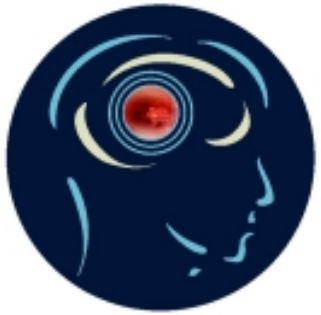
PETITE:
Pediatric Endovascular Therapy after Imaging in acuTE stroke

PIs: Gregory W Albers, MD, Sarah Lee, MD

Stanford Stroke Center / Stanford Children's Health

StrokeNet Steering Committee 6/12/19



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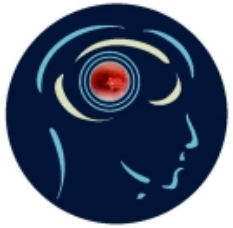
Background

- ~5000 children are diagnosed with ischemic stroke per year in the U.S.
- Stroke is an important cause of morbidity in children
  - 75% will have long-term disability
  - 65% with motor deficits, 50% neuropsychological sequelae, 1/3 epilepsy
- High cost of care (Lo et al, Stroke 2008)
  - Average adjusted 5-year cost for childhood stroke: $135,161
  - Annual cost of pediatric stroke hospitalization in the US: $42 million
- Identifying ways to reduce or eliminate disability in childhood stroke would have a significant impact on individual and society

Background

- Well-established guidelines exist for acute therapy in adult ischemic stroke, but no rigorous trials have been completed in children
- Multiple case series report excellent outcomes with thrombectomy in children, but widely varying inclusion criteria and inherent limitations (Cobb et al Stroke 2017, Bigi et al Ann Neurol 2018, Pacheco et al Eur J Paediatr Neurol 2018; Shoriah et al, JNIS 2018; Lee et al JNIS 2019; Sporns, et al, *submitted*)
- IPSS, TIPS trial and the rise of the pediatric stroke center make PETITE feasible, especially within a 24 hour time window
- TIPSTERS data (Lefond et al, *in preparation*) and multiple new case series suggest thrombectomy is increasingly being utilized in children after January 2018
- Survey of 23 pediatric stroke centers in the IPSS
  - 21/23 centers: 1-5 pediatric thrombectomies per year
  - 15/23 use MR perfusion



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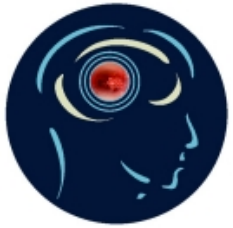
Feasibility

- Wilson, et al *(in preparation):* Online survey of the International Pediatric Stroke Study (IPSS) physician members in March 2019 to assess pediatric neurology attitudes toward thrombectomy since DAWN and DEFUSE 3
- Since January 2018, 20 responding institutions had treated a child with endovascular therapy: 11 (35.5%) had treated 1 child, 5 (16.1%) had treated 2 children, and 4 (12.9%) had treated 4 or more.
- 70% of respondents reported their practice changed after the 2018 AHA guidelines extended the time window for adults, making prospective studies more feasible
- StrokeNet Feasibility survey sent to participating centers

Study Design

- PETITE is a prospective, multi-center, Phase 2 cohort study designed to explore whether neuroimaging can identify pediatric patients who are more likely to benefit from thrombectomy.

- Broad inclusion criteria: all children age 5-17 presenting with stroke symptoms attributable to a large vessel occlusion with an acceptably small ischemic core volume (<50% of MCA territory) within 24 hours of last known well are eligible, regardless of presumed penumbra



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Study Aims

- Primary Aim: To determine if children who meet prespecified Target Mismatch (TMM) criteria on acute neuroimaging are more likely to benefit from endovascular reperfusion than those who do not
  - **Target Mismatch (TMM) profile** will be determined by the imaging core lab, blinded to all clinical data, using the following criteria:

MRI/MRA/MR Perfusion or CT/CTA/CT Perfusion*:
Core*: < 50 mL (age 5-10)
< 70 mL (age 11-17)
AND
Mismatch ratio** ≥ 1.8
AND
Mismatch volume ≥ 15 ml

MRI/MRA without perfusion:

DWI lesion volume < 25 mL

CT/CTA:

ICA, M1 or proximal M2 occlusion AND ASPECTS ≥ 8

*Core defined by ADC < 620 x10^{-6} mm^2/s (if MRI/MR perfusion is performed) or rCBF < 30% (if CT Perfusion is performed)
**Mismatch ratio = [(volume Tmax> 4 seconds)/(volume ischemic core)]

  - DICOM data for all images will be directly transferred to the neuroimaging core lab, where fully automated imaging analysis of the ischemic core and penumbral regions and ASPECTS when applicable will be performed with MR or CT RAPID, an image-post-processing system that has been validated in a number of studies.

