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The Black Box of Perinatal Ischemic Stroke Pathogenesis

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Abstract

An improved understanding of perinatal stroke epidemiology, classification, neuroimaging, and outcomes has emerged in recent years. Despite this, little is known regarding the pathophysiological mechanisms responsible for most cases. A multitude of possible associations and putative risk factors have been reported, but most lack definitive empirical evidence supporting primary causation. These include obstetrical and maternal factors, perinatal conditions, infectious diseases, prothrombotic abnormalities, cardiac disorders, medications, and many others. The bulk of evidence is weak, dominated by case reports and retrospective case series. Findings from the small number of case-control and cohort studies that exist are limited by heterogeneous populations and methodologies. The single largest barrier to ultimately understanding and potentially improving outcomes from this common and disabling condition is the lack of comprehensive, fully-powered risk factor studies required to definitively describe perinatal stroke pathogenesis. This review summarizes current evidence and suggests future directions for research.

Keywords

perinatal stroke; risk factors; cerebral palsy; neonate

Introduction

More than 100 years ago, Freud astutely hypothesized that much of cerebral palsy was secondary to perinatal stroke, specifically the “tearing, embolism, and thrombosis of cerebral vessels.”¹ By 1980, the body of evidence had grown surprisingly little and cerebral infarction in newborns was considered rare and most commonly resulting from venous sinus thrombosis or arterial embolization from a patent ductus arteriosus or placenta.² A more accurate, current reflection of our ignorance is Dr. Karin Nelson’s summary in 2003: “The known causes of cerebral palsy account for only a minority of the total cases.”³ In 2011, recent advances have improved our understanding of perinatal stroke epidemiology, classification, neuroimaging, and outcomes. Despite this, little remains known regarding the pathophysiological mechanisms responsible for most cases.

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Terminology and Classification

There is no doubt that perinatal stroke is common and the leading cause of hemiplegic cerebral palsy, with an incidence of 1:3000 live births or more.^{4,5} It is defined as “a group of heterogeneous disorders in which there is a focal disruption of cerebral blood flow secondary to arterial or venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, and confirmed by neuroimaging or neuropathological studies.”⁶

Recently proposed syndromic classifications have further advanced efforts to define specific perinatal stroke disease states based on mechanism and timing of both the injury and presentation (Figure 1.⁷ Neonatal arterial ischemic stroke refers to neonates with acute symptoms, usually seizures, leading to confirmation of an acute arterial ischemic stroke by neuroimaging (Figure 1A). The acute recognition of neonatal arterial ischemic stroke likely explains why risk factor studies to date have focused almost entirely on this population. In a similar fashion, neonatal cerebral sinovenous thrombosis also usually presents acutely,^{8,9} facilitating risk factor investigations. Neonatal cerebral sinovenous thrombosis is reviewed elsewhere.¹⁰

Alternatively, many children with no perinatal neurological history present later in infancy with neurological abnormalities, usually hemiparesis, that is attributable to remote focal infarction on neuroimaging (Figure 1B and 1C). Such presumed perinatal ischemic stroke is common but relatively unstudied. Recent advances in imaging classification have defined 2 patterns of injury that account for the vast majority of this type of perinatal stroke. When imaging reveals remote infarction in a known arterial territory, the term arterial presumed perinatal ischemic stroke may be applied (Figure 1B). Imaging⁷ and risk factor¹¹ studies have provided indirect evidence that arterial presumed perinatal ischemic stroke and neonatal arterial ischemic stroke may be the same disease, differing only in their age at presentation.

