Childhood moyamoya

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Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study

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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

Clinical and Radiological Recurrence After Childhood Arterial Ischemic Stroke

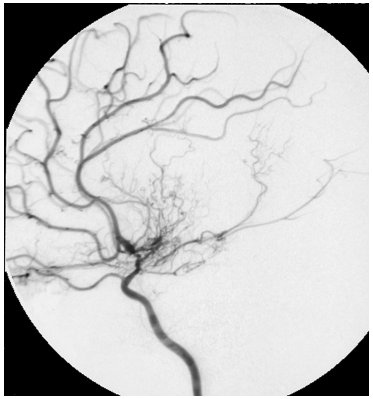
Vijeya Ganesan, MD; Mara Prengler, PhD; Angela Wade, PhD; Fenella J. Kirkham, MB, BCh

Background—Data on rates and risk factors for clinical and radiological recurrence of childhood arterial ischemic stroke (AIS) might inform secondary prevention strategies.

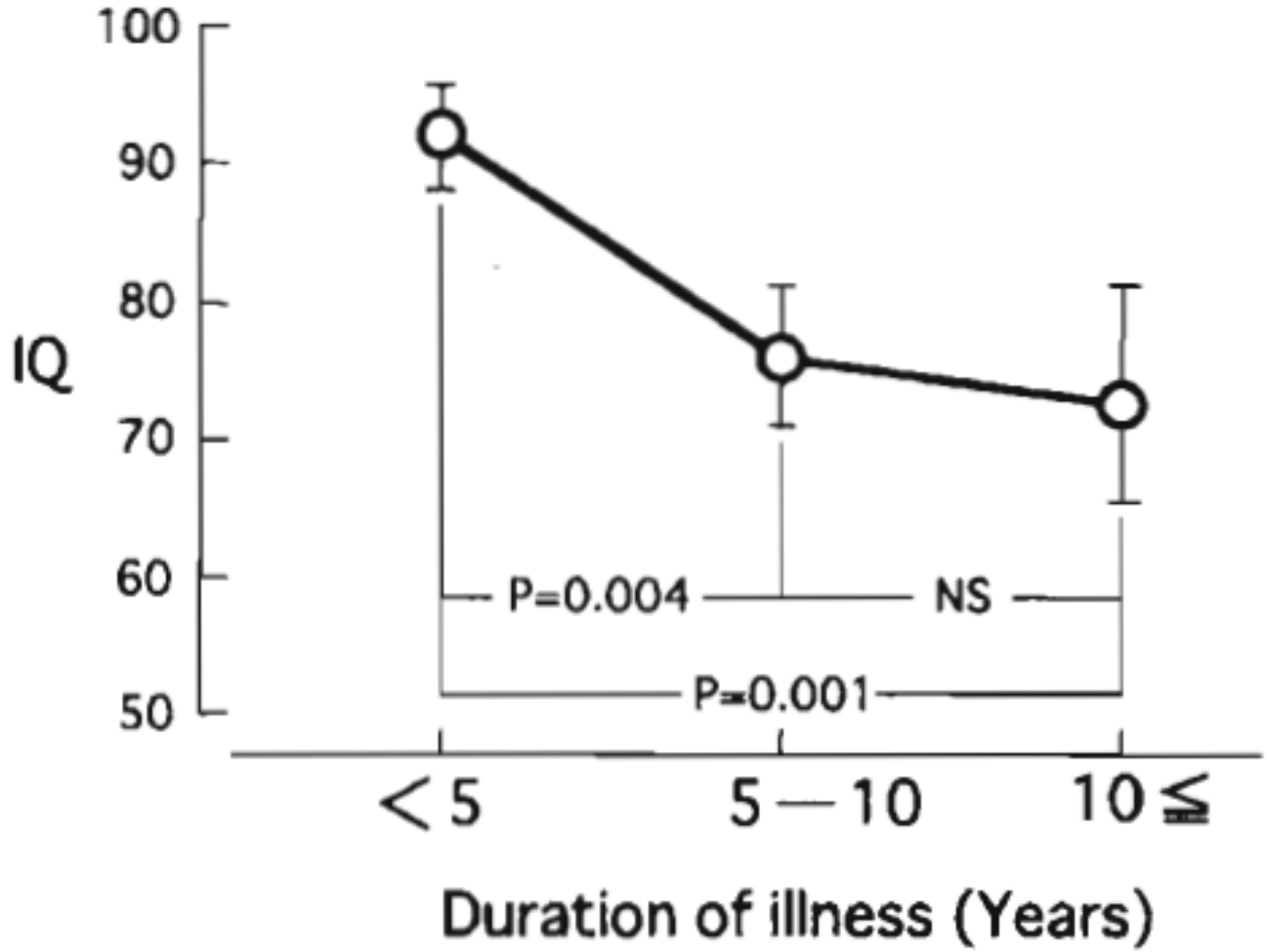
Methods and Results—Consecutive Great Ormond Street Hospital patients with first AIS were identified retrospectively (1978–1990) and prospectively (1990–2000). Patients underwent repeat neuroimaging at the time of clinical recurrence or, if asymptomatic, at least 1 year after AIS. Cox and logistic regression analyses were used to explore the relationships between risk factors and clinical and radiological recurrence, respectively. A total of 212 patients were identified, of whom 97 had another prior diagnosis. Seventy-nine children had a clinical recurrence (29 strokes, 46 transient ischemic attacks [TIAs], 4 deaths with reinfarction 1 day to 11.5 years (median 267 days) later); after 5 years, 59% (95% confidence interval, 51% to 67%) were recurrence free. Moyamoya on angiography and low birth weight were independently associated with clinical recurrence in the whole group. Genetic thrombophilia was associated with clinical recurrence in previously healthy patients, independent of the presence of moyamoya. Sixty of 179 patients who had repeat neuroimaging had radiological reinfarction, which was clinically silent in 20. Previous TIA, bilateral infarction, prior diagnosis (specifically immunodeficiency), and leukocytosis were independently associated with reinfarction. Previous TIA and leukocytosis were also independently associated with clinically silent reinfarction.

Conclusions—Clinical and radiological recurrence are common after childhood AIS. The risk of clinical recurrence is increased in children with moyamoya and, in previously healthy patients, in those with genetic thrombophilia. Preexisting pathology, including immunodeficiency, and persistent leukocytosis are risk factors for radiological recurrence, which suggests a potential role for chronic infection. (***Circulation***. **2006;114:2170-2177.**)

Moyamoya



- Most malignant radiological signature in AIS
- Commonest in E Asia
- May be idiopathic or secondary to both genetic & acquired conditions
- “Moyamoya” probably not single disease entity
- High rates of ischaemic brain injury, cognitive dysfunction & cerebral haemorrhage



Imazumi et al 1999

Intellectual ability and executive function in pediatric moyamoya vasculopathy

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AIM Moyamoya vasculopathy is characterized by progressive stenosis of the major arteries of the Circle of Willis, resulting in compromised cerebral blood flow and increased risk of stroke. The objectives of the current study were to examine intellectual and executive functioning of children with moyamoya and to evaluate the impact of moyamoya type, stroke (clinical or silent), vasculopathy laterality, and disease duration on neurocognitive abilities.

METHOD Thirty pediatric participants (mean age 10y 10mo, SD 4y; 18 females, 12 males) completed age-appropriate Wechsler Intelligence Scales before any therapeutic revascularization procedures. Reports of executive function were obtained from parents and teachers using the Behavior Rating Index of Executive Function.

