Prof. Adam Kirton – University of Calgary, Canada

Pediatric Stroke

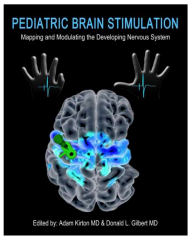
Cerebrovascular Injury in the Developing Brain

Prof. Adam Kirton, MD MSc FRCPC
Professor of Pediatrics, Radiology
Clinical Neurosciences
University of Calgary, Canada

1

Disclosures

- Brain stimulation is experimental
- Therapeutic applications off label
- Editor, *Pediatric Brain Stimulation*
- Boards and Scientific Advisory: HSFA, ICNA, BBC, CSBPG, CB
- Funding: CIHR, AIHS, HSFC, HSFA, CPRA, CPIRF, HBI, CSOM, VRPRI, NDN



2

Learning objectives

Recognize the presentations, causes, and management of stroke in neonates and children

Appreciate the role of developmental neuroplasticity in determining the diverse range outcomes that occur

3

Prof. Adam Kirton – University of Calgary, Canada

Strokes can happen at any age

Pediatric strokes can occur in infants, children, and even before birth

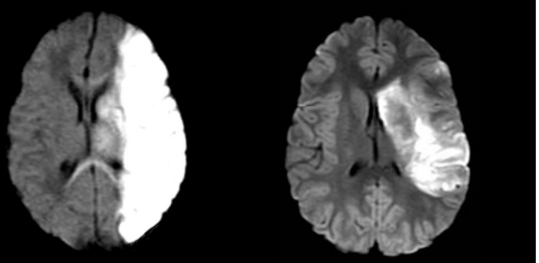
Perinatal stroke
Last few months of pregnancy to 1-month-old

Childhood stroke
1-month-old to 18 years

Last few months of pregnancy | 1-month-old | 18 years

4

Diffusion MRIs of young stroke patients



1-day-old | 12-year-old

5

"Pressing issues and promising directions"

Paediatric stroke: pressing issues and promising directions

Adam Kirton, Gabrielle deVeber — *Lancet Neurol* 2015; 14: 92-102

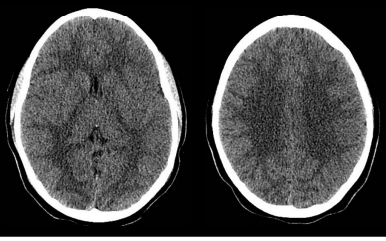
- Acute treatment dilemmas in childhood stroke
- Advances in childhood cerebral arteriopathy
- Neurorehabilitation: harnessing the plasticity of the developing brain
- Perinatal stroke: searching for disease biology
- Neonatal CSVT: diagnostic challenges in a treatable disease
- Translating knowledge: patients, parents, policy makers

6

Prof. Adam Kirton – University of Calgary, Canada

Example: 9-year-old

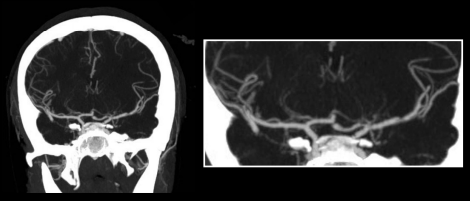
- 9-year-old girl
- Collapsed, weakness on her right side, drowsy, trouble speaking
- According to acute stroke protocol, she immediately went to CT scanning



7

Example: 9-year-old

- CT angiogram - acute ischemic stroke in the left MCA territory
- Treatment: inter-venous tPA and considered for interventional therapy (used in adults but it's still experimental in children)



Acute intervention in ischemic stroke

TIME IS BRAIN

8

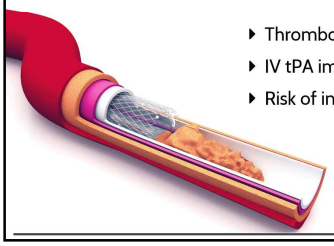
Prof. Adam Kirton – University of Calgary, Canada

Acute intervention in ischemic stroke

Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study

Catherine Amlie-Lefond, Gabrielle deVeber, Anthony K Chan, Susan Benedict, Timothy Bernard, Jessica Carpenter, Michael M Dowling, Heather Fullerton, Collin Hovinga, Adam Kirton, Warren Lo, Khaled Zamel, Rebecca Ichord, for the International Pediatric Stroke Study

Lancet Neurol 2009; 8: 530–36



- Thrombolysis is adult standard
- IV tPA improves outcomes (NNT ~6)
- Risk of intracerebral bleeding: 2-8%

Thrombolysis in Pediatric Stroke

Thrombolysis in Pediatric Stroke
…it's about time

International Paediatric Stroke Study
TIPS Trial

- Dose escalation safety trial
- Children 2-18 with severe stroke
- IV tPA within 4.5 hours

9

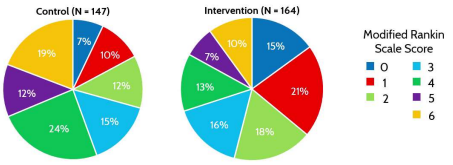
The ESCAPE trial

ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, T.G. Jovin, R.A. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, N.R. Kamal, W.J. Montanera, A.Y. Poppe, K.J. Ryckborst, F.L. Silver, A. Shuaib, D. Tampieri, D. Williams, O.Y. Bang, B.W. Baxter, P.A. Burns, H. Choe, J.-H. Heo, C.A. Holmstedt, B. Jankowitz, M. Kelly, G. Linares, J.L. Mandzia, J. Shankar, S.-I. Sohn, R.H. Swartz, P.A. Barber, S.B. Coutts, E.E. Smith, W.F. Morrish, A. Weill, S. Subramaniam, A.P. Mitha, J.H. Wong, M.W. Lowerison, T.T. Sajobi, and M.D. Hill for the ESCAPE Trial Investigators*

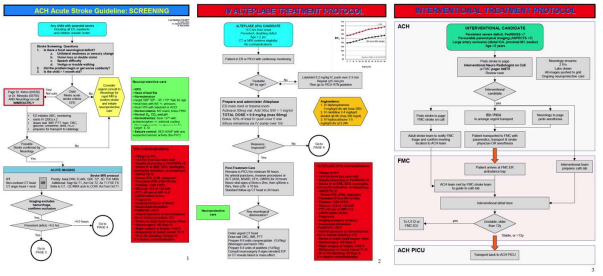
N ENGL J MED 372;11 NEJM.ORG MARCH 12, 2015



