A clinical approach to childhood stroke

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Stroke

- WHO 1971 - 2013: *"A clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin"*

An Updated Definition of Stroke for the 21st Century

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

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(*Stroke*. 2013;44:2064-2089)

Table 1. Definition of Stroke

The term "stroke" should be broadly used to include all of the following:

Definition of CNS infarction: CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on

1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes hemorrhagic infarctions, types I and II; see "Hemorrhagic Infarction.")

Definition of ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. (Note: Evidence of CNS infarction is defined above.)

Definition of silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Definition of intracerebral hemorrhage: A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. (Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types I and II—see "Hemorrhagic Infarction.")

Definition of stroke caused by intracerebral hemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Definition of silent cerebral hemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.

Definition of subarachnoid hemorrhage: Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).

Definition of stroke caused by subarachnoid hemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Definition of stroke caused by cerebral venous thrombosis: Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

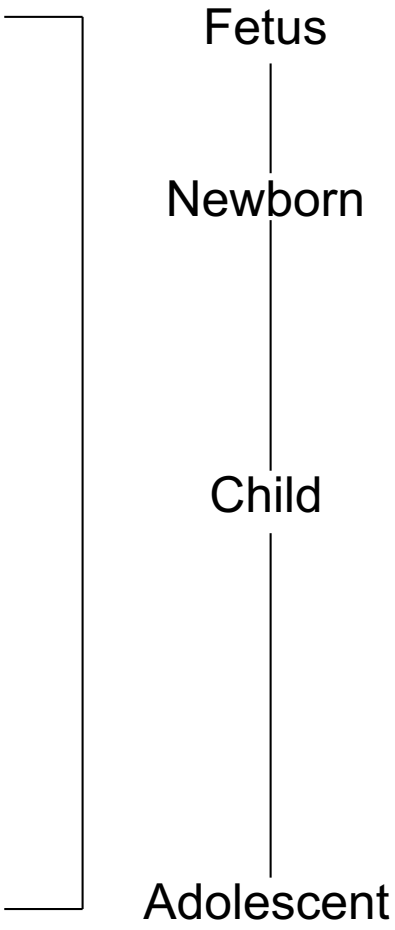
Definition of stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

Childhood stroke

- Important paediatric problem
  - incidence approx. 5/100 000/year
  - up to 1 000 children/year in UK
  - as common as brain tumour
  - one of the top 10 causes of childhood death
  - 2/3rds of survivors have residual morbidity
  - significant proportion of those with symptoms <24h will have cerebral infarction

Childhood stroke

- Arterial ischaemic stroke (AIS)
- Venous thrombosis
  - Sinovenous
  - Cortical venous
- Intracranial haemorrhage
  - Intraparenchymal
  - Intraventricular
  - Subarachnoid
  - Subdural
  - Extradural



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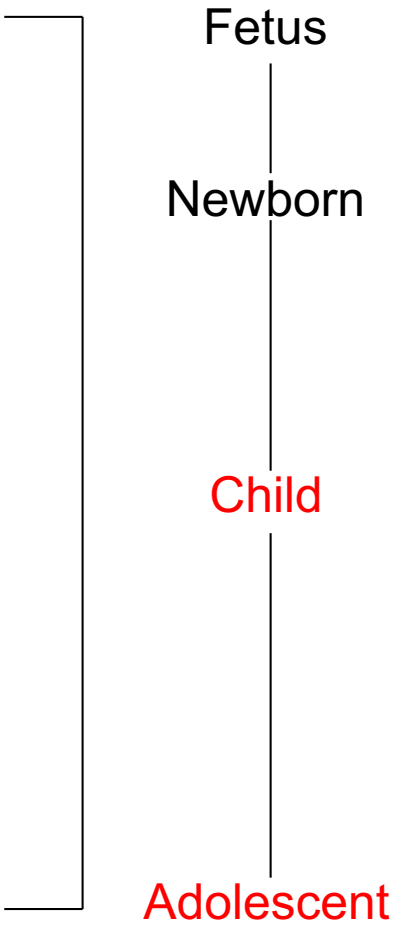
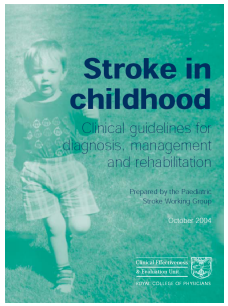


Clinical guidelines



CHEST

Official publication of the American College of Chest Physicians

Antithrombotic Therapy in Neonates and Children : American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Paul Monagle, Elizabeth Chalmers, Anthony Chan, Gabrielle deVeber, Fenella Kirkham, Patricia Massicotte and Alan D. Michelson

Chest 2008;133;887S-968S

Stroke

Journal of the American Heart Association

American Stroke Association

A Division of American Heart Association

Management of Stroke in Infants and Children: A Scientific Statement From a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young

E. Steve Roach, Meredith R. Golomb, Robert Adams, Jose Biller, Stephen Daniels, Gabrielle deVeber, Donna Ferriero, Blaise V. Jones, Fenella J. Kirkham, R. Michael Scott and Edward R. Smith

Stroke 2008;39:2644-2691; originally published online Jul 17, 2008;
DOI: 10.1161/STROKEAHA.108.189696

RCPCH

Royal College of Paediatrics and Child Health

Leading the way in Children's Health

Stroke association

RCPCH Childhood Stroke Guidelines (May 2017)

Childhood AIS: take home messages

- Acute hemiparesis commonest presentation
- May present with “soft signs” in children with SCD (commonest RF world wide)
- Posterior circulation only accounts for 15%
  - >90% male
  - >50% secondary to vertebral dissection

Stroke and nonstroke brain attacks in children

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ABSTRACT

Objectives: To determine symptoms, signs, and etiology of brain attacks in children presenting to the emergency department (ED) as a first step for developing a pediatric brain attack pathway.

Methods: Prospective observational study of children aged 1 month to 18 years with brain attacks (defined as apparently abrupt-onset focal brain dysfunction) and ongoing symptoms or signs on arrival to the ED. Exclusion criteria included epilepsy, hydrocephalus, head trauma, and isolated headache. Etiology was determined after review of clinical data, neuroimaging, and other investigations. A random-effects meta-analysis of similar adult studies was compared with the current study.

Results: There were 287 children (46% male) with 301 presentations over 17 months. Thirty-five percent arrived by ambulance. Median symptom duration before arrival was 6 hours (interquartile range 2–28 hours). Median time from triage to medical assessment was 22 minutes (interquartile range 6–55 minutes). Common symptoms included headache (56%), vomiting (36%), focal weakness (35%), numbness (24%), visual disturbance (23%), seizures (21%), and altered consciousness (21%). Common signs included focal weakness (31%), numbness (13%), ataxia (10%), or speech disturbance (8%). Neuroimaging included CT imaging (30%), which was abnormal in 27%, and MRI (31%), which was abnormal in 62%. The most common diagnoses included migraine (28%), seizures (15%), Bell palsy (10%), stroke (7%), and conversion disorders (6%). Relative proportions of conditions in children significantly differed from adults for stroke, migraine, seizures, and conversion disorders.

Conclusions: Brain attack etiologies differ from adults, with stroke being the fourth most common diagnosis. These findings will inform development of ED clinical pathways for pediatric brain attacks. *Neurology*® 2014;82:1434–1440

Step 1: Differentiate stroke from mimics

- Imaging is key
- MRI ideal but 2017 RCPCH guidelines recommend CT&CTA for those presenting within window for hyperacute treatment (4-6hours)
- CTA: arch to CoW for AIS; intracranial for ICH

Step 2: Identify underlying risk factors

- 50% have pre-morbid diagnosis e.g. congenital heart disease
- Antecedent intercurrent infection (incl. *varicella*), anaemia, minor head trauma common
- Thrombophilia/silent heart disease rare
- 80% have cerebral/cervical non-atherosclerotic arteriopathy

Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study

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Katherine J. Lee, MSc, PhD,[4] Gabrielle A. deVeber, MSc, MD,[5]
and Vijeya Ganesan, MD,[6] on behalf of the International Pediatric Stroke Study Group

Objective: To describe presumptive risk factors (RFs) for childhood arterial ischemic stroke (AIS) and explore their relationship with presentation, age, geography, and infarct characteristics.
Methods: Children (29 days–18 years) were prospectively enrolled in the International Pediatric Stroke Study. Risk factors, defined conditions thought to be associated with childhood AIS, were divided into 10 categories. Chi-square tests were used to compare RFs prevalence across regions and age; logistic regression was used to determine whether RFs were associated with particular features at presentation or infarct characteristics.
Results: A total of 676 children were included. No identifiable RFs was present in 54 (9%). RFs in others included arteriopathies (53%), cardiac disorders (CDs) (31%), infection (24%), acute head and neck disorders (AHNDs) (23%), acute systemic conditions (ASCs) (22%), chronic systemic conditions (CSCs) (19%), prothrombotic states (PTSs) (13%), chronic head and neck disorders (CHNDs) (10%), atherosclerosis-related RFs (2%), and other (22%). Fifty-two percent had multiple RFs. There was lower prevalence of arteriopathy in Asia, lower prevalence of CSCs in Europe and Australia, higher prevalence of PTSs in Europe, and higher prevalence of ASCs in Asia and South America. Prevalence of CDs and ASCs was highest in preschoolers, arteriopathies in children 5 to 9 years old, and CHNDs were highest in children aged 10 to 14 years. Arteriopathies were associated with focal signs and ASCs, CHNDs, and AHNDs with diffuse signs. Arteriopathies, CSCs, and ASCs were associated with multiple infarcts and CDs with hemorrhagic conversion.
Interpretation: RFs, especially arteriopathy, are common in childhood AIS. Variations in RFs by age or geography may inform prioritization of investigations and targeted preventative strategies.