RESULTS Children with moyamoya scored significantly lower than the test standardization samples on all indices of intelligence and ratings of executive functioning ($p<0.001$). Patients did not differ by type of moyamoya or history of stroke. Patients with bilateral disease and stroke scored significantly lower than those with unilateral disease on measures of overall intellectual function ($p=0.035$) and verbal comprehension ($p=0.04$). Deficits in metacognitive executive functions were also more pronounced in bilateral patients according to teacher ratings.

INTERPRETATION Children with moyamoya are at risk for intellectual and executive problems, exacerbated by bilateral disease and clinical stroke history.

ABSTRACT

Background and purpose Alteration of the cerebrovascular reserve (CVR) in the frontal lobes has been associated with cognitive dysfunction in adults with moyamoya disease (MMD). Elevation of the apparent diffusion coefficient (ADC) in normal-appearing white matter on conventional MRI may occur as a consequence of chronic haemodynamic failure. In the present study, the authors examined the relation of ADC with CVR and cognitive dysfunction in adults with MMD.

Methods The authors measured ADC and CVR in the normal-appearing frontal white matter. CVR was calculated using dynamic susceptibility contrast-enhanced MRI and the acetazolamide challenge. A standardised and validated neuropsychological assessment test battery focusing on executive function was used.

Results 14 patients, 9 women and 5 men (mean age 36.6±12.9 years), were included. The authors found executive dysfunction in 7 of 13 tested patients. ADC and CVR were negatively correlated (Spearman coefficient: −0.46; p=0.015). Elevation of ADC predicted executive dysfunction (area under receiver operating characteristic curve (95% CI): 0.85 (0.59 to 1.16); p=0.032).

Conclusion Elevation of ADC in the normal-appearing frontal white matter of adults with MMD was associated with reduced CVR and executive dysfunction. This preliminary study suggests that measurement of ADC might be used to detect patients at risk for cerebral ischaemia and cognitive impairment.

Executive dysfunction in adults with moyamoya disease is associated with increased diffusion in frontal white matter

Lionel Calviere,[1] Guillaume Ssi Yan Kai,[2] Isabelle Catalaa,[2] Fabienne Marlats,[1] Fabrice Bonneville,[2] V Larrue[1]

Moyamoya: histology

- Intimal thickening
- Media is thinned
- Tortuous internal elastic lamina

Moyamoya: genetics

- 9-15% cases familial in E Asia
- Likely heterogenous & multiple mechanisms
- Linkage to 5 loci: 3p24.2p26, 6q25, 8q23, 12p12 and 17q25
- RNF213 – founder effect in Asians
- NF1, trisomy 21 etc.

Paediatric stroke: genetic insights into disease mechanisms and treatment targets

Pinki Munot, Yanick J Crow, Vijeya Ganesan

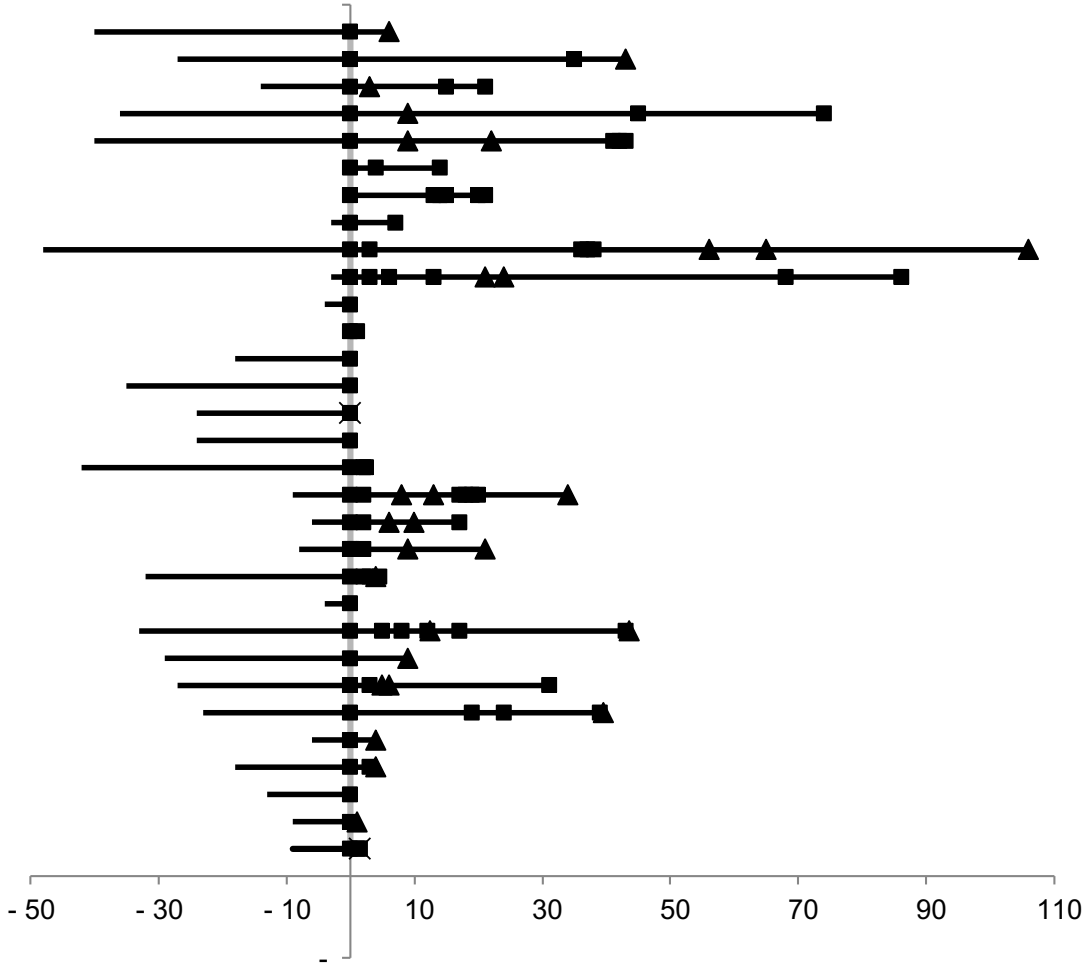
In children, stroke is as common as brain tumour and causes substantial mortality and long-term morbidity, with recurrence in up to 20%. There are three sets of international clinical guidelines relating to childhood stroke; however, acute and preventive treatment recommendations are based on interventions effective in adults, rather than data regarding efficacy in children. A wide spectrum of risk factors underlies childhood stroke, and these risk factors vary from those encountered in adults. Specific disease mechanisms implicated in childhood arterial ischaemic stroke have received little attention, but an increased understanding of disease pathogenesis could lead to novel targeted treatment approaches. Here, we consider insights into the pathogenesis of childhood arterial ischaemic stroke and cerebral arteriopathy, provided by current knowledge of Mendelian diseases that are associated with an increased risk of these conditions. We give particular attention to aspects of vascular development, homoeostasis, and response to environmental effects. Our analysis highlights a potential role for interventions already licensed for pharmaceutical use, as well as new therapeutic targets and avenues for further research.

