

Perinatal arterial ischaemic stroke: An update with literature review

Ibrahim Shahnaz Hamid, Zafar Abdul Mueed

Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan.

Abstract

Perinatal arterial ischaemic strokes are a major cause of morbidity in the neonatal period and leads to significant neurological morbidity. It is however under recognized as an entity and usually missed till the baby is 3-4 months of age when they first present with hemiplegia.

Perinatal arterial ischaemic strokes are not reported from our country and this may be due to the fact that neurodiagnostic modalities were not available until the last few years. Even now this is not available in the smaller cities of our country. In this review we will discuss the common issues related to etiology and pathogenesis in perinatal arterial ischaemic stroke. The management and the prognosis are also reviewed especially discussing the factors that affect the long term prognosis

Introduction

Cerebral palsy is a major cause of morbidity in our country. Although birth asphyxia plays a major role in its etiology, there are a small percentage of children that have sustained a perinatal ischaemic stroke. A country like ours where there is a dearth of medical facilities and imaging is not available in all centers it is important to recognize this as a possibility in term neonates, so that a more holistic approach is made in the management of these children. Perinatal arterial ischaemic stroke is under recognized and missed because the neonates may be completely asymptomatic at that time.¹ This holds true in our part of the world also where children present after 3 -4 months of age to the paediatrician with a history of weakness on one side. This is commonly related to either a vaccination or an injection given in the limb. Neuroimaging done at that time reveals an old ischaemic lesion which indicates a perinatal ischaemic infarct. Knowledge of the preexisting perinatal ischaemic stroke is therefore important for medico legal purposes also.

Cerebrovascular disorders are among the top 10 causes of mortality in children with the rates highest in first year of life.¹ Stroke is estimated to affect 1 in 4000 neonates based on CT scan findings² and is 17 times more common in the perinatal population as compared to rest of the paediatric population.³

Perinatal arterial ischaemic stroke (PAS), is

defined as "Cerebrovascular event occurring between 28 weeks of gestation and 28 days of post natal age with radiological or pathological evidence of focal arterial infarction of the brain".¹ It represents a specific entity in the spectrum of cerebrovascular events. It excludes generalized cerebral ischaemic events like watershed infarctions and border zone infarctions.^{1,4,5} Earlier the diagnosis of stroke was based on autopsy findings, but more recently this has been replaced by imaging. In a recent population-based study with relatively frequent neuroimaging, unilateral PAS was recognized in the neonatal period in 1 in 2300 term infants.⁶ Previous studies reporting the incidence of perinatal stroke has estimated it to be 24.7-35/100,000 live births or approximately 1/3000-1/4000 live births.^{2,7,8} The Canadian Childhood Stroke registry, a population-based study, that recorded all cases of neonatal and childhood stroke in Canada between 1992 and 1996, reported the figures of ischaemic arterial stroke to be about 93/100,000 live births. A quarter of these cases fell in the neonatal age group.⁹ The National Hospital Discharge Survey (NHDS) from 1980 through 1998 estimated the rate of neonatal stroke (<30 days of age) to be about 26.4/100,000 live births¹

Pathophysiology

Arterial ischemic stroke (AIS) commonly relates to a focal ischaemic lesion in the distribution of a major cerebral artery.

Neonates have been recognized as a specific population at high risk for stroke and PAS has been found to affect mostly term neonates with MCA (Middle cerebral artery) being most commonly involved.^{2,4,7,10,11} Miller et al reported MCA to be involved in 83% of cases and in 66% of these the left MCA was affected.⁷

The lesions are thought to occur either in the intracranial vessels, extra cranial vessels, the heart or the placenta. The thrombus originating in the placenta then undergoes a left to right shunt via the patent foramen ovale and lodges in the cerebral circulation. These are quite distinct from the changes seen in HIE (Hypoxic ischemic encephalopathy) which causes a water shed infarction, are more bilateral and reflect a systemic hypotensive event with poor cerebral perfusion.⁵

Rarely the infarcts may be multifocal reflecting embolic origin or sub cortical indicating small vessel involvement.