10

Prof. Adam Kirton – University of Calgary, Canada

Protocol for children presenting with acute stroke

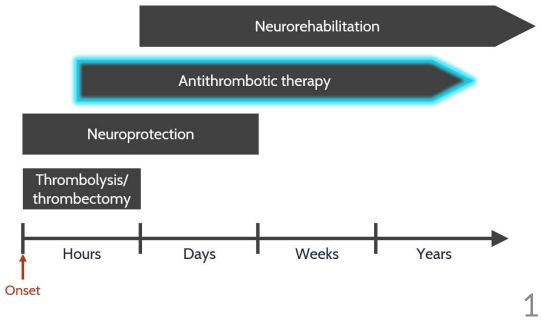


- Acute care pathways are being defined for children with stroke

11

See 'Links' tab for access

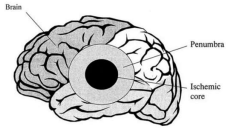
Stroke treatment timeline



12

Neuroprotection

- Airway and Breathing
- Circulation - CPP = MAP - ICP
- Sedation - minimize CMRO2
- Seizures - control, monitor
- Temperature - euthermia
- Infection - find and Tx
- Glucose - euglycemia
- ICP - medical, surgery



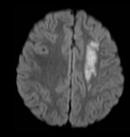
Hutchison *et al., Seminars in pediatric Neurology* . 2004;11:139–146

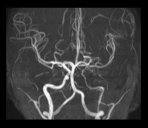
13

Prof. Adam Kirton – University of Calgary, Canada

Neuroprotection: 5-year-old

- 5-year-old boy
- Mild hemiparesis and unusual headache
- MRI - ischemic injury in the white matter, MRA - drop of flow in the internal carotid and middle cerebral arteries
- After 1 hour - completely hemiplegic and lost his ability to speak
- Treated according to principles of neuroprotection and fully recovered





14

Guidelines for childhood stroke

- Minimal evidence
- Moderate consensus

RCPCH Stroke association

Key recommendations for childhood stroke

NICE accredited

The Diagnosis and Acute Management of Childhood Stroke

CLINICAL GUIDELINE 2017

Antithrombotic Therapy in Neonates and Children*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

AHA Scientific Statement

Management of Stroke in Infants and Children

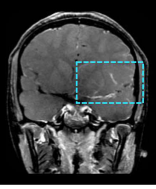
A Scientific Statement From a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young

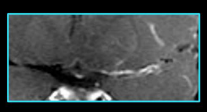
15

See '**Links**' tab for access

Example: 5-year-old with stroke

- 5-year-old boy
- MRI - big acute stroke in the left middle cerebral artery territory, MRA - drop of flow in the left internal carotid artery
- MRI with gadolinium demonstrated the sick arteries ICA and MCA which may be vasculitis disorder of these large arteries in the brain





16

Prof. Adam Kirton – University of Calgary, Canada

Steroids in acute Focal Cerebral Arteriopathy (FCA)

- Focal Cerebral Arteriopathy
  - General term
  - Exact mechanism unknown
  - 'Primary angiitis of the CNS'
  - 'Transient cerebral arteriopathy'
  - Postvaricella vasculopathy
- In an acute case presenting with inflammation, should we treat with anti-inflammatory drugs, specifically steroids?

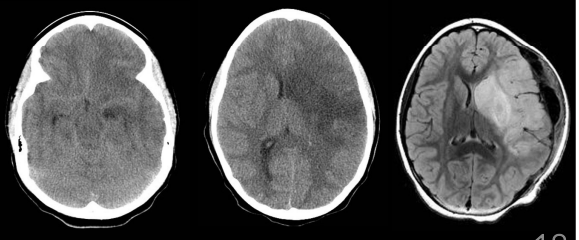
17

Steroids in acute Focal Cerebral Arteriopathy (FCA)

Risk	*vs.*	Benefit
Risk of serious steroid toxicity = low		Probably inflammation
Active infection unlikely		High risk of progression with increased morbidity and mortality
		Higher BP may help perfusion
		Steroids don't worsen outcomes in adult stroke
		Weak evidence safe, beneficial

Example of child that developed malignant cerebral edema

- Child - didn't receive steroids developed malignant cerebral edema

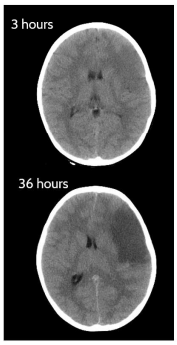


18

Prof. Adam Kirton – University of Calgary, Canada

Malignant cerebral edema

- 1-10% supra-tentorial strokes
- Swelling max at 36-72 hrs (1/3 < 24 hrs)
- ↑ brain : skull ratio in children
- Herniation syndromes
- 80% mortality in adults
- Treatment?



Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials

Katayoun Vahedi, Jeannette Hofmeijer, Eric Juettler, Eric Vicaut, Bernard George, Ale Algra, G Johan Amelink, Peter Schmiedek, Stefan Schwab, Peter M Rothwell, Marie-Germaine Bousser, H Bart van der Worp, Werner Hacke, for the DECIMAL, DESTINY, and HAMLET investigators

Lancet Neurol 2007; 6: 215–22

19

Epidemiology of AIS

- AIS has been fairly well-defined:

Cerebrovascular Disorders in Children

John Kylan Lynch, DO, MPH

Current Neurology and Neuroscience Reports 2004, 4:129–138

- 5 per 100,000 children per year
  - *E.g.* ~ 1 case per month in the city of Calgary

20

Clinical presentation of AIS

- Any *sudden* neurological deficit
- Maximal at onset
- TIA has occurred in ~33%
- Confounders more common in kids
- Complicated differential diagnosis

Mimics of Childhood Stroke: Characteristics of a Prospective Cohort

Renée A. Shellhaas, MD, Sabrina E. Smith, MD, PhD, Erin O'Tool, BS, Daniel J. Licht, MD, Rebecca N. Ichord, MD

PEDIATRICS Volume 118, Number 2, August 2006

21

Prof. Adam Kirton – University of Calgary, Canada

Pediatric AIS: etiology and risk factors

- Smoking, diabetes, hypertension, atherosclerosis, atrial fibrillation are NOT risk factors for pediatric AIS
- Vasculitic/inflammatory (20–30%)
- Cardiac (25%)
- Prothrombotic (10–20%)
- Traumatic (10–20%)
- Hematological (10–20%)
- Congenital/structural (10–20%)
- Other: migranous, metabolics, drugs
- Idiopathic in >20%

