Perinatal stroke

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- Classification
- Aetiological factors
- Clinical approach
- Outcomes

Axes of classification

- Age at injury
  - Gestational/postnatal
- Symptomatic vs. silent
- Arterial vs. venous

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

Tonse N. K. Raju, MD, DCH[a], Karin B. Nelson, MD[b], Donna Ferriero, MD[c], John Kylan Lynch, DO, MPH[b], and the NICHD-NINDS Perinatal Stroke Workshop Participants

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"a group of heterogeneous conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through twenty-eighth postnatal day confirmed by neuro-imaging or neuropathologic studies."

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

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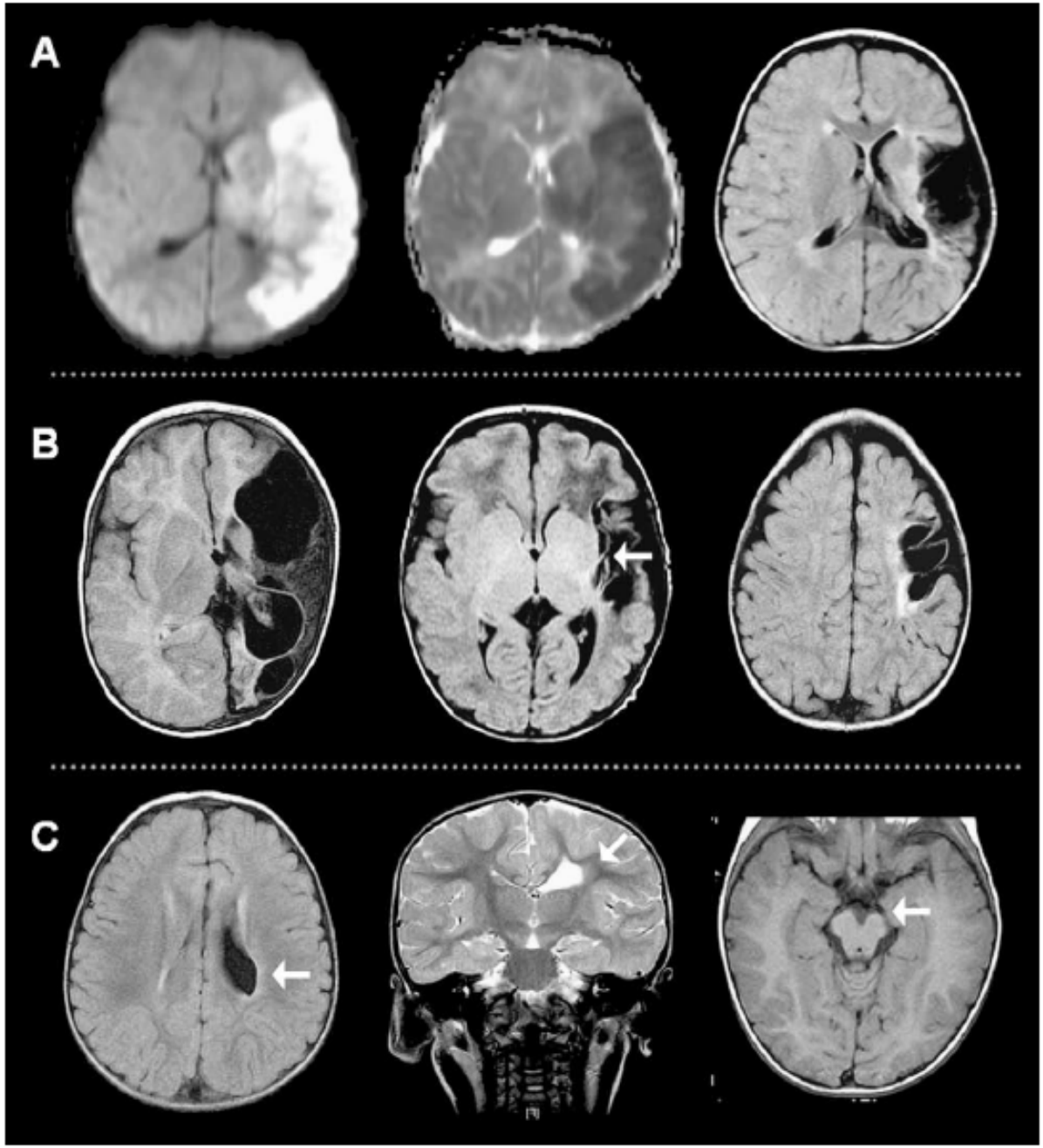
Because the timing of the vascular event leading to IPS is almost always unknown, it was suggested that the classification of IPS be based on the gestational or postnatal age at diagnosis. The suggested subcategories were