With the conventional CT, MRI and now with MR DWI images, it is possible to time these events quite accurately. In a recent large study of neonates with encephalopathy a proportion of whom had focal infarctions, all but one had the onset within a few days of life suggesting the onset to be very recent.¹² However there are other studies which would also point towards the onset occurring much earlier in the perinatal life.¹³

Etiology

Regarding the mechanism of neonatal stroke, several potential genetic and environmental factors have been implicated but unequivocal evidence about a definite mechanism is still lacking and an obvious precipitating factor has not been identified in as many as 25-47% of cases.⁹ This is because most of the information received are from case reports and large population based studies have not been conducted. Also in a large number of series, border zone infarcts have been included and these are now categorized as a separate entity. The risk factors for PAS can be divided into three categories; antenatal, peri-natal and neonatal.

Antenatal

Pregnancy related events have not been reported in all studies of PAS, but where they are implicated the incidence from antenatal complications account from 0-64%.¹⁴⁻¹⁷

Antenatal risk factors such as pre-eclampsia, IUGR (Intrauterine growth retardation), maternal diabetes, maternal pro-thrombotic disorders, maternal infection, antenatal trauma and maternal drug abuse have all been implicated in studies of neonatal stroke.¹⁴⁻¹⁷

Two case-control studies looking specifically at the association of maternal factors with PAS deserve mention at this point. The study by Estan and Hope (1997) included 12 cases and 24 controls and assessed a total of 16 antenatal and perinatal risk factors of PAS. Compared to controls the cases were more likely to have lower 1 minute APGAR scores and require assisted ventilation than the controls; however there was no difference in the 5 minute APGAR scores. No significant difference was found between cases and controls with respect to maternal age, pregnancy related complications, CTG (Continuous Tomogram) abnormalities, mode of delivery and umbilical cord acidosis.² The data reported by Lee et al. based on 40 cases of PAS and 120 controls describes primiparity (73% vs. 44%), abnormal CTG findings (46% vs. 14%),

chorioamnionitis (27% vs. 11%) oligohydramnios (14% vs. 3%) to be significantly higher in cases as compared to controls. After multivariate analysis, history of infertility (OR 7.5), pre-eclampsia (OR 5.3), and chorioamnionitis (OR 3.4) were found to be independently associated with PAS and the number of risk factors present had a direct relationship with the risk of PAS.¹⁸

Normal pregnancy is a pro-inflammatory and pro-coagulant state which translates into a greater risk of stroke in the pregnant state as compared to the non-pregnant state. Unfortunately factors that decrease the risk of haemorrhage after delivery increases the risk of stroke both in the mother and the baby. Pregnancy is a time of relative hyper coagulability during which protein S and APC (activated protein C) ratios are decreased and Protein C, Thrombin generation and fibrinogen levels are increased.¹⁹ The fVL (factor 5 Leiden) mutation has also been associated with pregnancy related thrombosis and pregnancy disorders i.e. pre-eclampsia, abruptio placenta, IUGR prematurity, neonatal stroke and foetal death. It is also well documented that acquired antiphospholipid antibody in the mother increases the risk of foetal loss.²⁰

On the foetal side, the foetus has a high haematocrit and high viscosity of blood, placenta has areas of low flow velocity favouring thrombotic tendency. The placenta has its own haemostatic mechanisms and is probably an important area of pathology in PAS.⁴ Other factors that may contribute to this are, damage to neonatal vessels during birth, dehydration, hypotension, infection and intravascular catheters. Prothrombotic disorders which include Factor V Leiden and prothrombin mutation, protein S, C and antithrombin 111 deficiency are factors which are responsible in more than half of the children with stroke.^[9] These are now being increasingly recognized as causative factors for neonatal strokes also.