In contrast, periventricular venous infarction is a common form of perinatal ischemic stroke with distinct timing and mechanism. Germinal matrix and intraventricular hemorrhage is well-described and common in infants delivered preterm. Subependymal hemorrhage may result in compressive obstruction of medullary veins that drain blood from the periventricular white matter.¹² Secondary venous infarction damages descending corticospinal tracts, resulting in hemiplegic cerebral palsy.^{12,13} This same process (“grade 4 intraventricular hemorrhage”) is now well-described as occurring in utero^{14,15} and can present as perinatal ischemic stroke.^{16,17} Magnetic resonance imaging (MRI)-based retrospective diagnosis of periventricular venous infarction is now feasible with detection of remote hemorrhage with gradient echo and susceptibility-weighted sequences.^{7,17} Perinatal hemorrhagic stroke is beyond the scope of this review and is discussed elsewhere.^{18,19}

The goal of this review is to critically summarize the evidence for possible perinatal stroke risk factors while considering the relative level of evidence and potential causal relationship for each. We suggest that a definitive cause for most cases remains elusive and propose future directions for research. Only with an improved understanding of pathophysiological mechanisms will the first steps toward prevention and treatment be realized.

Prothrombotic Factors

Thrombophilia has been a logical leading avenue of investigation given the reasonable likelihood of a cerebral thrombotic or thromboembolic mechanism in arterial perinatal stroke. Combined with the quantitative nature of such measurements, investigation of prothrombotic factors provides a solid historical example of how the exploration of disease

mechanisms can proceed. Case reports of perinatal stroke in association with prothrombotic risk factors have been published for several decades,²⁰ with multiple prothrombotic factors considered. Most early studies were case series and case reports, but the importance of such preliminary evidence is well-described in the study of new mechanisms of disease.²¹ Despite their anecdotal nature, the value of case descriptions is readily apparent in the literature on prothrombotic factors associated with perinatal stroke, with many factors first described in case reports or case series and later validated in case-control studies. Table 1 lists prothrombotic factors potentially associated with perinatal stroke across case reports, case series, case-control studies, and cohort studies.

Real answers to the role of prothrombotic factors, which abnormalities, and how they might combine with other factors to result in perinatal stroke is far from settled. Studies vary in their design, laboratory methods, and the panel of prothrombotic markers tested. Age at testing is another crucial variable, with developmental hemostasis creating a complex, constantly evolving system inherently difficult to measure.²² Rather than controls matched for essential variables such as age, gender, and stroke syndrome, some studies have used adult population controls.²³ Others have been unable to study specific disease states, instead grouping heterogeneous populations such as perinatal and childhood stroke,²⁴ arterial and cerebral sinovenous thrombosis²⁵ or hemorrhagic stroke,²⁶ various forms of cerebral palsy²⁷ or porencephaly,²⁸ or children with varied thromboembolic disorders including stroke.²³

A recent systematic review and meta-analysis of thrombophilia in pediatric ischemic stroke provides relative perspective on the current evidence base for this issue. Only 6 of 22 studies included perinatal stroke and the authors elected to combine both childhood and perinatal populations as well as arterial ischemic strokes with cerebral sinovenous thrombosis. While this creates some limitations in applicability to specific perinatal stroke diseases, the analysis did reveal significant associations with factor V Leiden (Odds Ratio [OR] 3.56; 95% confidence interval [CI], 2.29–5.53) and prothrombin 20210 gene mutation (OR 2.02; 95% CI, 1.02–3.99).²⁹

Two small studies have tried to compare prothrombotic factors between more specific perinatal disease states, namely neonatal arterial ischemic stroke and perinatal ischemic stroke. While under-powered, one suggested a greater number of inherited thrombotic abnormalities in perinatal ischemic stroke compared with neonatal arterial ischemic stroke³⁰ while the other found no difference.¹¹ Only one small study of 59 children with perinatal ischemic stroke has looked at thrombophilia in periventricular venous infarction; possible abnormalities were found in 5 of 9 cases.¹¹ Interestingly, associations between thrombophilia and preterm germinal matrix hemorrhage/periventricular venous infarction,^{31–33} including in utero occurrences, have been described.^{34–36} It is certainly possible that the venous stasis created by the germinal matrix hemorrhage might combine with inherent thrombophilia to predispose to periventricular venous infarction, but additional studies within this population are required.