(1) fetal ischemic stroke, diagnosed before birth by using fetal imaging methods or in stillbirths on the basis of neuropathologic examination,
(2) neonatal ischemic stroke, diagnosed after birth and on or before the 28th postnatal day (including in preterm infants), and
(3) presumed perinatal ischemic stroke (PPIS), diagnosed in infants >28 days of age in whom it is presumed (but not certain) that the ischemic event occurred sometime between the 20th week of fetal life through the 28th postnatal day.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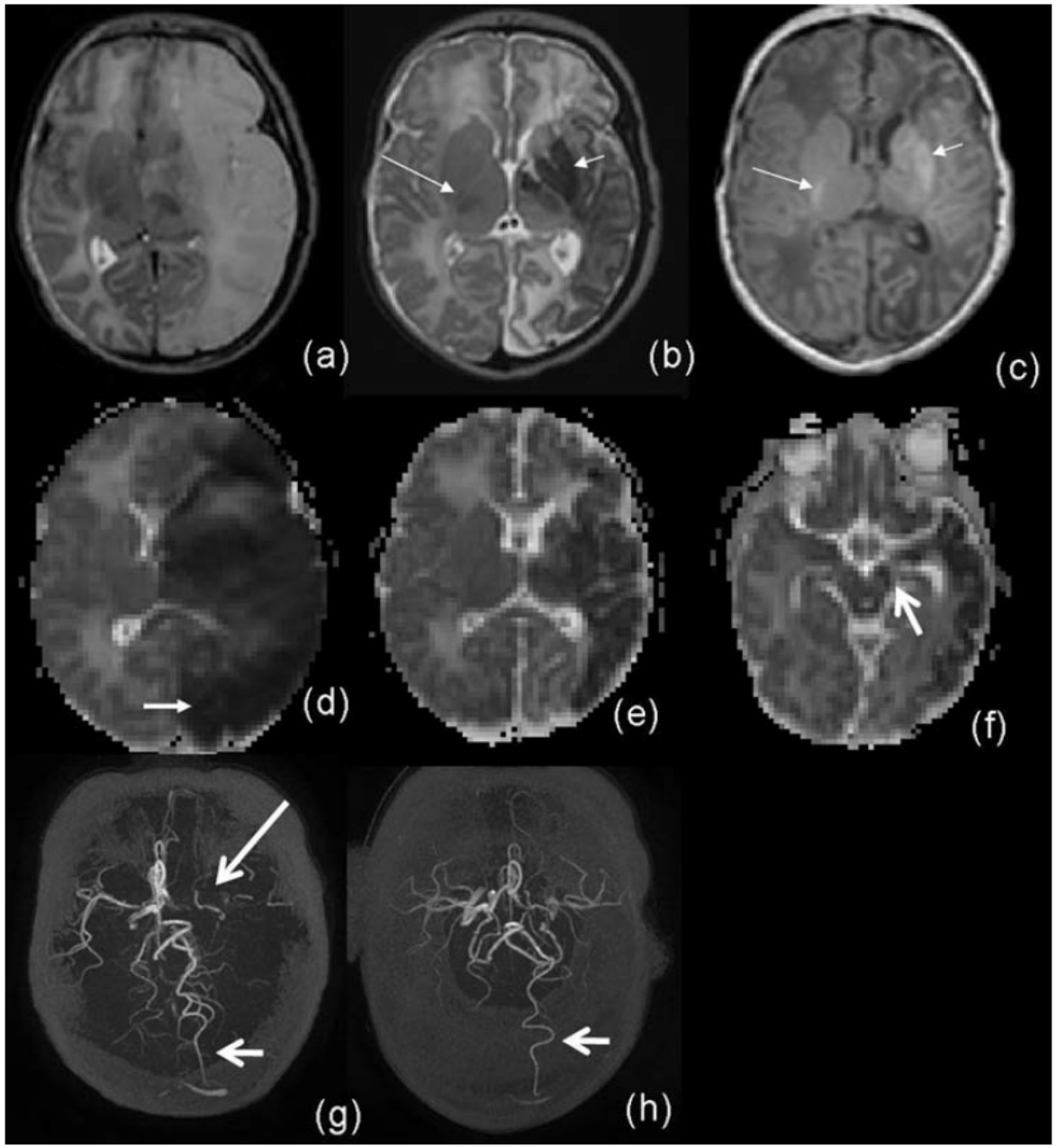
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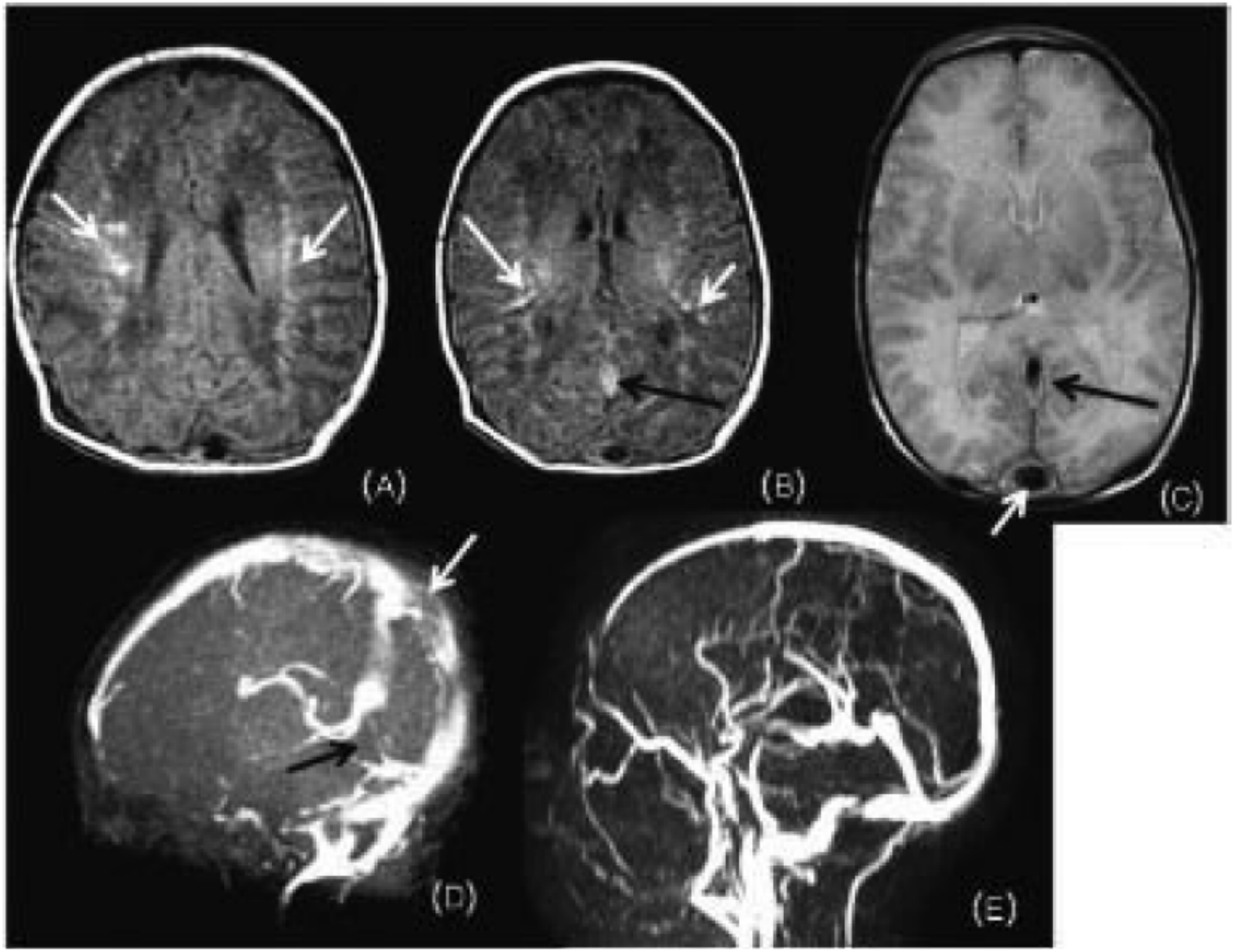
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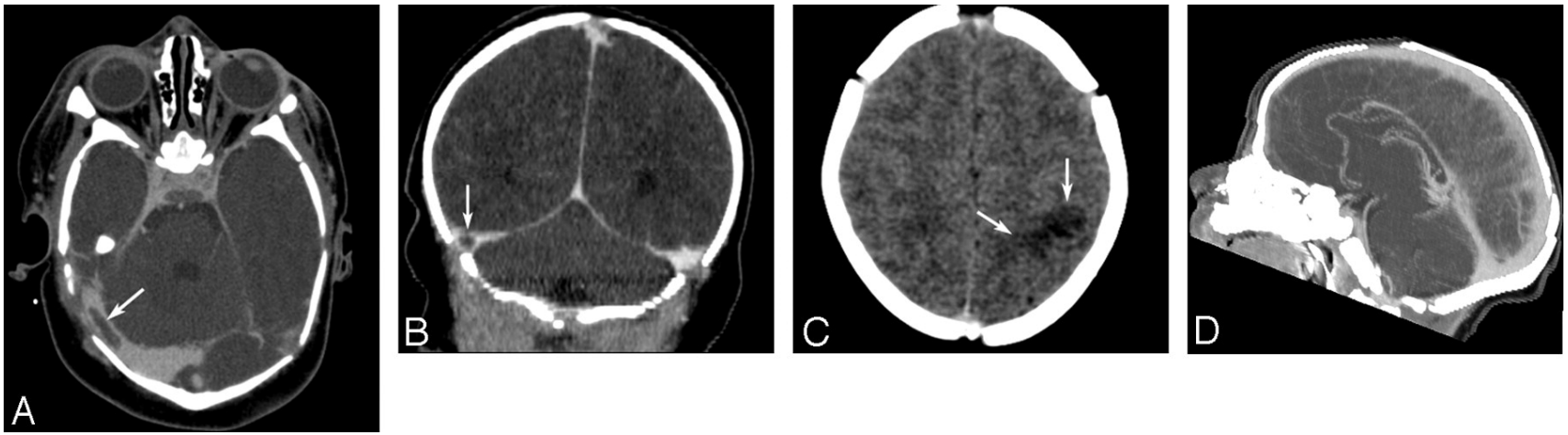
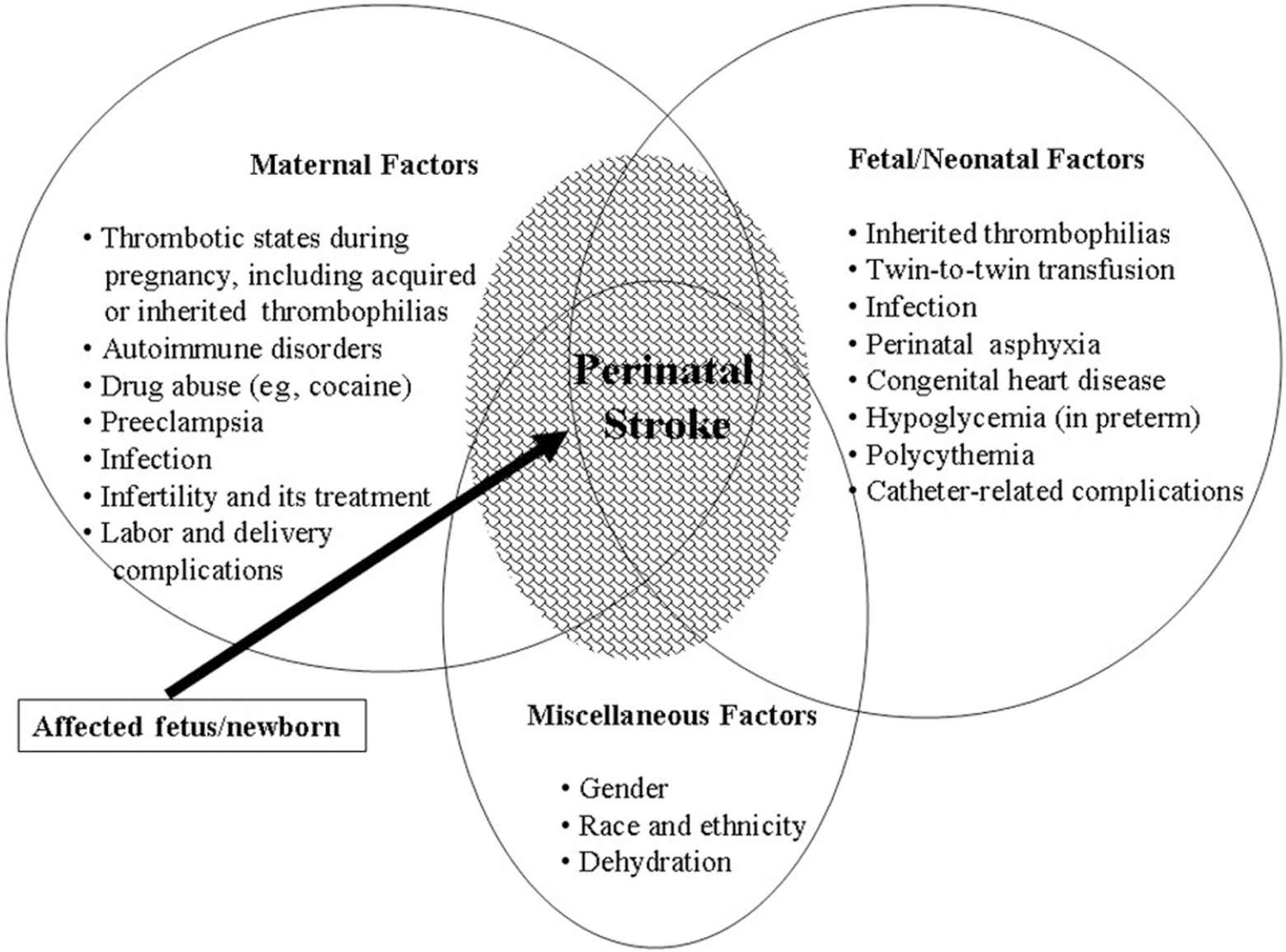