Perinatal factors

Factors contributing to the stroke in the perinatal period include assisted delivery, caesarean section, birth asphyxia and intra-partum trauma.⁵ The Canadian stroke registry, one of the largest studies on PAS, reported complicated birth/asphyxia to be present in about 18% of patients.^{9,10} Other studies have also found emergency caesarean section, vacuum extraction, prolonged rupture of membranes, prolonged stage II of labour and cord abnormalities to be potential risk factors for PAS.^{15,18} Contrary to these findings, the national hospital discharge survey (NHDS 1980-1998) recorded perinatal asphyxia in <5% of neonatal stroke.⁵ This factor has been questioned in recent studies and while there is good evidence of an association of asphyxia with border zone cerebral ischaemia, evidence to support a strong association with

focal infarction is lacking.⁵

Neonatal factors

Infections, dehydration and infection during the perinatal period are also a risk factor for stroke in the neonate.

Cardiac disorders: Although cardiac disorders are a known risk factor for childhood ischaemic stroke, it is less commonly implicated in the etiology of perinatal stroke. Cardiac defects contribute to the pathology by allowing venous clots to by pass the pulmonary filter.^{4,21} Neonatal pulmonary hypertension and extracorporeal membrane oxygenation (ECMO) have also been stated as a risk factor in some cases of PAS.^{8,22}

Catheterization: With the advent of intensive care management and the use of indwelling catheters, the obvious risk of thrombosis and subsequently of perinatal arterial strokes have increased.²³

Polycythemia: Polycythemias have been postulated to be an underlying mechanism in the development of PAS. This is presumably related to arterial red cell sludging in the cerebral circulation.²⁴ However, the case control study by Estan and Hope 1997,² did not show any difference in the haematocrit values of cases and controls.

Thrombophilia: Among all the risk factors of PAS, maternal and neonatal pro-thrombotic disorders are the ones that have been most extensively studied. This stems from the obvious deduction that pro-thrombotic disorders may play a role in cerebral thromboembolic phenomena. These disorders have been reported in 11%-64% of cases of PAS in different studies.^{9,10,17,25,26} Although maternal and neonatal thrombophilias can be logically implicated as a causative factor, unequivocal evidence about their causative role is yet to be defined. Much research has been focused on the study of genetic coagulation disorders in PAS but there is also evidence that additional environmental factors are present in up to 54% of cases²⁵ and occurrence of PAS in more than one singleton child in a sib-ship is a rare event. Screening of neonates for these thrombotic disorders will identify the cause but does not play a role in future management. The exceptions are the homozygous conditions of protein C, S and Antithrombin deficiency.

Clinical manifestations

Clinical signs and symptoms of cerebral injury are not as well defined in neonates as in older children and adults. The symptoms, if any, are usually subtle, present late and vary across individuals.^{2,4,10,16,27} Adding to it is the fact that a certain proportion may not manifest clinical

symptoms at all times.^{4,5} In view of these findings, it is not surprising that although these events mostly happen within 72 hours of birth, an estimated one-third cases of neonatal stroke are diagnosed retrospectively around the age of 4-5 months when they start voluntary motor activities.^{4,17}

Neonates with underlying cerebral ischaemia, rarely present with focal signs but may present with seizures, apneic spells, lethargy, poor feeding, birth asphyxia or hypotonia during the first 24-72 hours of life.^{2,4,10,16,27} Seizures have been reported as the most common presentation of neonatal stroke.² The Canadian Stroke Registry, has also reported similar findings; seizures in 85% of cases and hemiparesis in only 7% cases.⁹ Looking at this from a different perspective, only 12-14% of patients with seizures in the neonatal period were found to have an underlying stroke.^{2,14} Generalized hypotonia and lethargy has been found to be the most frequent findings on neurological examination.⁵ There is a differential susceptibility to ischaemic insult across different areas in the neonatal brain with the deep gray nuclei and peri-rolandic cortex being the most likely to be affected.^[28] Seizures and motor abnormalities may be better understood when viewed from this perspective.

Neonates with PAS and seizures may appear clinically well between episodes or may depict other signs of encephalopathy.⁴ Different areas of the brain have variable vulnerability to insults at different maturational stages.²⁹ This temporal variation in susceptibility to injury may translate into protean clinical signs and presentations reported in the literature.