- Secondary Aim #1: To establish the safety of thrombectomy in children

- Secondary Aim #2: To assess neuroimaging characteristics and clinical outcomes of children with LVO who do not meet inclusion criteria. All screened patients with large vessel occlusion that do not meet inclusion criteria may be enrolled in a registry arm, including (but not limited to) patients presenting >24 hours from last known well, younger patients (<5 years), patients with posterior circulation occlusion or multiple occluded vessels, patients with NIHSS<4, patients with significant disability at baseline and/or patients with large or completed infarcts.

Clinical inclusion criteria

- Signs and symptoms consistent with the diagnosis of an acute anterior circulation ischemic stroke
- Age 5-17 years
- Pediatric NIHSS ≥ 4, with deficits consistent with acute ischemic stroke
- Endovascular treatment can be initiated (femoral puncture) within 24 hours of stroke onset. Stroke onset is defined as the time the patient was last known to be at their neurologic baseline (wake-up strokes are eligible if they meet the above time limits).
- Pediatric modified Rankin Scale ≤ 2 (normal to moderate deficits) prior to stroke
- Informed consent from parent or legally authorized representative will be obtained prior to any study interventions.

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Clinical exclusion criteria

- Life expectancy of less than 6 months
- Pregnant
- Known allergy to iodine that precludes an endovascular procedure
- Treated with IV tPA >4.5 hours after time last known well
- Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL Baseline platelet count < 50,000/uL
- Severe, sustained hypertension (Systolic or Diastolic Blood Pressure 25% above 95th percentile for age)
- Current participation in another investigational drug or device study
- Presumed septic embolus; suspicion of bacterial endocarditis
- Known pre-existing condition causing cerebrovascular steno-occlusion secondary to vasculopathy such as Moyamoya disease, focal cerebral arteriopathy of childhood or post-radiation vasculopathy
- Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the subject if an endovascular procedure was performed

Neuroimaging inclusion criteria:

- Intracranial ICA (or extracranial ICA with tandem MCA), MCA-M1 or proximal MCA-M2 occlusion on MRA; AND
- DWI hyperintensity involving less than 1/2 of the MCA territory by visual inspection

Alternate Neuroimaging Inclusion Criteria If MRI is contraindicated or unavailable:

- Intracranial ICA (or extracranial ICA with tandem MCA), MCA-M1 or proximal MCA-M2 occlusion on CTA; AND
- CT hypodensity involving less than 1/3 of the MCA territory by visual inspection

Neuroimaging exclusion criteria:

- Evidence of intracranial tumor (except small meningioma), acute intracranial hemorrhage, neoplasm, or arteriovenous malformation
- Significant mass effect with midline shift
- Evidence of internal carotid artery dissection that is flow-limiting (>50%?) or aortic dissection
- Intracranial stent implanted in the same vascular territory that precludes the safe deployment/removal of the thrombectomy device
- Evidence of occlusion secondary to steno-occlusive cerebral vasculopathy such as vasculitis, Moyamoya disease or radiation vasculopathy
- Acute symptomatic arterial occlusions in more than one large vessel territory confirmed on CTA/MRA (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion).

PRIMARY OUTCOME: Pediatric Stroke Outcome Measure

SUMARY OF IMPRESSIONS Score SOI-Score PSOM-SNE

After completing the PSOM-SNE or equivalent detailed neurologic examination, summarize and grade your impressions in the following categories:

A. Sensorimotor Deficit (ANY motor or sensory abnormality including Cranial Nerve Deficits, Visual, and Hearing deficits)

	R side	L side
None	0	0
Mild but no impact on function	0.5	0.5
Moderate with some functional limitations	1	1
Severe or Profound with missing function	2	2
Not Tested	n/t	n/t

Select the Sensorimotor Deficits You Observed (select all that apply)

□ Global developmental delay □ Global hypotonia or hypertonia
□ Hemiparesis □ Hemifacial weakness □ Hemiataxia □ Dysarthria □ Other Motor deficit
□ Hemisensory deficit □ Other Sensory deficit
□ Difficulty with vision □ Difficulty with drinking, chewing or swallowing
□ Other, describe: _____

B. Language Deficit – Production (exclude dysarthria)

None	0
Mild but no impact on function	0.5
Moderate with some functional limitations	1
Severe or Profound with missing function	2
Not Tested	n/t

Describe the Language Production Deficits You Observed Here:

_____

C. Language Deficit - Comprehension

None	0
Mild but no impact on function	0.5
Moderate with some functional limitations	1
Severe or Profound with missing function	2
Not Tested	n/t

Describe The Language Comprehension You Observed Here:

_____

D. Cognitive or Behavioural Deficit (specify which)

□ **Cognitive** □ **Behavioural**

None	0
Mild but no impact on function	0.5
Moderate with some functional limitations	1
Severe or Profound with missing function	2
Not Tested	n/t