Majority will have multiple risk factors

22

Arteriopathy is the main cause of stroke

Prevalence of Risk Factors by Age at Time of AIS

Risk Factor Category	<5 Years	5–9 Years	10–14 Years	15–18 Years	p^*
Arteriopathy	106/229 (46%)	82/125 (66%)	57/106 (54%)	32/65 (49%)	0.006
Cardiac disorders	115/317 (36%)	39/141 (28%)	26/129 (20%)	24/80 (30%)	0.007
Chronic systemic conditions	49/321 (15%)	34/144 (24%)	26/129 (20%)	17/80 (21%)	0.15
Prothrombotic states	36/321 (11%)	16/144 (11%)	23/129 (18%)	12/80 (15%)	0.23
Acute systemic conditions	94/308 (31%)	25/142 (18%)	22/129 (17%)	7/79 (9%)	<0.0001
Chronic head and neck disorders	10/318 (3%)	17/142 (12%)	28/128 (22%)	12/79 (15%)	<0.0001
Acute head and neck disorders	81/306 (26%)	33/139 (24%)	19/124 (15%)	15/79 (19%)	0.07
Infection	72/321 (22%)	23/144 (16%)	24/130 (18%)	8/81 (10%)	0.05
At least 1 RF present	191/214 (89%)	110/118 (93%)	81/98 (83%)	59/63 (94%)	0.05

*Chi-square p value to test whether the proportion of children with each risk factor is independent of age group. RFs for atherosclerosis in adulthood were not included because they were recorded in few patients. Other RFs were not included because this category combines a range of risk factors.
AIS = arterial ischemic stroke; RF = risk factor.

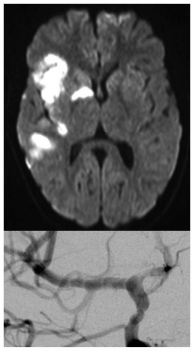
Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study

Mark T. Mackay, MBBS,[1] Max Wiznitzer, MD,[2] Susan L. Benedict, MD,[3] 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

ANN NEUROL 2011;69:130–140

23

Childhood cerebral arteriopathies



- Infection/inflammation?
  - Transient cerebral arteriopathy (TCA)
  - Focal cerebral arteriopathy (FCA)
  - Childhood primary angiitis of the CNS (cPACNS)
  - Post-varicella angiopathy (PVAR)
- Dissection
- Moyamoya
- Sickle cell
- Congenital/genetic

24

Prof. Adam Kirton – University of Calgary, Canada

The VIPS study

Infection, vaccination, and childhood arterial ischemic stroke

Results of the VIPS study

Heather J. Fullerton, MD, MAS; Nancy K. Hills, PhD; Mitchell S.V. Elkind, MD, MS; Michael M. Dowling, MD, PhD; Max Wintermark, MD; Carol A. Glaser, DVM, MD; Marilyn Tan, MD; Michael J. Rivkin, MD; Luigi Titomanlio, MD, PhD; A. James Barkovich, MD; Gabrielle A. deVeber,MD, MSc
On behalf of the VIPS Investigators

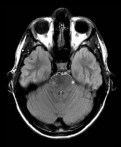
Neurology® 2015;85:1459–1466

- VIPS: Vascular Effects of Infection in Pediatric Stroke
- n=355
- Recent infection = 6.3-fold AIS risk
- Similar across stroke subtypes
- Vaccination = LOWER risk (OR 7.3)

25

Example: 15-year-old

- 15-year-old boy collapsed
- Decreased level of conciseness, multiple brainstem abnormalities
- MRA - occlusion of the distal basilar artery with signs of dissection
- MRI - small strokes throughout the posterior circulation
- Treatment: heparin, fully recovered



26

Arterial tortuosity as an imaging biomarker

Arterial Tortuosity: An Imaging Biomarker of Childhood Stroke Pathogenesis?

Felix Wei, Karl T. Diedrich, Heather J. Fullerton, Gabrielle deVeber, Max Wintermark, Jacquie Hodge, Adam Kirton ✉ and the Vascular Effects of Infection in Pediatric Stroke (VIPS) Investigators, MM Dowling, SL Benedict, TJ Bernard, CK Fox, NR Friedman, WD Lo, RN Ichord, MA Tan, MT Mackay, Chavez MI Hernandez, P Humphreys, LC Jordan, SM Sultan ... See all authors

Originally published 22 Mar 2016 | https://doi.org/10.1161/STROKEAHA.115.011331 | Stroke. 2016;47:1265–1270

- Kids with dissection and kids with FCA have higher arterial tortuosity
- The way arteries are built, and their structural integrity may be associated with the risk for stroke
- Tortuosity - an imaging biomarker

27

Prof. Adam Kirton – University of Calgary, Canada

Sickle-cell disease: primary and secondary prevention

- Trials conducted:
  - STOP trials
  - SWiTCH trial
  - TWiTCH trial
  - Small vessel trial
- Preventing stroke:
  - Transcranial Doppler (TCD)
  - Transfusion therapy

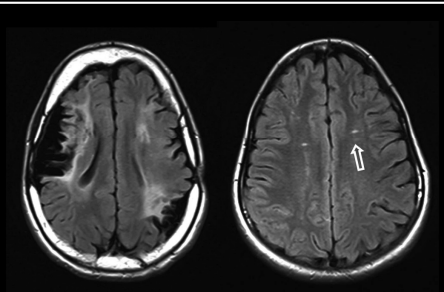
28

Example: 9-year-old

- 9-year-old girl with acute stroke and fever - endocarditis

29

Example: brother and sister

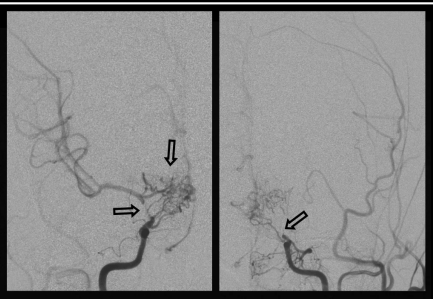


- Family history of moyamoya disease - slowly progressive disease

30

Prof. Adam Kirton – University of Calgary, Canada

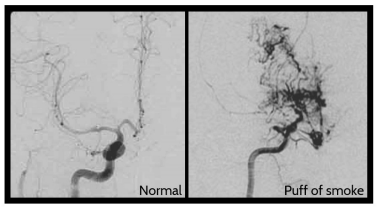
Example: brother and sister



- Family history of moyamoya disease - slowly progressive disease
- Treatable with revascularization surgery procedures