Lancet Neurol 2011; 10: 264–74

Gene mutations associated with childhood cerebral arteriopathy	**Disease mechanisms implicated**
COL4A1	Abnormal vessel wall integrity
ABC6	
	Abnormal vascular homeostasis
ACTA2	- SMC proliferation
NF1	
ELN	
NOTCH3	- NOTCH signalling
JAG1	
HTRA1	- TGFB pathway
SAMHD1	- ?
Pericentrin	
	Abnormal response to vascular injury
	- infection
	- trauma
APT7A	- oxidative stress
GLUT10	
Homocystinuria	Vascular injury due to
GLA	accumulation of abnormal metabolites
CECR1	Differentiation from monocytes to macrophages

Defining disease causation

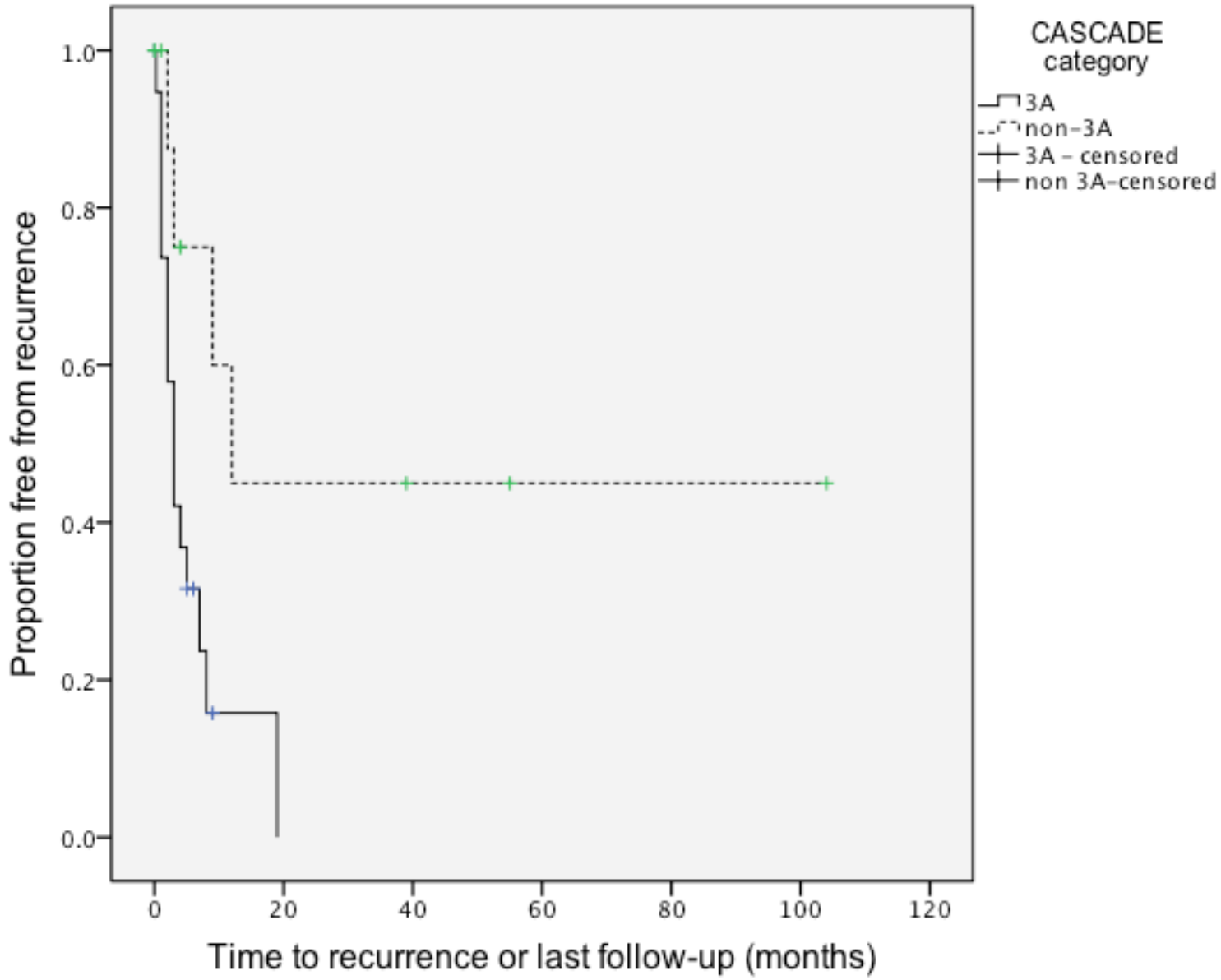
- Phenotypic characterisation is vital to defining and characterising homogenous disease entities & for genotype phenotype correlation
  - Clinical
    - Neurological
    - Cognitive
  - Biomarkers
    - Circulating
    - Radiological



Young onset = malignant disease course

Data from 31 children <5 with bilateral cerebral arteriopathies, showing time to recurrence (square boxes) relative to presentation.

Al-Yassin et al, (*Neurology*, in press)



Al-Yassin et al, (*Neurology*, in press)

ACTA2

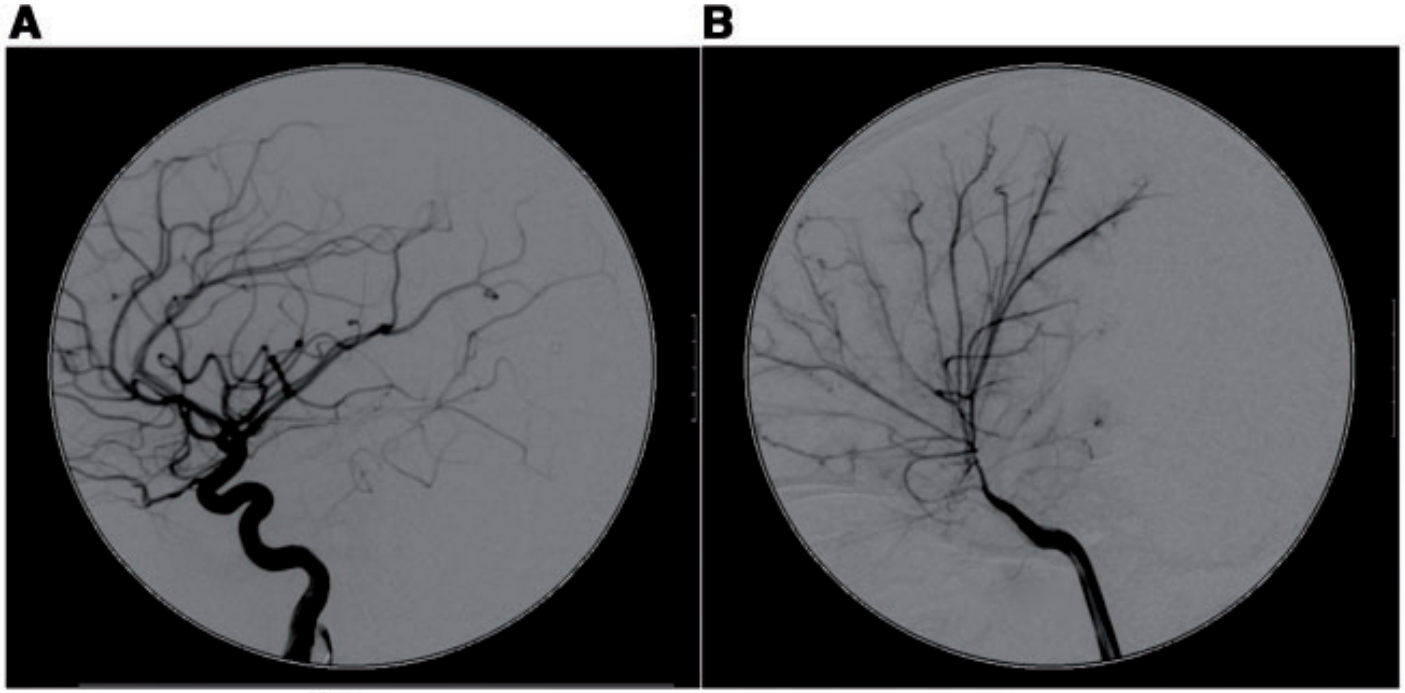
- Actin alpha 2 is major contractile protein in vascular smooth muscle
- Initial phenotype assoc. w mutations in *ACTA2* = thoracic aortic aneurysms and coronary artery disease
- Mutations lead to occlusive disease in elastin deficient vessels and aneurysms in large vessels
- R179 mutations said to be assoc. w “moyamoya”