ANN NEUROL 2011;69:130–140

Risk factor category	Frequency N (%)
Arteriopathy (n=525)	277 (53%)
Cardiac disorders (n=667)	204 (31%)
Chronic systemic disorders (n=674)	199 (30%)
Prothrombotic states (n=674)	87 (13%)
Acute systemic disorders (n=658)	148 (23%)
Chronic head & neck disorders (n=667)	68 (10%)
Acute head & neck disorders (n=648)	148 (23%)
Infection (n=676)	165 (24%)
Risk factors for atherosclerosis (n=676)	12 (2%)
Other AIS risk factor recorded	150 (22%)

Mackay et al 2011

Timing and number of minor infections as risk factors for childhood arterial ischemic stroke

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ABSTRACT

Objective: In a population-based case-control study, we examined whether the timing and number of minor infections increased risk of childhood arterial ischemic stroke (AIS).

Methods: Among 102 children with AIS and 306 age-matched controls identified from a cohort of 2.5 million children in a large integrated health care plan (1993–2007), we abstracted data on all medical visits for minor infection within the 2 years prior to AIS or index date for pairwise age-matched controls. We excluded cases of AIS with severe infection (e.g., sepsis, meningitis). Using conditional logistic regression, we examined the effect of timing and total number of minor infections on stroke risk.

Results: After adjusting for known pediatric stroke risk factors, the strongest association between infection and AIS was observed for infectious visits ≤3 days prior to stroke (odds ratio [OR] 12.1, 95% confidence interval [CI] 2.5, 57, $p = 0.002$). Respiratory infections represented 80% of case infections in that time period. Cases had more infectious visits, but not significantly so, for all time periods ≥4 days prior to the stroke. A greater cumulative number of infectious visits over 2 years did not increase risk of AIS.

Conclusions: Minor infections appear to have a strong but short-lived effect on pediatric stroke risk, while cumulative burden of infection had no effect. Proposed mechanisms for the link between minor infection and stroke in adults include an inflammatory-mediated prothrombotic state and chronic endothelial injury. The transient effect of infection in children may suggest a greater role for a prothrombotic mechanism. *Neurology*® 2014;83:890–897

Infection, vaccination, and childhood arterial ischemic stroke

Results of the VIPS study

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ABSTRACT

Objectives: Minor infection can trigger adult arterial ischemic stroke (AIS) and is common in childhood. We tested the hypotheses that infection transiently increases risk of AIS in children, regardless of stroke subtype, while vaccination against infection is protective.

Methods: The Vascular Effects of Infection in Pediatric Stroke study is an international case-control study that prospectively enrolled 355 centrally confirmed cases of AIS (29 days–18 years old) and 354 stroke-free controls. To determine prior exposure to infections and vaccines, we conducted parental interviews and chart review.

Results: Median (interquartile range) age was 7.6 years for cases and 9.3 for controls ($p = 0.44$). Infection in the week prior to stroke, or interview date for controls, was reported in 18% of cases, vs 3% of controls, conferring a 6.3-fold increased risk of AIS ($p < 0.0001$); upper respiratory infections were most common. Prevalence of preceding infection was similar across stroke subtypes: arteriopathic, cardioembolic, and idiopathic. Use of vasoactive cold medications was similarly low in both groups. Children with some/few/no routine vaccinations were at higher stroke risk than those receiving all or most (odds ratio [OR] 7.3, $p = 0.0002$). In an age-adjusted multivariate logistic regression model, independent risk factors for AIS included infection in the prior week (OR 6.3, $p < 0.0001$), undervaccination (OR 8.2, $p = 0.0004$), black race (compared to white; OR 1.9, $p = 0.009$), and rural residence (compared to urban; OR 3.0, $p = 0.0003$).

Conclusions: Infection may act as a trigger for childhood AIS, while routine vaccinations appear protective. Hence, efforts to reduce the spread of common infections might help prevent stroke in children. *Neurology*® 2015;85:1459–1466

Herpesvirus Infections and Childhood Arterial Ischemic Stroke

Results of the VIPS Study

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Background—Epidemiological studies demonstrate that childhood infections, including varicella zoster virus, are associated with an increased risk of arterial ischemic stroke (AIS). Other herpesviruses have been linked to childhood AIS in case reports. We sought to determine whether herpesvirus infections, which are potentially treatable, increase the risk of childhood AIS.

Methods and Results—We enrolled 326 centrally confirmed cases of AIS and 115 stroke-free controls with trauma (29 days to 18 years of age) with acute blood samples (≤3 weeks after stroke/trauma); cases had convalescent samples (7–28 days later) when feasible. Samples were tested by commercial enzyme-linked immunosorbent assay kits for immunoglobulin M/immunoglobulin G antibodies to herpes simplex virus 1 and 2, cytomegalovirus, Epstein-Barr virus, and varicella zoster virus. An algorithm developed a priori classified serological evidence of past and acute herpesvirus infection as dichotomous variables. The median (quartiles) age was 7.7 (3.1–14.3) years for cases and 10.7 (6.9–13.2) years for controls (P=0.03). Serological evidence of past infection did not differ between cases and controls. However, serological evidence of acute herpesvirus infection doubled the odds of childhood AIS, even after adjusting for age, race, and socioeconomic status (odds ratio, 2.2; 95% confidence interval, 1.2–4.0; P=0.007). Among 187 cases with acute and convalescent blood samples, 85 (45%) showed evidence of acute herpesvirus infection; herpes simplex virus 1 was found most often. Most infections were asymptomatic.

Conclusions—Herpesviruses may act as a trigger for childhood AIS, even if the infection is subclinical. Antivirals like acyclovir might have a role in the prevention of recurrent stroke if further studies confirm a causal relationship. **(*Circulation*. 2016;133:732-741. DOI: 10.1161/CIRCULATIONAHA.115.018595.)**

Step 3: Define the AIS subtype

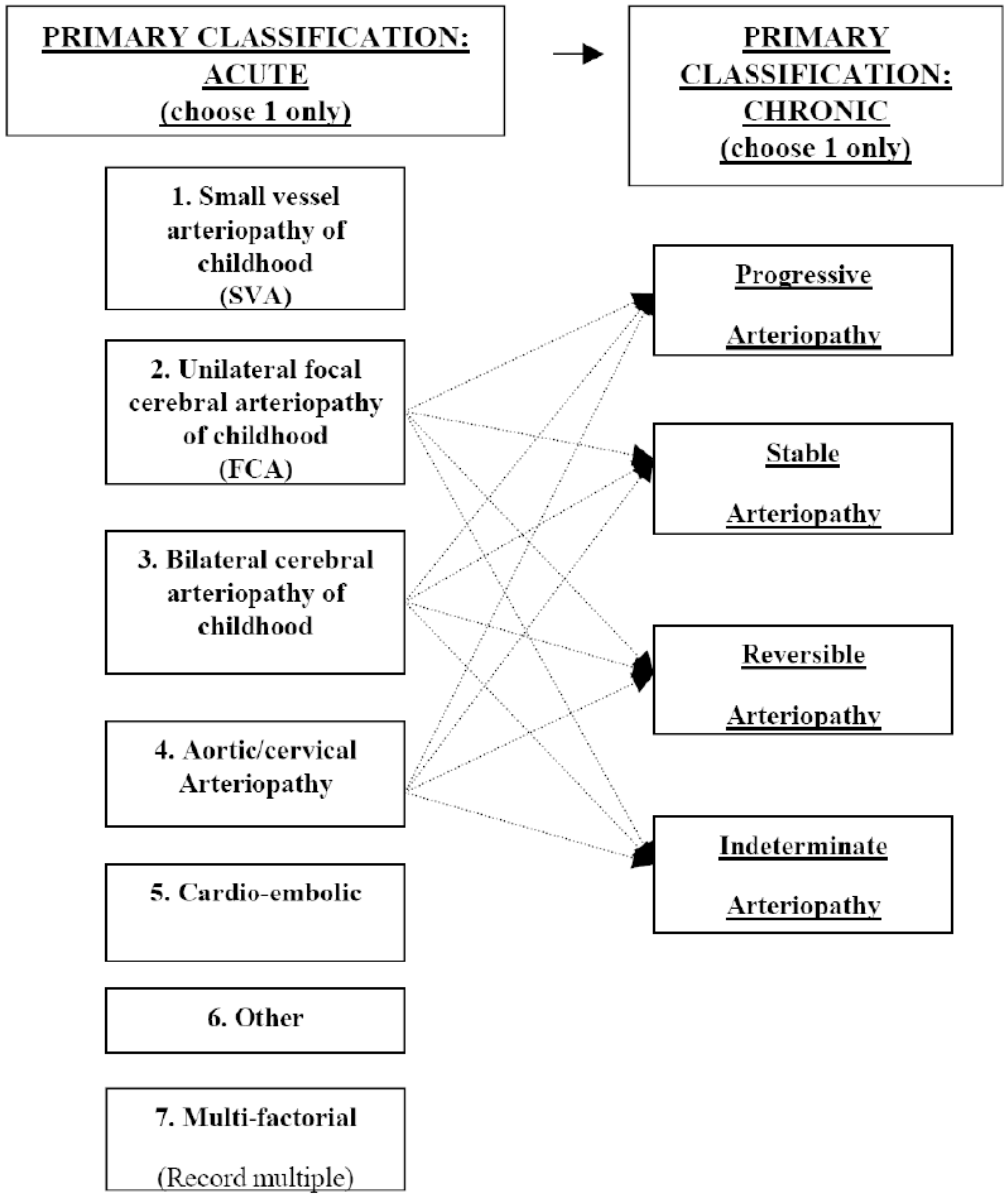
Classification of childhood cerebral arteriopathies