Prothrombotic abnormalities in both the fetus/newborn and mother must also be considered and 2 studies have addressed this. One study of 60 mother-child pairs with population comparative data found possible abnormalities in 50% of the children and 55% of the mothers. The same factors were not always present in both the child and the mother. Significant differences from population prevalence was seen for low protein S, elevated lipoprotein (a), and anticardiolipin antibodies (in mothers), prothrombin 20210 gene mutation (in children), and methylenetetrahydrofolate reductase homozygosity (in both).³⁷ Another study assessing prothrombotic factors evaluated 47 infants with stroke and 22 mothers and compared them with 145 healthy surgical neonates and 631 nulliparous pregnant women.³⁸ Eighteen of 23 mother-infant pairs had a prothrombotic abnormality. In

mothers, factor V Leiden heterozygosity conferred an 8.5-times increased risk (95% CI, 4.1–17.5) and antiphospholipid antibodies a 3.9-times increased risk (95% CI, 1.5–10.0) of a baby with stroke. For infants, the relative risk of stroke was 4.2 (95% CI, 1.5–11.3) for factor V Leiden heterozygosity, 12.2 (95% CI, 2.5 – 59.9) for protein C deficiency, and 4.1 (95% CI, 1.4 – 12.2) for antiphospholipid antibodies.³⁸

Does thrombophilia influence the generally very low risk of recurrent thrombotic events after perinatal stroke? One cohort study of 215 neonatal arterial ischemic stroke cases followed prospectively for recurrence of thrombosis included 127 (59%) with a possible prothrombotic abnormality (31, 14% with multiple abnormalities). Recurrence of any type of thrombotic event was rare (3.3% over a median of 3.5 years of follow-up) but most (5 of 7) had a prothrombotic abnormality.³⁹ Understanding the role of prothrombotic factors in recurrence after perinatal stroke is certainly important, although the very rare event rate complicates such studies and questions the clinical relevance or any opportunity for an intervention/prevention study.

Prothrombotic factors likely play a role in perinatal ischemic stroke. Several questions remain: (1) which prothrombotic factors in a rigorous, case-controlled, population-based study of well-defined perinatal stroke types will rise to clinical significance; (2) which prothrombotic factor abnormalities in mothers and which in the newborn confer significant risk for perinatal stroke; and (3) what are the normal values for prothrombotic factors in newborns and postpartum mothers? Evidence for true causation must come from fully powered, methodically executed, case-control studies of carefully defined perinatal stroke populations.

Placental Abnormalities

While thrombophilia is probably the most studied potential risk factor, placental disease is perhaps the least studied major suspect in perinatal stroke. Multiple observations support the possibility that placental disease with systemic embolization into the newborn cerebral circulation could be responsible for arterial perinatal strokes. Nearly all such strokes are once-in-a-lifetime events, suggesting unique perinatal factors are responsible. Modern neuroimaging, specifically diffusion-weighted MRI, can now confirm close proximity to labor and delivery in neonatal arterial ischemic stroke cases. Such sensitive imaging also frequently detects bilateral and/or multifocal lesions, suggesting a proximal embolic source. Other such proximal sources of emboli are usually otherwise not apparent, with cardiac disease in <20% of cases (below) and systemic venous thrombosis that could embolize via a patent foramen ovale rarely detected.

Studies examining placental pathology in perinatal stroke are challenging, resulting in minimal evidence to date. Case reports and small series do provide possible insight. Neonatal arterial ischemic stroke has been reported with chorioangioma,^{40,41} chorioamnionitis,^{42,43} placental infarcts,⁴³ and fetal thrombotic vasculopathy.⁴⁴ Two large series have examined the association of placental infarction and histologic brain ischemia, though most are global injuries rather than focal strokes. An autopsy study of fetuses who died in utero documented a high rate of cerebral ischemia in those with placental infarction.⁴⁵ A second study reviewed autopsy cases of stillborn neonates with intrauterine growth restriction. Thirty-one of 37 brains examined had evidence of ischemic changes and 27 of those 31 cases had evidence of placental ischemia.⁴⁶ Although these findings support the link between placental and cerebral ischemic disease, the brain changes seen histologically were typically global and not focal ischemic infarcts.

