

# Perinatal stroke



Ronald van Toorn



# Classification

3 key factors: the type of vessel affected; the timing, and the clinical presentation

## **Perinatal Arterial Ischemic Stroke (AIS)**

Prenatal/fetal AIS<sup>a</sup>

Neonatal AIS (NAIS)<sup>a</sup>

Preterm

Term

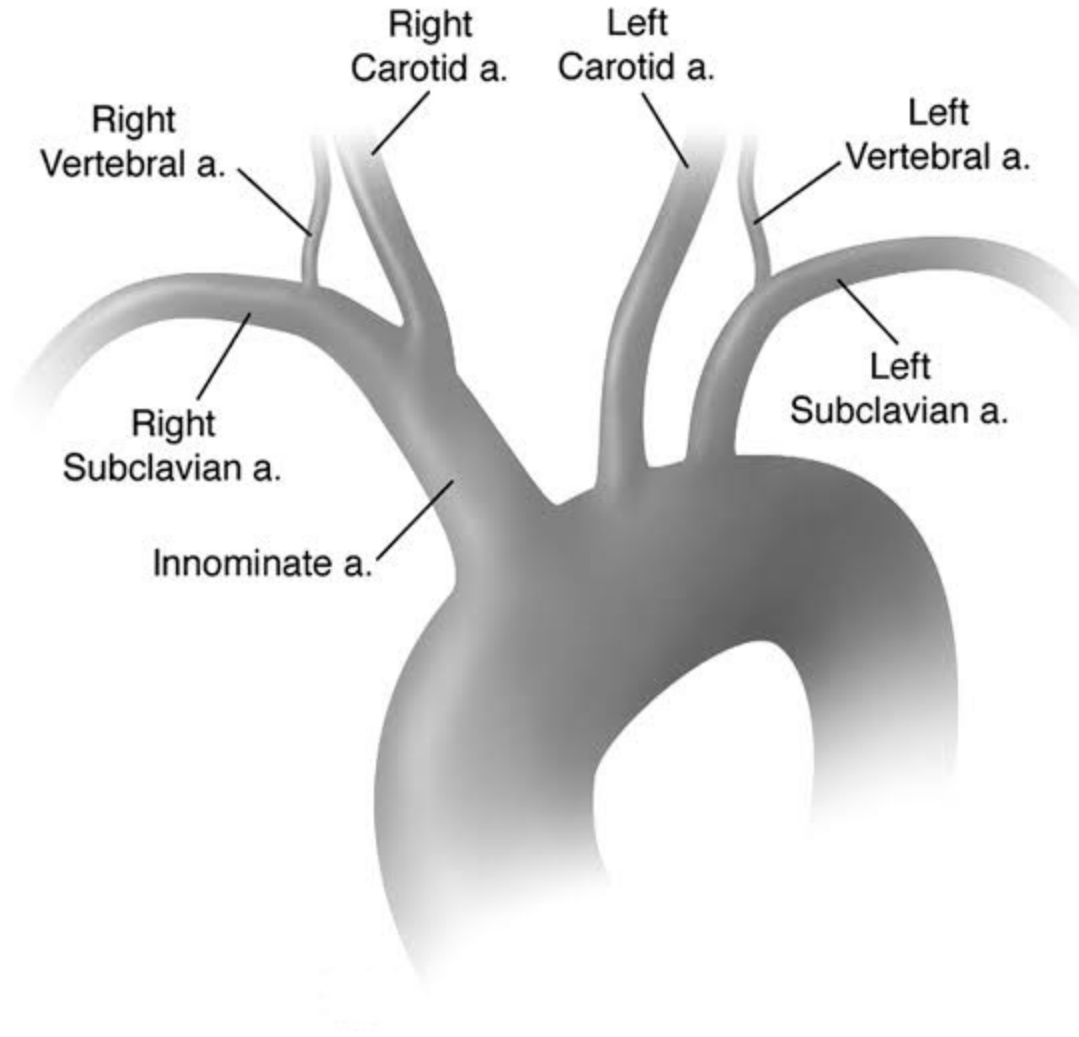
Presumed perinatal AIS

**Perinatal Cerebral Sinovenous Thrombosis (CSVT)<sup>a</sup>**

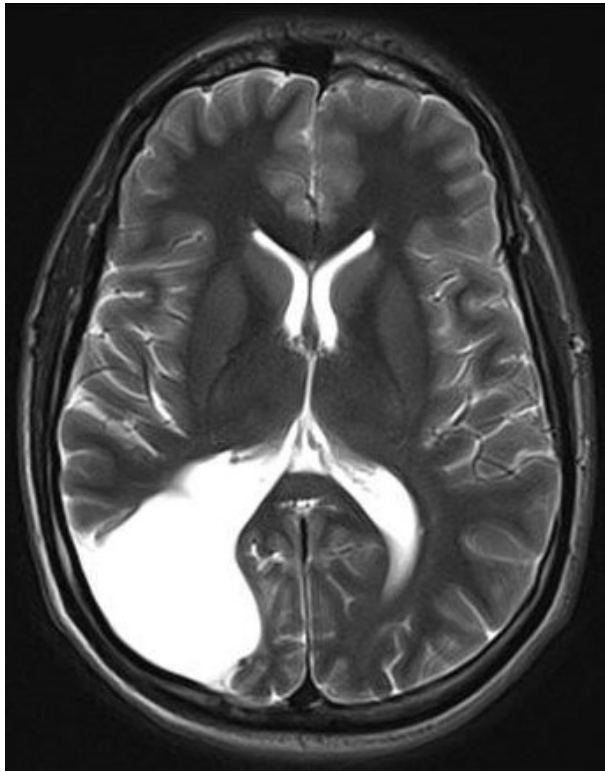
# Topography of infarction in arterial distribution

<b>TOPOGRAPHY OF INFARCTION</b>	<b>PERCENTAGE OF TOTAL (%)</b>
<b>Laterality</b>	
Unilateral	75
Bilateral	25
<b>Vascular distribution</b>	
Left MCA	55
Right MCA	30
Bilateral MCA	10
Other arteries	5

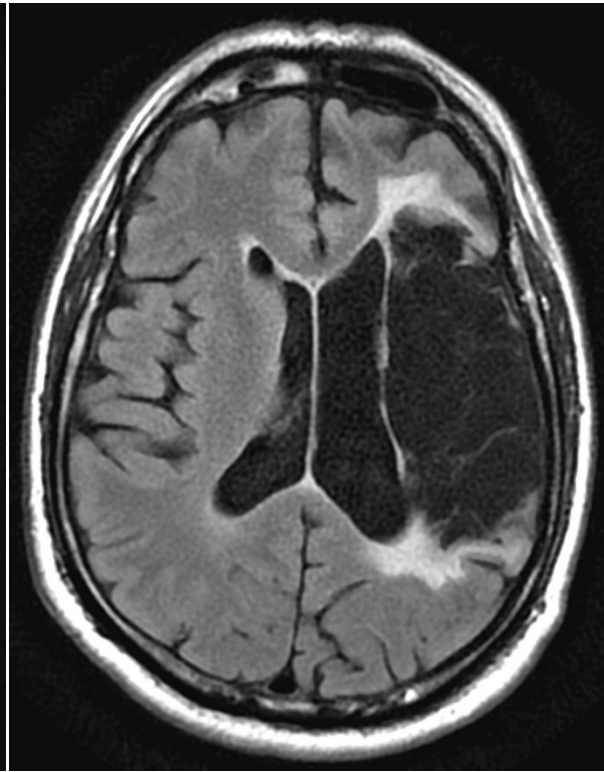
# Left MCA more commonly affected?



