Risk Factors and Presentations of Periventricular Venous Infarction vs Arterial Presumed Perinatal Ischemic Stroke

Adam Kirton, MD, MSc, FRCPC; Manohar Shroff, MD; Ann-Marie Pontigon, BScH; Gabrielle deVeber, MD, MHSc, FRCPC

Objective: To determine whether clinical presentations and risk factor profiles differ between periventricular venous infarction (PVI) and arterial presumed perinatal ischemic stroke (APPIS).

Design: Retrospective cohort study.

Participants: A total of 59 children with presumed perinatal ischemic stroke (PPIS) from the SickKids Children’s Stroke Program who were carried to term (63% boys).

Setting: Single tertiary care center subspecialty program.

Interventions: Participants had validated magnetic resonance imaging classification to define PVI and APPIS subgroups.

Main Outcome Measures: Clinical presentations, times to parental and physician concern, age at diagnosis, and standardized risk factor evaluations including maternal, fetal, obstetrical, neonatal, and prothrombotic variables. Patients with PVI and APPIS were compared using χ² or Fisher exact tests and Wilcoxon rank sum or Mann-Whitney U tests.

Results: A total of 12 children (20%) had PVI and 47 (80%) had APPIS. Median parental concern was 5 months, with delays to physician concern (7 months) and diagnosis (12 months). Delays were longer in PVI cases compared with APPIS (P = .002). Most presented with asymmetrical motor development but children with APPIS were more likely to present with seizures or nonmotor delays (P = .01). Children with APPIS were more likely to have acute perinatal risk factors (66% vs 17%; P = .002) including fetal distress, emergency caesarian section, or neonatal resuscitation. Cardiac evaluations were unremarkable. Prothrombotic abnormalities were common (44%) including protein S deficiency, lupus anticoagulant, and elevated factor IX but were comparable between APPIS and PVI subgroups.

Conclusions: Diagnosis of PPIS is often delayed. The association of acute perinatal risk factors with APPIS compared with PVI supports distinct timing of these diseases. Prospective, case-control risk factor studies of PPIS subtypes are required to develop prevention strategies.

Arch Neurol. 2010;67(7):842-848.

Perinatal stroke is a leading cause of cerebral palsy in children carried to term.¹ Most studies have focused on symptomatic neonatal strokes that present acutely (usually with seizures), though this only represents a fraction of all cases. Presumed perinatal ischemic strokes (PPIS) defines a child with a normal perinatal neurological history with neurological deficits attributable to remote focal infarction on neuroimaging later in infancy.²⁻³ Presumed perinatal ischemic strokes may be the most common perinatal stroke but are the least studied, with only 1 previous dedicated study.³ We recently defined imaging-based vascular classifications of PPIS and correlated them with neurological outcomes.⁴ Most PPIS are arterial (APPIS) in middle cerebral artery distributions. The typical cortical/subcortical injury (Figure 1A) is indistinguishable from many symptomatic neonatal arterial ischemic strokes, suggesting that APPIS are acute perinatal events.

Periventricular venous infarction (PVI) has emerged as a distinct and common cause of PPIS and hemiplegic cerebral palsy.⁵⁻⁶ The proposed mechanism includes unique timing and pathophysiology, with important implications for prevention. Germinal matrix hemorrhage prior to 34 weeks’ gestation may compress medullary veins, causing focal venous infarction of the periventricular white matter (Figure 1B).⁷ This injury is well described in infants delivered preterm but occurrence in utero may also occur, presenting as PPIS in infancy following term birth. Differences in risk factor profiles between PVI and APPIS are unknown but

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could support the unique mechanism of PVI while identifying interventional opportunities.

We hypothesized that risk factor profiles differ between PVI and APPIS, with acute perinatal factors being more common in the latter. We used the largest PPIS cohort to date to characterize these risk factor profiles and clinical presentations.