Moyamoya disease

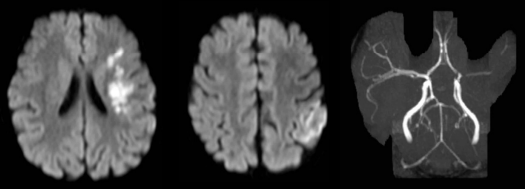
- Progressive ICA occlusion
- SCD, NF1, T21, R/T
- TIA's with crying or HV
- Stroke: Ischemic or bleed
- Treatments
  - Medical
  - Surgical



31

Example: 5-year-old with dwarfism

- Sudden onset right-sided weakness and dysphasia

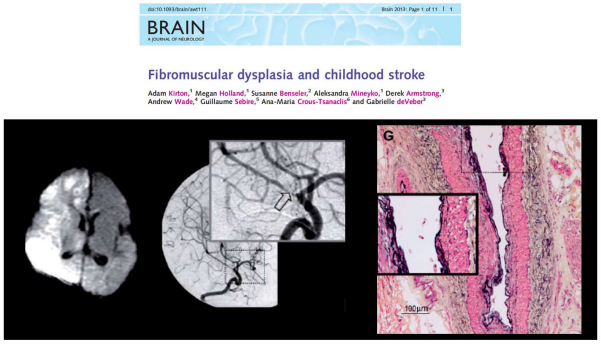


32

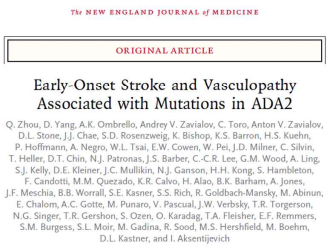
Prof. Adam Kirton – University of Calgary, Canada

Fibromuscular dysplasia in children

33



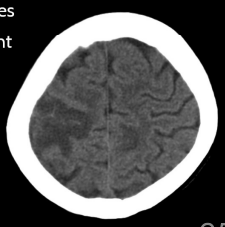
ADA2 can cause recurrent small strokes in children



34

Example: 12-year-old

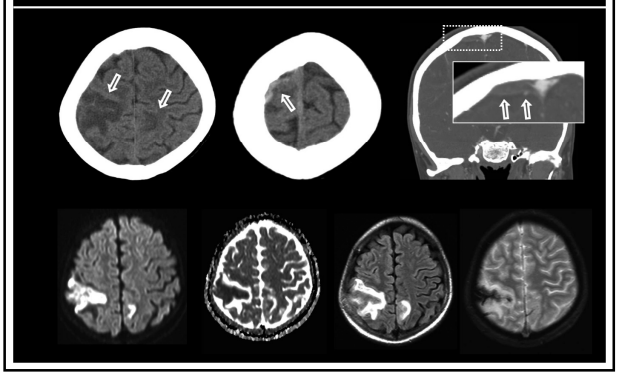
- 12-year-old boy with inflammatory bowel disease, on steroids, bloody diarrhea, and iron-deficient
- Left side weakness, and new headaches
- CT scan - hypodense infarct in the right and left hemisphere



35

Prof. Adam Kirton – University of Calgary, Canada

Example: 12-year-old



Cerebral sinovenous thrombosis (CSVT) in children

CEREBRAL SINOVENOUS THROMBOSIS IN CHILDREN

GABRIELLE DEVEBER, M.D., MAUREEN ANDREW, M.D., COLEEN ADAMS, M.B., BRUCE BJORNSON, M.D., FRANCES BOOTH, M.D., DAVID J. BUCKLEY, M.B., CH.B., CAROL S. CAMFIELD, M.D., MICHÈLE DAVID, M.D., PETER HUMPHREYS, M.D., PIERRE LANGEVIN, M.D., E. ATHEN MACDONALD, M.D., AND JANE GILLETT, M.D., FOR THE CANADIAN PEDIATRIC ISCHEMIC STROKE STUDY GROUP*

N Engl J Med, Vol. 345, No. 6 · August 9, 2001

Different presentations	Different risk factors
Slower progression	Infection
Headache	Dehydration
Increased ICP	Chronic disease
Seizures	Blood clotting disorders

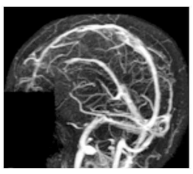
36

Cerebral sinovenous thrombosis (CSVT) in children

CEREBRAL SINOVENOUS THROMBOSIS IN CHILDREN

GABRIELLE DEVEBER, M.D., MAUREEN ANDREW, M.D., COLEEN ADAMS, M.B., BRUCE BJORNSON, M.D., FRANCES BOOTH, M.D., DAVID J. BUCKLEY, M.B., CH.B., CAROL S. CAMFIELD, M.D., MICHÈLE DAVID, M.D., PETER HUMPHREYS, M.D., PIERRE LANGEVIN, M.D., E. ATHEN MACDONALD, M.D., AND JANE GILLETT, M.D., FOR THE CANADIAN PEDIATRIC ISCHEMIC STROKE STUDY GROUP*

N Engl J Med, Vol. 345, No. 6 · August 9, 2001



Prof. Adam Kirton – University of Calgary, Canada

Pediatric CSVT: diagnosis

CT Venography (CTV)

MR Venography (MRV)

37

Thrombophilias are associated with childhood CSVT

Impact of Thrombophilia on Risk of Arterial Ischemic Stroke or Cerebral Sinovenous Thrombosis in Neonates and Children

A Systematic Review and Meta-Analysis of Observational Studies

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

Circulation. 2010;121:1838–1847

- Family history and thrombophilic testing may be necessary in children with CSVT

38

Anticoagulants in pediatric CSVT

Anticoagulants in Pediatric Cerebral Sinovenous Thrombosis

A Safety and Outcome Study

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

ANN NEUROL 2010;67:590–599

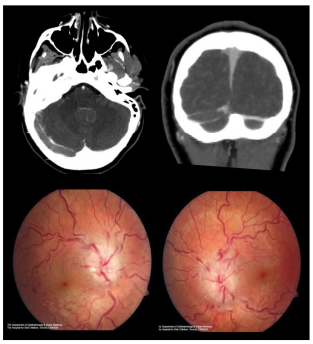
- 162 children with CSVT
- 85 anticoagulated
- 28-37% untreated propagated thrombus
- 4-7% treated propagated
- Propagation = infarcts, poor outcome
- Bleed rate 2-6%, same outcomes