# Sequela of infarction



Porencephaly



Multicystic encephalomalacia



Hydranencephaly

Significant glial response > 28 weeks

High content of water  
Relative paucity of tightly packed, myelinated fiber bundles  
Deficient astroglial response

# 1. Major causes of PAIS

## **Focal and multifocal cerebrovascular occlusion-insufficiency**

### **Vascular abnormality (prenatal)**

Vascular maldevelopment

Vasculopathy

Familial, proliferative

*Collagen IV A1* mutation

Isoimmune thrombocytopenia

Vasospasm

Cocaine

Vascular distortion

### **Embolus (prenatal or neonatal)**

Placental thromboses or tissue fragments, detritus (twin pregnancy with dead co-twin)

Involuting fetal vessels (thrombi)

Catheterized vessels (thrombi or air)

Cardiac: congenital heart disease with right-to-left shunt, patent foramen ovale, atrial myxoma, rhabdomyoma (tuberous sclerosis),

## 2. Major causes of PAIS

### **Thrombus (arterial or venous) (prenatal or neonatal)**

Meningitis with arteritis or phlebitis

Trauma

Dissection

Fibromuscular dysplasia

Vascular ligation-manipulation: extracorporeal membrane oxygenation (ECMO)

Disseminated intravascular coagulation (e.g., sepsis, twin pregnancy with dead co-twin)

Prothrombotic/hypercoagulable, endogenous factors: factor V Leiden mutation, protein C deficiency, protein S deficiency, prothrombin mutation, antithrombin III deficiency, antiphospholipid antibodies, *MTHFR* mutation, elevated lipoprotein  $\alpha$ , elevated factor VIIIc

Hypernatremia-dehydration

Polycythemia

### **Generalized systemic circulatory insufficiency**

#### **Prenatal**

Maternal hypotension or cardiac arrest

Maternal trauma (?)

#### **Neonatal**

Perinatal asphyxia

Systemic hypotension or cardiac arrest

Congenital heart disease with cardiac failure (exclusive of thromboembolic phenomena)

## **Maternal risk factors**

**Autoimmune abnormalities  
Chorioamnionitis/infection  
Cocaine abuse  
Diabetes  
History of infertility and its  
treatment  
Labor and delivery  
complications  
Placental thrombosis/abruption  
Preeclampsia  
Prolonged rupture of  
membranes  
Prothrombotic abnormalities**

# **PERINATAL STROKE**

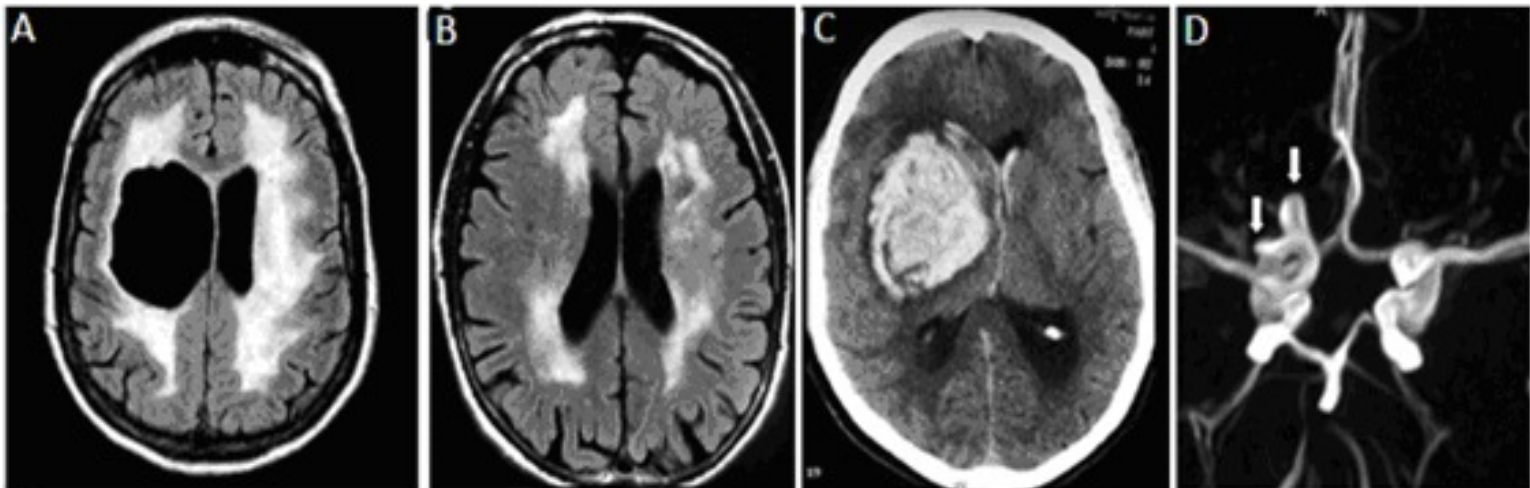
## **Fetal/neonatal risk factors**

**Congenital heart disease  
Dehydration  
Hypoglycemia  
Infection  
Neonatal encephalopathy  
Polycythemia  
Prothrombotic disorders  
(inherited)  
Twin-twin transfusion**



# Collagen 4A1 mutation

Collagen 4 is critical for vascular basement membrane stability and function  
Mutation results in abnormal vascular development  
At risk of diverse cerebrovascular diseases including cerebral microbleeds,  
porencephaly and fatal intracerebral haemorrhage (ICH).  
AD inheritance pattern



# Are neonatal stroke and HIE related ?

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

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

**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 abnormal cardiotocography (67% vs 21%). Male sex (OR 2.8), family history of seizures (OR 6.5) or neurologic diseases (OR 4.9), and  $\geq 1$  (OR 5.8) and  $\geq 2$  (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).