Toward the definition of cerebral arteriopathies of childhood

Guillaume Sébire[a], Heather Fullerton[b], Emilie Riou[a] and Gabrielle deVeber[c]

Current Opinion in Pediatrics 2004; 16: 617

- Non-inflammatory vasculopathies
  - Dissection
  - Moyamoya (primary/secondary)
  - Transient cerebral arteriopathy
  - SCD
  - Congenital hypoplasia/dysplasia
  - FMD
  - Drugs
- Primary vasculitides w CNS involvement
  - incl primary CNS angiitis
- Secondary vasculitides w CNS involvement
  - Collagen vascular diseases
  - Infection



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Towards a Consensus-based Classification of Childhood Arterial Ischemic Stroke

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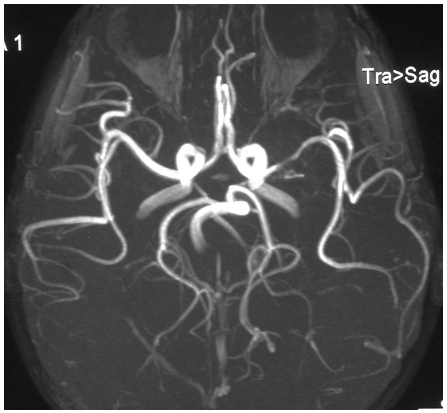
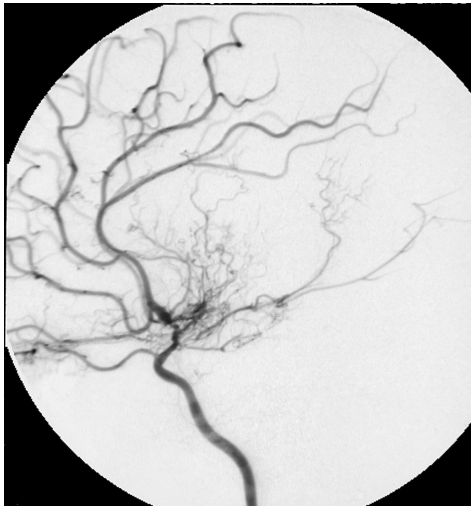
Figure 2.
CASCADE Criteria (Childhood AIS Standardized Classification and Diagnostic Evaluation)

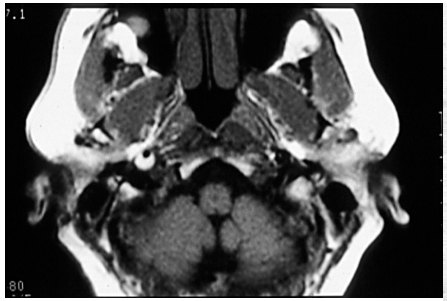
Childhood AIS: key investigations that change management

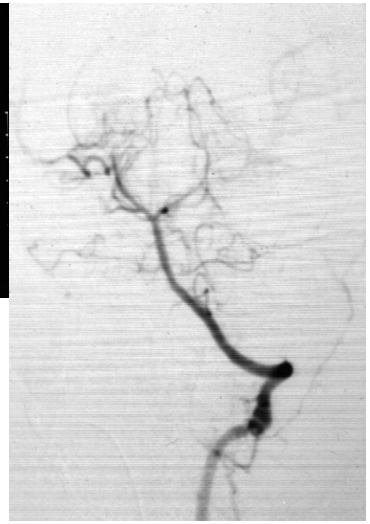
- Clinical examination
  - Neurocutaneous
  - Heart/pulses/bruit
  - Blood pressure
  - Horner's syndrome
- MRA: arch to CoW
- Echocardiogram
- ?LP

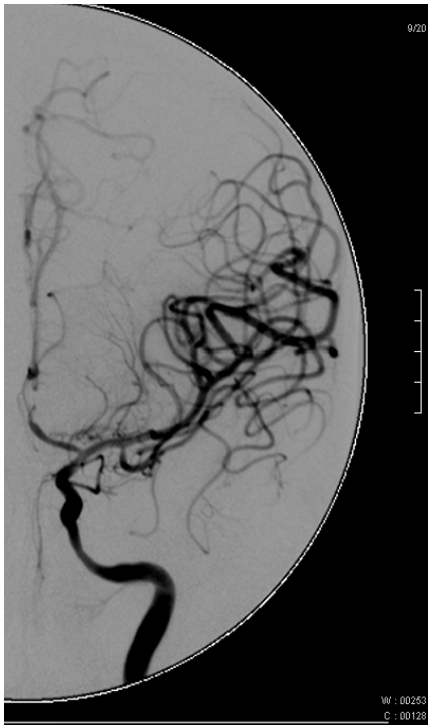


Arteriopathy in childhood AIS

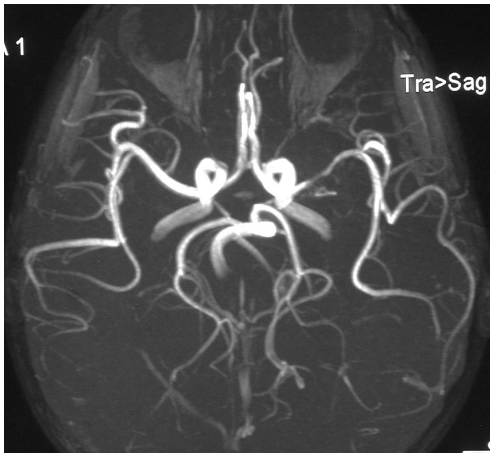






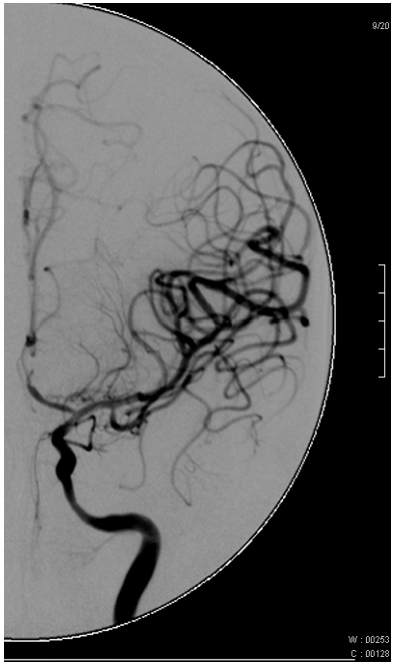


TCA/FCA



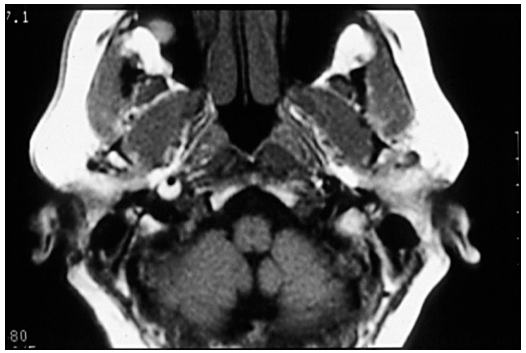
- Most commonly identified arteriopathy associated with childhood AIS
- Occlusive disease of TICA/proximal MCA – i.e. intracranial
- +/- associated with antecedent *varicella* infection
- Initial imaging may be normal
- Focal and monophasic (though FCA diagnosis can be made on single scan)