Additional smaller placental studies have focused on arterial strokes. A case-control study described 29 cases of placentas with avascular villi, 4 of which had cerebral infarcts.⁴⁷

Variable results have been reported in case-control studies examining the potential association between perinatal stroke and clinical chorioamnionitis. Some have not found clinical significance,^{48,49} while others have.⁵⁰ A recent international study of 248 neonatal arterial ischemic stroke cases only had placental data on 20 (8%) but 16 (80%) of these were reported as “abnormal.”⁵¹ A recent case series found placental pathology available in 12 cases (5 with neonatal arterial ischemic stroke and 7 with cerebral sinovenous thrombosis) of 186 neonatal strokes in the Canadian Pediatric Ischemic Stroke Registry. All 5 placentas were reported as abnormal, with decreased placental reserve, thromboinflammatory process, and sudden catastrophic events as the described histopathological abnormalities.⁵²

There are few studies of placental pathology in perinatal stroke and often the placental findings are a small subanalysis of much larger observational studies. The single largest barrier is the time that elapses between birth and typical presentation and diagnosis, often 24 to 48 hours or later, when the placenta has already been destroyed. As it is unusual for perinatal stroke patients to die in the neonatal period and progress to autopsy, pathological studies in perinatal stroke are rare. Ideally, prospective case-control studies of placental pathology in neonatal arterial ischemic stroke could yield important findings regarding pathogenesis but would require an extensive, organized, and large-scale placental banking system. The primary question to be asked is what conditions affecting the fetal side of the placenta could result in embolization of thrombotic, or even placental, tissue into the newborn circulation?

Genetic Factors

Genetic susceptibility for perinatal stroke is a complex, poorly understood issue. Recurrences within families are rare, but this does not exclude the possibilities of spontaneous mutations, low penetrance or expressivity rates, or multiple gene interactions. Aside from studies of genetic prothrombotic factors (above), studies are limited. Isolated case reports provide examples of recurrences within families with complex, multifactorial genotypes.^{53,54} Single gene mutations such as *COL4A1* have recently been reported in association with both arterial perinatal strokes and periventricular venous infarction,⁵⁵ perhaps suggesting that alterations in vascular integrity or structure are important. A case-control study comparing candidate gene polymorphisms regulating thrombosis, nitric oxide, cytokines, vascular tone, and cell adhesion in neonatal arterial and venous stroke was negative.²⁵ Application of modern genetic methodologies such as genome-wide screening and whole exome sequencing are required and may well yield valuable clues regarding perinatal stroke pathophysiology.

Cardiac Factors

Obvious cardioembolic sources of perinatal stroke have been described and should always be considered.^{56–59} However, one series reviewing risk factors associated with presumed perinatal stroke⁶⁰ and another large prospective cohort study of 100 newborns with neonatal arterial ischemic stroke found no significant cardiac abnormalities.⁶¹

A prospective cohort study of neonates with transposition of the great arteries enrolled 29 term neonates; 19 required balloon atrial septostomy prior to surgery. All patients with focal brain injury on MRI had balloon atrial septostomy (12 of 19 with balloon atrial septostomy versus 0 of 10 without balloon atrial septostomy). Most (11 of 12) were embolic in nature and no patients were symptomatic.⁶²

Cardiac causes of perinatal stroke, although not likely the most common, are an important risk factor as they may potentially change the recurrence risk profile and acute management.^{63–65} Data from cohort and case-control studies are usually incomplete. Future

studies, particularly in neonatal arterial ischemic stroke cohorts, should include echocardiograms for all subjects, and if possible, for controls.