M. Teksam et al. AJNR Am J Neuroradiol 2008;29:1961-1965

Incidence

- All perinatal AIS: 1:2300-4000 deliveries
- Neonatal AIS – 15% preterm
- AIS is diagnosis in 10-15% of neonatal seizures

- CVST 1-2.7/100 00 newborns


Maternal Factors
• Thrombotic states during pregnancy, including acquired or inherited thrombophilias
• Autoimmune disorders
• Drug abuse (eg, cocaine)
• Preeclampsia
• Infection
• Infertility and its treatment
• Labor and delivery complications
Fetal/Neonatal Factors
• Inherited thrombophilias
• Twin-to-twin transfusion
• Infection
• Perinatal asphyxia
• Congenital heart disease
• Hypoglycemia (in preterm)
• Polycythemia
• Catheter-related complications
Perinatal Stroke
Miscellaneous Factors
• Gender
• Race and ethnicity
• Dehydration
Affected fetus/newborn

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

Gili Kenet, MD*; Lisa K. Lütkhoff*; Manuela Albisetti, MD; Timothy Bernard, MD; Mariana Bonduel, MD; Leonardo Brandao, MD; Stephane Chabrier, MD; Anthony Chan, MD; Gabrielle deVeber, MD, MAS; Barbara Fiedler, MD; Heather J. Fullerton, MD, MAS; Neil A. Goldenberg, MD, PhD; Eric Grabowski, MD; Gudrun Günther, MD; Christine Heller, MD; Susanne Holzhauer, MD; Alfonso Iorio, MD; Janna Journeycake, MD; Ralf Junker, MD; Fenella J. Kirkham, MD; Karin Kurnik, MD; John K. Lynch, MD; Christoph Male, MD; Marilyn Manco-Johnson, MD; Rolf Mesters, MD; Paul Monagle, MD; C. Heleen van Ommen, MD; Leslie Raffini, MD; Kevin Rostásy, MD; Paolo Simioni, MD; Ronald D. Sträter, MD; Guy Young, MD; Ulrike Nowak-Göttl, MD

Background—The aim of this study was to estimate the impact of thrombophilia on risk of first childhood stroke through a meta-analysis of published observational studies.

Methods and Results—A systematic search of electronic databases (Medline via PubMed, EMBASE, OVID, Web of Science, The Cochrane Library) for studies published from 1970 to 2009 was conducted. Data on year of publication, study design, country of origin, number of patients/control subjects, ethnicity, stroke type (arterial ischemic stroke [AIS], cerebral venous sinus thrombosis [CSVT]) were abstracted. Publication bias indicator and heterogeneity across studies were evaluated, and summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with fixed-effects or random-effects models. Twenty-two of 185 references met inclusion criteria. Thus, 1764 patients (arterial ischemic stroke [AIS], 1526; cerebral sinus venous thrombosis [CSVT], 238) and 2799 control subjects (neonate to 18 years of age) were enrolled. No significant heterogeneity was discerned across studies, and no publication bias was detected. A statistically significant association with first stroke was demonstrated for each thrombophilia trait evaluated, with no difference found between AIS and CSVT. Summary ORs (fixed-effects model) were as follows: antithrombin deficiency, 7.06 (95% CI, 2.44 to 22.42); protein C deficiency, 8.76 (95% CI, 4.53 to 16.96); protein S deficiency, 3.20 (95% CI, 1.22 to 8.40), factor V G1691A, 3.26 (95% CI, 2.59 to 4.10); factor II G20210A, 2.43 (95% CI, 1.67 to 3.51); *MTHFR* C677T (AIS), 1.58 (95% CI, 1.20 to 2.08); antiphospholipid antibodies (AIS), 6.95 (95% CI,

Factor V Leiden and Antiphospholipid Antibodies in Either Mothers or Infants Increase the Risk for Perinatal Arterial Ischemic Stroke

Michal J. Simchen, MD; Gal Goldstein, MD; Aaron Lubetsky, MD; Tzipi Strauss, MD; Eyal Schiff, MD; Gili Kenet, MD

Background and Purpose—The objective was to investigate the role of infant and maternal thrombophilia in a cohort of mothers and infants presenting with perinatal arterial ischemic stroke.

Methods—Forty-seven infants with clinically and radiologically confirmed perinatal arterial ischemic stroke underwent thrombophilia workup: factor V Leiden (FVL), PII20210A mutation, Methylene-tetrahydrofolate reductase 677T polymorphism, protein C, protein S, antithrombin, FVIII, and antiphospholipid antibodies. Thrombophilia data were available for 23 mother–infant pairs and compared with control populations to evaluate the risk for PAS.

Results—Thirty of 47 (64%) infants and 15 of 22 mothers (68%) had evidence of thrombophilia. In 18 of 23 (78%) mother–infant pairs, there was at least 1 thrombophilic risk factor, but 15 pairs were mismatched in pathology. Among infants, FVL, protein C deficiency, and presence of antiphospholipid antibodies prevailed (OR, 4.2; 95% CI, 1.5–11.3; OR, 12.2; 95% CI, 2.5–59.9; OR, 4.1; 95% CI, 1.4–12.2, respectively). Interestingly FVL prevailed in almost one-third of mothers (OR, 8.5; 95% CI, 4.1–17.5) and 18% of mothers had antiphospholipid antibodies (OR, 3.8l; 95% CI, 1.5–10.0).