Diagnostic modalities

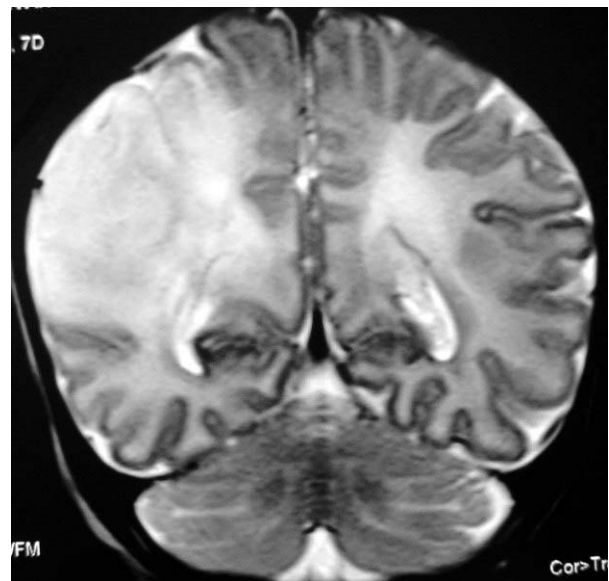


Figure 1. MRI of a neonate 3 days old. Coronal image showing a large ischemic area in the distribution of the right middle cerebral artery consistent with Perinatal arterial ischemic stroke

The lack of well defined clinical signs leaves diagnostic Neuroimaging as the only reliable choice for identification of PAS.^{4,5} Diagnostic imaging procedures for cerebral pathology in the neonates include magnetic resonance imaging (MRI), computerized tomography (CT) and cranial ultrasonography (USS).

USS is the most widely used form of screening modality in the newborn but the yield of USS in detection of PAS is not encouraging.^{4,5} USS failed to identify 75% of neonates in whom the pathology was diagnosed on CT scan.² Although CT scan has better sensitivity than cranial USS; it may not identify abnormalities in the early phase of an acute ischaemic event leaving MRI as the preferred modality for the diagnosis of PAS as it would be able to identify the focal area of ischaemia which would be diagnostic (Figure 1). Currently, diffusion weighted MRI (DW MRI) is regarded the most sensitive technique for early detection of acute infarction due to its ability to identify cytotoxic cerebral oedema which is the earliest abnormality seen in case of an infarction.^{30,31}

Electroencephalography (EEG) is a frequently used diagnostic modality in paediatric neurological problems which may have a potential role in PAS. Periodic Lateralized Epileptiform Discharges (PLED) may be associated with a localized cerebral lesion such as stroke and have been implicated as pointers towards PAS before diagnostic imaging is done.³²

Management

There are no randomized trials that address the acute management of neonatal stroke or its primary or secondary prevention. The American College of Chest Physicians recommend the use of heparin or low molecular weight heparin for the cardio embolic strokes. However it is not recommended for the non-cardio embolic strokes.³³ This may be because of the fact that a large number are identified quite late after the event has occurred. Some authors suggest the use of thromboprophylaxis in the mother as a primary prevention of PAS. This is debatable till further studies elucidate the mechanisms better.

Prognosis and outcome

Neuroimaging and EEG findings have been used in the prediction of long term neurological outcome.¹ Mercuri et al found an association of development of hemiplegia with the extent of lesion on MRI. Lesions involving, internal capsule were associated with development of hemiplegia later on while involvement of other regions were less reliable.³⁴ Trauner et al have found that children with early unilateral damage exhibit prosodic

deficits and the side of the lesion is related to the affective comprehension³⁵ but the association between occipital lesions and visual field defects or between parietal lobe involvement and fixation shift abnormalities does not appear to be consistent.¹

Mercuri et al. also reported the potential predictive value of EEG for long term outcome. They reported that changes in background activity suggesting generalized brain involvement may predict the development of hemiparesis whereas seizure activity alone was associated with a better outcome.³⁴