doi:10.1093/brain/aws172 Brain 2012: 135; 2506–2514 | 2506

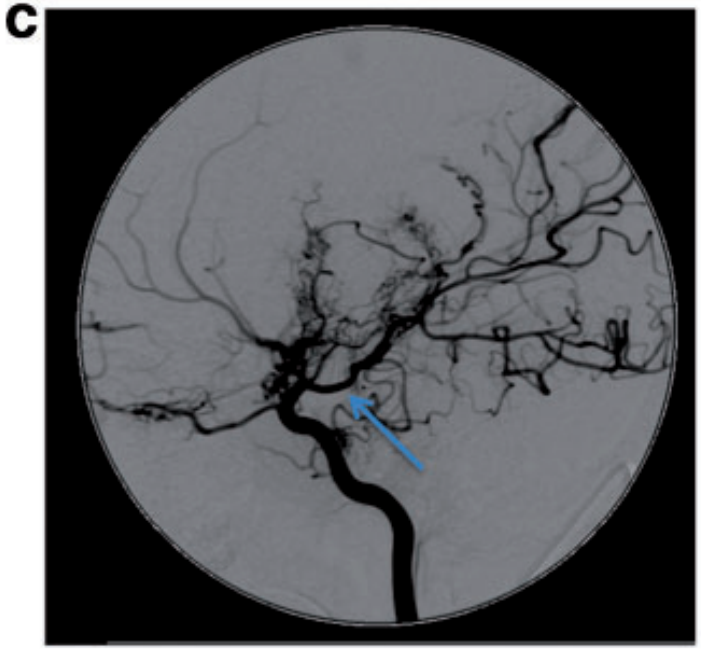
BRAIN
A JOURNAL OF NEUROLOGY

A novel distinctive cerebrovascular phenotype is associated with heterozygous Arg179 *ACTA2* mutations

Pinki Munot,[1] Dawn E. Saunders,[2] Dianna M. Milewicz,[3] Ellen S. Regalado,[3] John R. Ostergaard,[4] Kees P. Braun,[5] Timothy Kerr,[6] Klaske D. Lichtenbelt,[7] Sunny Philip,[8] Christopher Rittey,[9] Thomas S. Jacques,[10,11] Timothy C. Cox[2] and Vijeya Ganesan[1,12]