Conclusions—Maternal and neonatal thrombophilia, especially presence of FVL or antiphospholipid antibodies, may be important in the pathogenesis of perinatal arterial ischemic stroke. The nature of thrombophilic mother–infant risk potential interactions warrants further investigation. (***Stroke*. 2009;40:65-70.**)

Risk Factors for Perinatal Arterial Stroke: A Study of 60 Mother-Child Pairs

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The objective of the present study was to examine demographic, historical, and prothrombotic risk factors in infants with perinatal arterial stroke and their mothers. Risk factors were evaluated in 60 mother-child pairs with perinatal arterial stroke. Prothrombotic factors analyzed included the DNA mutations factor V Leiden, prothrombin 20210, MTHFR C677T and A1298C; serum activity levels for protein C, protein S, and antithrombin III; serum levels of lipoprotein(a); and, in the mothers, antiphospholipid antibodies. Boys predominated, 36:24. There were four twin sets. Sixty percent were term and 22% were post-date. Ten were large for gestational age. Five mothers had abdominal trauma. Nine mothers (15%) had preeclampsia. Emergency caesarean section was performed in 17 cases (28%). Eight placental exams revealed seven with abnormalities. Seizures were the presenting sign in 70%, and 30% presented with early handedness or cerebral palsy. Prothrombotic risk factors were found in 28 of 51 mothers (55%) and 30 of 60 children (50%). Forty-one pairs (68%) had at least one abnormality in mother, child, or both. Long-term sequelae included cerebral palsy (40 of 51; 78%), cognitive impairment (35 of 51; 68%), seizures (23 of 51; 45%), and microcephaly (26 of 51; 51%). Perinatal arterial stroke is the result of multifactorial, synergistic fetal and maternal factors among which the prothrombotic factors, both fetal and maternal, appear significant.

Neonatal arterial ischaemic stroke: obstetric issues

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Perinatal arterial ischaemic stroke (PAIS) is increasingly recognised as an important cause of neurological morbidity in children. The aetiology remains unclear although perinatal risk factors have been identified from limited case series. Risk factors for PAIS in term infants are different from those in preterm infants. Maternal primiparity, infertility, cocaine use, prothrombotic disorders, prolonged rupture of membranes, abnormal cardiotocograph, instrumental deliveries and emergency caesarean sections are reported risk factors in term infants. Uncomplicated vaginal delivery and prelabour caesarean section are uncommon in cases of PAIS. The presence of multiple risk factors increases the odds of developing PAIS. For preterm babies, fetal heart abnormalities, twin–twin transfusion and hypoglycaemia are recognised risk factors. Larger cohort studies are required to elucidate further the multifactorial pathway to perinatal arterial stroke.

Risk Factors for Neonatal Arterial Ischemic Stroke: The Importance of the Intrapartum Period

Miriam Martinez-Biarge, PhD[1,*], Jeanie L. Y. Cheong, MD[1,2,*], Jesus Diez-Sebastian, PhD[3], Eugenio Mercuri, PhD[1,4], Lilly M. S. Dubowitz, MD[1], and Frances M. Cowan, PhD[1]

Objective To investigate risk factors for neonatal arterial ischemic stroke (NAIS), and compare them with those present in term controls and infants with hypoxic-ischemic encephalopathy (HIE).

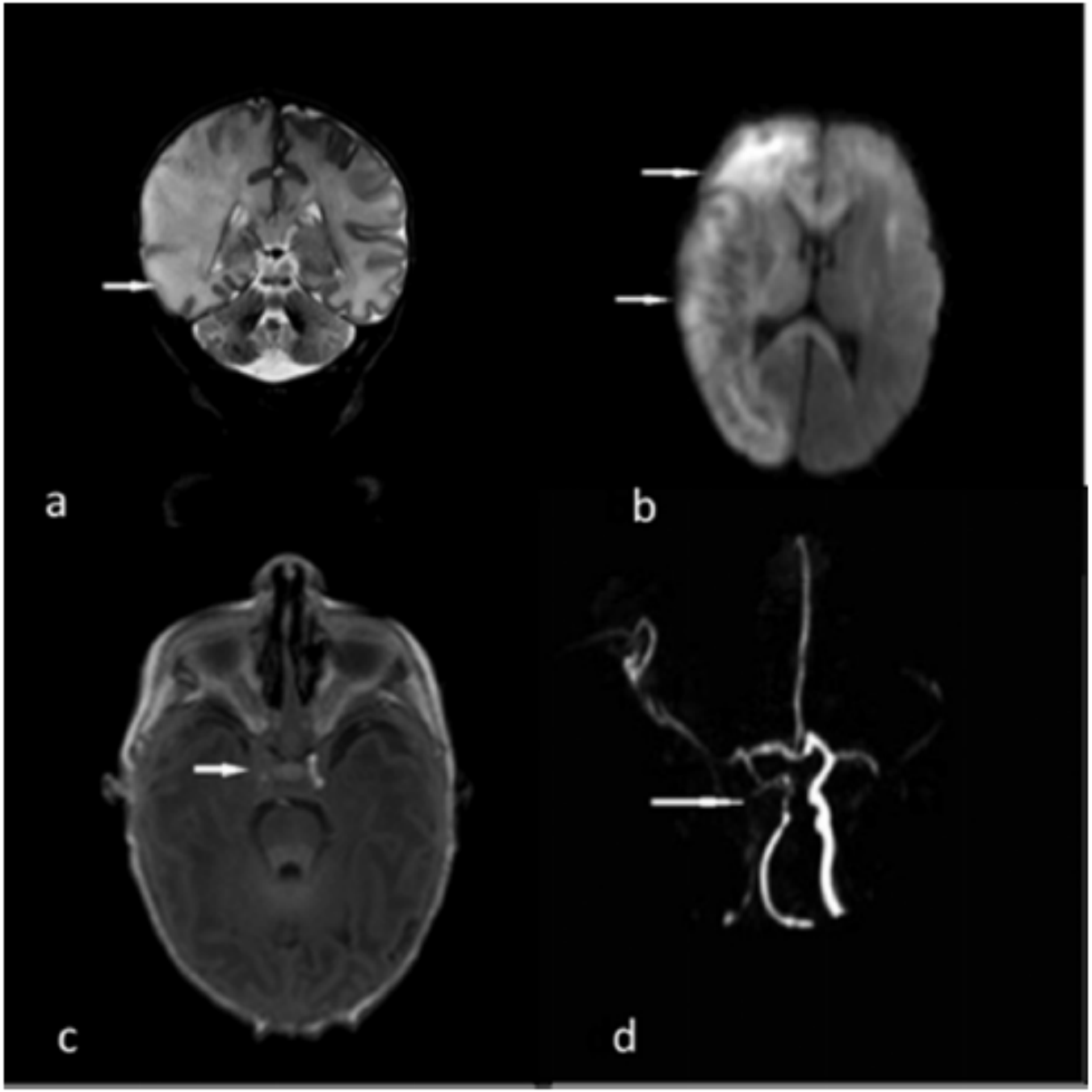
Study design Antepartum and intrapartum data were collected at presentation from 79 infants with NAIS and compared with 239 controls and 405 infants with HIE. The relationships between risk factors and NAIS were explored using univariable and multivariable regression.

Results Compared with controls, infants with NAIS more frequently had a family history of seizures/neurologic diseases, primiparous mothers, and male sex. Mothers of infants with NAIS experienced more intrapartum complications: prolonged rupture of membranes (21% vs 2%), fever (14% vs 3%), thick meconium (25% vs 7%), prolonged second stage (31% vs 13%), tight nuchal cord (15% vs 6%), and abnorm8al cardiotocography (67% vs 21%). Male sex (OR 2.8), family history of seizures (OR 6.5) or neurologic diseases (OR 4.9), and ≥1 (OR 5.8) and ≥2 (OR 21.8) intrapartum complications were independently associated with NAIS. Infants with NAIS and HIE experienced similar rates though different patterns of intrapartum complications. Maternal fever, prolonged rupture of membranes, prolonged second stage, tight nuchal cord, and failed ventouse delivery were more common in NAIS; thick meconium, sentinel events, and shoulder dystocia were more frequent in HIE. Abnormal cardiotocography occurred in 67% of NAIS and 77.5% of infants with HIE. One infant with NAIS and no infant with HIE was delivered by elective cesarean (10% of controls).