Describe the Cognitive or Behavioural Deficits You Observed Here:

_____

TOTAL SCORE: ___/10

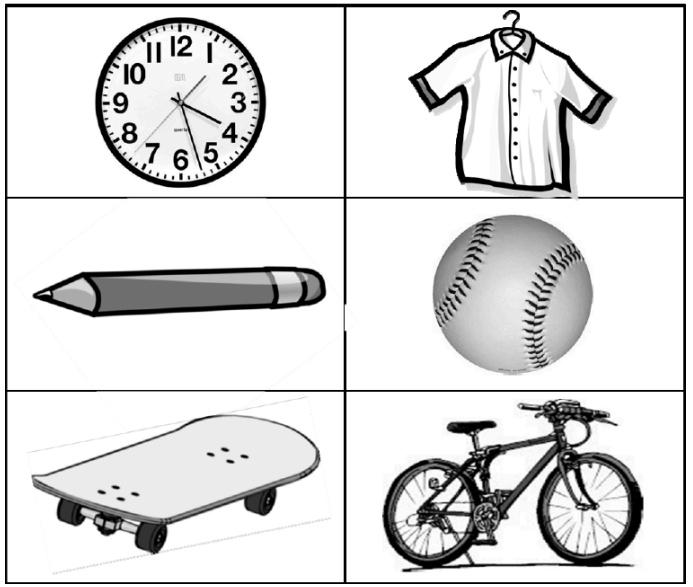
Severity	Total PSOM criteria
Normal	0-0.5 in all subdomains
Mild	1 in 1-2 subdomains and <1 in remaining subdomains
Moderate	1 in ≥3 subdomains OR 2 in 1 subdomain and <2 in all remaining subdomains
Severe	2 in ≥2 subdomains
Death	

Kitchen, et al Stroke 2012

Slim et al, Poster presentation, Child Neurology Society meeting 2018, Chicago, IL

Secondary Outcomes

- Clinical outcomes
  - Pediatric NIHSS (discharge, 3 months, 1 year)
  - Pediatric modified Rankin Scale (baseline, 3 months, 1 year)
  - Vineland Adaptive Behavior Scale II (1 year)
  - Death



- Imaging outcomes
  - % ischemic core growth
  - Vessel re-thrombosis
  - Recurrent stroke
  - Clinically significant hemorrhage (PH2)
  - Complications of the neurointerventional procedure (dissection, groin hematoma, lower limb ischemia, anesthesia-related complications)

Ichord et al Stroke 2011
Felling et al *in preparation*

Schedule of events

	Screening	Baseline	Enrollment	Endovascular Procedure	24 hours post (+/- 6 hours)	5 days post (+/- 24 hours) or prior to discharge	Day 5 or Hospital Discharge	Day 30* Phone call (+/- 7 days)	Day 90 (+/- 14 days)	1 year (+/- 2 months)
Screen Failure Log	X									
Informed Consent			X							
Subject Enrollment			X							
Inclusion and Exclusion Criteria		X								
MRI/MRA or CT/CTA		X			X++ Clinical scan	X++ DWI and FLAIR Research scan				Standard here
Medical History		X								
Vital Signs		X								
Lab Evaluation**		X				X				
Pediatric NIH Stroke Scale		X			X		X		X	X
Pediatric Modified Rankin Scale***		X					X	X	X	X
Pediatric Stroke Outcome Measure		X					X	X Clinic visit is desirable but not required	X	X
PedNIHSS/NIHSS		X					X		X	X
Vineland Behavioral Scale-II										X
Endovascular Therapy				X						
Adverse Event Assessment				X	X		X		X	X

*30 day follow-up can be performed by phone (clinic visit if feasible)

** CBC with Platelets, Creatinine, Glucose, INR, activated PTT, and Pregnancy test (if applicable).

***Modified Rankin Scale adapted for pediatric patients

++ Patients will preferably undergo a limited sequence, short MRI/MRA/MR Perfusion at 24 hours and MRI (DWI and FLAIR) at 5 days; if an MR cannot be performed safely, a CT +/- CTA can be substituted.

Statistical Design

- Estimate: 90 patients with satisfactory imaging who receive endovascular treatment will be needed based on the following assumptions:
  - Power of 88% to test the primary hypothesis
  - 60% of patients will have TMM profile (extrapolated from DEFUSE2/3 data, where TMM+ 50%)
  - 75% of patients will achieve successful reperfusion in both groups*
  - 37% difference in proportion of patients with favorable clinical outcome between TMM+ patients with and without reperfusion (67% vs 30%)**
  - No difference in the proportion of TMM- patients with and without reperfusion who have a favorable clinical response OR = 1 (conservative estimate based on DEFUSE2 data)