39

Prof. Adam Kirton – University of Calgary, Canada

Pediatric CSVT: treatment

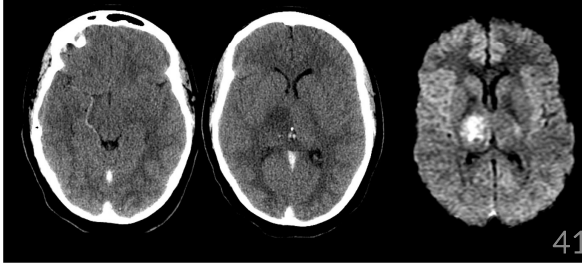
- Anticoagulation
  - Safe
  - Effective
  - Neonates
  - Contraindications
- Thrombolysis?
- Neuroprotection
- ICP and vision: Diamox



40

Pediatric CSVT example: 15-year-old

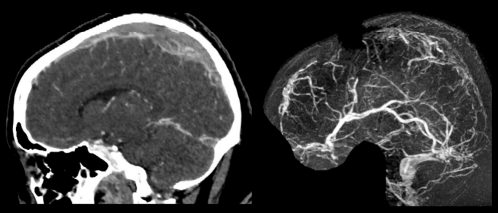
- 15-year-old girl with obesity, dehydration, on OCP with coma, papilledema



41

Pediatric CSVT example: 15-year-old

- Treatment: anticoagulant, with 48 hrs she improved
- Completely resolved the thrombosis



Prof. Adam Kirton – University of Calgary, Canada

Example: 13-year-old

- 13-year-old girl, collapsed, with a new headache and dense hemiparesis
- CT scan, decompressed
- Underlying arteriovenous malformation

42

Hemorrhagic stroke: epidemiology

Cerebrovascular Disorders in Children

John Kylan Lynch, DO, MPH

Current Neurology and Neuroscience Reports 2004, 4:129–138

- HS also occurs in children
- Possibly lower incidence than ischemic stroke
- Typical clinical presentation

43

Hemorrhagic stroke: clinical presentation

- Location-dependent
  - IP >> SAH, IVH, EDH, SDH
  - Supra > infratentorial
  - Cortical > 80%
- Signs & symptoms
  - Headache: thunderclap
  - Vomiting, altered LOC, seizures
  - Focal deficits

44

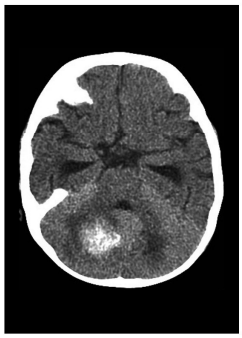
Lynch, CNNR 2004; Meyer-Heim, Brain Dev 2003

Prof. Adam Kirton – University of Calgary, Canada

Hemorrhagic stroke: etiology

45

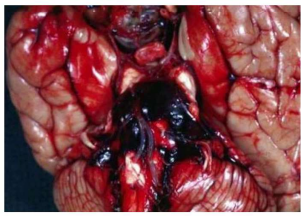
- Vascular malformations
  - AVM (30-80%)
  - Cavernous malformations
- Aneurysms
- Arteriopathies
- CSVT
- Blood disorders (10-30%)
  - Leukemia, platelets, SCD, iatrogenic
- Malignancy (2-20%)
- Trauma
- Idiopathic



Lynch, CNNR 2004; Meyer-Heim, Brain Dev 2003

Hemorrhagic stroke: investigation

- CT Head
- Lumbar puncture
- CBC, PTT, INR +/- other
- MRI
  - Blood sensitive sequences
  - MRA, MRV
- Conventional angiography

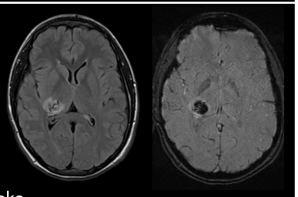


46

Lynch, CNNR 2004; Meyer-Heim, Brain Dev 2003

Example: 15-year-old

- 15-year-old boy, sudden onset headache, left-sided hemisensory change and weakness
- MRI - acute lesion in the right thalamus
- Hemorrhage - hemorrhagic stroke



47

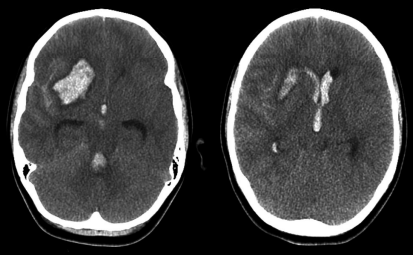
Prof. Adam Kirton – University of Calgary, Canada

Example: 15-year-old

- 15-year-old boy, sudden onset headache, left-sided hemisensory change and weakness
- MRI - acute lesion in the right thalamus
- Hemorrhage - hemorrhagic stroke

Example: 14-year-old

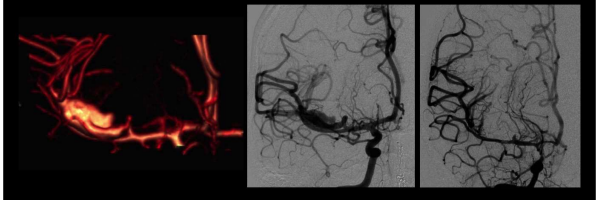
- 14-year-old girl, left-sided weakness, headache, decreased level of consciousness, with large hemorrhage in the right frontal lobe



48

Example: 14-year-old

- 14-year-old girl, left-sided weakness, headache, decreased level of consciousness, with large hemorrhage in the right frontal lobe
- CTA - unique aneurysm malformation of the right cerebral artery

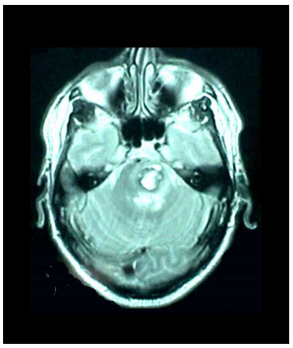


Prof. Adam Kirton – University of Calgary, Canada

Cerebral Cavernous Malformations (CCM)