Conclusions NAIS is multifactorial in origin and shares risk factors in common with HIE. Intrapartum events may play a more significant role in the pathogenesis of NAIS than previously recognized. *(J Pediatr 2016;173:62-8).*

Genetics

- COL4A1 (High CK, calcification)
- COL4A2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Article

Perinatal Arterial Ischemic Stroke Is Associated to Materno-Fetal Immune Activation and Intracranial Arteritis

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Abstract: The medium-size intra-cranial arteries arising from the carotid bifurcation are prone to perinatal arterial ischemic strokes (PAIS). PAIS' physiopathology needs to be better understood to develop preventive and therapeutic interventions that are currently missing. We hypothesized that materno-fetal inflammation leads to a vasculitis affecting selectively the carotidian tree and promoting a focal thrombosis and subsequent stroke. Dams were injected with saline or lipopolysaccharide (LPS) from *Escherichia coli*. A prothrombotic stress was applied on LPS-exposed vs. saline (S)-exposed middle cerebral arteries (MCA). Immunolabeling detected the inflammatory markers of interest. In S-exposed newborn pups, a constitutive higher density of macrophages combined to higher expressions of tumor necrosis factor-α (TNF-α), and interleukin 1β (IL-1β) was observed within the wall of intra- vs. extra-cranial cervicocephalic arteries. LPS-induced maternal and placental inflammatory responses mediated by IL-1β, TNF-α and monocyte chemotactic protein 1 (MCP-1) were associated with: (*i*) increased density of pro-inflammatory macrophages (M1 phenotype); and (*ii*) pro-inflammatory orientation of the IL-1 system (IL-1β/IL-1 receptor antagonist (IL-1Ra) ratio) within the wall of LPS-, vs. S-exposed, intra-cranial arteries susceptible to PAIS. LPS plus photothrombosis, but not sole photothrombosis, triggered ischemic strokes and subsequent motor impairments. Based on these preclinical results, the combination of pro-thrombotic stress and selective intra-cranial arteritis arising from end gestational maternal immune activation seem to play a role in the pathophysiology of human PAIS.

Clinical presentation

- Symptomatic
  - 90% in 1st 3 days
  - Seizures
  - Diffuse signs common
  - Co-morbidities common
- Emergent hemiparesis

Clinical approach

- Haematology
- Sepsis
- echocardiogram
- MRI/MRA (MRV)
- EEG

Treatment

- Supportive
- AHA guidelines recommend anticoagulation for NAIS w cardioembolic source
- Anticoagulation in CVST controversial; anticoagulation recommended by ACCP guidelines

Anticoagulants in Pediatric Cerebral Sinovenous Thrombosis

A Safety and Outcome Study

Mahendranath D. Moharir, MBBS,[1] Manohar Shroff, MD,[2]
Derek Stephens, MSc,[3] Ann-Marie Pontigon, MBA,[3]
Anthony Chan, MBBS,[4] Daune MacGregor, MD,[1] David Mikulis, MD,[5]
Margaret Adams, BScN[3] and Gabrielle deVeber, MD[1,3]

Objective: Clinical trials are lacking in pediatric cerebral sinovenous thrombosis (CSVT). Neonates and children increasingly receive anticoagulant therapy (ACT) based on adult studies. Safety data for ACT in pediatric CSVT are scant and urgently needed. The objective was to assess the safety and outcome of ACT in pediatric CSVT.
Methods: In a single-center prospective study, neonates and children with CSVT received ACT (standard/low molecular weight heparin, warfarin) by standardized protocol. A study neuroradiologist (M.S.) assessed all initial and follow-up neuroimaging for intracranial hemorrhage (ICH), thrombus propagation, and recanalization. Clinical outcome was assessed with the Pediatric Stroke Outcome Measure.
Results: Among 162 pediatric patients, 85 received ACT at diagnosis, including 29/83 (35%) neonates and 56/79 (71%) children. Major hemorrhage occurred in 6% (6/99) of treated patients, including 14% (3/21 neonates, 2/15 children) with and 2% (0/17 neonates, 1/46 children) without pretreatment ICH. ACT-associated bleeds were all nonfatal, and clinical outcome was favorable in 50%, similar to the remaining patients (53%). Early follow-up imaging demonstrated thrombus propagation in 11/57 neonates (10/35 [28%] without and 1/22 [4%] with ACT [$p = 0.037$]) and 10/63 children (7/19 [37%] without and 3/44 [7%] with ACT [$p = 0.006$]). Propagation was associated with new venous infarcts in 10% neonates and 40% children and worse clinical outcome in children ($p = 0.053$). Recanalization occurred earlier and more completely in neonates ($p = 0.002$). Clinical outcome was unfavorable in 47%.
Interpretation: In pediatric CSVT, ACT appears safe. Nontreatment with ACT is associated with thrombus propagation, observed in $\frac{1}{4}$ of untreated neonates and over $\frac{1}{3}$ of children. Anticoagulants merit strong consideration in pediatric CSVT.

ANN NEUROL 2010;67:590–599

Recurrent Thromboembolism in Infants and Children Suffering From Symptomatic Neonatal Arterial Stroke

A Prospective Follow-Up Study

Karin Kurnik, MD; Andrea Kosch, MD; Ronald Sträter, MD; Rosemarie Schobess, MD; Christine Heller, MD; Ulrike Nowak-Göttl, MD; for the Childhood Stroke Study Group

Background and Purpose—The present study was performed to evaluate the rate of recurrent symptomatic thromboembolism with respect to prothrombotic risk factors and underlying clinical conditions.

Methods—In a series of 215 consecutively enrolled neonates with arterial ischemic stroke (AIS), the factor V G1691A mutation, factor II G20210A variant, methylenetetrahydrofolate reductase (MTHFR) T677T genotype, lipoprotein (Lp)(a), antithrombin, protein C, protein S, and anticardiolipin antibodies (ACA) were investigated. Patient median follow-up was 3.5 years (range, 1 to 8 years).

Results—During follow-up, 7 infants and children (3.3%) showed recurrent symptomatic thromboembolism (AIS, n=4; venous sinus thrombosis, n=2; deep vein thrombosis of the leg, n=1). The factor V mutation, factor II variant, elevated Lp(a) >30 mg/dL, protein C deficiency, and protein S or antithrombin deficiency were associated with first stroke onset. In 5 of 7 cases (71.4%), prothrombotic risk factors [MTHFR T677T, elevated Lp(a), hyperhomocysteinemia, protein C deficiency] were involved at the time of recurrence. Furthermore, a second thromboembolic event was triggered additionally by underlying diseases (71%), eg, cardiac malformation and immobilization, diarrhea, mastoiditis, and moyamoya syndrome.

Conclusions—Data shown here give evidence that symptomatic recurrent thromboembolism is not common in children with neonatal AIS. The risk of a second event, however, is increased when underlying diseases occur and prothrombotic risk factors are involved. (***Stroke***. **2003;34:2887-2893.**)

Presumed Perinatal Ischemic Stroke: Vascular Classification Predicts Outcomes

Adam Kirton, MD, MSc, FRCPC,[1] Gabrielle deVeber, MD, MHSc, FRCPC,[2] Ann-Marie Pontigon, BScH,[2] Daune Macgregor, MD, FRCPC,[2] and Manohar Shroff, MD[3]