Infection

Infections may result in perinatal stroke through several pathophysiological mechanisms. Infection of the placenta may lead to thromboembolic events, and a link to clinical chorioamnionitis has been described.^{42,48–50,66} Sepsis and meningitis of the newborn has also been reported in association with perinatal stroke.^{59,67}

One review of 63 cases of neonatal meningitis over a 5-year period found no cases with cerebral infarctions.⁶⁸ Another review over a 5-year period identified 5 neonates with cerebral infarction and meningitis but only one had arterial ischemic stroke; the other 4 had cerebral sinovenous thrombosis.⁶⁹ A consecutive case series of neonatal bacterial meningitis over a 3-year period found 6 of 8 neonates with bacterial meningitis who were diagnosed with stroke.⁷⁰ Studies predating the advent of modern neuroimaging, particularly diffusion-weighted MRI, may have underestimated focal ischemic mechanisms of injury. For example, a recent case series of neonates with Group B streptococcal meningitis who received early diffusion-weighted imaging found distinct patterns of cerebral infarction, including common involvement of lenticulostriate arteries and deep gray matter infarcts.⁷¹ Therefore, infection is not only one of the few directly treatable causes of neonatal arterial ischemic stroke but specific mechanisms of injury may be definable that could help advance additional therapeutic interventions.

Maternal/Obstetrical Factors

Multiple maternal, obstetrical, and peripartum factors have been proposed as possible risks for perinatal stroke. Many of these are described in case series or examined in case-control studies. Given the overlapping features of many of these factors and their complex interplay, they are difficult to always clearly attribute solely to one of these specific categories. Thus, some will be discussed here as well as in the following section of acute illnesses of the newborn.

Although many patients are the products of healthy, uncomplicated pregnancies, many risk factors, such as post-date deliveries, maternal smoking, and eclampsia, have been described in pregnancies preceding perinatal stroke, according to anecdotal reports.⁴³ A series of 22 cases of perinatal ischemic stroke found 18 mothers with gestational or obstetrical risk factors, including preeclampsia, maternal infection, gestational diabetes, bleeding during pregnancy, breech presentation, and forceps delivery.⁶⁰ A recent comparison of risk factors in arterial presumed perinatal ischemic stroke and periventricular venous infarction revealed no difference between prenatal, maternal, or perinatal risk factors.¹¹

Case reports of perinatal stroke in twins are reported.^{72–74} A series from one center found 4 of 35 children with perinatal stroke were twins. None had co-twin demise, and none of the co-twins had stroke.⁷⁵ Twinning may confer a unique risk for perinatal stroke. Population-based studies would help establish prevalence of perinatal stroke in twin pregnancies.

Case-control studies have demonstrated associations with preeclampsia,^{48,49} primiparity, oligohydramnios, decreased fetal movements, prolonged rupture of membranes, prolonged second-stage labor, fetal heart rate abnormality, cord abnormality, vacuum extraction, and emergency caesarean section. In multivariate analysis, history of infertility, preeclampsia, prolonged rupture of membranes, and clinically diagnosed chorioamnionitis have been shown to be statistically significant.⁵⁰ A large, prospective cohort study of 100 newborns with neonatal arterial ischemic stroke showed a statistically significant association with

previous fetal loss, first pregnancy, primiparity, caesarean section, and premature rupture of membranes.⁶¹

Trauma and potentially traumatic deliveries have also attracted significant attention. Interested parties include clinicians, researchers, and parents searching for answers to their child's brain injury, as well as lawyers looking for those who might be held accountable. Cases of newborns with neonatal arterial ischemic stroke and vacuum-assisted or "traumatic" delivery have been described^{2,59,76-79} but the commonplace occurrence of such procedures complicates defining any causal association. In fact, multivariate logistic regression analysis in a recent international study of 248 cases of neonatal arterial ischemic stroke found that caesarean section was actually protective against the presence of neurological deficits at discharge.⁵¹ Although pathophysiology in some cases has been shown either pathologically² or radiologically⁷⁹ to be due to arterial dissection, cervical vessels remain angiographically uninvestigated in most cases. Although diagnostic yield is low, newborns having diagnostic imaging could benefit from complete vascular imaging.

