcomes, and reviewing both traditional therapies as well as the future of perinatal stroke care. Unlike most prior reviews in this area, the authors give specific attention to the parental and family impact of a stroke diagnosis with reference to family-oriented resources, which provide critical information for all medical providers who care for these neonates and their families.

From our perspective as neonatologists, perinatal stroke is not an uncommon diagnosis, but it is always recognized as a *fait accompli* in otherwise healthy, term neonates¹. The lack of specific factors to predict its occurrence contribute to the need for a high index of suspicion to diagnose perinatal stroke in a timely fashion². Protocols, like the ones proposed in this review, provide an invaluable tool to effectively navigate the diagnostic path and treatment algorithm for perinatal stroke. In the hours or days following birth, neonates with perinatal stroke may present with abnormal movements with concerns or seizures, vital sign changes, or overt encephalopathy. With these signs, the neonate requires immediate stabilization and treatment. Neonates with perinatal stroke can be born at hospitals with advanced imaging capabilities and the benefits of a multidisciplinary neurological neonatal intensive care (NeuroNICU) program, but often they are born at community hospitals without these resources. Similarly, if presentation occurs

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outside the immediate postnatal course, these neonates arrive at local emergency rooms for initial stabilization.

We emphasize that the immediate course after onset of signs of perinatal stroke is critical and involves specific key steps including, 1) ensuring a stable airway and regular breathing, 2) cessation of seizures, and 3) timely imaging. Airway protection can become compromised in neonates with seizures or those with acute blood loss such as with hemorrhagic stroke, thus, clinicians should consider stopping enteral feeds and starting the neonate on intravenous fluids when stroke is suspected. Apnea (defined as respiratory pauses greater than 20 seconds) or respiratory distress leading to hypoxemia and bradycardia can be a presenting sign of seizures in neonates and may occur with or without an overt clinical correlation. Seizures manifesting as apnea may require immediate initiation of respiratory support including possible intubation. Given the risks associated with multiple attempts at endotracheal intubation in neonates³, the most experienced medical provider should attempt intubation, if it becomes necessary. Alternate airways such as the laryngeal mask airway should be available in case intubation with endotracheal tube is unsuccessful. Secondly, the treatment of clinical seizures acutely has specific caveats. In the neonate without intravenous access, an intranasal benzodiazepine such as lorazepam or midazolam is quick and effective and should be considered as the first line if continuous video electroencephalogram (EEG) has not been initiated yet⁴. The short-acting nature of these drugs allows easier interpretation of the electroencephalogram once it is placed, compared to the longer-acting medications which can cause background slowing and disguise

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the post-ictal stigmata of EEG leaving the medical team to question whether the event was indeed a seizure. In neonates with intravenous access or those who do not respond to benzodiazepines, a loading dose of phenobarbital is typically used to stop seizures. Reversible causes of seizure and encephalopathy should be excluded with immediate point-of-care testing of blood glucose, sodium, and calcium levels followed by septic evaluation and initiation of antimicrobials at meningitic dosing including coverage for herpes simplex virus.

After initial stabilization, imaging is a priority. Importantly, neuroimaging should be performed before placement of EEG leads, because most are not compatible with magnetic resonance scanners. The expertise of pediatric neuroradiologists is a critical component of the care of neonates with stroke. In this review, the authors also discuss the importance of ruling out other pathologies that present similarly to perinatal stroke including hypoxic ischemic encephalopathy (HIE). The key distinction between perinatal stroke and HIE is the absence of a perinatal event to explain the signs of encephalopathy and/ or seizures in perinatal stroke. For neonates with HIE, there is no postnatal period of normalcy and the birth history often reveals a need for advanced resuscitation after delivery. Neonatal blood gas and/ or arterial cord blood gas are recommended to facilitate the evaluation.

The role of the placenta in perinatal brain injury is the focus of ongoing research efforts in our group⁵⁻⁷. The placenta is vastly under-appreciated for its contributions to the hemodynamic, hormonal, and gas diffusing functions that directly contribute to fetal brain development, and in some cases, neuropathology. The placenta is an important component of the investigation for

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potential causes in perinatal arterial ischemic stroke⁸, and the impetus to send the placenta for pathologic exam must come from the medical team caring for the infant. This can be time-intensive and require persistent detective work to determine if the placenta is still available and how to route it appropriately. If possible, the preserved placenta or slides of the placental tissue should be shipped to the referral center with the baby to ensure a thorough evaluation using the Amsterdam Workshop classification system of placental pathology by pediatric placental pathologists⁹. Since the placenta is the most frequent source of embolic stroke in neonates, placental evaluation can provide the critical information that families seek regarding the possibility of this tragic event recurring for their child¹⁰.