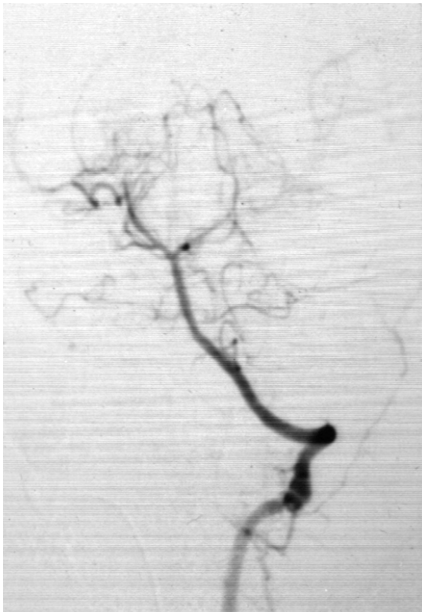
Childhood PACNS



- Inflammatory cerebrovascular disorder confined to cerebral circulation
- Absence of systemic inflammation
- Controversy as to distinction between cPACNS & TCA/FCA (e.g. Aviv et al 2006)
- Early results suggest that markers of endothelial injury & repair might distinguish between these

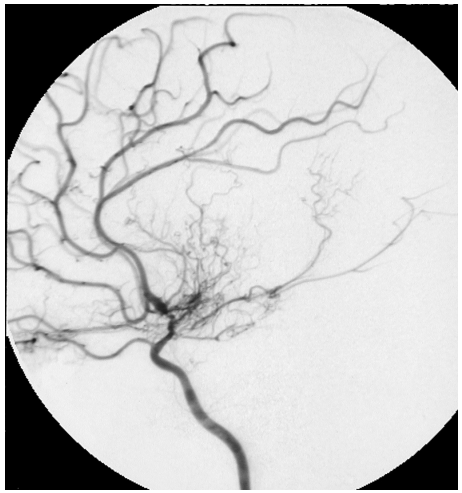
Arterial dissection





- Up to 15% AIS in young people
- Traumatic vs. non-traumatic
- Rarely associated with systemic connective tissue disorder (e.g. vascular EDS) but 50% have cutaneous connective tissue abnormalities
- Association with recent infection
- CADISS suggests no benefit to anticoag over aspirin

Moyamoya



- Terminal ICA occlusion with basal collaterals
- Radiological rather than clinical entity
- Primary vs. secondary
- Ethnicity
- Associated with genetic conditions: NF1, trisomy 21 etc.
- High rate recurrence
- Surgical revascularisation

Subtypes of arteriopathy

- IPSS, n = 277/525 had abnormal vascular imaging

Arteriopathy	n	%
FCA*	69	25
Moyamoya (primary or secondary)†‡	61	22
Arterial dissection‡	56	20
Vasculitis	33	12
Sickle cell disease arteriopathy	21	8
Postvaricella angiopathy	19	7
Other§	10	4
Unspecified vasculopathy	9	3

Table II: Ischaemic stroke subtypes according to TOAST classification

Ischaemic stroke subtype	*Children (n=36)*	*Adults (n=50)*
Large artery atherosclerosis	0	4
Cardioembolic	3	6
Small vessel	0	17
Other determined aetiology	29	8
SCD	8	1
Arterial dissection	3	0
Large vessel vasculopathy	11	0
Moyamoya disease	3	0
Migraine	1	5
MELAS	1	0
Anticardiolipin antibodies	0	2
Meningitis	1	0
Direct ICA trauma	1	0
Multiple probable aetiologies	1	3
Undetermined aetiology	3	12

SCD, sickle cell disease; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke like episodes; ICA, internal carotid artery. TOAST, Trial of Org 10172 in Acute Stroke Therapy (Adams et al. 1993).

IPSS, AIS, n = 661

- 3% mortality
- 74% neurological morbidity at time of discharge
- Arteriopathy, bilateral injury, reduced LOC predictive of adverse outcome

Outcome and Recurrence 1 Year after Pediatric Arterial Ischemic Stroke in a Population-Based Cohort

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Finbar J. O'Callaghan, MBChB,PhD[2,12]

Objective: Arterial ischemic stroke (AIS) is an important cause of acquired brain injury in children. Few prospective population-based studies of childhood AIS have been completed. We aimed to investigate the outcome of childhood AIS 12 months after the event in a population-based cohort.

Methods: Children aged 29 days to < 16 years with radiologically confirmed AIS occurring over a 1-year period residing in southern England (population = 5.99 million children) were eligible for inclusion. Outcome was assessed during a home visit using the Pediatric Stroke Outcome Measure (PSOM). Parental impressions of recovery were assessed using the Pediatric Stroke Recurrence and Recovery Questionnaire. PSOM score was estimated via telephone interview or clinician interview whenever home visit was not possible.

Results: Ninety-six children with AIS were identified. Two children were lost to follow-up. Nine of 94 (10%) children died before the 12-month follow-up. One child had an AIS recurrence. PSOM scores were available for 78 of 85 living children at follow-up. Thirty-nine of 78 (50%) had a good outcome (total PSOM score < 1), and 39 of 78 (50%) had a poor outcome. Seizures at onset of AIS were associated with a poor outcome (odds ratio = 3.5, 95% confidence interval = 1.16–10.6). Twenty-eight of 73 (38%) children were judged by their carers to have fully recovered. Ten of 84 (12%) children had recurrent seizures, and 17 of 84 (20%) reported recurrent headaches.

Interpretation: AIS carries a significant risk of mortality and long-term neurological deficit. However, the rates of mortality, recurrence, and neurological impairment were markedly lower in this study than previously published figures in the United Kingdom.

ANN NEUROL 2016;79:784–793

Stroke Prevalence, Mortality and Disability-Adjusted Life Years in Children and Youth Aged 0–19 Years: Data from the Global and Regional Burden of Stroke 2013

Conclusions: Globally, between 1990 and 2013, there was a significant increase in the absolute number of prevalent childhood strokes, while absolute numbers and rates of both deaths and DALYs declined significantly. The gap in childhood stroke burden between developed and developing countries is closing; however, in 2013, childhood stroke burden in terms of absolute numbers of prevalent strokes, deaths and DALYs remained much higher in developing countries. There is an urgent need to address these disparities with both global and country-level initiatives targeting prevention as well as improved access to acute and chronic stroke care.

Neuroepidemiology 2015;45:177–189
DOI: 10.1159/000441087

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Prolonged or recurrent acute seizures after pediatric arterial ischemic stroke are associated with increasing epilepsy risk

CHRISTINE K FOX[1,2] | MARK T MACKAY[3,4] | MICHAEL M DOWLING[5,6] | PAOLA PERGAMI[7] | LUIGI TITOMANLIO[8] | GABRIELLE DEVEBER[9] | ON BEHALF OF THE SIPS INVESTIGATORS*

AIM To determine epilepsy risk factors after pediatric stroke.

METHOD A cohort of children with arterial ischemic stroke (birth–18y) was enrolled at 21 centers and followed for 1 year. Acute seizures (≤7d after stroke) and active epilepsy (at least one unprovoked remote seizure plus maintenance anticonvulsant at 1y) were identified. Predictors were determined using logistic regression.

RESULTS Among 114 patients (28 neonates and 86 children) enrolled, 26 neonates (93%) and 32 children (37%) had an acute seizure. Acute seizures lasted longer than 5 minutes in 23 patients (40%) and were frequently recurrent: 33 (57%) had 2 to 10 seizures and 11 (19%) had more than 10. Among 109 patients with 1-year follow-up, 11 (10%) had active epilepsy. For each year younger, active epilepsy was 20% more likely (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.6–0.99, p=0.041). Prolonged or recurrent acute seizures also increased epilepsy risk. Each additional 10 minutes of the longest acute seizure increased epilepsy risk fivefold (OR 4.7, 95% CI 1.7–13). Patients with more than 10 acute seizures had a 30-fold increased epilepsy risk (OR 30, 95% CI 2.9–305).

INTERPRETATION Pediatric stroke survivors, especially younger children, have a high risk of epilepsy 1 year after stroke. Prolonged or recurrent acute seizures increase epilepsy risk in a dose-dependent manner.