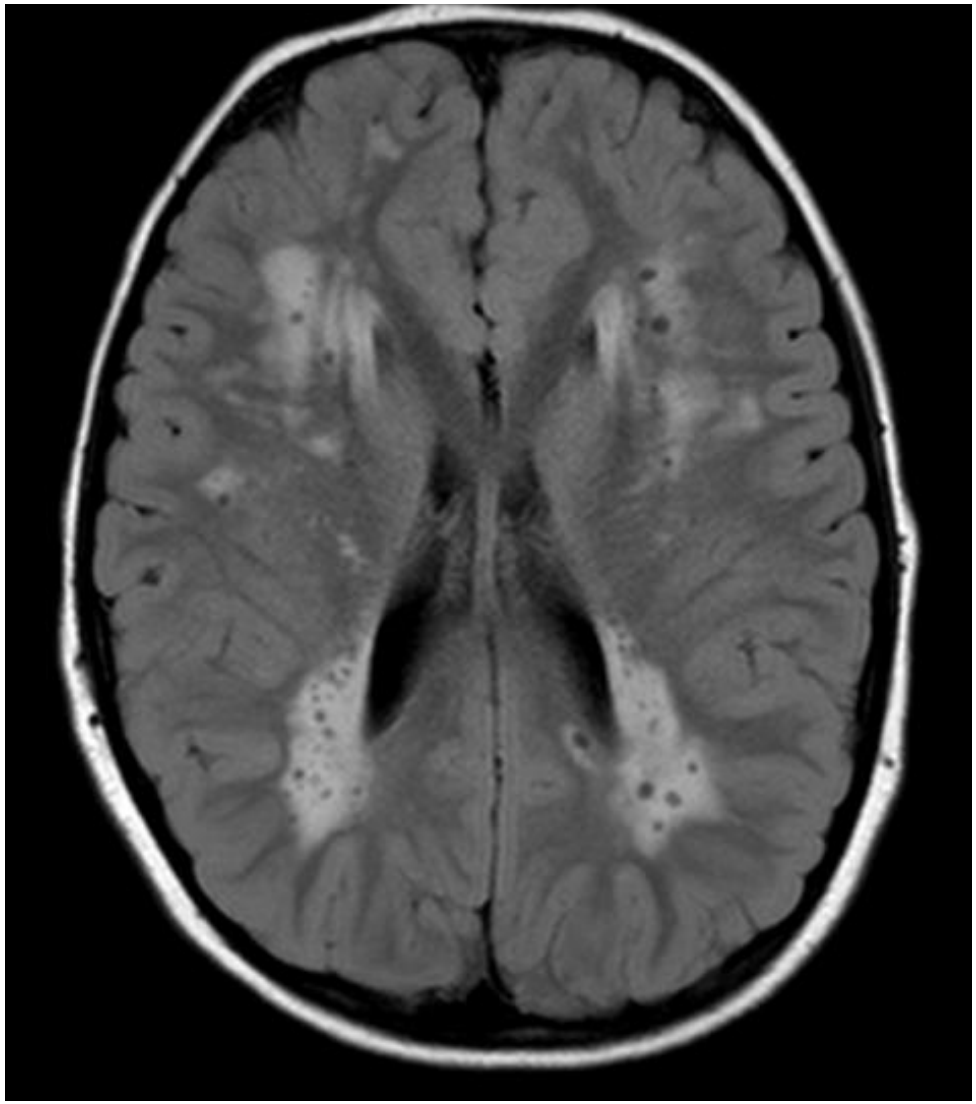


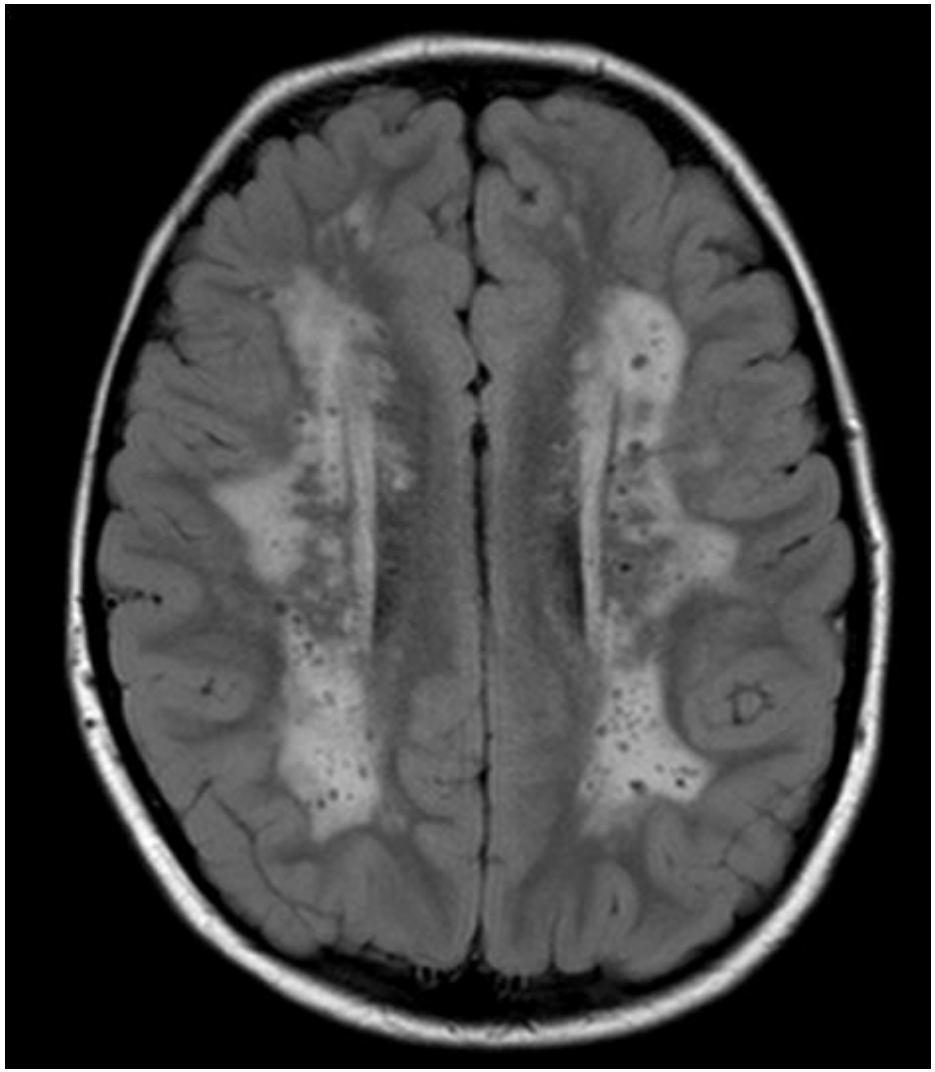
ACTA2 Arg179

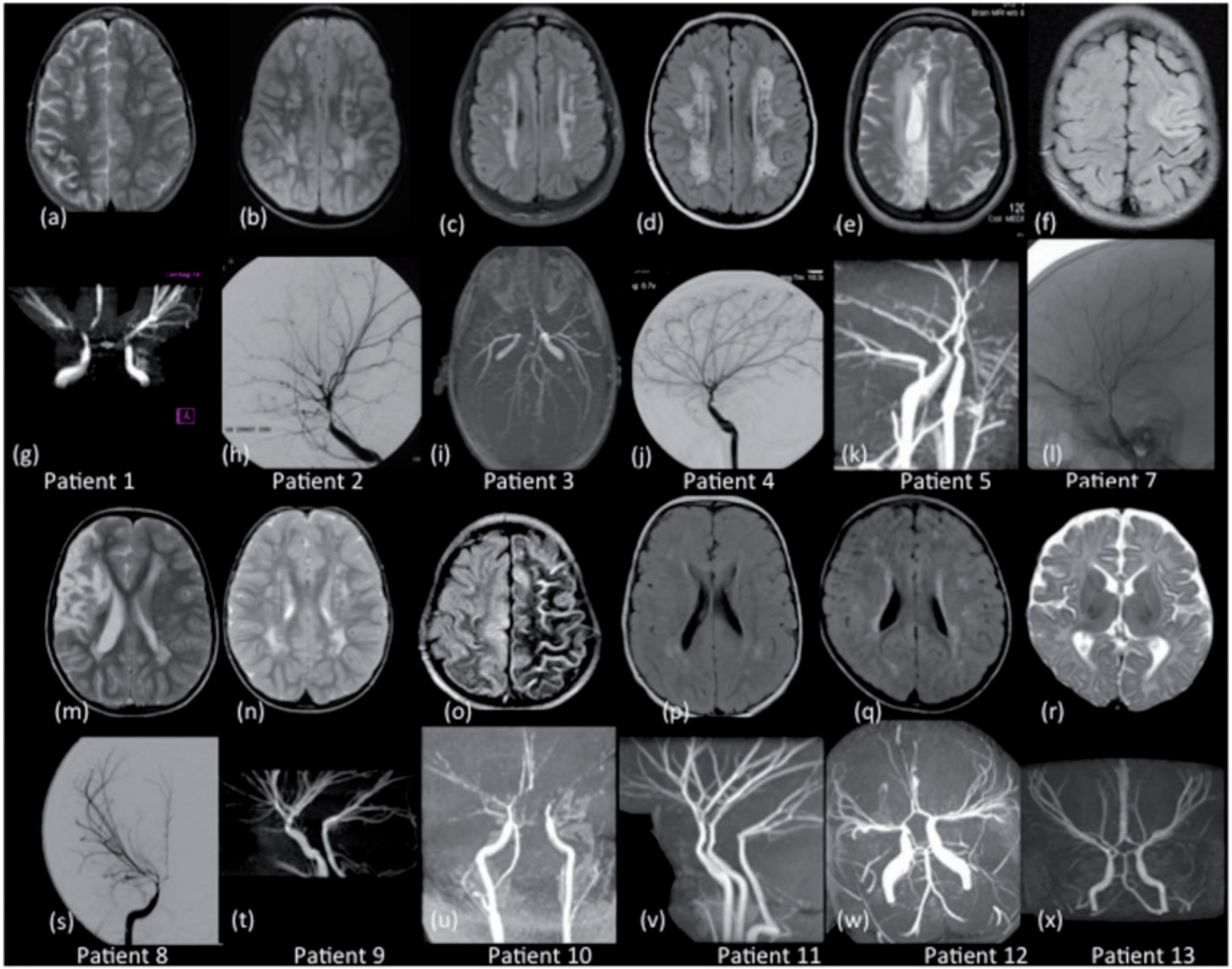


Moyamoya

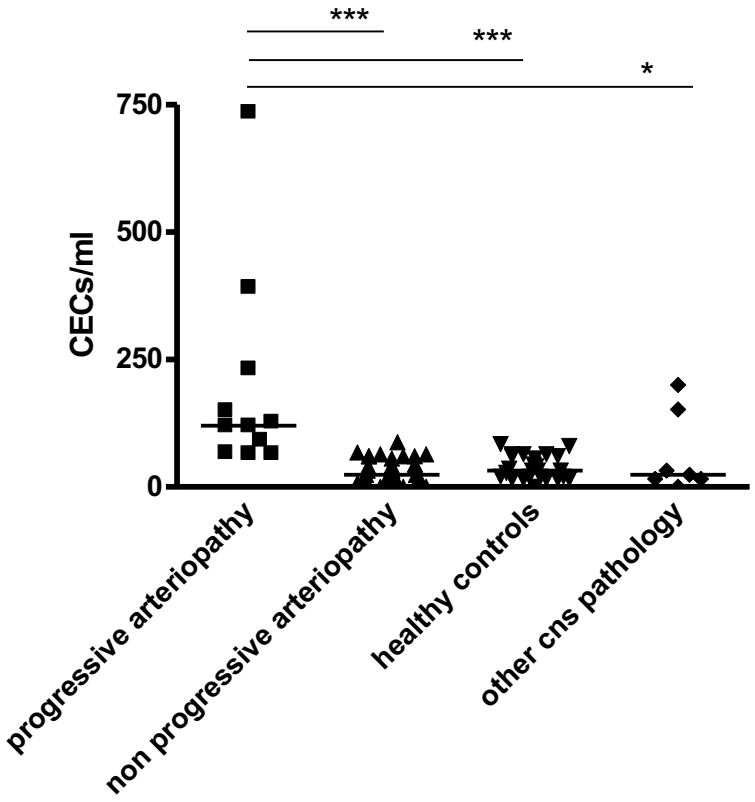
Munot et al 2013

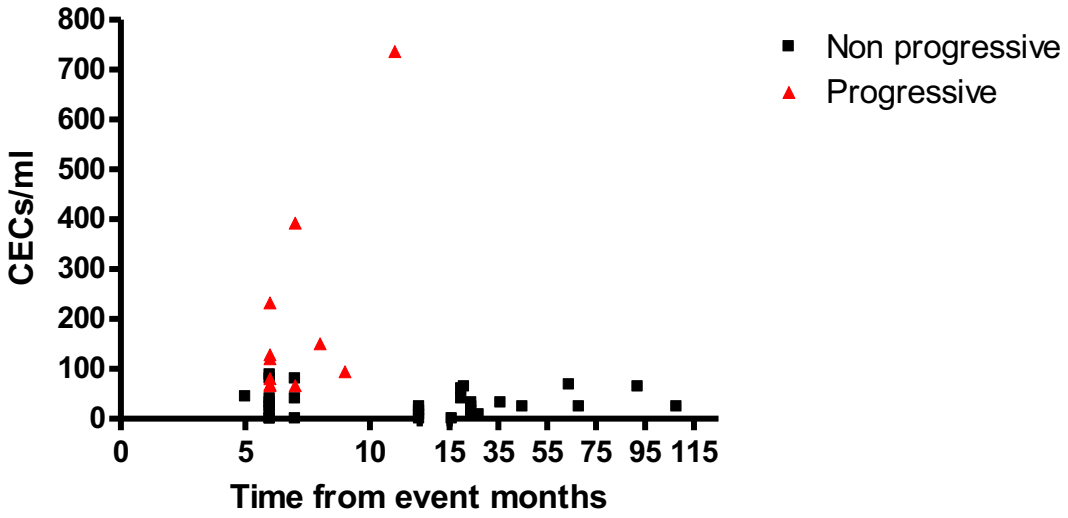





(a)
(b)
(c)
(d)
(e)
(f)
(g)
Patient 1
(h)
Patient 2
(i)
Patient 3
(j)
Patient 4
(k)
Patient 5
(l)
Patient 7
(m)
(n)
(o)
(p)
(q)
(r)
(s)
Patient 8
(t)
Patient 9
(u)
Patient 10
(v)
Patient 11
(w)
Patient 12
(x)
Patient 13

CECs detect ongoing endothelial injury in progressive cerebral arteriopathy





D Eleftheriou

Surgical revascularisation

- Direct vs. indirect
- Aim to provide alternate source of blood to the brain
- Indications unclear
- GOSH: established tendency to recurrence/progression
- Challenging populations: SCD, asymptomatic

AHA childhood stroke guidelines 2008

1. Different revascularization techniques are useful to effectively reduce the risk of stroke resulting from moyamoya disease (Class I, Level of Evidence B). However, despite a vast literature on moyamoya, there are no controlled clinical trials to guide the selection of therapy.

2. Indirect revascularization techniques are generally preferable and should be used in younger children whose small-caliber vessels make direct anastomosis difficult, whereas direct bypass techniques are preferable in older individuals (Class I, Level of Evidence C).