PAS is significant with respect to long term outcomes. Hemiplegic cerebral palsy is the most common outcome and occurs in 37% of children whose strokes were diagnosed in the neonatal period and in 82% of children whose stroke was diagnosed retrospectively.³⁶ In addition, seizure disorders, delayed language development, cognitive impairment and behavioural disorders can occur.^{4,36} 57% of children with neonatal stroke develop some neurological morbidity.¹⁰ Estan and Hope found a low rate of occurrence of complications (no motor, cognitive or seizure disorder in 11/12 cases) during follow-up for a median of 33 months.² Other studies have reported at least one neurological complication in 37-94% of patients.^{10,36} this apparent discordance could be due to the fact that a majority of these cases are not diagnosed in the neonatal period and complications have been found to be higher in retrospectively diagnosed cases.^{17,36} Differences in duration of follow-up, outcomes measured and population studied have also been proposed to contribute to this disparity among different reports.¹⁰

Fortunately, PAS carries a low mortality and rate of recurrence. Mortality after neonatal stroke is estimated to be less than 10% in the Canadian pediatric stroke study.¹⁰ Risk of recurrence is also reported to be 3-5%.¹⁰

More than 95% of neonates with stroke survive into the adulthood. This may lead to considerable effects on the patient, family and the society as a whole. There is a pressing need for standardization of diagnostic criteria, biochemical measurements as well as establishment of causative mechanisms and temporal relations between insult and symptoms to not only identify the pathology at an early stage but also to mark a window period for potential intervention and prevention.^{1,5} This calls for a better liaison across different disciplines involved in the care of the neonate and mother.

Conclusion

Perinatal arterial strokes are uncommon and under recognized. The use of diagnostic modalities may lead to

early detection and treatment. Prognosis for complete neurological recovery is poor.