Childhood AIS: outcome

- Most children with AIS will
  - Walk out of hospital
  - Go to mainstream school
  - Live independently as adults

- Outcome not predictable on the basis of lesion characteristics/aetiology/age
- Risk-benefit of high risk interventions undefined

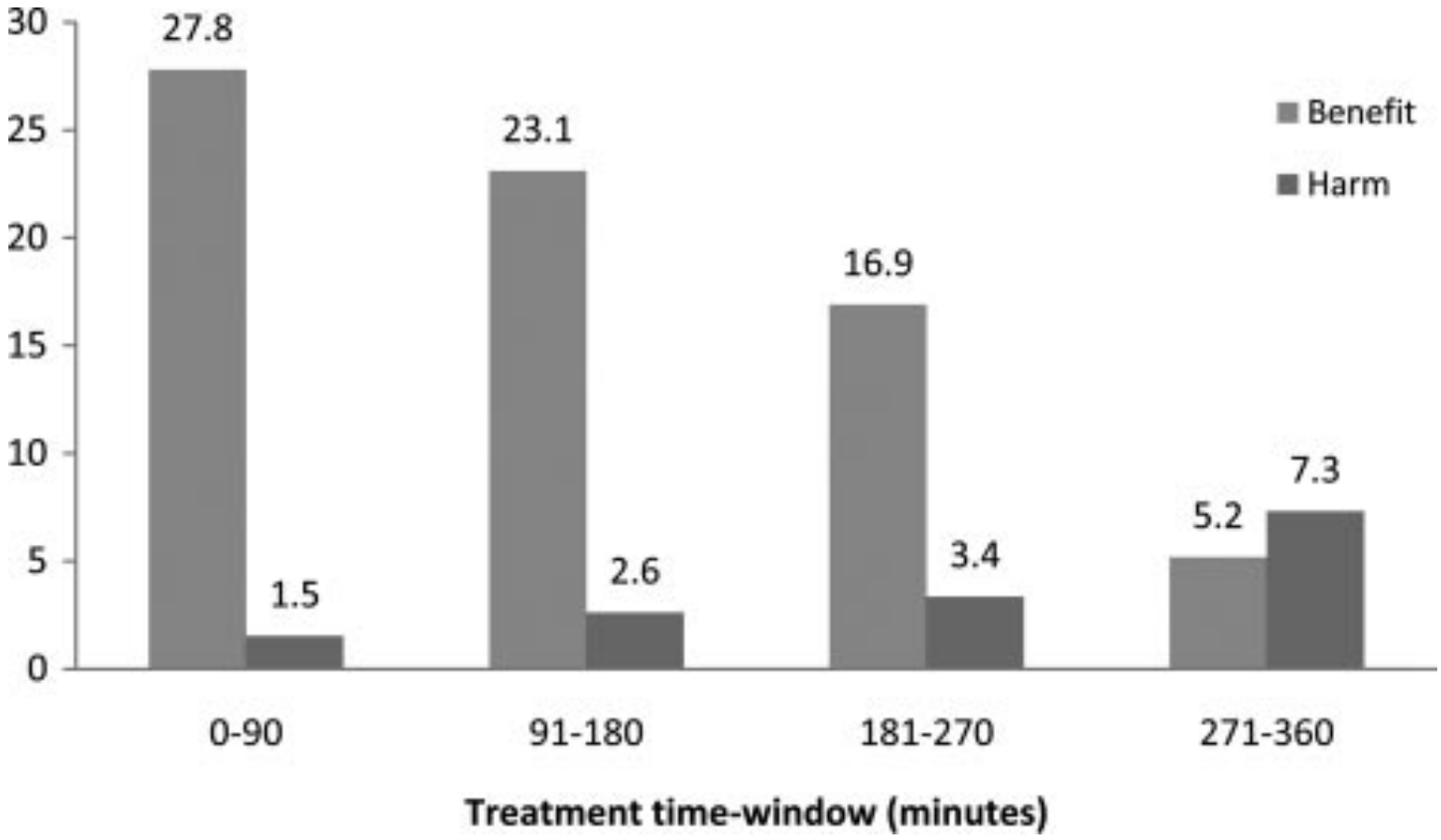
Childhood AIS: economic impact

- Acute treatment costs approx $70 000 USD/child
- At 5y healthcare costs = $135 000 USD
- Societal impact not quantified

Childhood AIS: acute treatment

- Maintain homeostasis (BP, temperature, treat sz)
- Exchange transfusion for SCD
  - HbS <30%, Hb >10

Thrombolysis & adult AIS



Randomized trials of endovascular therapy for stroke — impact on stroke care

Maxim Mokin[1], Haydy Rojas[2] and Elad I. Levy[3]

Abstract | Five trials that investigated the efficacy of modern endovascular therapies for stroke — MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND IA and REVASCAT — have been published within the past year, changing the landscape of acute stroke management. The trials used a variety of imaging modalities and combinations of treatment approaches, including the mandatory use of intravenous thrombolysis before the initiation of endovascular therapy. All five trials provided strong evidence to support the use of thrombectomy that is initiated within 6 h of stroke onset, prompting worldwide changes in the guidelines for management of acute stroke by endovascular treatment. The benefits of endovascular therapy were observed irrespective of a patient's age, their NIH Stroke Scale score, or whether they received intravenous thrombolysis. In this article, we review the main findings of these recent trials, focusing on key aspects of their designs, and discuss their impact on the future management of patients with acute stroke that results from large-vessel occlusion. We discuss the values of noncontrast CT ASPECTS, perfusion imaging and angiography for selecting patients to receive endovascular interventions. We also consider the role of thrombectomy beyond 6 h after stroke onset, and in patients with posterior circulation strokes.

Acute presentation

- Hemiparesis commonest presentation of AIS in all ages

- Of 50 children w acute hemi & final diagnosis of AIS
  - 75% present to a doctor <6hours
  - 35% not scanned in first 24 hours
  - 85% took >24 hours to have MRI
- Similar data from USA, Australia & Canada

Diagnosis

- Logistics of diagnostic imaging in children
  - Access to hyperacute MRI
  - GA/sedation
  - Expertise in interpretation
  - Expertise in paediatric neuroangiography
  - Radiation

Aetiology

- 80% have non-atheromatous cerebral arteriopathy
  - Most FCA/TCA
  - Most anterior circulation
- Childhood AIS multifactorial, no single risk factor dominant
- Of 185 children with AIS seen @ GOSH 1978 – 2000, 30 had occluded artery (16%)
- Fullerton et al (California): 6/52 (12%) occluded artery

Paediatric thrombolysis

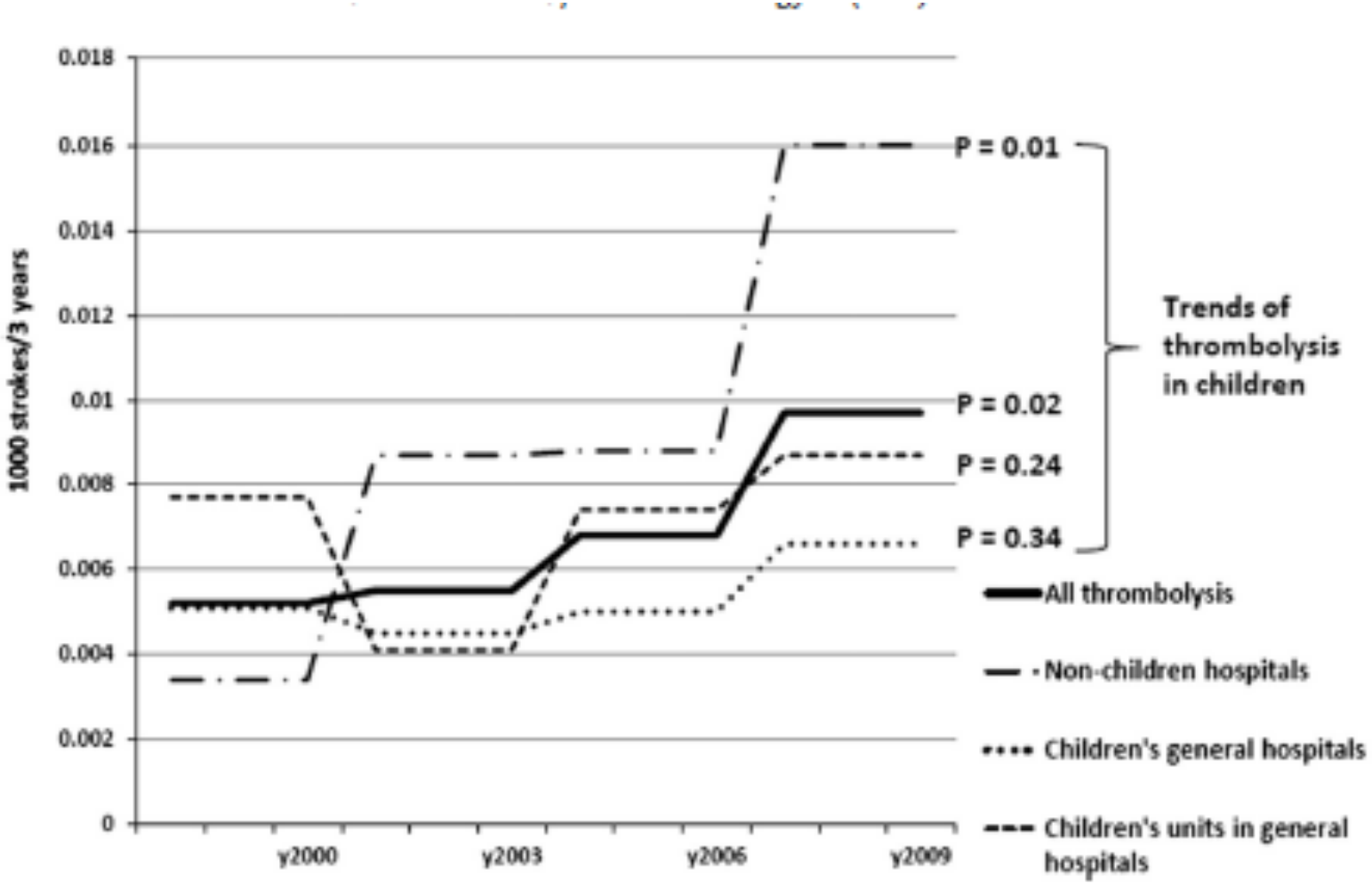
- Gupta et al 2001:
  - n = 80 (65 AIS)
  - Some degree of clot resolution in 85%
  - 70% had complications related to tPA