**Table IV.** Antenatal and perinatal factors in infants with NAIS and HIE and controls

<b>Antepartum factors</b>	<b>Controls N = 239</b>	<b>OR</b>	<b>HIE N = 405</b>	<b>OR (95% CI)</b>	<b>NAIS N = 79</b>	<b>OR (95% CI)</b>	<b>P (<math>\chi^2</math>)</b>	<b>P (linear-by-linear)</b>
Male sex	50.8%	1	56.5%	1.26 (0.9-1.7)	70%	2.21 (1.3-3.8)	.014	.005
Family history of seizures	3.4%	1	6.8%	2 (0.9-4.8)	16.2%	5.5 (2.1-14)	.001	<.001
Family history of neurological diseases	2.6%	1	4.7%	1.9 (0.7-5.5)	15%	6.6 (2.4-18.7)	<.001	<.001
Birthweight <third percentile	1.7%	1	5.8%	3.51 (1.2-10.3)	6.6%	4 (1.05-15.3)	.041	.020
Primiparity	51.7%	1	60.4%	1.42 (1.03-1.9)	76.6%	3.06 (1.7-5.5)	<.001	<.001
<b>Intrapartum factors*</b>	<b>Controls N = 239</b>	<b>OR</b>	<b>HIE N = 405</b>	<b>OR (95% CI)</b>	<b>NAIS N = 79</b>	<b>OR (95% CI)</b>	<b>P (<math>\chi^2</math>)</b>	<b>P (linear-by-linear)</b>
Maternal pyrexia	3%	1	4.3%	1.47 (0.5-3.7)	14%	5.4 (2-14.5)	<.001	.001
PROM	2.2%	1	10%	4.8 (1.8-12.6)	20.8%	11.5 (4-33)	<.001	<.001
Prolonged second stage	13%	1	16.5%	1.33 (0.8-2.2)	32%	3.18 (1.5-6.4)	.004	.004
Tight nuchal cord	6.3%	1	11.4%	1.9 (1.03-3.5)	15.2%	2.6 (1.18-5.9)	.036	.010
Failed vacuum delivery	1.7%	1	8%	5 (1.7-14.3)	14%	9.4 (2.9-30.6)	<.001	<.001
<b>Intrapartum factors<sup>†</sup></b>	<b>Controls N = 239</b>	<b>OR</b>	<b>NAIS N = 79</b>	<b>OR (95% CI)</b>	<b>HIE N = 405</b>	<b>OR (95% CI)</b>	<b>P (<math>\chi^2</math>)</b>	<b>P (linear-by-linear)</b>
Thick meconium	7%	1	24.4%	4.3 (2.09-8.9)	29%	5.5 (3.1-9.6)	<.0001	<.0001
Sentinel event	0.8%	1	3.8%	4.6 (0.7-28.5)	22%	33.3 (8.1-137)	<.0001	<.0001
Shoulder dystocia	0.4%	1	3.8%	9.4 (0.9-91.6)	7.3%	18.8 (2.5-139)	<.0001	<.0001
Abnormal CTG	21.5%	1	66%	7.13 (3.7-13.4)	77.5%	12.6 (8.3-19.1)	<.001	<.0001

# Association between Hypoxia and Perinatal Arterial Ischemic Stroke: A Meta-Analysis

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## Abstract

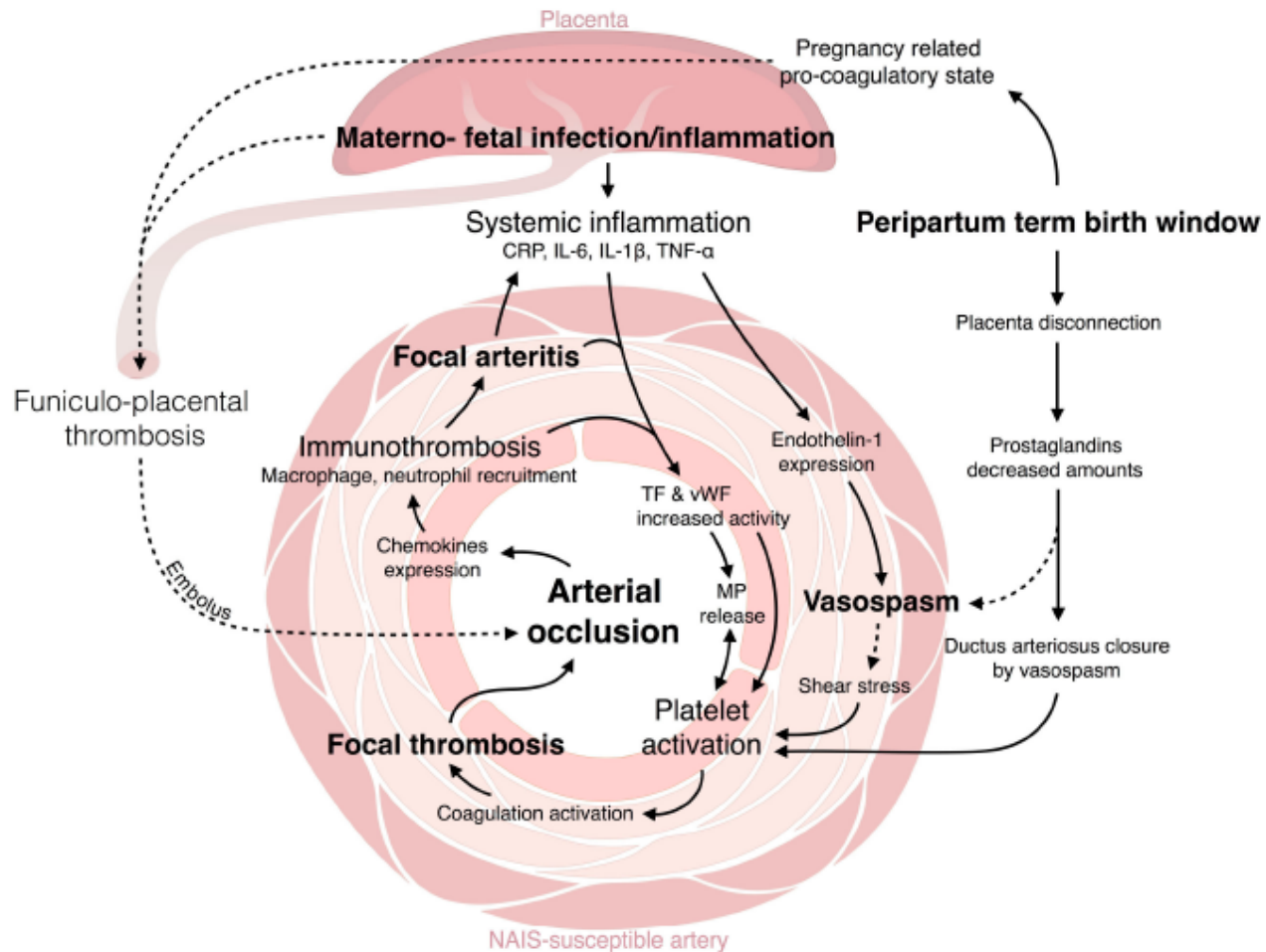
**Background:** Perinatal arterial ischemic stroke (AIS) occurs in an estimated 17 to 93 per 100000 live births, yet the etiology is poorly understood. Although investigators have implicated hypoxia as a potential cause of AIS, the role of hypoxia in AIS remains controversial. The aim of this study was to estimate the association between perinatal hypoxia factors and perinatal arterial ischemic stroke through a meta-analysis of published observational studies.

**Patients and methods:** A systematic search of electronically available studies published through July 2013 was conducted. Publication bias 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.

**Results:** A total of 8 studies describing the association between perinatal hypoxia factors and neonatal arterial ischemic stroke (AIS) met inclusion criteria, and 550 newborns with AIS were enrolled. The associations were found for AIS: preeclampsia (OR 2.14; 95% CI, 1.25 to 3.66), ventouse delivery (OR 2.23; 95% CI, 1.26 to 3.97), fetal heart rate abnormalities (OR 6.30; 95% CI, 3.84 to 10.34), reduced fetal movement (OR 5.35; 95% CI, 2.17 to 13.23), meconium-stained liquor (OR 3.05; 95% CI, 2.02 to 4.60), low Apgar score (OR 5.77; 95% CI, 1.66 to 20.04) and resuscitation at birth (OR 4.59; 95% CI, 3.23 to 6.52). Our data did not show any significant change of the mean risk estimate for oxytocin induction (OR 1.33; 95% CI, 0.84 to 2.11) and low arterial umbilical cord pH (OR 4.63; 95% CI 2.14 to 9.98).