**METHODS**

**DEFINITIONS**

According to a recent National Institute of Neurological Disorders and Stroke workshop on perinatal stroke, PPIS is defined as a term-born child with normal neonatal neurological history presenting at 29 days of age or older with neurological deficit or seizure referable to focal, chronic infarction(s) on neuroimaging. Focal infarction specifies stroke (arterial or venous) while excluding global ischemic injuries such as hypoxic-ischemic encephalopathy, watershed infarction, or periventricular leukomalacia. Chronicity is confirmed by imaging (encephalomalacia, gliosis, atrophy, absence of restricted diffusion).

**PATIENT POPULATION**

Patients were identified through the SickKids Children's Stroke Program in Toronto, Canada. A comprehensive research database (1992-2006) in the Canadian Pediatric Ischemic Stroke Registry was screened for PPIS. Inclusion criteria were PPIS with complete neuroimaging and neurological follow-up for more than 12 months with the Pediatric Stroke Outcome Measure. Exclusions included (1) global brain injury or other neurological abnormality, (2) incomplete imaging, (3) neonatal neurological concerns, and (4) preterm birth (<37 weeks). The age at diagnosis was either the date at magnetic resonance imaging, reported as showing focal ischemia or infarction or, if not reported, subsequent determination by a pediatric neuroradiologist (without specification as APPIS or PVI). Limited clinical and risk factor data from 22 children and the vascular classification of this cohort are previously published. Ethical approval and informed consent were obtained.

**NEUROIMAGING**

Neuroimaging analysis followed previously validated methods. A, standardized PPIS classification scoring tool determined the following classifications: (1) middle cerebral artery arterial ischemic strokes (proximal M1/distal M1/anterior trunk/posterior trunk/lateral lenticulostriate), (2) other arterial ischemic strokes (eg, posterior cerebral artery), or (3) PVI. Diagnosis of PVI requires unilateral periventricular white matter infarction in medullary venous territory with 4 or more of the following: (1) focal periventricular encephalomalacia, (2) T2 prolongation in the posterior limb of the internal capsule, (3) cortical sparing, (4) hemosiderin (within lesion, ventricle, and/or germinal matrix) on susceptible sequences, and (5) relative sparing of the basal ganglia (lesser volume than cranial white matter lesion). Imaging was reviewed by a pediatric neuroradiologist (A.K.) and neuroradiologist (M.S.) experienced in perinatal stroke and blinded to outcome, with discrepancies resolved by discussion per previously validated methods.

**RISK FACTORS**

Historical variables were collected from prenatal records, perinatal and birth records, hospital admissions, and historical reviews, with parents attending the SickKids Children's Stroke clinic. Data were extracted and collected on standardized capture forms by experienced research personnel. Prenatal and maternal factors included maternal health including preexisting medical conditions, parity, infertility, antepartum bleeding or infection, recurrent early pregnancy loss (≥3 spontaneous abortions), gestational hypertension/preeclampsia, gestational diabetes, abnormalities of routine prenatal investigations, fetal position and version maneuvers, and exposures during pregnancy (smoking, alcohol, illicit drugs, trauma).
Perinatal, obstetrical, and neonatal factors included need for induction, failure to progress, assisted delivery (vacuum or forceps), and caesarian section (urgent or elective). Neonatal factors included fetal distress, nonreassuring status, intrapartum hemorrhage, neonatal resuscitation (assisted ventilation, intubation, chest compressions, or cardiac medication), neonatal acidosis (cord pH, ≤7.1), low APGAR scores (≤7 at 5 minutes), neonatal or maternal fever, abnormal birth weight, neonatal intensive care unit admission, and neonatal systemic illnesses (eg, sepsis). A positive family history included a first-degree relative with perinatal stroke, stroke, or prothrombotic disorder (confirmed and/or treated with anticoagulation).