Paediatric Stroke Guidelines & thrombolysis

- RCP 2004 – not discussed; Chest 2008 – not recommended
- AHA 2009
  - thrombolysis not recommended for neonates
  - consider in some CVST
  - not recommended for AIS outside a trial
  - no consensus on adolescents who meet tPA criteria

Alshekhlee et al., 2013

- National Kids Inpatient Database: 67/ 9257 given thrombolysis for AIS 1998-2009
- Tended to be older
- In adjusted logistic regression analysis, thrombolysis assoc. w ICH (OR 4.28, 1.3 – 14) but not assoc. with in-hospital mortality (OR 1.77, 0.86 – 3.64)
- General increase in thrombolysis per 3year interval


0.018
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
1000 strokes/3 years
y2000
y2003
y2006
y2009
P = 0.01
P = 0.02
P = 0.24
P = 0.34
Trends of thrombolysis in children
All thrombolysis
Non-children hospitals
Children's general hospitals
Children's units in general hospitals

Thrombolysis in Pediatric Stroke Study

Michael J. Rivkin, MD; Gabrielle deVeber, MD, MHSc; Rebecca N. Ichord, MD; Adam Kirton, MD, MSc; Anthony K. Chan, MBBS; Collin A. Hovinga, PharmD, MS; Joan Cox Gill, MD; Aniko Szabo, PhD; Michael D. Hill, MD; Kelley Scholz, MSW; Catherine Amlie-Lefond, MD

(*Stroke*. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.008210.)

Table 1. TIPS Inclusion and Exclusion Criteria

Inclusion criteria
Aged 2 to 17 y
Acute ischemic stroke defined as acute-onset neurological deficit with a pattern consistent with arterial ischemia
PedNIHSS ≥4 and ≤24
Treatment can be administered within 4.5 h of stroke onset
Radiological confirmation of an acute ischemic stroke by:
(a) MR showing acute stroke on diffusion imaging plus MRA showing partial arterial or complete arterial occlusion of the corresponding intracranial artery
(b) CT and CT angiogram confirmation showing a normal brain parenchyma or minimal early ischemic change plus partial or complete arterial occlusion of the corresponding intracranial artery
No evidence of any intracranial hemorrhage
Children with seizure at onset may be included as long as they fulfill the criteria above

TIPS

- 17/25 planned sites activated at study closure
- Active for mean of 9 months
- Closed Dec 2013
- 93 screened, 1 enrolled

Table 3. Characteristics of 93 Patients Aged 2 to 17 y Screened for TIPS

Screens	No (%)	Reason Patient Not Enrolled
43 (46%) confirmed stroke	21 (22)	Medical contraindications ± time to presentation >12 h
	5 (5)	PedNIHSS <6 (2, 2, 3, 4, <6)
	10 (11)	Diagnosed at 4.5 to 12 h
	4 (5)	PedNHSS <6 and outside time window
	2 (2)	Without clot visualized
	1 (1)	Not applicable, child was enrolled
50 (54%) stroke mimics	38 (41)	Benign mimic
	12 (13)	Nonbenign mimic
		2-hemorrhagic stroke
		3-mass lesion
		2-infection
		2-methotrexate toxicity
		2-posterior reversible encephalopathy syndrome

PedNIHSS indicates pediatric version of the NIH Stroke Scale.

Are children with acute arterial ischaemic stroke eligible for hyperacute thrombolysis? A retrospective audit from a tertiary UK centre

CLARA MARECOS[1] | ROXANA GUNNY[2] | ROBERT ROBINSON[1] | VIJEYA GANESAN[1,3]

AIM The aim of this study was to evaluate the number of children with acute arterial ischaemic stroke (AIS) who would have been eligible for hyperacute thrombolysis in the authors' unit (Great Ormond Street Hospital, London, UK) and to identify barriers to this treatment.
METHOD We compared the characteristics of children with a diagnosis of acute AIS, identified from neuroimaging databases, seen at our centre between January 2006 and December 2011. The criteria for hyperacute thrombolysis were predefined by us: age ≥8y; imaging-confirmed diagnosis of acute AIS and arrival at our centre within 6 hours of symptom onset; occluded major artery on computed tomography (CT) or magnetic resonance angiography; no contraindications. Factors that precluded therapy were examined.
RESULTS Of a total of 107 children with acute AIS identified on MRI (*n*=64; 33 females, 31 males; median age 4y, range 1mo–17y) or CT databases (*n*=43; 14 females, 29 males; median age 1y, range 1mo–15y), none would have been eligible for hyperacute thrombolysis. The major barriers to this were (1) delayed diagnosis, (2) delayed transfer to the tertiary centre, (3) age, and (4) medical comorbidities. Of 107 children, three (2.8%) would have been eligible for thrombolysis if diagnosis and transfer had occurred in a timely manner. An additional 11 children (10.3%) would have been eligible if the age criterion was 28 days or more and if diagnosis and transfer had occurred promptly.
INTERPRETATION Although hyperacute thrombolysis is, as yet, an unproven treatment in childhood AIS, at least a subset of patients could potentially benefit. This audit has identified that clinical factors preclude treatment in a high percentage of children. Furthermore, in our specialist unit, without an emergency department, we identified major logistic barriers that will need to be addressed to enable access to hyperacute therapies. These results could inform future trial design and service delivery.

RCPCH Childhood Stroke Guidelines (May 2017)

- Out for consultation
- Likely to recommend IV tPA for >8y within 4.5h
  - w +DWI on MRI or ”normal” CT
  - AND large vessel occlusion on CTA/MRA
  - NIHSS >4
- Consider IV tPA in 2-8y
- Thrombectomy <4.5h (or <24h if posterior circulation)

Concurrent Validity and Reliability of Retrospective Scoring of the Pediatric National Institutes of Health Stroke Scale

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Background and Purpose—The Pediatric National Institutes of Health Stroke Scale (PedNIHSS), an adaptation of the adult National Institutes of Health Stroke Scale, is a quantitative measure of stroke severity shown to be reliable when scored prospectively. The ability to calculate the PedNIHSS score retrospectively would be invaluable in the conduct of observational pediatric stroke studies. The study objective was to assess the concurrent validity and reliability of estimating the PedNIHSS score retrospectively from medical records.

Methods—Neurological examinations from medical records of 75 children enrolled in a prospective PedNIHSS validation study were photocopied. Four neurologists of varying training levels blinded to the prospective PedNIHSS scores reviewed the records and retrospectively assigned PedNIHSS scores. Retrospective scores were compared among raters and to the prospective scores.

Results—Total retrospective PedNIHSS scores correlated highly with total prospective scores (R^2=0.76). Interrater reliability for the total scores was "excellent" (intraclass correlation coefficient, 0.95; 95% CI, 0.94–0.97). Interrater reliability for individual test items was "substantial" or "excellent" for 14 of 15 items.

Conclusions—The PedNIHSS score can be scored retrospectively from medical records with a high degree of concurrent validity and reliability. This tool can be used to improve the quality of retrospective pediatric stroke studies. (***Stroke*****. 2012;43:341-345.)**

Item
1a. LOC
1b. LOC questions
1c. LOC commands
2. Best gaze
3. Visual
4. Facial palsy
5a. Motor arm left
5b. Motor arm right
6a. Motor leg left
6b. Motor leg right
7. Limb ataxia
8. Sensory
9. Best language
10. Dysarthria
11. Extinction/ inattention

Pediatric NIHSSS

The PedNIHSS has the same examination elements as the adult scale including 11 neurological domains and 15 scored items. The PedNIHSS (for children aged 2–18 years) adapts the tasks the child performs so that they are appropriate for the child's age and development. The total score for the PedNIHSS ranges from 0 (least severe) to 42 (most severe).[11]

Arterial ischaemic stroke: recurrence

- Clinical recurrence in 5% - 37%; >60% in children with SCD
- Re-infarction in 33%, clinically silent in 11%
- Risk factors :
  - vascular pathology (esp. moyamoya)
  - protein C deficiency/increased lipoprotein (a)
  - immunodeficiency
  - thrombophilia in previously healthy

Risk of Recurrent Arterial Ischemic Stroke in Childhood

A Prospective International Study

Heather J. Fullerton, MD, MAS; Max Wintermark, MD; Nancy K. Hills, PhD; Michael M. Dowling, MD, PhD; Marilyn Tan, MD; Mubeen F. Rafay, MD; Mitchell S.V. Elkind, MD, MS; A. James Barkovich, MD; Gabrielle A. deVeber, MD, MSc; and the VIPS Investigators*

Background and Purpose—Published cohorts of children with arterial ischemic stroke (AIS) in the 1990s to early 2000s reported 5-year cumulative recurrence rates approaching 20%. Since then, utilization of antithrombotic agents for secondary stroke prevention in children has increased. We sought to determine rates and predictors of recurrent stroke in the current era.