**Conclusions:** There is a significant association between perinatal hypoxia factors and AIS. The result indicates that perinatal hypoxia maybe one of causes of AIS. Large scale prospective clinical studies are still warranted.

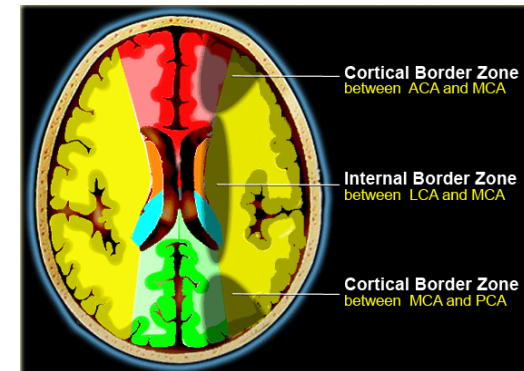
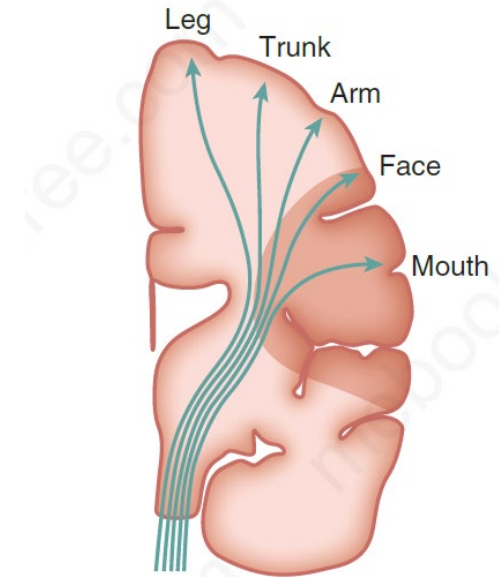
# Perinatal inflammation



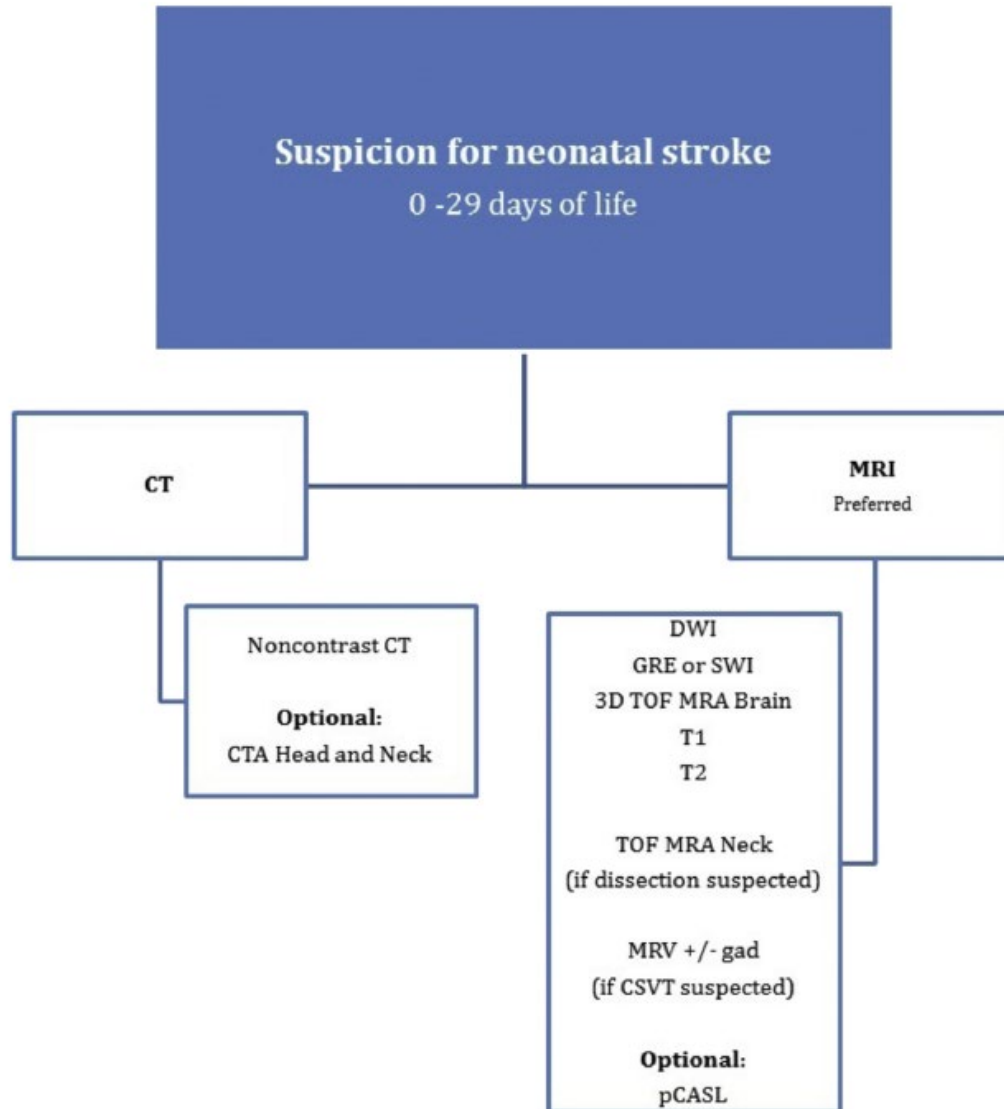
# Clinical manifestations of NAIS

<b>Neonatal arterial ischemic stroke</b>	<b>Hypoxic ischemic encephalopathy</b>
Seizures, especially focal seizures, with onset after 12 hours of life.	Seizures most often within 12 hours of life
10% exhibited encephalopathy, most often mild in nature	
Preterm infants: commonly asymptomatic 83% respiratory difficulties/apnea 30% seizures	

MCA	Arm face > leg
Parietal and occipital lobes	Sensory deficits
PCA	Visual defects
Parasagittal injury	Hypotonia and weakness of the proximal extremities. Upper limbs, especially shoulder girdle more affected than lower limbs



# Diagnosis of NAIS





# Thrombophilia Studies

Prothrombotic factors associated with neonatal arterial stroke in 30%–70% of cases

Most common factors: factor V Leiden mutation, prothrombin mutation, *MTHFR* mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, antiphospholipid antibodies, elevated lipoprotein *a*, elevated factor VIIIc

Usually (50%–80%) associated with other pathogenetic factors (i.e., preeclampsia, gestational diabetes, placental vasculopathy, chorioamnionitis, signs of “perinatal asphyxia,” sepsis, congenital heart disease)

Protein C functional assay<sup>a</sup>

Protein S functional assay<sup>a</sup>

Factor V Leiden functional assay or factor V Leiden gene mutation

Prothrombin gene mutation on (20210)

Antithrombin functional assay

Serum homocysteine level

Serum lipoprotein (a)

Serum lupus anticoagulant<sup>b</sup>

Anti-cardiolipin antibodies<sup>b</sup>

Anti-B2 glycoprotein antibodies<sup>b</sup>

<sup>a</sup>Proteins C and S reach adult levels at 6 to 12 months of life. If levels are only slightly low in the newborn, a repeat level should be obtained later in the first year.