3. Revascularization surgery is useful for moyamoya (Class I, Level of Evidence B). Indications for revascularization surgery include progressive ischemic symptoms or evidence of inadequate blood flow or cerebral perfusion reserve in an individual without a contraindication to surgery (Class I, Level of Evidence B).

Table 1 Surgical outcomes

Outcomes	Indirect procedures	Direct procedures	Combined (direct and indirect procedures)	Surgical group as a whole
Clinical	*N*=669	*N*=9	*N*=56	*N*=1,156
Asymptomatic	379	1	24	592
Improvement	203	5	24	411
Static	74	2	4	122
Deterioration	13	1	4	31
Development	*N*=72			
Improve	20 (28)	–	–	
Static	38 (53)	–	–	
Deteriorate	14 (19)	–	–	
Quality of life	*N*=204	–	*N*=35	*N*=272
Independent	142 (70)	–	26 (74)	187
Partially dependent	45 (22)	–	8 (23)	64
Totally dependent	17(8)	–	1 (3)	21
Angiography	*N*=864	*N*=7	*N*=101	*N*=1,005
Good[a]	719	6	97	851
Poor[b]	145	1	4	135

Fung et al 2005

Table 2 Complication rates. *RIND* reversible ischemic neurological deficit, *TIA* transient ischaemic attacks

Complication	Combined[a] (*N*=89)	Indirect (*N*=327)	Surgical group as a whole (*N*=680)
Stroke	1 (1.1)	19 (5.8)	30 (4.4)
RIND	1 (1.1)	7 (2.1)	13 (2.4)
TIA	9 (10.1)	18 (5.5)	28 (3.7)
Seizures	0	4 (1.2)	7 (1.0)
Hemorrhage	0	5 (1.5)	12 (1.7)
Infection	0	1 (0.3)	1 (0.2)
Others	2 (2.2)	4 (1.2)	7 (1.0)