With a significant number of existing studies examining very similar clinical elements of pregnancy and delivery, a meta-analysis might provide insight into the role of these factors.

Acute Systemic Illnesses of the Newborn

The classical description of the newborn with stroke is that of an otherwise well baby with a focal seizure, and this is certainly a common neonatal arterial ischemic stroke presentation.^{80,81} Most presumed perinatal strokes also have unremarkable neonatal histories.⁶ However, there is increasing recognition that subsets of perinatal stroke cases are associated with acute illness approximating the time of birth. Determining which neonatal illnesses are associated with perinatal stroke may lead to a better understanding of mechanisms and opportunities for intervention.

A large, prospective cohort of 100 newborns with neonatal arterial ischemic stroke compared neonatal characteristics associated with symptomatic stroke to >45 000 newborns from the general population. Perinatal factors more frequent in stroke cases included the need for emergency cesarean section, Apgar scores ≤ 7 at 1 minute, need for resuscitation at birth, and immediate transfer to a neonatal unit.⁶¹ Several case-control studies have shown that patients with perinatal stroke are more likely to have intrauterine growth restriction,^{48,82} be delivered by emergency caesarean section,⁵⁰ be diagnosed with asphyxia,^{49,50} have Apgar scores < 7 at 5 minutes,^{49,50} have a cord pH < 7.0 ,⁴⁹ require resuscitation at birth,^{49,50} and require neonatal intensive care unit admission.⁴⁹ Additional small case series and case reports provide additional support for these associations as well as disseminated intravascular coagulation and multisystem organ failure.⁵⁹

A retrospective cohort study that compared perinatal ischemic stroke subtypes found that acute perinatal risk factors (defined as fetal distress or nonreassuring status, urgent caesarean section, intrapartum hemorrhage, neonatal or maternal fever, neonatal resuscitation, neonatal acidosis [cord pH < 7.1], low Apgar scores [< 7 at 5 minutes], or neonatal intensive care unit admission) were significantly more common in arterial presumed perinatal ischemic stroke than periventricular venous infarction (66% vs. 17%, $P = .003$).¹¹ While this evidence is indirect, it supports the notion that many cases of arterial presumed perinatal ischemic stroke occur in the immediate neonatal period and may be the same disease as neonatal arterial ischemic stroke.

Additional, fully powered case-control studies differentiating specific stroke types may help further define the role of acute illness in perinatal stroke. That the "clinical" factors listed above, including maternal, obstetrical, and neonatal considerations, have been relatively

consistent among case-control studies in both their definitions and potential associations suggests a meta-analysis may also provide useful evidence to guide future studies.

Medications/Drugs

Reported associations of medications and perinatal stroke in pregnant women or neonates should be interpreted with caution, particularly with commonly administered drugs and a high incidence of perinatal stroke.^{4,5} Furthermore, identification of a definitive risk factor is so often lacking in perinatal stroke that families are typically left wondering what caused their child's stroke and may be quick to attribute causation to any present factor such as a medication. It is important to not overemphasize unlikely culprits while critically considering those medications with a possible theoretical basis for increased stroke risk. Randomized control trials for medications usually exclude pregnant women and prospective cohort studies are lacking, although pregnancy drug registries may be helpful. At this time, no specific medications have been clearly linked to perinatal stroke and potentially coincidental associations described in individual cases must be put in the appropriate context.