Methods—The Vascular Effects of Infection in Pediatric Stroke (VIPS) study enrolled 355 children with AIS at 37 international centers from 2009 to 2014 and followed them prospectively for recurrent stroke. Index and recurrent strokes underwent central review and confirmation, as well as central classification of causes of stroke, including arteriopathies. Other predictors were measured via parental interview or chart review.

Results—Of the 355 children, 354 survived their acute index stroke, and 308 (87%) were treated with an antithrombotic medication. During a median follow-up of 2.0 years (interquartile range, 1.0–3.0), 40 children had a recurrent AIS, and none had a hemorrhagic stroke. The cumulative stroke recurrence rate was 6.8% (95% confidence interval, 4.6%–10%) at 1 month and 12% (8.5%–15%) at 1 year. The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold when compared with an idiopathic AIS (hazard ratio, 5.0; 95% confidence interval, 1.8–14). The 1-year recurrence rate was 32% (95% confidence interval, 18%–51%) for moyamoya, 25% (12%–48%) for transient cerebral arteriopathy, and 19% (8.5%–40%) for arterial dissection.

Conclusions—Children with AIS, particularly those with arteriopathy, remain at high risk for recurrent AIS despite increased utilization of antithrombotic agents. Therapies directed at the arteriopathies themselves are needed. **(*Stroke*. 2016;47:53-59. DOI: 10.1161/STROKEAHA.115.011173.)**

Evolution of Cerebral Arteriopathies in Childhood Arterial Ischemic Stroke

Nasuda Danchaivijitr, MD,[1] Timothy C. Cox, MB,[1] Dawn E. Saunders, MD,[1] and Vijeya Ganesan, MD[2]

Objective: **To investigate evolution of cerebral arteriopathy in children with arterial ischemic stroke (AIS) and its influence on recurrence.** ***Methods:*** **Arteriopathy severity was graded on serial magnetic resonance angiograms from 50 children with first AIS; diagnostic categories were assigned.** ***Results:*** **Arteriopathy affected 72 arteries in 43 of 50 children. Five had clinical recurrence, with reinfarction in four; another had clinically silent reinfarction. Twelve children (24%; 4 with recurrence) had progressive arteriopathy. Arteriopathy improved in 24 patients (including 1 with recurrent transient ischemic attacks) and was stable in 7 patients. Magnetic resonance angiograms remained normal in seven patients; one had recurrent stroke. Diagnoses were transient cerebral arteriopathy (n = 24), chronic cerebral arteriopathy (n = 11), arterial dissection (n = 3), possible moyamoya (n = 2), primary moyamoya (n = 1), dysplastic arteriopathy (n = 1), and cerebral vasculitis (n = 1). Some of the first two categories could represent thromboembolic arterial occlusion with recanalization. The hazard of recurrence was three times higher when arterial disease had progressed (Cox regression hazard ratio, 3.2; 95% confidence intervals, 0.5–20.3; $p = 0.22$). After adjustment for age and number of AIS risk factors, the hazard ratio was 3.1 (95% confidence interval, 0.4–22.2; $p = 0.27$).** ***Interpretation:*** **Arteriopathy frequently progresses after childhood AIS. Further studies are needed to examine the relationship between progressive arteriopathy and recurrence.**

Ann Neurol 2006;59:620–626

Risk of Recurrent Arterial Ischemic Stroke in Childhood

A Prospective International Study

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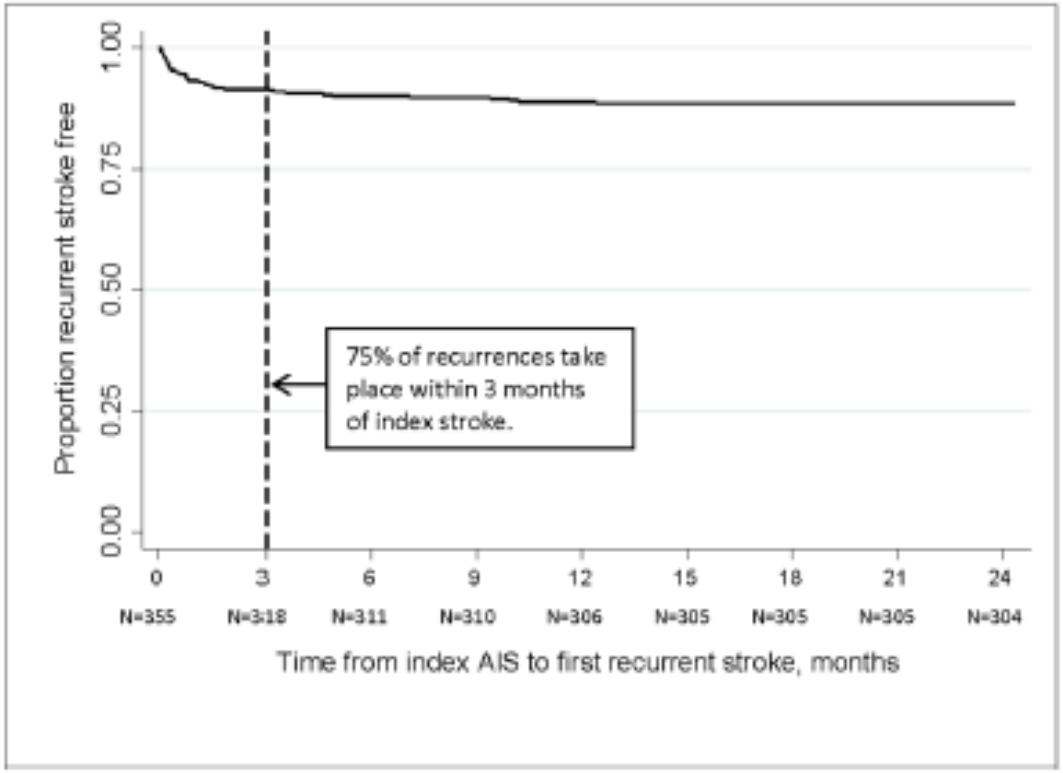
Conclusions—Children with AIS, particularly those with arteriopathy, remain at high risk for recurrent AIS despite increased utilization of antithrombotic agents. Therapies directed at the arteriopathies themselves are needed. **(*Stroke*. 2016;47:53-59. DOI: 10.1161/STROKEAHA.115.011173.)**



Risk of Recurrent Arterial Ischemic Stroke in Childhood: A Prospective International Study

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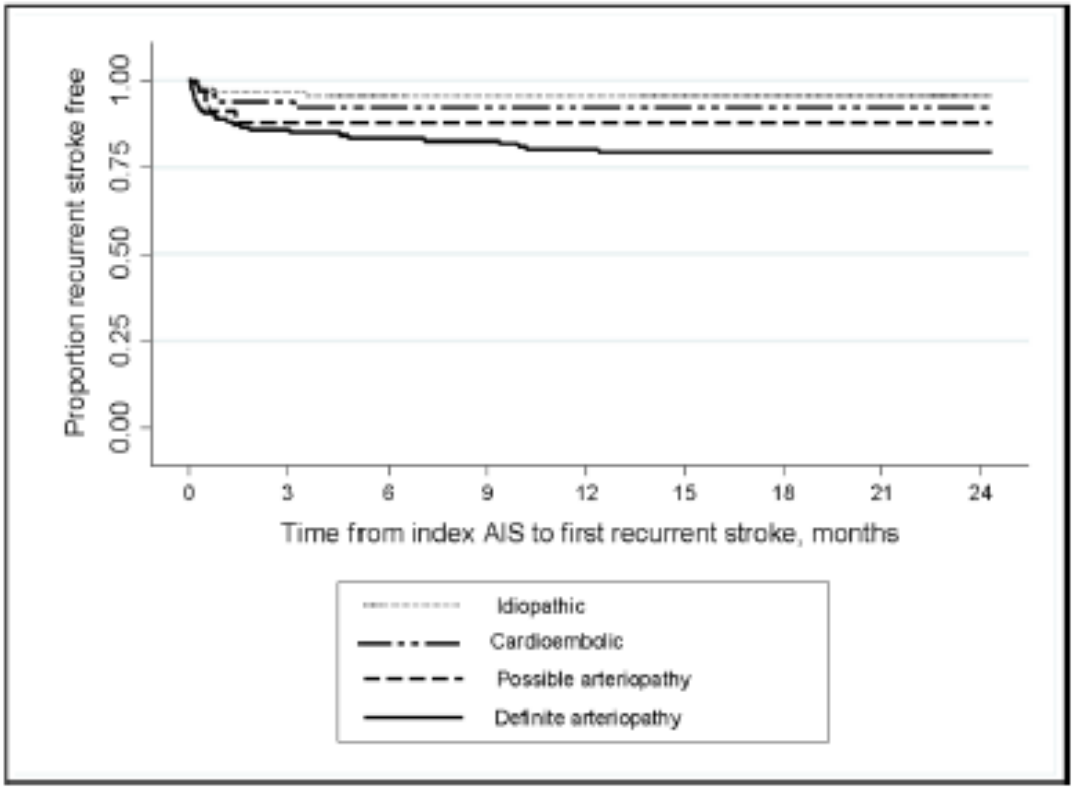
Stroke. 2016 January ; 47(1): 53–59. doi:10.1161/STROKEAHA.115.011173.