<sup>b</sup>Antiphospholipid antibodies—can be tested in mother or infant.

# OR for thrombophilic stroke risk factors

**Table 3. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity ( $I^2$ ), Noncombinability, and Publication Bias for Thrombophilic Risk Factors Associated With a First AIS/CSVT Onset in Children**

Genetic Traits (No. of Studies)	Patients/Control Subjects, n	OR/95% CI (Fixed-Effects or Random-Effects Model)	$I^2$ , %; $P$	Bias Indicator (Harbord et al <sup>73</sup> , $P$ )
Genetic risk factors				
Antithrombin deficiency (6)	826/1153	7.06/2.44–22.42 (F)	27; 0.23	0.53
Protein C deficiency (10)	1031/1468	9.31/4.81–18.02 (F)	0; 0.94	0.76
Protein S deficiency (6)	761/941	3.20/1.22–8.40 (F)	47; 0.09	0.57
Lipoprotein(a) (5)	722/727	6.27/4.52–8.69 (F)	0.0; 0.91	0.64
Factor V G1691A (21)	1625/2842	3.26/2.59–4.10 (F)	0; 0.67	0.42
Factor II G20210A (17)	1409/2613	2.43/1.67–3.51 (F)	0; 0.76	0.86
$\geq 2$ Genetic traits (12)	926/1720	11.86/5.93–23.73 (F)	19; 0.25	0.52

# Coagulation testing indicated?

The association between thrombophilia markers and arterial perinatal stroke is minimal. Therefore, it is likely that **no added prognostic or treatment information** will be gained from routinely performing thrombophilia profiles in infants with either acute NAIS or presumed perinatal ischemic stroke.

Exceptions: strong family history of thrombotic disease or multiple sites or a large burden of thrombosis

# Routine testing in children indicated?

## Thrombophilia risk is not increased in children after perinatal stroke

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### Key Points

- Thrombophilia in children with perinatal stroke is rare, with rates similar to those in the normal population.
- Routine testing in childhood is not indicated.

**Perinatal stroke causes cerebral palsy and lifelong disability. Specific diseases are definable, but mechanisms are poorly understood. Evidence suggests possible associations between arterial perinatal stroke and prothrombotic disorders, but population-based, controlled, disease-specific studies are limited. Understanding thrombophilia in perinatal stroke informs pathogenesis models and clinical management. We conducted a population-based, prospective, case-control study to determine the association of specific perinatal stroke diseases with known thrombophilias. Children with idiopathic magnetic resonance imaging–classified neonatal arterial ischemic stroke (NAIS), arterial presumed perinatal ischemic stroke (APPIS), or fetal periventricular**

**venous infarction (PVI) were recruited. Standardized thrombophilia evaluations were performed after 12 months of age on stroke cases and controls, including quantified proteins C and S, antithrombin, factors VIII/IX/XI, fibrinogen, lipoprotein(a), homocysteine, lupus anticoagulant, anticardiolipin antibodies and genotyping of factor V Leiden (FVL), factor II G20210A (FII), and methylenetetrahydrofolate reductase C677T. A total of 212 children were studied: 46 with NAIS, 34 with APPIS, 55 with PVI, and 77 controls (male, 53%; median age, 4.8 years). Of 14 parameters, no differences were observed in 12, including all common thrombophilias. Mean prothrombin time was shorter in arterial strokes ( $P < .001$ ). Rates of antiphospholipid antibodies were low, comparable to those in controls, and resolved on repeat testing. FVL and FII rates were comparable to population norms. Total number of possible abnormalities did not differ between cases and controls. Our prospective, population-based, controlled, disease-specific study suggests minimal association between perinatal stroke and thrombophilia. This does not exclude the possibility of disordered coagulation at the time of stroke but suggests testing in childhood is not indicated. (*Blood*. 2017;129(20):2793-2800)**

# Acute management of NAIS

Evidence based management strategies are limited/consensus derived

Neuroprotection: normoglycemia; ventilation/oxygenation, avoidance of hyperthermia , seizure management (aEEG)

Hypothermia: trials pending

Antiplatelet therapy (Aspirin) and anticoagulation (LMWH UFH) is rarely indicated because of low risk of recurrence.

However, it must be considered in neonates with ongoing cardioembolic risk

Thrombolytic agents not recommended

Erythropoietin: Trails pending

Stem cells: phase 1 clinical trial

# Later therapies

Early implementation of physical, occupational and speech therapy  
Trial: Early therapy in Perinatal Stroke (eTIPS)-a parent delivered home based complex intervention first 6 months.

Constraint induced movement therapy & extensive gait training  
Non-invasive neuromodulation: inhibitory repetitive transcranial magnetic stimulation



# Prognosis of NAIS

Magnetic resonance imaging is valuable in estimation of prognosis by determining both the extent of the unilateral lesion and the presence of milder injury of the contralateral hemisphere.

Hemiparesis occurs in approximately 25%–35% of survivors. Hemiparesis occurs in nearly 100% if the lesion involves the distribution of the *stem* of the middle cerebral artery (cerebral cortex—white matter—basal ganglia—posterior limb of the internal capsule).

The presence of concomitant, albeit milder injury to the contralateral hemisphere sharply increases the likelihood of hemiparesis.