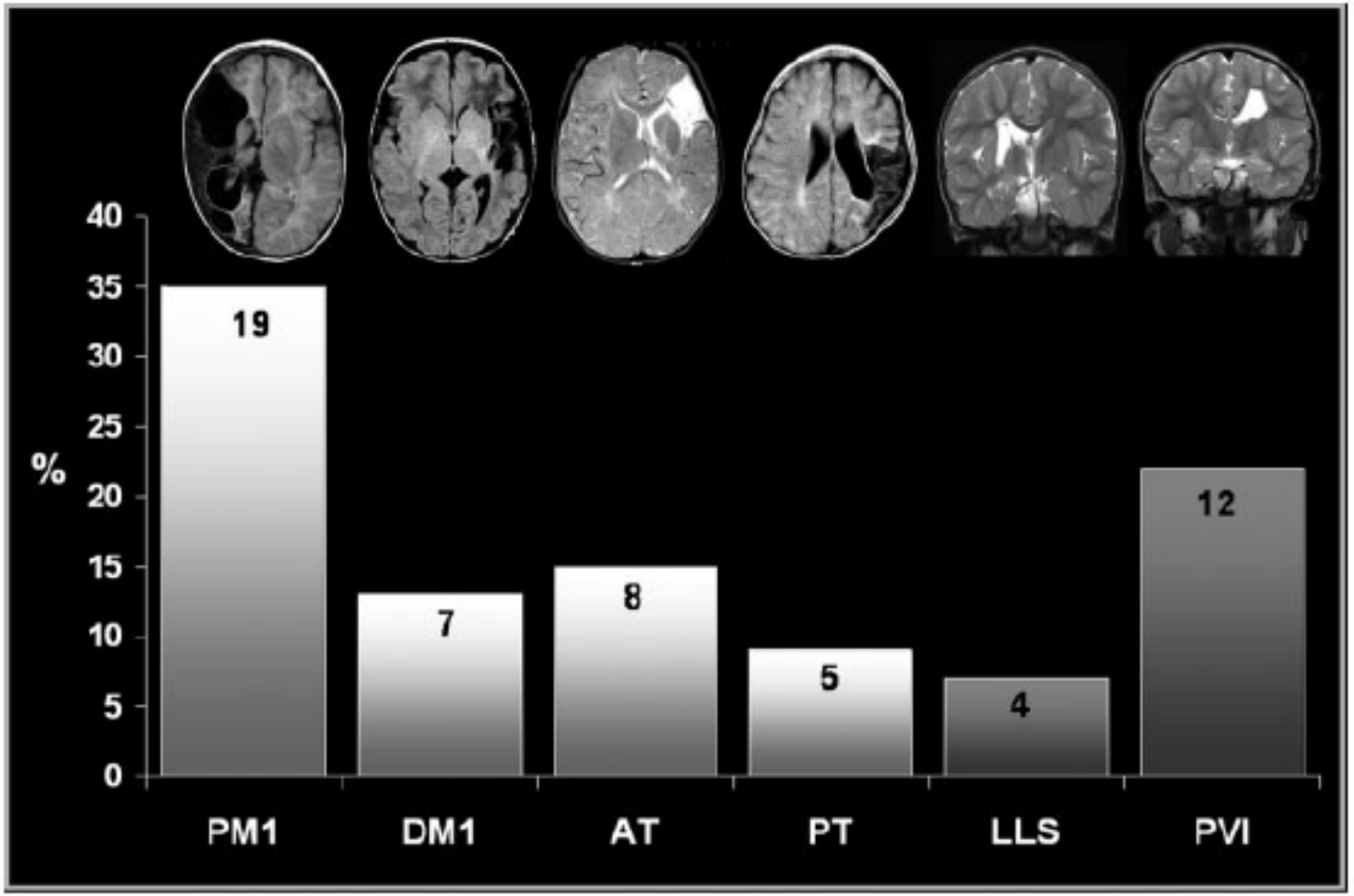
Objective: Perinatal stroke commonly causes childhood neurological morbidity. Presumed perinatal ischemic stroke (PPIS) defines children presenting outside a normal perinatal period with chronic, focal infarction on neuroimaging. Infarcts are assumed to represent arterial strokes, but recent evidence suggests the periventricular venous infarction (PVI) of infants born preterm may also occur in utero and present as PPIS. Using the largest published cohort, we aimed to define arterial and PVI PPIS syndromes and their outcomes.

Methods: A PPIS consecutive cohort was identified (SickKids Children's Stroke Program, 1992–2006). Systematic neuroradiological scoring executed by blinded investigators included previously defined arterial stroke syndromes. PVI criteria included unilateral injury with at least four of the following conditions: (1) focal periventricular encephalomalacia, (2) internal capsule T2 prolongation, (3) cortical and (4) relative basal ganglia sparing, and (5) remote hemorrhage. Arterial and PVI classifications were validated and correlated with neurological outcomes (Pediatric Stroke Outcome Measure).

Results: In 59 PPISs (64% male), 94% of lesions fell within potential middle cerebral artery territories. Although arterial proximal M1 infarction was most common (n = 19; 35%), venous PVI was second (n = 12; 22%) and accounted for 75% of subcortical injuries. Motor outcomes (mean follow-up, 5.3 years) were predicted by basal ganglia involvement including leg hemiparesis, spasticity, and need for assistive devices ($p < 0.01$). Nonmotor outcomes were associated with cortical involvement, including cognitive/behavioral outcomes, visual deficits, and epilepsy ($p < 0.01$). Classification interrater reliability was excellent (correlation coefficients > 0.975).

Interpretation: Recognizable PPIS patterns predict long-term morbidity and may guide surveillance, therapy, and counseling. PVI is an underrecognized cause of PPIS and congenital hemiplegia.

Ann Neurol 2008;63:436–443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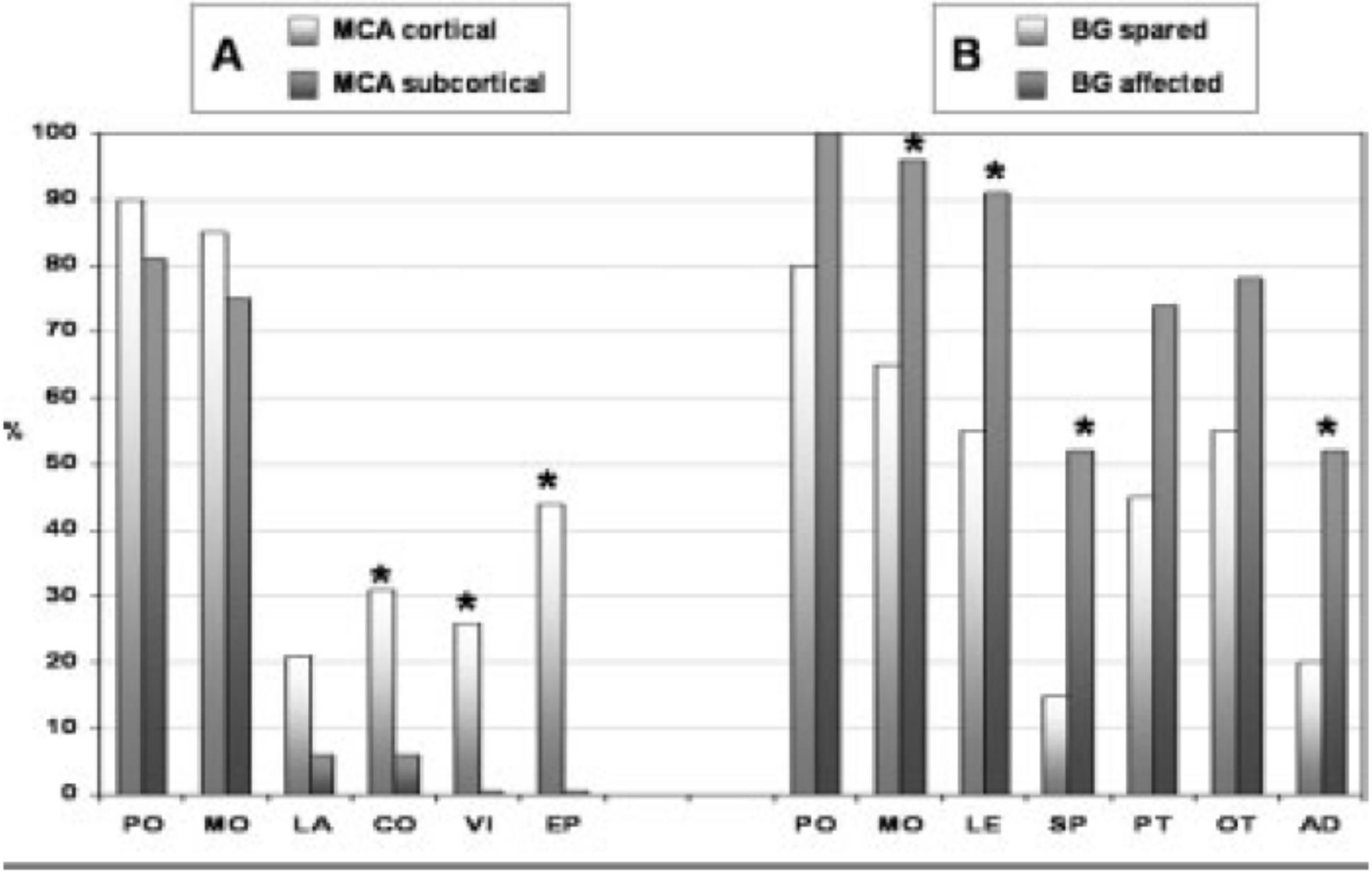
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Early Prognostic Indicators of Outcome in Infants With Neonatal Cerebral Infarction: A Clinical, Electroencephalogram, and Magnetic Resonance Imaging Study

Eugenio Mercuri*; Mary Rutherford*‡; Frances Cowan*; Jackie Pennock‡; Serena Counsell‡; Maria Papadimitriou*; Denis Azzopardi*; Graeme Bydder‡; and Lilly Dubowitz*

ABSTRACT. *Objective.* The aim of this study was to identify prognostic factors in newborns with cerebral infarction.