Prothrombotic testing was completed according to research protocols that were updated as new evidence, and laboratory methods became available during the study. Recognizing controversies regarding thrombophilia in perinatal stroke, test results were interpreted relative to age reference values when possible. Testing included low levels of protein C, protein S, antithrombin III, or plasminogen; elevated levels of factor VIII, factor IX, lipoprotein(a) (>35 mg/dl; to convert to micromoles per liter, multiply by 0.0357), fibrinogen, or homocysteine (>1.62 mg/L; to convert to micromoles per liter, multiply by 7.397); single positive lupus anticoagulant or elevated anticardiolipin antibody (IgG > 4500 mg/dl; to convert to grams per liter, multiply by 0.01); or positive molecular assay for factor V Leiden or activated protein C resistance, homozygous methylene tetrahydrofolate reductase, or G20210A prothrombin gene mutations.

Two additional, prespecified subclassifications of risk factors were implemented to test specific hypotheses. First, if APPIS events are specific to the immediate perinatal period, they should associate with “acute perinatal factors,” which were defined as a priori as fetal distress or nonreassuring status, urgent caesarian 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. Second, the presence or absence of factors potentially present at fewer than 34 weeks’ gestation (ie, maternal and prenatal but not obstetrical or neonatal variables) were documented to examine potential associations with the earlier injury of PVI.

STATISTICAL ANALYSIS

Comparisons of the APPIS and PVI subgroups used χ² and Fisher exact tests for dichotomous variables and Wilcoxon rank sum and Mann-Whitney U tests for continuous variables. Our sample size of 59 patients (with 20% PVI cases) was 80% powered to detect a 40% difference in the proportion of our primary variable of interest (acute perinatal factors) between PVI and APPIS (type 1 error P = .05). Analysis was performed using Statistical Package for the Social Sciences, version 13.0 (SPSS Inc, Chicago, Illinois).

RESULTS

POPULATION

Of 91 children with possible PPIS, 32 were excluded because of hypoxic-ischemic encephalopathy (6), PVL (4), trauma (2), malformation (2), retrospectively identified neonatal neurological concerns (eg, possible seizures) (9), and insufficient imaging (9). The study population of 59 children included a higher proportion of males (37; 63%) including APPIS (64%) and PVI (58%). With all events considered perinatal, the age at study and duration of follow-up were considered the same, with a mean (SD) of 5.3 (0.7) years and median of 3.7 years. Most were white (62%), though ethnicity data were limited (73% of cases).

Lesions due to APPIS were found in 47 cases (80%), with the remaining 12 (20%) being due to PVI. Left hemisphere lesions were more common (59%) but accounted for only 5 of 12 PVI lesions (42%). Lesions due to APPIS were subclassified according to validated methods. Most (43 of 47 lesions; 91%) conformed to middle cerebral artery vascular territories including proximal M1 (19), distal M1 (7), anterior trunk (8), posterior trunk (5), and lenticulostriate (4) occlusions. Other APPIS lesions included posterior cerebral artery (2), anterior choroidal artery (1), and recurrent artery of Huebner (1) infarcts. Details of lesion classification and correlation with outcomes are published elsewhere.

DELAY TO DIAGNOSIS

Delay from first parental concern to final diagnosis was common. The median age at parental concern was 5.0 months (interquartile range, 3.0-8.5 months; range, 1.3-77 months). The median age at physician concern was 7 months (interquartile range, 4.5-17.5 months; range, 1.3-86 months). The median age at diagnosis was 12 months (interquartile range, 8.0-30 months; range, 1.4-120 months), with a median time to diagnosis from parental concern of 6 months (interquartile range, 2.0-12 months; range, 0-96 months). No differences in diagnostic intervals were apparent between left and right hemispheric lesions.