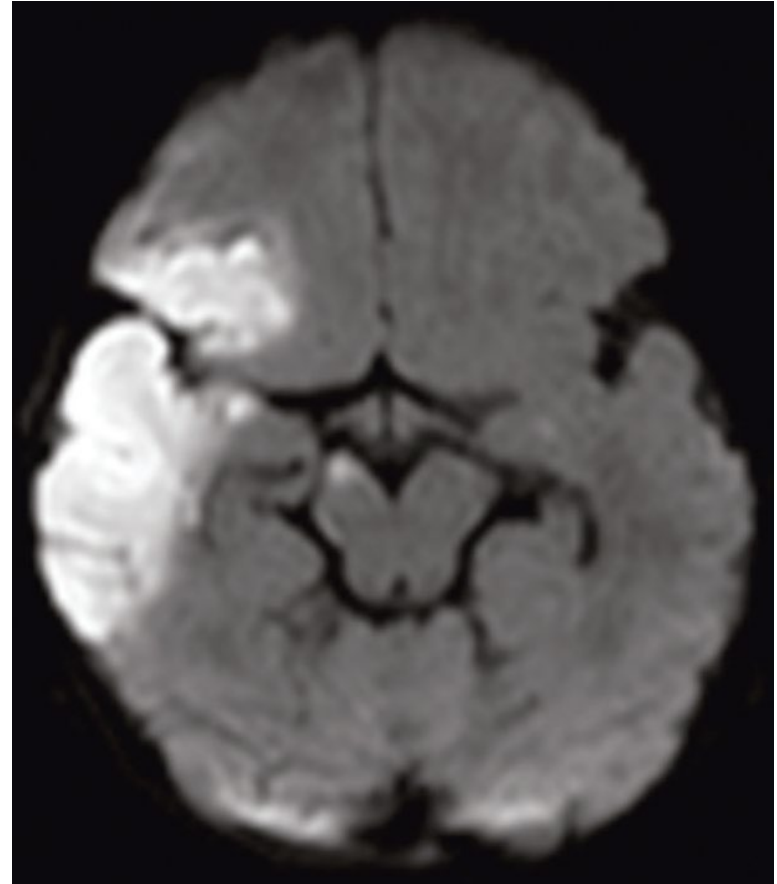
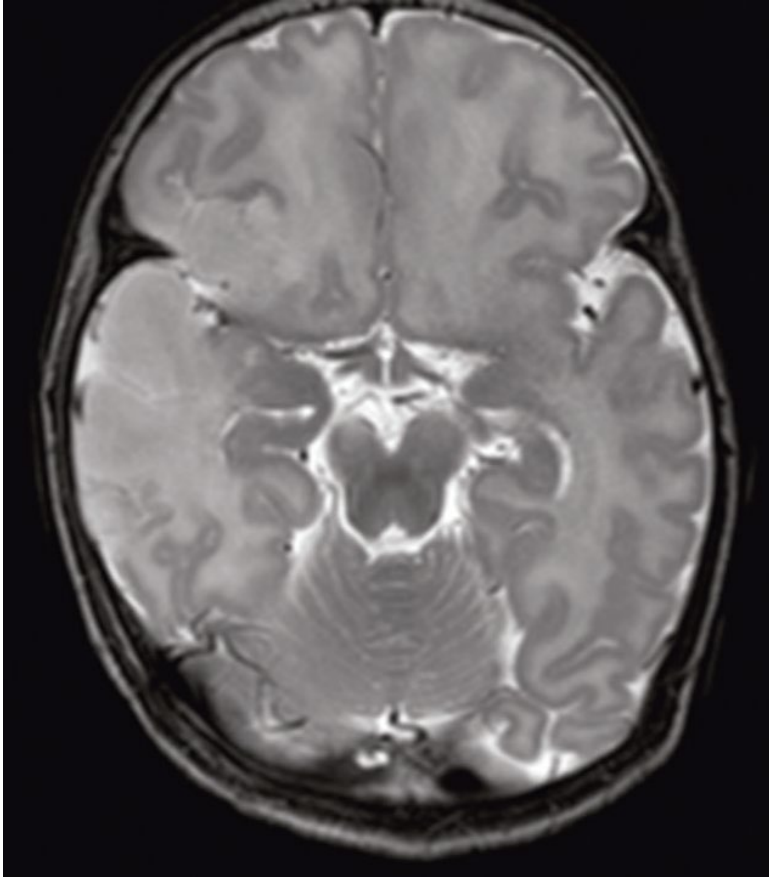
Cognitive deficits occur approximately in 50%–70% of survivors when studied at *school age*.

Epilepsy occurs in approximately 15%–40% of survivors

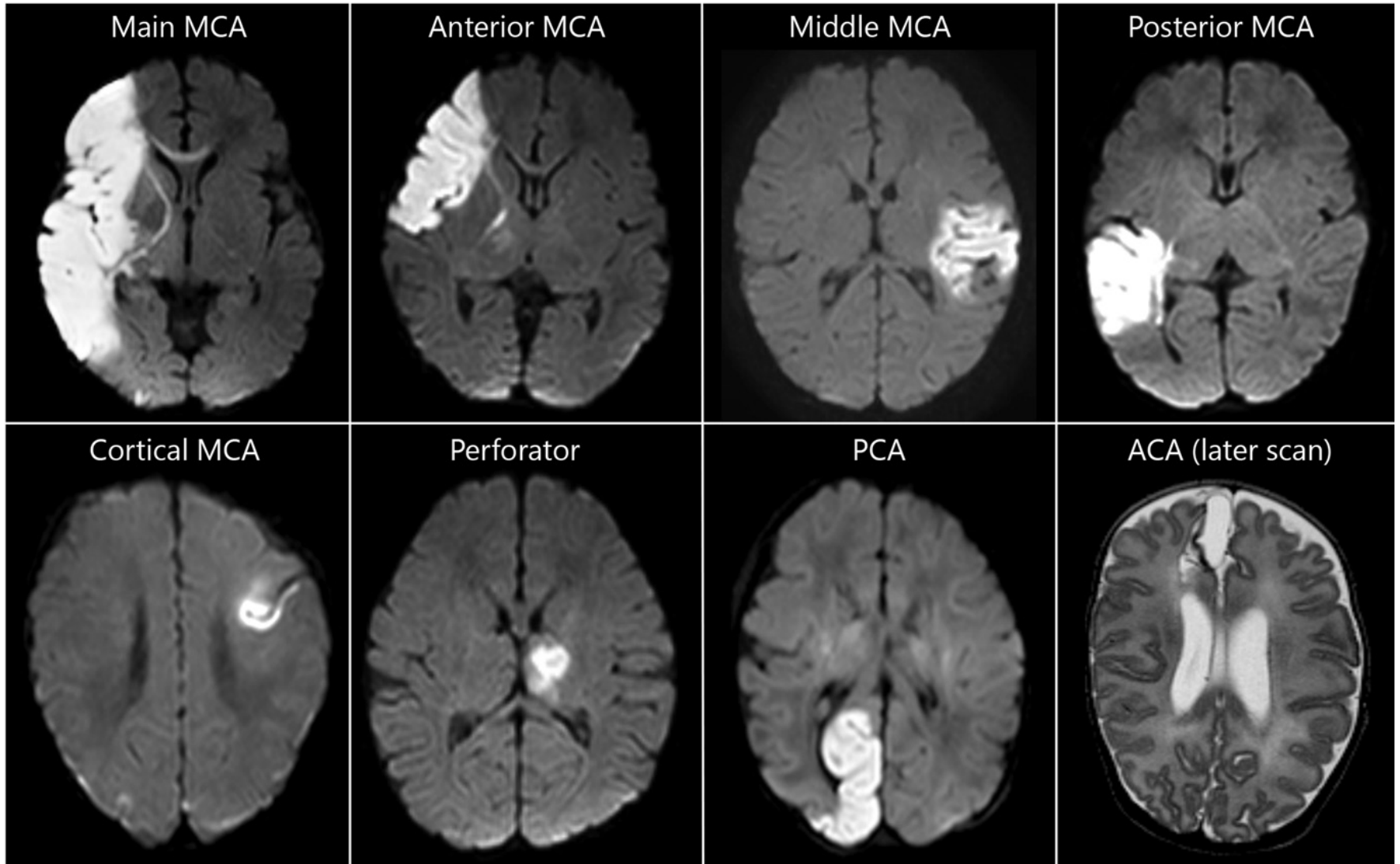
<b>Extent of the lesion</b>	<b>Likelihood of hemiparesis</b>
Distribution of the MCA stem (cerebral cortex-white matter-basal ganglia-PLIC)	Nearly 100%
Hemisphere contralateral to the infarction is affected, even not severely	Close to 100%
Cortical branch or only the lenticulostriate vessels affected	Less than 10%
Internal capsule together with either basal ganglia or cerebral cortical involvement	Rare