In addition to placental pathologic examination, pediatric hematologists are important members of the care team to guide the diagnostic approach for the possibility of rare thrombotic disorders or bleeding diatheses as the etiology of the stroke¹¹. Pediatric hematologists can determine the appropriate timing of this testing for the neonate as well as specific laboratory testing required in the mother (such as testing for antiphospholipid syndrome and systemic lupus erythematosus). Neonates with congenital heart disease are at increased risk of embolic stroke, thus, echocardiogram is part of the diagnostic evaluation that we agree should be included for all neonates with perinatal arterial ischemic stroke¹². As neonatal echocardiography differs greatly from the targeted views in adult echocardiograms, technicians with expertise in this age group are preferred, to ensure optimal views for the pediatric cardiologist to determine if there is structural heart disease that contributed to the stroke event. In some cases, the presence of

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even a minor structural heart defect in the setting of perinatal stroke provokes a discussion about long-term treatment with aspirin to prevent future episodes ¹³.

In conclusion, the pediatrician and neonatologist should always consider stroke in the differential diagnosis of a seizing or encephalopathic neonate. Immediate steps should focus on stabilization, evaluation for reversible causes of seizure, and imaging to arrive at a timely diagnosis. The authors of this review delineate a useful imaging algorithm and management flowchart for future reference. The care of neonates with perinatal stroke requires multidisciplinary coordination and thus, optimally should be provided at centers with established NeuroNICU programs, dedicated 24-hour continuous video EEG monitoring, and the expertise of neonatologists, pediatric neurologists, pediatric hematologists, pediatric cardiologists, pediatric neuroradiologists, and placental pathologists ^{14,15}. Patients transferred to these referral centers will benefit from the latest in perinatal stroke care including the possibility of enrolling in one of the many ongoing clinical trials. Recruitment is currently underway in clinical trials investigating treatment of perinatal arterial ischemic stroke with mesenchymal stem cells (NCT03356821) and darbopoietin (NCT03171818), as well as trials involving transcranial magnetic stimulation to promote brain reorganization after perinatal stroke (NCT02743728).

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References

- 1 Raju, T. N., Nelson, K. B., Ferriero, D., Lynch, J. K. & Participants, N.-N. P. S. W. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics* **120**, 609-616, doi:10.1542/peds.2007-0336 (2007).
- 2 Ferriero, D. M. *et al.* Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke* **50**, e51-e96, doi:10.1161/STR.000000000000183 (2019).
- 3 Foglia, E. E. *et al.* Neonatal Intubation Practice and Outcomes: An International Registry Study. *Pediatrics* **143**, doi:10.1542/peds.2018-0902 (2019).
- 4 Soul, J. S. Acute symptomatic seizures in term neonates: Etiologies and treatments. *Seminars in fetal & neonatal medicine* **23**, 183-190, doi:10.1016/j.siny.2018.02.002 (2018).
- 5 Mir, I. N. *et al.* Impact of multiple placental pathologies on neonatal death, bronchopulmonary dysplasia, and neurodevelopmental impairment in preterm infants. *Pediatric research* **87**, 885-891, doi:10.1038/s41390-019-0715-y (2020).
- 6 Mir, I. N. *et al.* Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcomes following hypothermia. *American journal of obstetrics and gynecology* **213**, 849 e841-847, doi:10.1016/j.ajog.2015.09.072 (2015).
- 7 Leon, R. L. *et al.* Neuroplacentology in congenital heart disease: placental connections to neurodevelopmental outcomes. *Pediatric research*, doi:10.1038/s41390-021-01521-7 (2021).
- 8 Roy, B. *et al.* The Role of the Placenta in Perinatal Stroke: A Systematic Review. *Journal of child neurology*, 883073820929214, doi:10.1177/0883073820929214 (2020).
- 9 Khong, T. Y. *et al.* Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. *Arch Pathol Lab Med* **140**, 698-713, doi:10.5858/arpa.2015-0225-CC (2016).
- 10 Bemister, T. B., Brooks, B. L., Dyck, R. H. & Kirton, A. Parent and family impact of raising a child with perinatal stroke. *BMC Pediatr* **14**, 182, doi:10.1186/1471-2431-14-182 (2014).
- 11 Kenet, G. *et al.* Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation* **121**, 1838-1847, doi:10.1161/CIRCULATIONAHA.109.913673 (2010).
- 12 Asakai, H. *et al.* Arterial ischemic stroke in children with cardiac disease. *Neurology* **85**, 2053-2059, doi:10.1212/WNL.0000000000002036 (2015).
- 13 Leon, R. L., Zaban, N. B., Schamberger, M. S., Ho, C. Y. & Mietzsch, U. Cyanosis and Stroke due to Functional Cor Triatriatum Dexter in a Neonate. *Neonatology* **113**, 231-234, doi:10.1159/000485829 (2018).
- 14 Bonifacio, S. L., Glass, H. C., Peloquin, S. & Ferriero, D. M. A new neurological focus in neonatal intensive care. *Nat Rev Neurol* **7**, 485-494, doi:10.1038/nrneurol.2011.119 (2011).

15 Glass, H. C., Ferriero, D. M., Rowitch, D. H. & Shimotake, T. K. The neurointensive nursery: concept, development, and insights gained. *Current opinion in pediatrics* **31**, 202-209, doi:10.1097/MOP.0000000000000733 (2019).