Delays to diagnosis differed between APPIS and PVI (Figure 2). The median age at parental concern was similar (APPIS, 4.5 months; PVI, 5.8 months; P = .36). However, the interval between parental concern and both physician concern and final diagnosis of PVI increased over time. Physician reaction to parental concern was faster in APPIS, with a shorter median time to referral or investigation (2.0 months) compared with PVI (6.3 months; P = .04). Final diagnosis occurred at an older median age.
in PVI (18.0 months vs 11.0 months for APPIS; \(P = .03\)), with a longer interval from first parental concern (14.9 months for PVI vs 5.0 months for APPIS; \(P = .002\)).

**CLINICAL PRESENTATION**

Asymmetrical early motor development or early hand preference was most common (44 children; 75%). Seizures were second, present in 10 children (17%), while nonmotor developmental delays were the concern in the remaining 5 (8%). Presentations differed between PVI and APPIS cases (Figure 3). Ninety-two percent of children with PVI presented with isolated motor asymmetry compared with 70% of those with APPIS (\(P = .12\)). Children with APPIS were more likely to present with seizures or nonmotor delay (25% vs 0% for PVI; \(P = .01\)). Motor asymmetry was noted by parents at a mean (SD) of 5.7 (+4.8) months and almost always within the first year (91%). In contrast, mean (SD) seizure presentations varied widely (30[31] months; range, 1-96 months). Presentation with seizures appeared to expedite investigations, with shorter times from parental concern to diagnosis (13.4 vs 3.6 months; \(P = .02\)).

**RISK FACTORS**

**Historical**

Complete historical risk factor data were available (n=59). Total proportions and comparisons between APPIS and PVI are summarized in Table 1. Chronic maternal conditions were present in 21 cases (35%) including hypertension (5), recurrent miscarriage (5), antepartum bleeding (3), and prenatal infection (3). A trend toward increased chronic maternal factors was observed for PVI (50% vs 32% for APPIS; \(P = .20\)). Unfortunately, data resolution was insufficient to subclassify chronic risk factors as present or not prior to 34 weeks to address our secondary hypothesis.

Perinatal, obstetrical, and neonatal factors were common (76%), with acute perinatal factors present in 33 cases (56%). Consistent with our primary hypothesis, the presence of one or more acute perinatal factor was significantly more common in APPIS (31 of 47 cases; 66%) compared with PVI (2 of 12 cases; 17%; \(P = .003\)). Delivery by cesarean section appeared greater than typical rates (42%) and was similar between APPIS and PVI (\(P = .54\)). Emergent cesarean section occurred in 15% (17% APPIS; 9% PV; \(P = .41\)). Neonatal interventions were documented in 14 cases (24%), usually consisting of brief respiratory support only and only 3 endotracheal intubations (all in APPIS cases). A trend toward increased neonatal intervention was observed in APPIS compared with PVI (28% vs 9%; \(P = .15\)). No differences were detected between APPIS and PVI in terms of induction, assisted delivery, fetal distress, or neonatal intensive care unit admission.

Thrombophilia

Thrombophilia data were available for 50 patients (85%), with most (80%) receiving 3 or more investigations (Table 2). Possible prothrombotic abnormalities were detected in 21 of 48 cases (44%). Most common were elevated factor IX (22%), lupus anticoagulant (17%), protein S deficiency (15%), and factor V Leiden (10%). These 4 most common abnormalities were tested for in most children (mean, 33; range, 24-40 patients). Infrequent (<5%) or entirely absent prothrombotic abnormalities included protein C deficiency, prothrombin gene mutation, and abnormalities of plasminogen, factor VIII, or factor XI.

Presence of prothrombotic abnormalities did not differ between APPIS (41%) and PVI (60%; \(P = .34\)). While possible differences in certain disorders are suggested (Table 2), the small sample size of the tested PVI group was limiting. Multiple prothrombotic risk factors were found in 8 children (16%). One child demonstrated 3 prothrombotic abnormalities (protein S, factor IX, and activated protein C resistance), one had highly positive anticardiolipin antibodies and elevated lipoprotein(a), one had protein S deficiency and factor V Leiden, and another had protein S deficiency and elevated lipoprotein(a). These children all had APPIS, while only a single child with PVI harbored multiple prothrombotic abnormalities (protein S and lupus anticoagulant).