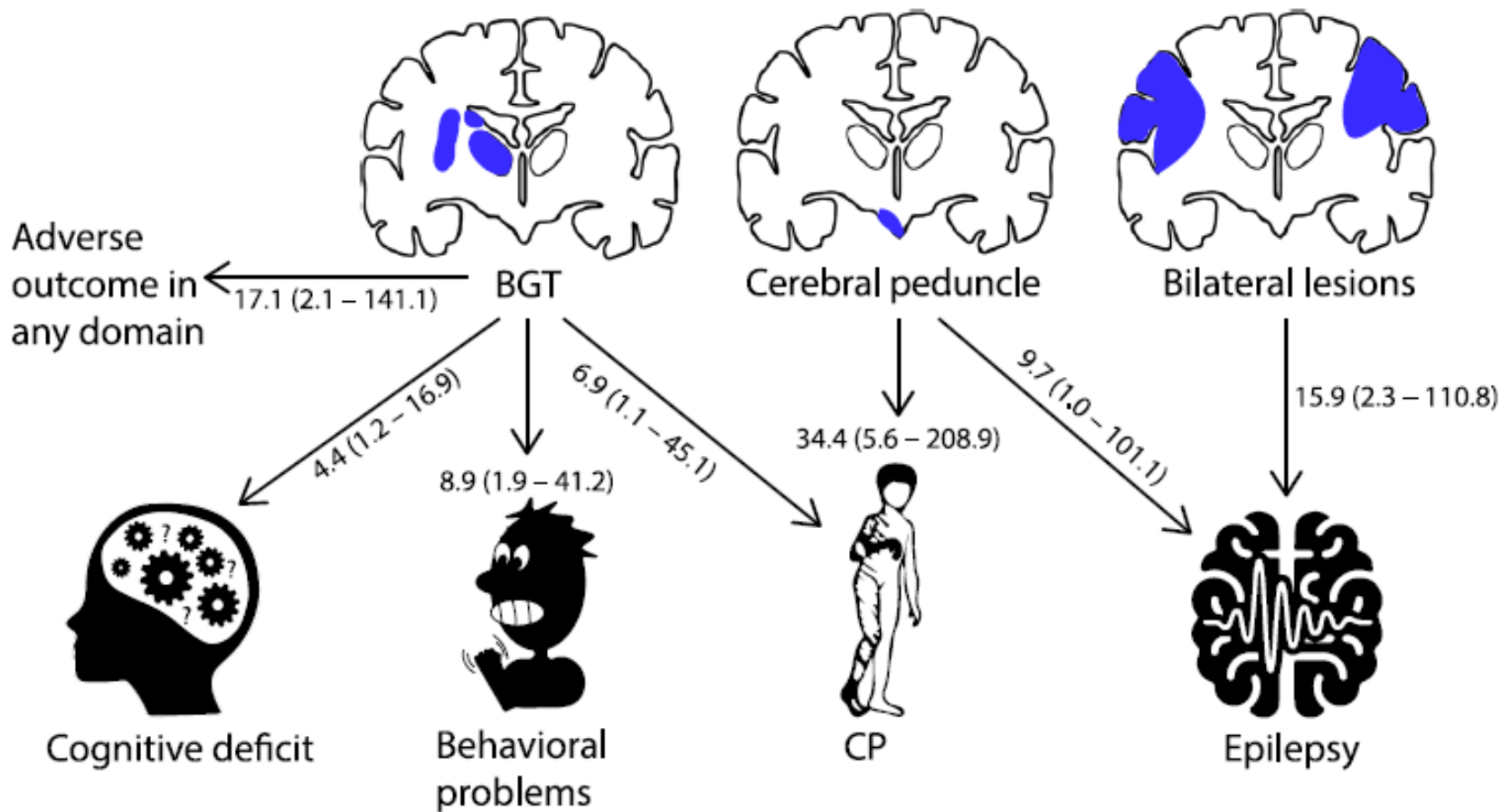
# Likelihood of hemiparesis ?



# Stroke territory subtypes



PAIS Type and Outcomes (No. With Data)	Total ( <i>n</i> = 161), <i>n</i> (%)	Main MCA ( <i>n</i> = 31), <i>n</i> (%)	Anterior MCA Branch ( <i>n</i> = 17), <i>n</i> (%)	Middle MCA Branch ( <i>n</i> = 21), <i>n</i> (%)	Posterior MCA Branch ( <i>n</i> = 28), <i>n</i> (%)	Cortical MCA Branch ( <i>n</i> = 21), <i>n</i> (%)	Perforator Branch ( <i>n</i> = 27), <i>n</i> (%)	PCA or ACA ( <i>n</i> = 16), <i>n</i> (%)
CP, <i>N</i> = 161	49 (30)	31 (100)	2 (12)	4 (19)	6 (21)	0 (0)	4 (15)	2 (13)
Cognitive deficit, <i>n</i> = 160	37 (23)	17 (57)	1 (6)	3 (14)	8 (29)	3 (14)	2 (7)	3 (19)
Language delay, <i>n</i> = 145	34 (23)	15 (58)	4 (25)	2 (10)	5 (20)	3 (17)	3 (11)	2 (17)
Postneonatal epilepsy, <i>n</i> = 151	18 (12)	12 (41)	1 (6)	0 (0)	3 (12)	0 (0)	0 (0)	2 (13)
Behavioral problems, <i>n</i> = 126	31 (25)	10 (37)	4 (31)	1 (6)	6 (25)	2 (13)	3 (17)	5 (42)
Visual field defect, <i>n</i> = 96	17 (18)	12 (48)	0 (0)	0 (0)	2 (14)	0 (0)	0 (0)	3 (27)
Combination of adverse outcomes, <i>n</i> = 161	50 (31)	26 (84)	3 (18)	2 (10)	8 (29)	2 (10)	2 (7)	7 (44)
Within normal range, <i>n</i> = 161	74 (46)	0 (0)	9 (53)	13 (62)	12 (43)	15 (71)	18 (67)	7 (44)



# Fatigue in children with perinatal stroke: clinical and neurophysiological associations

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## ABBREVIATIONS

AHA	Assisting Hand Assessment
MEP	Motor evoked potential
PedsQL	Pediatric Quality of Life Inventory Version 3.0
RMT	Resting motor threshold
TMS	Transcranial magnetic stimulation

**AIM** To characterize fatigue in children with hemiparesis with perinatal stroke and explore associations with measures of motor performance and corticospinal excitability.

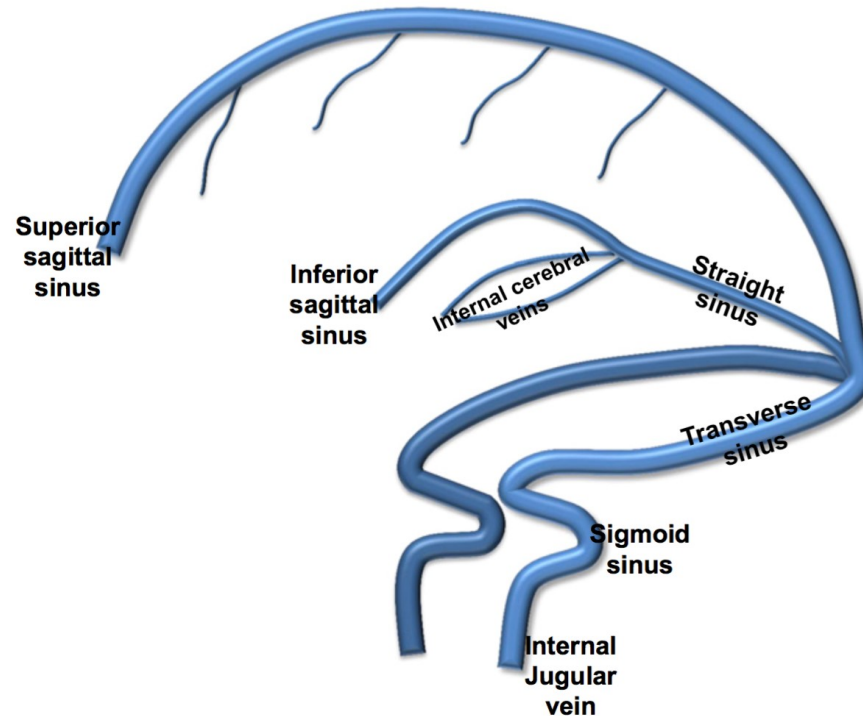
**METHOD** Forty-five children (16 females, 29 males), aged 6 to 18 years (mean [SD] 12y [4]), with magnetic resonance imaging-confirmed perinatal stroke participated. Associations between fatigue (Pediatric Quality of Life Inventory Version 3.0 cerebral palsy module fatigue subscale), motor performance (Assisting Hand Assessment [AHA], Box and Blocks Test, grip strength), and excitability of corticospinal projections to both hands were examined using ranked tests of correlation, robust regression, and the Mann-Whitney *U* test.