- Capillary malformations
- Focal deficits, seizures, ICH
- Tx: resection

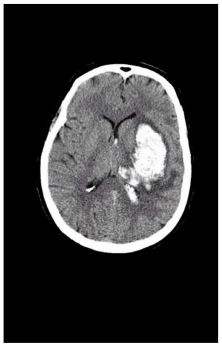
- AD
- KRIT-1
- CCM2
- PCDC10



49

Hereditary hemorrhagic telangiectasia (HHT)

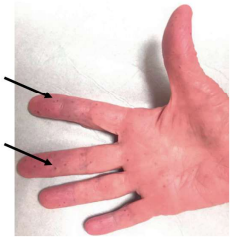
- AD
  - TGF-beta superfamily
  - Endoglin (HHT1)
  - ACVRL1 (HHT2)
- Systemic telangiectasia
  - Pulmonary (50%)
  - Liver (30%)
  - Brain (10%)



50

Hereditary hemorrhagic telangiectasia (HHT)

- AD
  - TGF-beta superfamily
  - Endoglin (HHT1)
  - ACVRL1 (HHT2)
- Systemic telangiectasia
  - Pulmonary (50%)
  - Liver (30%)
  - Brain (10%)



Prof. Adam Kirton – University of Calgary, Canada

Strokes can happen at any age

Pediatric strokes can occur in infants, children, and even before birth

Perinatal stroke
Last few months of pregnancy to 1-month-old

Childhood stroke
1-month-old to 18 years

Last few months of pregnancy

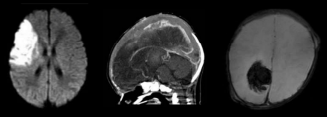
1-month-old

18 years

51

Perinatal stroke syndromes

Acute symptomatic

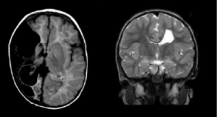


Neonatal Arterial Ischemic Stroke (NAIS)

Neonatal Cerebral Sinovenous Thrombosis (CSVT)

Neonatal Hemorrhagic Stroke (NHS)

Presumed perinatal ischemic stroke



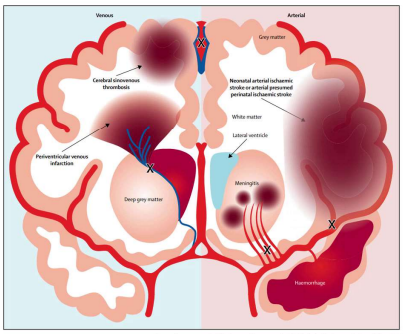
Arterial Presumed Perinatal Ischemic Stroke (APPIS)

Periventricular Venous Infarction (PVI)

52

Kirton and deVeber, *Stroke*. 2013; **44**:3265–3271

Perinatal stroke syndromes

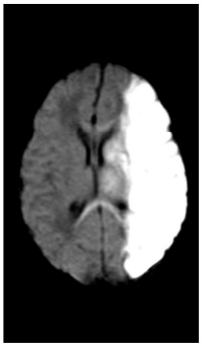


53

Dunbar and Kirton, *Lancet Child Adolesc Health*. 2018 2(9):666-676

Prof. Adam Kirton – University of Calgary, Canada

Perinatal stroke



- 1-day-old child with seizure, huge stroke
- Common
- No prevention
- Normal language
- Morbidity, cerebral palsy, weakness on one side, epilepsy
- No treatment?
- Poor outcomes
- Maximal developmental plasticity

54

Alberta Perinatal Stroke Project (APSP)

- > 1:1500 live births
- *You will not incur a more focused period of risk for ischemic stroke than the week you are born*

APSP
ALBERTA PERINATAL STROKE PROJECT

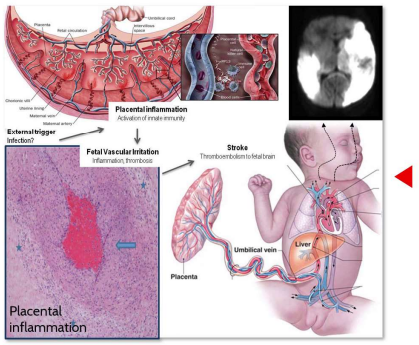
55

What causes perinatal stroke? Possible risk factors

56

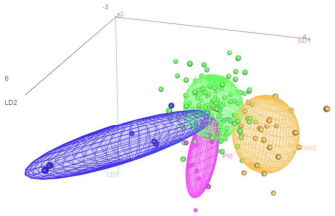
Prof. Adam Kirton – University of Calgary, Canada

Placenta as a top risk factor



57

Acute inflammatory profiles of perinatal stroke



Linear Discriminant Analysis, 65 cytokines (n=186)

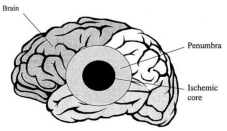
	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value
Class: APPIS	0.86	0.99	0.86	0.99
Class: Control	0.95	0.73	0.91	0.83
Class: NAIS	0.77	0.97	0.83	0.96
Class: PVI	0.58	0.99	0.78	0.97

58

Mineyko *et al.*, in preparation

Neuroprotection

- **Seizures** - control, monitor
- **Temperature** - euthermia
- **Infection** - find and Tx
- **Glucose** - euglycemia
- Airway and breathing?
- Circulation - CPP = MAP - ICP ?
- Sedation - minimize CMRO2?
- ICP?



Hutchison *et al.*, *Seminars in pediatric Neurology* . 2004;11:139–146

59

Prof. Adam Kirton – University of Calgary, Canada

Neuroprotection: erythropoietin

60

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Feasibility and Safety of Erythropoietin for Neuroprotection after Perinatal Arterial Ischemic Stroke

Manon J. Benders, MD, PhD[1], Niek E. van der Aa, MD[1], Maurice Roks, MPA[1], Henrica L. van Straaten, MD, PhD[2], Ivana Isgum, PhD[3], Max A. Viergever, PhD[3], Floris Groenendaal, MD, PhD[1,2], Linda S. de Vries, MD, PhD[1], and Frank van Bel, MD, PhD[1]

High-Dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial

PEDIATRICS Volume 137, number 6, June 2016

DINOSAUR Darbepoetin for Ischemic Neonatal Stroke to Augment Regeneration

Journal of Perinatology (2017) 00, 1–6 © 2017 Nature America, Inc., part of Springer Nature. All rights reserved 0743-8346/17 www.nature.com/jp