Fung et al 2005

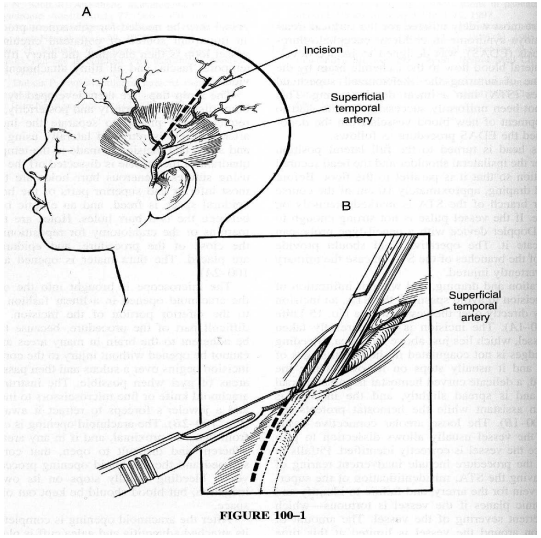


FIGURE 100–1

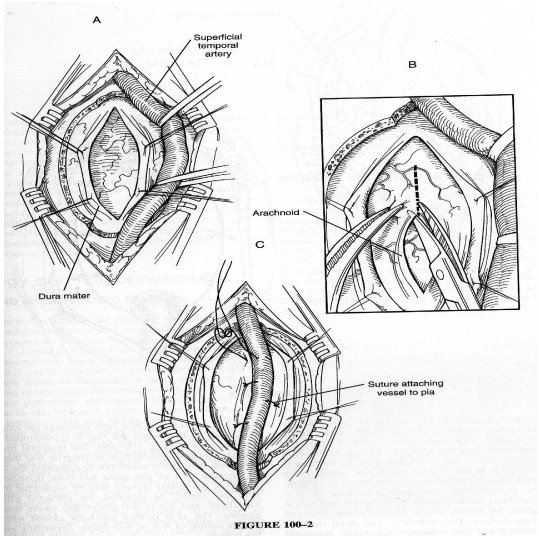
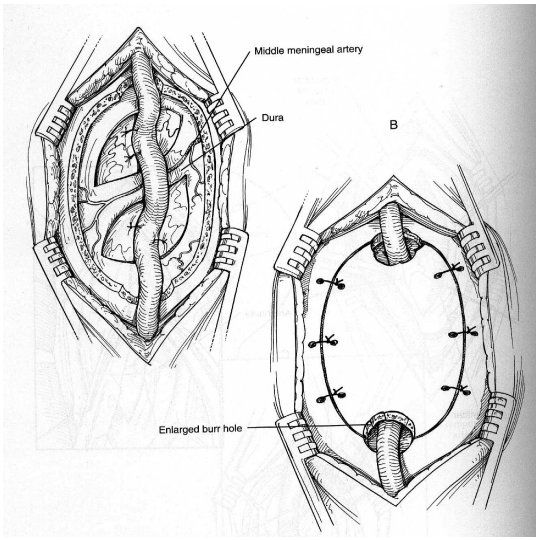
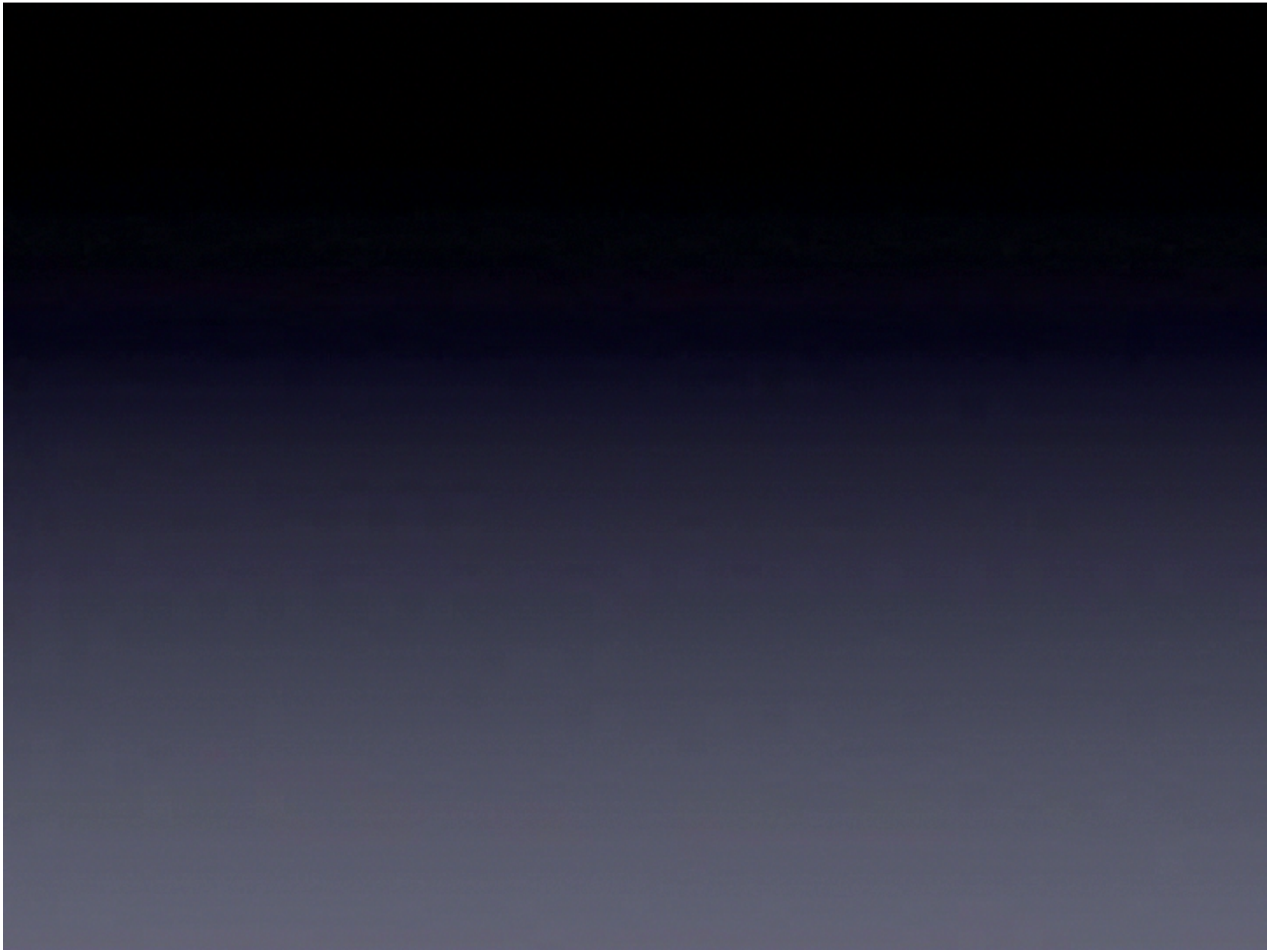
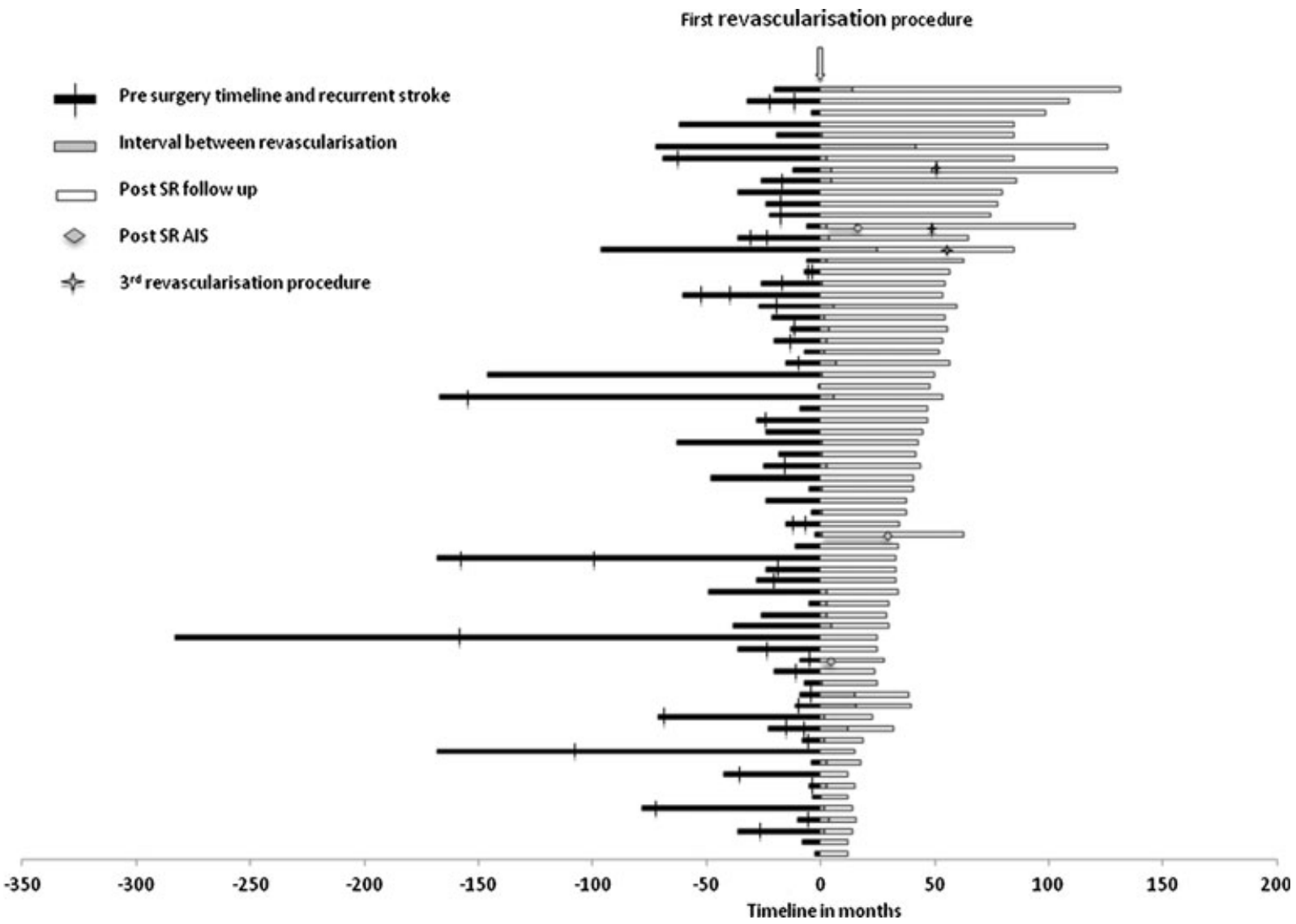