**RESULTS** Nearly half of the participants ( $n=21$ ) reported experiencing fatigue in the previous month. Function in the less affected hand (Box and Blocks Test, grip strength) was correlated with fatigue scores. Participants with preserved ipsilateral projections to the more affected hand had less fatigue, and scores correlated with the excitability of these projections. Fatigue scores were not associated with age, sex, or AHA score.

**INTERPRETATION** Fatigue is common in children with hemiparesis with perinatal stroke and is associated with motor performance and the presence and excitability of ipsilateral corticospinal projections from the contralesional hemisphere to the more affected hand.

# Neonatal Cerebral Sinovenous Thrombosis

Superior sagittal sinus involvement in 65% of patients, lateral sinus thrombosis in 50% or deep venous system in 50%; multiple sites 50%  
Infarction present in 40-80% and hemorrhagic in most, IVH 35-55%;  
Hemorrhage in caudate and thalamus less common



# Clinical presentation

Non-specific with lethargy, irritability and seizures

Seizures initial presentation 60-70% of cases

The presence of seizures does not predict the occurrence of long-term epilepsy.

# Risk and causes

Pathogenesis often involves multiple factors

Most often: preeclampsia, maternal diabetes, perinatal stress,  
Congenital cardiac disease, ECMO, sepsis, dehydration or prothrombotic  
coagulation defect

Although these factors are commonly thought of as risk factors, no  
controlled studies have proved the associations



# Investigations

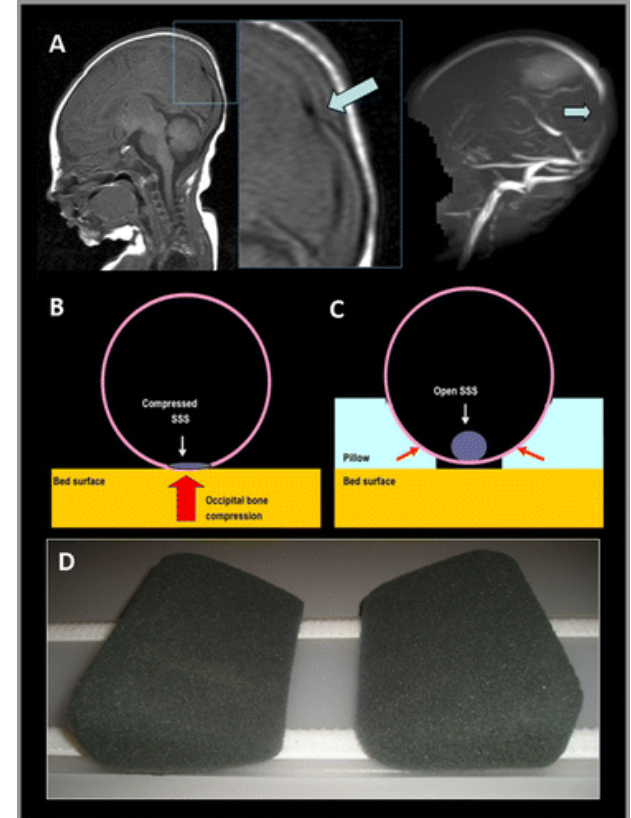
Diagnosis is best made by MRI/MRV

Thrombophilia evaluation in the neonate has limited clinical utility because levels of protein C, protein S, anti-thrombin, and factor XI are normally decreased to 30% of adult levels.

# Management of CSVT

Acute management of CSVT is similar to NAIS  
Prompt treatment of sepsis, meningitis and  
dehydration.

Decompression pillow alleviates occipital  
compression → increase blood flow in sigmoid sinus  
and superior sagittal sinus.



# Anticoagulant therapy in CSVT

No worldwide consensus but a distinct tendency towards increased use has developed in recent years

**Reason:** prevention of clot propagation which occurs 30% of cases, most often in the 1<sup>st</sup> week after the primary insult.

**Benefit:** reduces the rate to 3%

**Safety:** No apparent increased risk of bleeding

**Recommendation:** CSVT without hemorrhage & CSVT with thalamic hemorrhage  
LMW Heparin for 6 weeks

Follow-up imaging study: recanalization complete → discontinue

recanalization not complete → additional 6 weeks

# Anticoagulation in the management of neonatal cerebral sinovenous thrombosis: a systematic review and meta-analysis

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## ABBREVIATIONS

ACT	Anticoagulation therapy
CSVT	Cerebral sinovenous thrombosis
ICH	Intracerebral haemorrhage

**AIM** To determine whether anticoagulation therapy (ACT) in the treatment of neonatal cerebral sinovenous thrombosis (CSVT) improves outcomes, in the presence or absence of pre-existing intracerebral haemorrhage (ICH).

**METHOD** We searched CENTRAL, MEDLINE, Embase, CINAHL, the Web of Science, and clinical trial databases. We considered data from retrospective and prospective cohort studies, case series, and randomized controlled studies evaluating outcomes of CSVT treated with anticoagulation or no anticoagulation. Studies were included if they involved infants either younger than 28 days of age or younger than 44 weeks postmenstrual age at the time of diagnosis of CSVT in which ACT was considered.

**RESULTS** Seven non-randomized studies were included in meta-analysis. ACT had no significant effect on mortality before discharge either in the presence or absence of pre-existing ICH, nor on the incidence of extension of pre-existing ICH. ACT was associated with a reduced risk of propagation of thrombus (risk ratio 0.14, 95% confidence interval 0.03–0.72).

**INTERPRETATION** There are no randomized trials assessing the safety and efficacy of ACT in the treatment of neonatal CSVT. The results of this meta-analysis would justify a position of equipoise and support the need for well-designed randomized controlled trials of ACT in this population.

# Prognosis of CSVT

Mortality 10-20%

Individuals with venous infarction and those with seizures at the time of diagnosis tend to experience more serious neurological sequelae.

Recurrence risk of CSVT appears to be low

# Conclusions

An incomplete understanding of the causes of all forms of neonatal stroke limits our ability to develop preventative strategies.

Although there is some observational evidence that antithrombotic agents might benefit selected neonates with AIS or CSVT, clinical trials are lacking.