Design. Antenatal and perinatal factors and early clinical, electroencephalogram (EEG), and magnetic resonance imaging (MRI) findings were compared with neurodevelopmental outcome in 24 children with evidence of cerebral infarction on neonatal MRI.

Results. Out of 24 infants, 19 had an infarction in the territory of a major cerebral vessel and 5 in the borderzone between cerebral arteries. Neuromotor outcome was normal in 17 and abnormal in 7 infants. Of these 7 infants, 5 infants showed a definite hemiplegia, whereas the other 2 showed some asymmetry of tone or function but no definite hemiplegia.

None of the adverse antenatal or perinatal factors was significantly associated with abnormal outcome. Neonatal clinical examination was also not always predictive of the outcome. The extent of the lesion on MRI was a better predictor. In particular, it was the concomitant involvement of hemisphere, internal capsule and basal ganglia that was always associated with an abnormal outcome whereas the involvement of only one or two of the three tended to be associated with a normal outcome.

EEG was also very helpful. Abnormal background activity either unilateral or bilateral was found in 6 infants and 5 out of 6 developed hemiplegia. In contrast, the presence of seizure activity in presence of a normal background was not related to abnormal outcome.

Conclusions. Early MRI and EEG can help to identify the infants with cerebral infarction who are likely to develop hemiplegia. *Pediatrics* 1999;103:39–46; *newborn, cerebral infarction, brain, neurological examination, magnetic resonance imaging, electroencephalogram.*

Cognitive Outcome at Early School Age in Term-Born Children With Perinatally Acquired Middle Cerebral Artery Territory Infarction

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Background and Purpose—To assess cognitive outcome at early school age in term-born children with middle cerebral arterial (MCA) territory infarction of perinatal onset and examine the correlation between cognitive abilities and the extent of lesions as seen on neonatal MRI, epilepsy, and hemiplegia.

Methods—Thirty-one children were seen as newborns with an acutely evolving MCA territory infarction documented on neonatal MRI scan. IQ was assessed (WIPPSI/WISC where appropriate) and they had a standardized neurological examination at early school age. Lesion(s) site was recorded from the neonatal images.

Results—Twenty-eight of 31 children were assessed (median age 5.75 range 5.33 to 10.33 years); 1 child died and 2 were abroad. IQ was within the normal range (mean 104, range 82 to 144) in 21 (78%); 1 child did not complete all tests but had a normal PIQ; 3 had a low and 3 an exceptionally low IQ. Verbal IQs were more varied and lower than performance IQs especially in children from multilingual backgrounds. There was no consistent association between cognitive impairment, side, or extent of the MCA lesion. Cognitive impairments were more frequent in children with seizures or hemiplegia. All 6 children with low IQ also had behavioral problems or unusual associated clinical or scan features.

Conclusions—In our cohort a low IQ at early school age did not occur in children with the common presentation of neonatal unilateral MCA territory infarction. Cognitive impairment appeared more frequently when an MCA arterial territory infarction, even if relatively small, was associated with other risk factors. (***Stroke*. 2008;39:403-410.**)

A Prospective Outcome Study of Neonatal Cerebral Sinovenous Thrombosis

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Abstract

Neonatal cerebral sinovenous thrombosis is a frequent contributor to neonatal mortality and morbidity. Treatment is controversial and reported clinical outcomes vary widely. Newborns with radiologically confirmed neonatal cerebral sinovenous thrombosis from 1992–2009 were prospectively followed in our Children's Stroke Clinic for standardized outcomes, including the Pediatric Stroke Outcome Measure. Outcomes were available in 90/104 (87%) neonates. Early outcomes included cerebral sinovenous thrombosis-associated death (5) and thrombus propagation [15 (6 associated with new venous infarcts)]. Lack of anticoagulation predicted propagation (RR = 13, $P = .0007$). Complete thrombus recanalization occurred in 90% by 3 months. Late outcomes (median, 2.5 years) were epilepsy (15) and neurological disability (50), which included moderate-severe language (43), sensorimotor (38), and cognitive/behavioral (24) deficits. Overall, 61% had poor outcome (death/any deficit). Concurrent neurological comorbidity at diagnosis (odds ratio = 2.8, $P = .029$) predicted poor outcome. Clinical trials are urgently needed to establish more effective treatment strategies.

Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke

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ABSTRACT

Objectives: To determine incidence rates and risk factors of remote seizure after perinatal arterial ischemic stroke.

Methods: We retrospectively identified a population-based cohort of children with perinatal arterial ischemic stroke (presenting acutely or in a delayed fashion) from a large Northern Californian integrated health care system. We determined incidence and predictors of a remote seizure (unprovoked seizure after neonatal period, defined as 28 days of life) by survival analyses, and measured epilepsy severity in those with active epilepsy (≥1 remote seizure and maintenance anticonvulsant treatment) at last follow-up.

Results: Among 87 children with perinatal stroke, 40 (46%) had a seizure in the neonatal period. During a median follow-up of 7.1 years (interquartile range 3.2–10.5), 37 children had ≥1 remote seizure. Remote seizure risk was highest during the first year of life, with a 20% (95% confidence interval [CI] 13%–30%) cumulative incidence by 1 year of age, 46% (CI 35%–58%) by 5 years, and 54% (CI 41%–67%) by 10 years. Neonatal seizures increased the risk of a remote seizure (hazard ratio 2.8, CI 1.3–5.8). Children with neonatal seizures had a 69% (CI 48%–87%) cumulative incidence of remote seizure by age 10 years. Among the 24 children with active epilepsy at last follow-up, 8 (33%) were having monthly seizures despite an anticonvulsant and 7 (29%) were on more than one anticonvulsant.

Conclusions: Remote seizures and epilepsy, including medically refractory epilepsy, are common after perinatal stroke. Neonatal seizures are associated with nearly 3-fold increased remote seizure risk. *Neurology*® 2016;86:2179–2186

Age at stroke onset influences the clinical outcome and health-related quality of life in pediatric ischemic stroke survivors

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AIM Stroke in children occurs across different phases of brain development. Age at onset may affect outcome and health-related quality of life (HRQL). We evaluated the influence of age at stroke onset on the long-term neurological outcomes and HRQL of pediatric stroke survivors.

METHOD Children with ischemic stroke were recruited into three groups according to their age at onset of stroke (presumed perinatal, neonatal, and childhood). Neurological outcomes were assessed using the Pediatric Stroke Recovery and Recurrence Questionnaire. HRQL was evaluated using proxy report versions (2–18y) of the Pediatric Quality of Life Inventory (PedsQL 4.0). A χ^2/Fisher's exact test and multivariable logistic regression analysis was performed for the neurological outcomes. HRQL scores from the different age groups were compared using linear regression.

RESULTS Ninety participants (presumed perinatal stroke, n=31; neonatal stroke, n=36; childhood stroke, n=23) were enrolled. Median age at the onset of stroke was 0.5 days and 3.7 years in neonatal and childhood participants respectively. Of the three groups, participants with presumed perinatal stroke demonstrated the worst global (p<0.002) and motor (p<0.001) outcomes and the lowest level of independence in daily activities (p<0.001). Parents reported the best global outcome and overall HRQL (p=0.007) after neonatal stroke.