FIGURE 100–2



Pial synangiosis




First revascularisation procedure
Pre surgery timeline and recurrent stroke
Interval between revascularisation
Post SR follow up
Post SR AIS
3rd revascularisation procedure
-350
-300
-250
-200
-150
-100
-50
0
50
100
150
200
Timeline in months

Ng et al 2012

Table 4 Comparison of children with moyamoya revascularised in centres outside East Asia

Centre	Thompson Great Ormond Street Hospital	Steinberg Stanford University Hospital [20]	Scott Boston Children's Hospital [13]	Ibrahimi John Hopkins Hospital [21]	Yilmaz, Indiana [22]	Chui, Texas [23]	Khan, Europe [24]	Darwish, Sydney [25]
No. of patients (age range, years)	73 (0.6–14.5)	96 (1–17.9)	143 (0.5-21)	14 (0.1–13.9)	7 (under 18)	13 (1–18)	20 (1–18)	16
No. of initial procedures	131	168	271	23	31	17	38 total (no. in children only not available)	21
Direct (%)	37.6	76.2	0	0	6.4	27	100	57
Indirect (%)	62.4	23.8	100	87	93.6	63	0	43
Combined (%)	0	0	0	13 (STA + EDAMS)	0	0	0	0
Moyamoya disease (%)	61.6	83	46	57.1	–	–	6	56.2
Moyamoya syndrome (%)	38.4	17	54	43.9	–	–	40	44.8
Post-operative <30 days	AIS—0; TIA—8.2 %	AIS—2 %; haemorrhage—1 %	AIS—7.7 %; TIA—3 %	AIS—0	AIS—13 %	–	0	–
Mortality	0	2	2	0	13 %	0	–	–
Post-operative stroke <1 year	2.8 %	–	–	–	–	–	–	–
Post-operative stroke >1 year	1.4 % (1 silent)	1.4 %	3.1 %		6.4 %			
Post-operative stroke >5 years	0	–	4.3 %	–	–	–	–	–
TIA	Decrease or resolution in 79.2 % at last follow-up	93 % TIA free at >1 year	Decrease	–	–	–	Resolution or decrease at in 36 out of 38 both adults + children at 3 months follow-up	10 out of 13 still experience TIA at 1 year

Abstract

Background: Clinical research on moyamoya disease (MMD) has focused on symptomatic outcome such as transient ischemic attacks. Neurocognitive function in children critically affects social outcome and is closely related to quality of life. This study is the first to analyze the neurocognitive profiles of children with MMD before and after surgery. ***Methods:*** Sixty-five patients were selected out of 137 who underwent surgery for MMD between 2006 and 2008. The preoperative and postoperative neurocognitive function was tested using the Korean version of the Wechsler Intelligence Scale for Children-Revised (KEDI-WISC-R) and the Bender Gestalt Test (BGT). Pre- and postoperative profiles of patients with or without major infarctions were compared. Patients with borderzone infarctions were analyzed as well. ***Results:*** Preoperatively, patients had age-appropriate full-scale intelligence quotient (FSIQ) and verbal IQ (VIQ) scores, which were maintained after surgery. There was significant improvement in performance IQ (PIQ) ($p = 0.01$) and BGT scores postoperatively ($p < 0.01$). Among the subtests, Coding showed significant improvement postoperatively ($p < 0.01$). Preoperatively, patients with major infarctions had significantly lower FSIQ ($p < 0.01$), VIQ ($p = 0.01$) and PIQ ($p < 0.01$) scores compared with those without infarctions. The pre- and postoperative neurocognitive profiles of the patients with borderzone infarctions fell between those of patients with absolutely no infarctions and those of patients with major infarctions. ***Conclusions:*** Considering the natural history of MMD, which leads to a drastic decline in neurocognitive functions, the present findings indicate a role for early active surgery to save the intellectual abilities of children with MMD.

Neurocognitive Profiles of Children with Moyamoya Disease before and after Surgical Intervention

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Min-Sup Shin[b] Seung-Ki Kim[a]

[a]Division of Pediatric Neurosurgery and [b]Department of Psychiatry and Behavioral Science, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

National paediatric moyamoya registry

- National study w 23 sites
- Aim to identify all UK paediatric MM 2004-2014
- Mostly non-Asian patients
- Reduce referral bias
- Clinical interview to ascertain presentation & disease course
- Centralised imaging review

National paediatric moyamoya registry

- 94 patients reported; 88 consented and verified
- 71 from GOSH
- 55 treated w surgery
- Good outcome (mRS & school type) in 39

Prognostic predictors- Multivariable analysis

Predictor	Odds ratio (95% CI)	p value
Initial presentation		
AIS (baseline)	1 (odds= 5.6)	-
TIA	**0.09 (0.02-0.35)**	**0.001**
Cerebral haemorrhage	257148282 (0)	1.000
Seizure	0.50 (0.04-6.56)	0.593
Headache	**0.10 (0.02-0.58)**	**0.010**
Chorea	0 (0)	0.999
Other	**0.08 (0.01-0.68)**	**0.021**
Posterior cerebral circulation involvement	**4.22 (1.23-15.53)**	**0.022**
Moyamoya risk factor*	2.45 (0.64-9.36)	0.189
*risk factors include Down's syndrome, neurofibromatosis type I, sickle cell disease and cranial radiotherapy/proton beam therapy		

Surgery <u>not</u> predictive of prognosis

Conclusions

- “Moyamoya” probably encompasses a range of pathologies, including distinctive genetic disorders
- Natural history is variable
- Completed stroke is rare after surgery
- Surgical selection criteria remain undefined