References

1. Lynch JK, Hirtz DG, De Veber G, Nelson KB. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. *Pediatrics*. 2002; 109: 116-23.
2. Estan J, Hope P. Unilateral neonatal cerebral infarction in full term infants. *Arch Dis Child Fetal Neonatal* Ed.1997; 76: F88-93.
3. Wu YW, Lynch JK, Nelson KB. Perinatal arterial stroke: understanding mechanisms and outcomes. *Semin Neurol*.2005; 25: 424-34.
4. Nelson KB. Perinatal ischemic stroke. *Stroke*. 2007; 38: 742-55.
5. Chalmers EA. Perinatal stroke-risk factors and management. *Br J Haematol*. 2005; 130: 333-43.
6. Schulzke S, Weber P, Luetsch J, Fahrenstich H. Incidence and diagnosis of unilateral arterial cerebral infarction in newborn infants. *J Perinat Med*. 2005; 33: 170-75.
7. Perlman JM., Rollins NK, Evans D. Neonatal stroke: clinical characteristics and cerebral blood flow velocity measurements. *Pediatr Neurol*. 1994; 11: 281-84.
8. Govaert P, Matthys E, Zecic A, Roelens F, Oostra A, Vanzieleghem B. Perinatal cortical infarction within middle cerebral artery trunks. *Arch Dis Child Fetal Neonatal* Ed. 2000; 82: F59-63.
9. DeVeber G, Monagle P, Chan A, MacGregor D, Curtis R, Lee S ,et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. *Arch Neurol*. 1998; 55: 1539-43.
10. DeVeber, G.A., MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol*. 2000; 15: 316-24.
11. Miller V. Neonatal cerebral infarction. *Semin Pediatr Neurol*. 2000; 7: 278-88.
12. Cowan FM, Pennock JM, Hanrahan JD, Manji K P, Edwards A D. Early detection of cerebral infarction and hypoxic ischemic encephalopathy in neonates using diffusion-weighted magnetic resonance imaging. *Neuropediatrics*. 1994; 25: 172-75.
13. Scher MS, Belfar H, Martin J, Painter MJ. Destructive brain lesions of presumed fetal onset: antepartum causes of cerebral palsy. *Pediatrics*. 1991; 88: 898-906.
14. Levy SR , Abroms IF, Marshall PC, Rosquete EE. Seizures and cerebral infarction in the full-term newborn. *Ann Neurol*. 1985; 17: 366-70.
15. Koelfen W, Freund M, Varnholt V. Neonatal stroke involving the middle cerebral artery in term infants: clinical presentation, EEG and imaging studies and outcome. *Dev Med Child Neurol*. 1995; 37: 204-12.
16. Fujimoto S, Yokochi K, Togari H, Nishimura Y, Inukai K, Futamura M, et al. Neonatal cerebral infarction: Symptoms, CT findings and prognosis. *Brain Dev*. 1992; 14: 48-52.
17. Golomb MR, MacGregor DL, Domi T, Armstrong DC, McCrindle BW, Mayank S, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol*. 2001; 50: 163-68.
18. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, et al., Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *Jama*. 2005; 293: 723-29.
19. Delorme MA, Burrows RF, Ofosu FA, Andrew M. Thrombin regulation in mother and fetus during pregnancy. *Semin Thromb Hemost*. 1992; 18: 81-90.
20. Heilmann L, von Tempelhoff GF, Pollow K., Antiphospholipid syndrome in obstetrics. *Clin Appl Thromb Hemost*. 2003; 9: 143-50.
21. Pellicer A, Cabanas F, Garcia-Alix A, Perez-Higueras A, Quero J. Stroke in neonates with cardiac right-to-left shunt. *Brain Dev*. 1992; 14: 381-85.
22. Klesh KW, Murphy T F, Scher MS, Buchanan DE, Maxwell EP, Guthrie R D. Cerebral infarction in persistent pulmonary hypertension of the newborn. *Am J Dis Child*.1987;141: 852-57.
23. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics*. 1995; 96: 939-43.
24. Amit M, Camfield PR.Neonatal polycythemia causing multiple cerebral infarcts. *Arch Neurol*. 1980; 37: 109-10.
25. Gunther G, Junker R, Strater R, Schobess R, Kurnik K,Heller C, et al. Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. *Stroke*. 2000; 31: 2437-41.
26. Mercuri E, Cowan F, Gupte G, Manning R, Laffan M, Rutherford M, et al Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. *Pediatrics*. 2001; 107: 1400-04.
27. Sreenan C, Bhargava R, Robertson CM, Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr*. 2000; 137: 351-55.
28. Ferriero DM, Arcavi LJ, Sagar SM, McIntosh TK, Simon RP. Selective sparing of NADPH-diaphorase neurons in neonatal hypoxia-ischemia. *Ann Neurol*.1988; 24: 670-76.
29. McQuillen PS, Ferriero DM. Selective vulnerability in the developing central nervous system. *Pediatr Neurol*.2004; 30: 227-35.
30. Venkataraman A, Kingsley PB, Kalina P, Pavlakis SG, Buckwald S, Spinazzola R,et al. Newborn brain infarction: clinical aspects and magnetic resonance imaging. *CNS Spectr*. 2004; 9: 436-44.
31. Mader I, Schoning M, Klose U, Kuker W. Neonatal cerebral infarction diagnosed by diffusion-weighted MRI: pseudonormalization occurs early. *Stroke*. 2002; 33: 1142-45.
32. Rando T, Ricci D, Mercuri E, Frisone MF, Luciano R, Tortorolo G, et al.Periodic lateralized epileptiform discharges (PLEDs) as early indicator of stroke in full-term newborns. *Neuropediatrics*. 2000; 31: 202-5.
33. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson A D. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004; 126: 645S-87S.
34. Mercuri E, Rutherford M, Cowan F, Pennock J, Counsell S, Papadimitriou M, et al., Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram and magnetic resonance imaging study. *Pediatrics*. 1999; 103: 39-46.
35. Trauner DA, Ballantyne A, Friedland S, Chase C. Disorders of affective and linguistic prosody in children after early unilateral brain damage. *Ann Neurol*. 1996; 39: 361-67.
36. Lee J, Croen LA, Lindman C, Nash KB, Yoshida CK, Ferriero DM, et al., Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol*. 2005; 58: 303-08.