Cardiac evaluation including echocardiography was completed in 23 cases (39%). Noncomplex cardiac abnormalities were detected in 4 patients (18%), all of whom had APPIS (\(P = .68\)). Abnormalities included atrial septal defect and patent foramen ovale in 2 patients each. None had a history of additional cardiac problems or intervention. Positive family history was present in 18 patients (31%) and was comparable between APPIS and PVI (\(P = .27\)).

**COMMENT**

We describe the largest series of PPIS clinical presentations and risk factors. Our primary finding is that risk...
profiles differ between the 2 leading PPIS syndromes. This provides the first indirect evidence that APPIS events are often asymptomatic, acute, neonatal arterial strokes, while PVI occur earlier in gestation. Our results add to previous studies demonstrating the utility of clinical-radiographic perinatal stroke classifications based on timing of injury (fetal vs neonatal), clinical presentation (acute or delayed), and vessel involved (arterial or venous). Consistent use and refinement of these syndromes will further define specific disease states, an improved un-

**Table 1. PPIS Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All PPIS (n = 59)</th>
<th>APPIS (n = 47)</th>
<th>PVI (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prenatal/maternal</td>
<td>21 (35)</td>
<td>15 (32)</td>
<td>6 (50)</td>
<td>.20</td>
</tr>
<tr>
<td>REPL</td>
<td>9 (15)</td>
<td>7 (15)</td>
<td>2 (18)</td>
<td>.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (8)</td>
<td>3 (6)</td>
<td>2 (17)</td>
<td>.66</td>
</tr>
<tr>
<td>Bleeding&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (5)</td>
<td>2 (4)</td>
<td>1 (9)</td>
<td>.73</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>2 (17)</td>
<td>.73</td>
</tr>
<tr>
<td>breech</td>
<td>4 (7)</td>
<td>3 (6)</td>
<td>1 (9)</td>
<td>.61</td>
</tr>
<tr>
<td>Any perinatal/neonatal</td>
<td>45 (76)</td>
<td>37 (79)</td>
<td>8 (67)</td>
<td>.44</td>
</tr>
<tr>
<td>Induction</td>
<td>9 (15)</td>
<td>8 (17)</td>
<td>1 (9)</td>
<td>.73</td>
</tr>
<tr>
<td>Fetal distress&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11 (19)</td>
<td>10 (21)</td>
<td>1 (9)</td>
<td>.28</td>
</tr>
<tr>
<td>Assisted delivery</td>
<td>5 (8)</td>
<td>4 (8)</td>
<td>1 (9)</td>
<td>.73</td>
</tr>
<tr>
<td>Neonatal intervention&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14 (24)</td>
<td>13 (28)</td>
<td>1 (9)</td>
<td>.15</td>
</tr>
<tr>
<td>NICU admit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 (8)</td>
<td>7 (15)</td>
<td>1 (9)</td>
<td>.48</td>
</tr>
<tr>
<td>Any CS</td>
<td>25 (42)</td>
<td>19 (41)</td>
<td>6 (50)</td>
<td>.54</td>
</tr>
<tr>
<td>Urgent CS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9 (15)</td>
<td>8 (17)</td>
<td>1 (9)</td>
<td>.41</td>
</tr>
<tr>
<td>Acute perinatal&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33 (56)</td>
<td>31 (66)</td>
<td>2 (17)</td>
<td>.003</td>
</tr>
<tr>
<td>Family history</td>
<td>18 (31)</td>
<td>13 (28)</td>
<td>5 (42)</td>
<td>.27</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4/23 (18)</td>
<td>4/21 (19)</td>
<td>0/2 (0)</td>
<td>.58</td>
</tr>
</tbody>
</table>

Abbreviations: APPIS, arterial PPIS; CS, cesarean section; NICU, neonatal intensive care unit; PPIS, presumed perinatal ischemic stroke; PVI, periventricular venous infarction; REPL, recurrent early pregnancy loss.