ORIGINAL ARTICLE

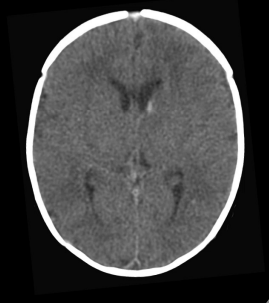
Erythropoietin monotherapy in perinatal asphyxia with moderate to severe encephalopathy: a randomized placebo-controlled trial

RR Malla[1], R Asim[2], MA Tek[3], F Shaheen[3] and MA Bhat[1]

Cerebral Palsy ALLIANCE RESEARCH FOUNDATION

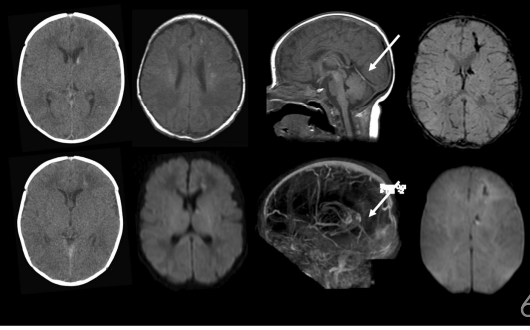
Example: 6-day-old term neonate

- 6-day-old baby with seizures
- CT scan - little hemorrhage



61

Example: 6-day-old term neonate

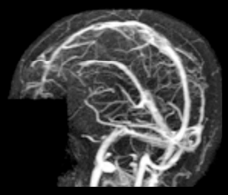


62

Prof. Adam Kirton – University of Calgary, Canada

CSVT visualization

- Treatment: anticoagulation



63

Anticoagulants in pediatric CSVT

Anticoagulants in Pediatric Cerebral Sinovenous Thrombosis
A Safety and Outcome Study

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

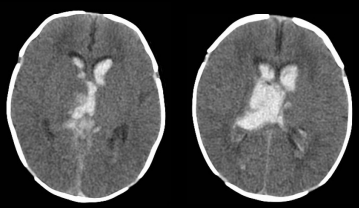
ANN NEUROL 2010;67:590–599

- 162 children with CSVT
- 85 anticoagulated
- 28-37% untreated propagated thrombus
- 4-7% treated propagated
- Propagation = infarcts, poor outcome
- Bleed rate 2-6%, same outcomes

64

Example: 8-day-old neonate

- 8-day-old baby with posturing and seizure
- 3 weeks later, increasing head circumference
- CT scan and MRI - deep sinovenous thrombosis

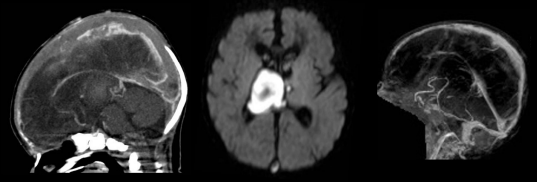


65

Prof. Adam Kirton – University of Calgary, Canada

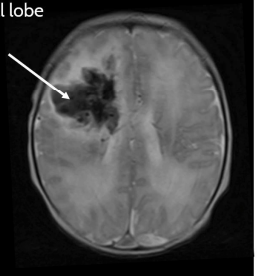
Example: 8-day-old neonate

- 8-day-old baby with posturing and seizure
- 3 weeks later, increasing head circumference
- CT scan and MRI - deep sinovenous thrombosis



Example: brain hemorrhage in a neonate

- Term baby with seizure
- Large hemorrhage in the right frontal lobe



66

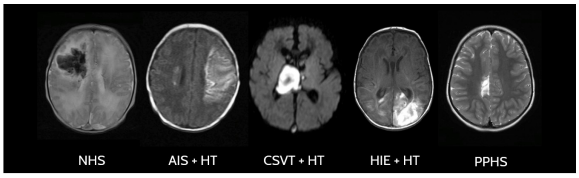
Neonatal hemorrhagic stroke research

Research

JAMA Pediatrics | Original Investigation

Population-Based Epidemiologic Study of Neonatal Hemorrhagic Stroke

Lauran Cole, BScH; Deborah Dewey, PhD; Nicole Letourneau, PhD; Bonnie J. Kaplan, PhD; Kathleen Chaput, PhD; Clare Gallagher, MD, PhD; Jacquie Hodge, MSc; Amalia Floer, MD; Adam Kirton, MD

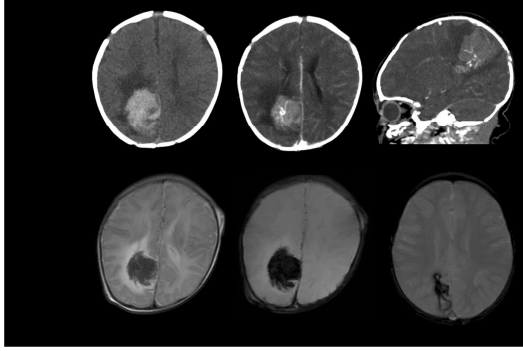


NHS + PPHS incidence: ~1:8880 live births

67

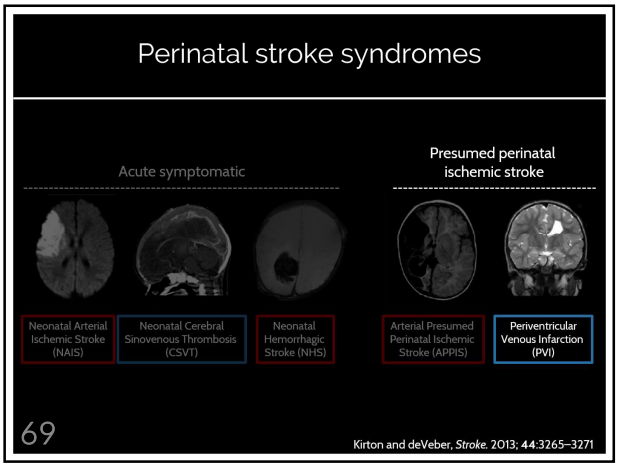
Prof. Adam Kirton – University of Calgary, Canada