A report of 2 cases of neonatal arterial ischemic stroke whose mothers had received codeine in the last 2 weeks of pregnancy illustrates the issue.⁸³ However, the biological effects of codeine are well-established⁸⁴ and do not include a predisposition to thrombosis or stroke and, despite widespread use over many decades, no such association has been established. More is known about the effect of cocaine in pregnancy and possible associations with stroke. Despite this, convincing evidence of a strong association is lacking. Several cases of neonatal arterial ischemic stroke in infants exposed to cocaine in utero are reported.^{80,85,86} However, case-control studies of complications of fetal cocaine exposure have yielded conflicting results, with any association being weak at most.⁸⁷⁻⁸⁹ Complimentary and alternative medications also need to be considered. Blue cohosh (*Caulophyllum thalictroides*), a "natural remedy" for labor induction, has been reported in association with neonatal arterial ischemic stroke in one patient.⁹⁰

Conclusion

The strength of evidence addressing the causative mechanisms of perinatal stroke is limited. Establishing disease causation remains one of the most challenging goals of clinical research and a relatively uncommon occurrence coupled with a multitude of biologically plausible candidates exacerbates the issue in perinatal stroke. Studies to date have provided an important preliminary foundation but suffer from limitations that range from inconsistent definitions and heterogeneous populations in the best case-control studies to the biases and possible chance associations promoted by case reports and small series.

We suggest that future efforts to unravel the mechanisms of perinatal stroke should consider the following principles:

1. Careful, imaging-based classification of *specific disease states* (perinatal stroke syndromes) is essential.
2. Adequately powered, case-control methodology with multisource data collection is required to define the relative role of most previously considered factors.
3. For laboratory outcome variables such as thrombophilia, careful comparisons of case measurements to controls matched for essential clinical variables (most notably age at testing) using consistent laboratory methodology is an important, difficult requirement.

4. Novel or previously understudied (but highly suspicious) candidates such as the placenta should be emphasized where original approaches such as large-scale, prospective tissue banking will likely be required.
5. The application of modern and emerging technologies, most notably genetic testing capabilities, must cast light into areas previously inaccessible in perinatal stroke.
6. Of equal importance, suggested but untrue associations with common factors potentially blamed for perinatal stroke must be clarified to minimize maternal guilt, misdirected legal actions, and other adverse consequences that exacerbate perinatal stroke morbidity.

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Figure 1. Perinatal stroke syndromes. (A) Neonatal arterial ischemic stroke. Diffusion-weighted magnetic resonance image (MRI) of a neonate presenting with a focal seizure demonstrates restricted diffusion in the right middle cerebral artery territory consistent with an acute infarct. (B) Arterial presumed perinatal ischemic stroke. T1-weighted MRI of an infant who presented with early handedness demonstrates remote infarction in the right middle cerebral artery territory. (C) Coronal T2-weighted MRI in another child with congenital hemiparesis demonstrates periventricular venous infarction.

Table 1

Prothrombotic Abnormalities Potentially Associated with Perinatal Stroke

Maternal ^{20,37,38,91–93} and infant ^{38,39,60,94–96} antiphospholipid antibodies
Methylenetetrahydrofolate reductase gene C677T mutation (heterozygous, ^{39,97} homozygous, ^{37,53,60,98} and compound heterozygous ⁵⁴)
Factor V Leiden gene mutation (heterozygous), ^{23,27–30,38,39,53,54,60,99–103} maternal ³⁸
Prothrombin gene mutation/factor II G20210A ^{27,29,30,37,39}
Protein C deficiency ^{30,38,39,66,94,96,102}
Protein S deficiency ^{30,37,39,94,96,102}
Antithrombin III ^{30,39,94,96}
Homocysteine ^{26,39,66}
Lipoprotein (a) ^{37,39,102,103}
Factor VIIIc ^{39,99}
Plasminogen ⁹⁴
Activated protein C resistance ^{60,94}
Plasminogen activator inhibitor ⁵⁴

Factors listed in bold have been reported in case control or cohort studies.