<sup>a</sup> All denominators are the values shown in the top panel except where indicated.

<sup>b</sup> Difference between APPIS and PVI subgroups (<sup>H2</sup> or Fisher exact test).

<sup>c</sup> Acute perinatal risk factors (see text for details) were significantly more common in APPIS than PVI.

**Table 2. Prothrombotic Risk Factors in PPIS**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All PPIS (n = 50)</th>
<th>APPIS (n = 41)</th>
<th>PVI (n = 9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. PS</td>
<td>6/39 (15)</td>
<td>4/30 (14)</td>
<td>2/9 (24)</td>
<td>.43</td>
</tr>
<tr>
<td>J. PC</td>
<td>0/38 (0)</td>
<td>0/29 (0)</td>
<td>0/9 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>J. ATIII</td>
<td>1/35 (3)</td>
<td>1/26 (4)</td>
<td>0/9 (0)</td>
<td>.75</td>
</tr>
<tr>
<td>PV/L/APCR</td>
<td>4/40 (10)</td>
<td>4/31 (13)</td>
<td>0/9 (0)</td>
<td>.34</td>
</tr>
<tr>
<td>PTG</td>
<td>0/40 (0)</td>
<td>0/31 (0)</td>
<td>0/9 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>↑ ACLA</td>
<td>3/39 (8)</td>
<td>2/20 (10)</td>
<td>1/9 (12)</td>
<td>.56</td>
</tr>
<tr>
<td>LAC +</td>
<td>4/24 (17)</td>
<td>2/19 (11)</td>
<td>2/5 (40)</td>
<td>.18</td>
</tr>
<tr>
<td>↑ Fibrinogen</td>
<td>1/34 (2)</td>
<td>0/30 (0)</td>
<td>1/4 (25)</td>
<td>.14</td>
</tr>
<tr>
<td>↑ Plasminogen</td>
<td>0/22 (0)</td>
<td>0/20 (0)</td>
<td>0/2 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>↑ Lipoprotein (a)</td>
<td>2/30 (7)</td>
<td>2/25 (8)</td>
<td>0/5 (0)</td>
<td>.69</td>
</tr>
<tr>
<td>MTHFR</td>
<td>1/8 (12)</td>
<td>1/9 (12)</td>
<td>0/0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>↑ Homocysteine</td>
<td>2/40 (5)</td>
<td>1/32 (3)</td>
<td>1/8 (16)</td>
<td>.36</td>
</tr>
<tr>
<td>↑ Factor VIII</td>
<td>1/27 (4)</td>
<td>1/24 (4)</td>
<td>0/3 (0)</td>
<td>.89</td>
</tr>
<tr>
<td>↑ Factor IX</td>
<td>6/27 (22)</td>
<td>6/24 (25)</td>
<td>0/3 (0)</td>
<td>.46</td>
</tr>
<tr>
<td>↑ Factor XI</td>
<td>0/27 (0)</td>
<td>0/24 (0)</td>
<td>0/3 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Multiple PTS</td>
<td>8/50 (16)</td>
<td>7/41 (17)</td>
<td>1/9 (13)</td>
<td>.74</td>
</tr>
<tr>
<td>Any PTS</td>
<td>21/48 (44)</td>
<td>16/39 (41)</td>
<td>5/9 (60)</td>
<td>.34</td>
</tr>
</tbody>
</table>

Abbreviations: ACLA, anticardiolipin antibody; APPIS, arterial PPIS; ATIII, antithrombin III; FVL/APCR, factor V Leiden mutation or activated protein C resistance; LAC +, positive for lupus anticoagulant; MTHFR, methylene tetrahydrofolate reductase mutation (homozygous); NA, not applicable; PC, protein C; PPIS, presumed perinatal ischemic stroke; PS, protein S; PTG, prothrombin 20210 mutation; PTS, prothrombotic state; PVI, periventricular venous infarction; ↓, decreased; ↑, increased.