Risk of Recurrent Arterial Ischemic Stroke in Childhood: A Prospective International Study

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Stroke. 2016 January ; 47(1): 53–59. doi:10.1161/STROKEAHA.115.011173.

Characteristic	Recurrent stroke (N=40) n	(%)	No recurrent stroke (N=315) n	(%)	HR	95% CI	p-value
Bachelor's degree	6	(15.0)	62	(19.7)	0.6	(0.2, 1.9)	0.4
Graduate education	4	(10.0)	34	(10.8)	0.8	(0.2, 2.7)	0.68
Missing	2	(5.0)	12	(3.8)			
STROKE CLASSIFICATION*							
No arteriopathy	10	(25.0)	184	(58.4)			
Idiopathic	4	(10.0)	86	(27.3)	Ref	-	-
Cardioembolic†	5	(12.5)	60	(19.0)	1.8	(0.5, 6.8)	0.37
Other	1	(2.5)	38	(12.1)	0.6	(0.1, 5.1)	0.61
Possible arteriopathy	4	(10.0)	30	(9.5)	2.9	(0.7, 11.6)	0.13
Definite arteriopathy	26	(65.0)	101	(32.1)	5.0	(1.8, 14.4)	0.003
Transient cerebral arteriopathy	6	(15.0)	19	(6.0)	6.3	(1.8, 22.4)	0.004
Arterial dissection	5	(12.5)	21	(6.7)	5.0	(1.3, 18.5)	0.02
Moyamoya	10	(25.0)	24	(7.6)	7.4	(2.3, 23.5)	0.001
Secondary vasculitis	1	(2.5)	14	(4.4)	1.5	(0.2, 13.8)	0.7
Other	4	(10.0)	23	(7.3)	3.3	(0.8, 13.2)	0.09
MARKERS OF INFECTION							
Infection in the week prior to index stroke	6	(15.0)	58	(18.4)	0.8	(0.3, 1.9)	0.59
Poorly vaccinated‡ (some/few/none routine vaccines)	2	(5.1)	25	(8.3)	0.6	(0.2, 2.6)	0.54
TREATMENT							
Antithrombotic treatment after index stroke							
Anti-platelets	15	(37.5)	132	(41.9)	0.98	(0.4, 2.7)	0.98
Anticoagulation	13	(32.5)	85	(27.0)	1.3	(0.5, 3.7)	0.58
Both	7	(17.5)	56	(17.8)	1.1	(0.3, 3.4)	0.91
Neither	5	(12.5)	42	(13.3)	Ref	-	-
Antithrombotic treatment at the time of recurrence							
Anti-platelets	15	(37.5)	-		-		-
Anticoagulation	14	(35.0)	-		-		-

Risk of Recurrent Arterial Ischemic Stroke in Childhood: A Prospective International Study

Heather J. Fullerton, MD, MAS[1,2], Max Wintermark, MD[3], Nancy K. Hills, PhD[1,4], Michael M. Dowling, MD, PhD[5], Marilyn Tan, MD[6], Mubeen F. Rafay, MD[7], Mitchell S. V. Elkind, MD, MS[8], A. James Barkovich, MD[1,9], Gabrielle A. deVeber, MD, MSc[10], and the VIPS Investigators*

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Table 3. Treatment guidelines for paediatric stroke: antithrombotic treatments.

	RCP guidelines	RCP grading	ACCP guidelines	ACCP grading	AHA Stroke Council	AHA Stroke Council grading
Acute childhood AIS						
General	Aspirin 5 mg/kg/day	Strong consensus	UFH or LMWH for 5 – 7 days and until cardioembolic and dissection have been excluded as causes	2C	The administration of LMWH or UFH may be considered in children for up to 1 week after an ischaemic stroke pending further evaluation to determine the cause of the stroke	Class IIb, C
Sickle cell disease	Exchange transfusion to HbS < 30%	Strong consensus	Intravenous hydration and exchange transfusion to HbS < 30%	1C	Inravenous hydration exchange transfusion to reduce HbS to < 30% total haemoglobin	Class IIa, C
Thrombolysis	Not recommended		Not recommended		Not recommended	
Maintenance therapy in childhood AIS						
General	Aspirin 5 mg/kg/day	Strong consensus	For all children with AIS treat with ASA 2 – 5 mg/kg/day after anticoagulation therapy has been stopped	2C	Aspirin 3 – 5 mg/kg/day when infarction is not due to SCD and no risk of recurrent embolism or a severe hypercoagulable disorder	Class IIa C
Dissection	Consider anticoagulation until evidence of vessel healing or up to 6 months	Strong consensus	After 5 – 7 days UFH or LMWH, treat with LMWH or warfarin for 3 – 6 months	2C	For extracranial dissection LMWH or warfarin for 3 – 6 months or an antiplatelet agent should be considered. Extend therapy beyond 6 months for individuals who develop recurrent symptoms or when there is radiographic evidence of a residual abnormality of the dissected artery. Anticoagulation not recommended for intracranial dissection	Class IIa, C Class III, C
Cardioembolic	Consider anticoagulation	Strong consensus	After 5 – 7 days UFH or LMWH, treat with LMWH or warfarin for 3 – 6 months	2C	Cardioembolic unrelated to PFO after initial therapy with UFH or LMWH, treat with LMWH or warfarin for 3 – 6 months. For children with a suspected cardiac embolism unrelated to a PFO with a lower or unknown risk of stroke, it is reasonable to begin aspirin and to continue it for at least 1 year	Class IIa, B Class IIa, C

Secondary prevention in childhood AIS

- Blood transfusion for SCD
- Anticoagulation for cardioembolic
- Aspirin for arteriopathy (?duration)
- Surgical revascularisation for moyamoya

Conclusions

- Childhood hemiparesis has a wide differential diagnosis
- The cause is non-vascular in 1/3rd
- Childhood ischaemic stroke has distinctive presentations, aetiologies and outcomes according to age

Conclusions

- Clinical guidelines are available to guide management of childhood AIS
- There is a dearth of evidence underpinning these

- As well as medical therapies, surgical and endovascular treatments may have a role in some patients; a multidisciplinary approach is helpful

Inter-Rater Reliability of the CASCADE Criteria

Challenges in Classifying Arteriopathies

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Background and Purpose—There are limited data about the reliability of subtype classification in childhood arterial ischemic stroke, an issue that prompted the IPSS (International Pediatric Stroke Study) to develop the CASCADE criteria (Childhood AIS Standardized Classification and Diagnostic Evaluation). Our purpose was to determine the CASCADE criteria's reliability in a population of children with stroke.

Methods—Eight raters from the IPSS reviewed neuroimaging and clinical records of 64 cases (16 cases each) randomly selected from a prospectively collected cohort of 113 children with arterial ischemic stroke and classified them using the CASCADE criteria. Clinical data abstracted included history of present illness, risk factors, and acute imaging. Agreement among raters was measured by unweighted κ statistic.

Results—The CASCADE criteria demonstrated a moderate inter-rater reliability, with an overall κ statistic of 0.53 (95% confidence interval [CI]=0.39–0.67). Cardioembolic and bilateral cerebral arteriopathy subtypes had much higher agreement (κ=0.84; 95% CI=0.70–0.99; and κ=0.90; 95% CI=0.71–1.00, respectively) than cases of aortic/cervical arteriopathy (κ=0.36; 95% CI=0.01–0.71), unilateral focal cerebral arteriopathy of childhood (FCA; κ=0.49; 95% CI=0.23–0.76), and small vessel arteriopathy of childhood (κ=–0.012; 95% CI=–0.04 to 0.01).

Conclusions—The CASCADE criteria have moderate reliability when used by trained and experienced raters, which suggests that it can be used for classification in multicenter pediatric stroke studies. However, the moderate reliability of the arteriopathic subtypes suggests that further refinement is needed for defining subtypes. Such revisions may reduce the variability in the literature describing risk factors, recurrence, and outcomes associated with childhood arteriopathy. **(*Stroke*. 2016;47:2443-2449. DOI: 10.1161/STROKEAHA.116.013544.)**