INTERPRETATION The age at stroke onset has important implications regarding long-term clinical outcomes and HRQL for survivors. Individuals with presumed perinatal stroke should be considered at high-risk for poor outcomes.

Transcranial direct current stimulation for children with perinatal stroke and hemiparesis

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ABSTRACT

Objective: To determine whether the addition of transcranial direct current stimulation (tDCS) to intensive therapy increases motor function in children with perinatal stroke and hemiparetic cerebral palsy.

Methods: This was a randomized, controlled, double-blind clinical trial. Participants were recruited from a population-based cohort with MRI-classified unilateral perinatal stroke, age of 6 to 18 years, and disabling hemiparesis. All completed a goal-directed, peer-supported, 2-week after-school motor learning camp (32 hours of therapy). Participants were randomized 1:1 to 1 mA cathodal tDCS over the contralesional primary motor cortex (M1) for the initial 20 minutes of daily therapy or sham. Primary subjective (Canadian Occupational Performance Measure [COPM]), objective (Assisting Hand Assessment [AHA]), safety, and secondary outcomes were measured at 1 week and 2 months after intervention. Analysis was by intention to treat.

Results: Twenty-four participants were randomized (median age 11.8 ± 2.7 years, range 6.7–17.8). COPM performance and satisfaction scores doubled at 1 week with sustained gains at 2 months ($p < 0.001$). COPM scores increased more with tDCS compared to sham control ($p = 0.004$). AHA scores demonstrated only mild increases at both time points with no tDCS effects. Procedures were safe and well tolerated with no decrease in either arm function or serious adverse events.

Conclusion: tDCS trials appear feasible and safe in hemiparetic children. Lack of change in objective motor function may reflect underdosing of therapy. Marked gains in subjective function with tDCS warrant further study.

Original article

Advancing non-invasive neuromodulation clinical trials in children: Lessons from perinatal stroke

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A B S T R A C T

Applications of non-invasive brain stimulation including therapeutic neuromodulation are expanding at an alarming rate. Increasingly established scientific principles, including directional modulation of well-informed cortical targets, are advancing clinical trial development. However, high levels of disease burden coupled with zealous enthusiasm may be getting ahead of rational research and evidence. Experience is limited in the developing brain where additional issues must be considered. Properly designed and meticulously executed clinical trials are essential and required to advance and optimize the potential of non-invasive neuromodulation without risking the well-being of children and families. Perinatal stroke causes most hemiplegic cerebral palsy and, as a focal injury of defined timing in an otherwise healthy brain, is an ideal human model of developmental plasticity. Advanced models of how the motor systems of young brains develop following early stroke are affording novel windows of opportunity for neuromodulation clinical trials, possibly directing neuroplasticity toward better outcomes. Reviewing the principles of clinical trial design relevant to neuromodulation and using perinatal stroke as a model, this article reviews the current and future issues of advancing such trials in children.

Conclusions

- There are diverse stroke syndromes in the perinatal period
- These are distinct according to gestational age & nature of vascular involvement
- Co-morbidities significantly influence outcome
- Most are single, non-recurrent events

ABSTRACT. *Objective.* The aim of this study was to assess neuromotor function at school age in children who had cerebral infarction on neonatal magnetic resonance imaging (MRI).

Design. Twenty-two children with evidence of cerebral infarction on neonatal brain MRI (18 with arterial infarction and 4 with border-zone lesions) were assessed at school age with a structured neurologic examination and the Movement Assessment Battery for Children, a battery of tests designed to assess motor function.

Results. Of the 22 children, 6 (30%) had hemiplegia and a further 7 (30%) showed some neuromotor abnormality such as asymmetry on the neurologic examination ($n = 4$) or poor scores on the neuromotor test without any sign of asymmetry ($n = 3$). The remaining 9 children had a normal motor outcome. Hemiplegia was found only in children who had concomitant involvement of hemisphere, internal capsule, and basal ganglia on brain MRI. Children with involvement of the internal capsule, associated either with basal ganglia or hemispheric lesions, did not show hemiplegia but still had motor difficulties.

Conclusions. Our results suggest that although hemiplegia occurs in a relatively small proportion of children with neonatal cerebral infarction, other signs of neuromotor impairment can be present, and these become more obvious at school age when a more specific assessment can be performed. These results also suggest that the involvement of the internal capsule on neonatal MRI can predict the presence of these abnormalities. *Pediatrics* 2004;113:95–100; *Mov ABC, MRI, hemiplegia, neonatal cerebral infarction.*

Neonatal Cerebral Infarction and Neuromotor Outcome at School Age

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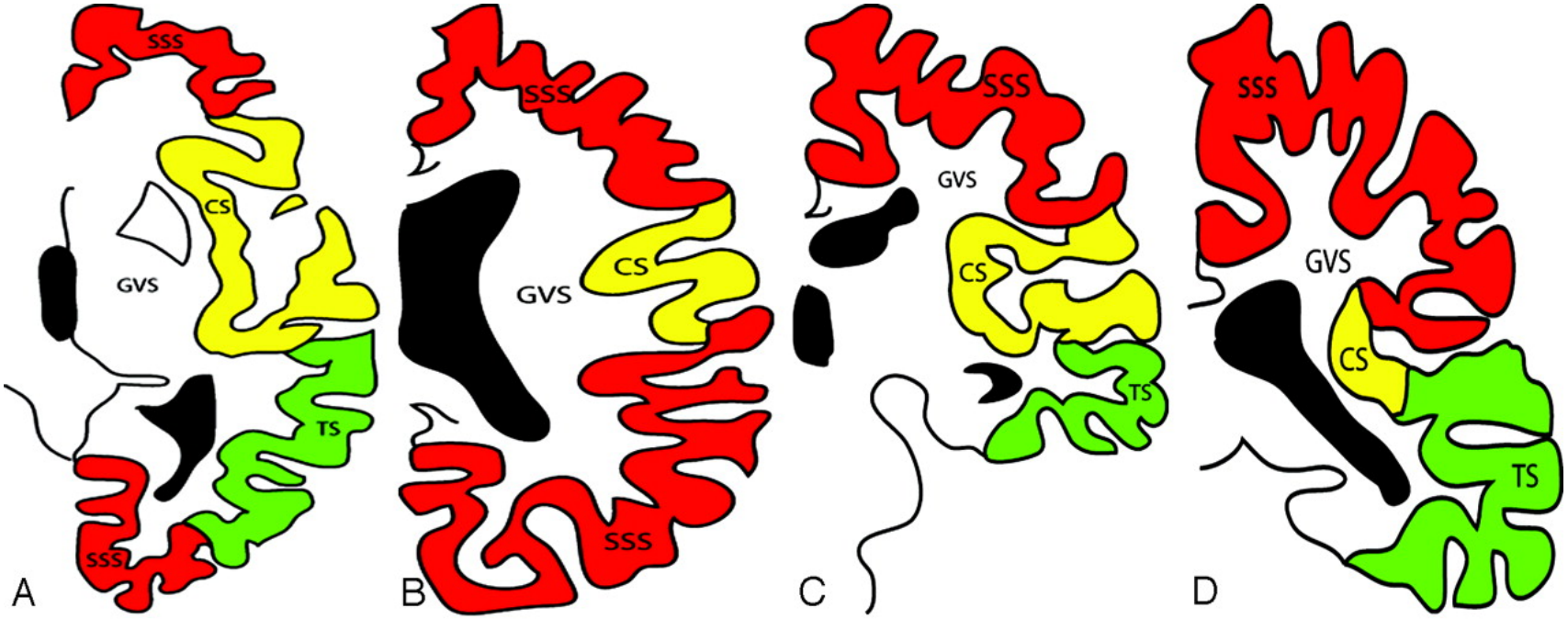
Diagrammatic representation of the cerebral venous territories.7 Transverse diagrams at the level of the basal ganglia (A) and (B) at the level of the corona radiata, coronal diagrams at the level of the basal ganglia (C) and (D) at the level of thalami.



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