<sup>a</sup> Denominator is the total number of tests performed under numerator of abnormal results. As the same child may have more than 1 abnormality, the total number in each column may be less than the sum of each abnormal test.

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understanding of which could afford new treatment and prevention strategies. Such classification is now readily available thanks to modern neuroimaging and is an important component of future perinatal stroke research.

We describe frequent occurrences of multiple biologically plausible risk factors in a well-characterized PPIS population. However, such associations still fall far short of proving definitive causative roles. Additional limitations include the retrospective nature of our study, particularly the collection of historical variables months to years later. Our data resolution was limited where, for example, we were unable to analyze prenatal risk factors as chronologically present before or after 34 weeks’ gestation. Such simple distinctions could provide important evidence regarding PPIS pathophysiology but will only be achieved by larger, prospective, case-control studies.

Our results demonstrate that PPIS diagnosis, particularly PVI, is usually delayed more than 6 months from the first parental concern. This supplements previous studies that characterize diagnostic delays in older children with stroke, 

suggesting increased education of primary care pediatric physicians is required. A clear hand preference noted by parents in the first year is likely pathological and requires prompt magnetic resonance imaging and/or referral to child neurology. Whether additional factors such as access to pediatricians, child neurologists, or neuroimaging influence time to diagnosis requires further study. We previously demonstrated that imaging-based classification of these PPIS syndromes facilitates accurate and early estimations of long-term neurological outcome. 

Timely diagnosis will be particularly important in motor rehabilitation in which strategies including constraint-induced therapy 

and noninvasive brain stimulation are increasingly supported and may be of maximal benefit earlier in development. The other common morbidities of perinatal stroke including disorders of language and cognitive development might also benefit from earlier diagnosis.

Similar to the only previous dedicated study of PPIS, 

thrombophilias were commonly detected in our cohort, though numerous limitations must be acknowledged. Inherent testing variability in young children of different ages must be considered, though we endeavored to use standardized testing protocols and age-defined normative values. The incomplete and variable collection of many prothrombotic variables is a major limitation, owing primarily to the retrospective nature of the study and subject collection for many years, during which testing options changed regularly. Previous evaluations of prothrombotic abnormalities in perinatal stroke populations are limited, suffering from similar limitations and population heterogeneity, but suggest comparable prevalence (20%-70%). 

Further distinguishing our PPIS population were abnormalities including protein S deficiency, lupus anticoagulant, and elevated factor IX, none of which have shown strong associations in previous studies in which protein C deficiency, lipoprotein(a), and factor V Leiden have predominated. Standardized, case-control studies of well-classified PPIS syndromes are required to establish the role of thrombophilia in perinatal stroke.

Cardiac abnormalities were rare in PPIS compared with other perinatal stroke subtypes. 

No complex congenital heart lesions were uncovered, which is not unexpected given the long delays to diagnosis. Our detection rate of 18% of simple patent foramen ovale or atrial septal defect does not seem excessive, and these lesions would seem unlikely to have contributed to the stroke. We suggest that cardiac evaluations be considered in children with PPIS but could be guided by clinical concern as opposed to acute symptomatic neonatal arterial stroke when cardiac evaluation is indicated.

In summary, the association of acute perinatal risk factors in APPIS compared with PVI provides evidence of distinct timing for each lesion: arterial strokes within the immediate perinatal period and PVI earlier in gestation. Diagnosis of PPIS is usually delayed, and improved education is required. Prospective, case-control studies of specific PPIS syndromes will further establish disease mechanisms and prevention opportunities.

Accepted for Publication: December 28, 2009.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by the Alberta Heritage Foundation for Medical Research and the American Academy of Neurology Foundation (Dr Kirton).

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