Example: 1-day-old neonate with seizures on day 1



68

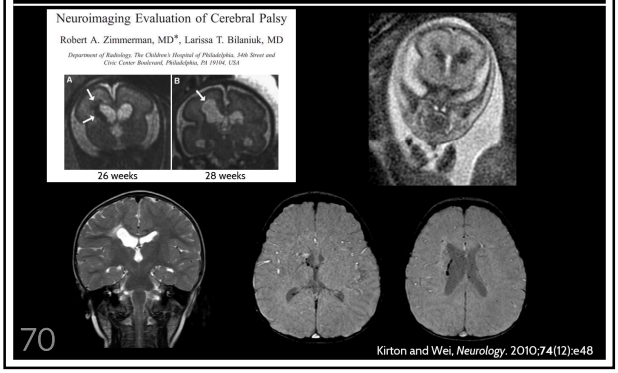
Perinatal stroke syndromes



69

Kirton and deVeber, *Stroke*. 2013; 44:3265–3271

Periventricular Venous Infarction (PVI)



70

Kirton and Wei, *Neurology*. 2010;74(12):e48

Prof. Adam Kirton – University of Calgary, Canada

Learning objectives

Recognize the presentations, causes, and management of stroke in neonates and children

Appreciate the role of developmental neuroplasticity in determining the diverse range outcomes that occur

71

Perinatal stroke outcomes

72

- Hemiparetic CP #1
- Epilepsy
- Cognitive
- Language
- Psych

~30%

- Sensory?
- Vision: <20%
- Recurrence: <1%

Life After Perinatal Stroke

Adam Kirton, MD, MSc; Gabrielle deVeber, MD, MHSc

Stroke. 2013;44:3265-3271.

Ballantyne *et al., Brain*. 2008;131(Pt 11):2975-85; Nelson, *Lancet Neurol* 2007; Trauner *et al., Pediatr Neurol*. 1993;9(5):383-6; Kirton *et al., Ann Neurol*. 2008;63(4):436-43; Lee *et al., Ann Neurol*. 2005;58(2):303-8.

Outcomes in childhood AIS

- Most suffer lifelong disability
- Factors: age, location, size, plasticity, others...

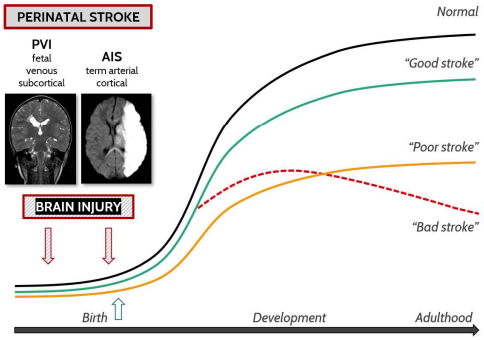
Motor	Hemiparesis #1, dystonia
Cognitive	Neuropsychological testing
Behavioral	ADHD
Epilepsy	15–20%, SIPS study
Mental health	QOL, family

73

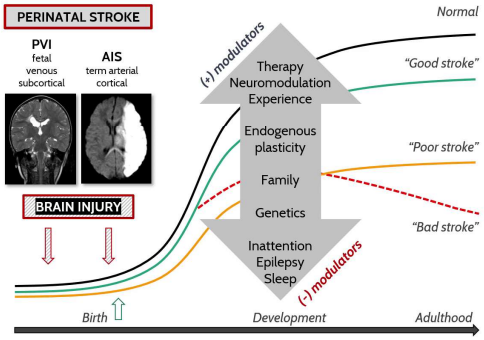
Prof. Adam Kirton – University of Calgary, Canada

Stroke outcomes can be modulated throughout development

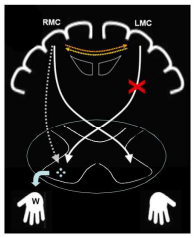
74

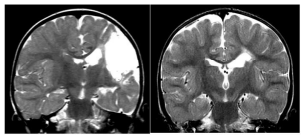


Stroke outcomes can be modulated throughout development



Motor recovery after stroke





Review Article

Modeling Developmental Plasticity After Perinatal Stroke: Defining Central Therapeutic Targets in Cerebral Palsy

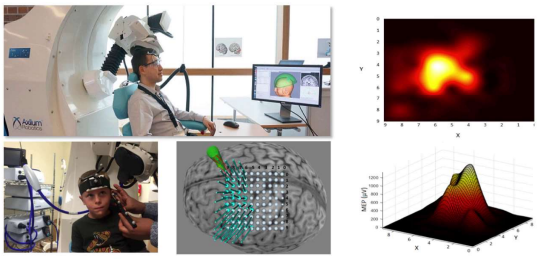
Adam Kirton MD, MSc

Calgary Pediatric Stroke Program, Alberta Children's Hospital Research Institute, and Section of Neurology, Department of Pediatrics and Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada

75

Prof. Adam Kirton – University of Calgary, Canada

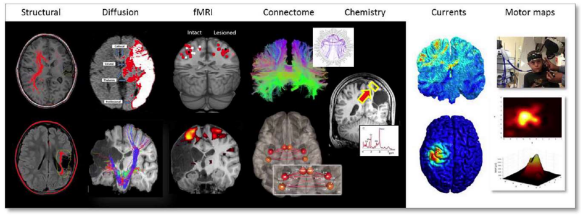
Robotic TMS mapping of motor cortex



76

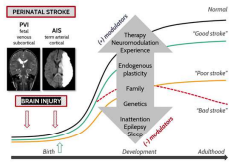
Grab *et al., J Neurosci Methods.* 2018;309:41-54

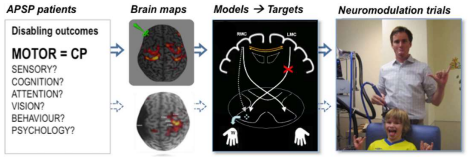
Perinatal stroke plasticity imaging



77

From imaging to neuromodulation

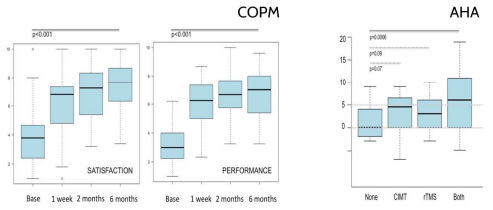




78

Prof. Adam Kirton – University of Calgary, Canada

The PLASTIC CHAMPS trial



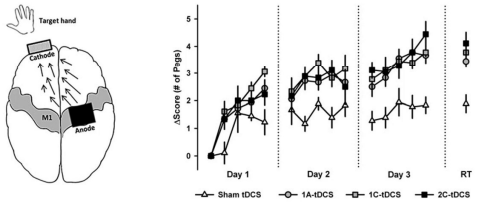
Kids *think* they are better at 6 months

rTMS + CIMT gain most

79

Kirton *et al., Neurology.* 2016;**86**(18):1659-67

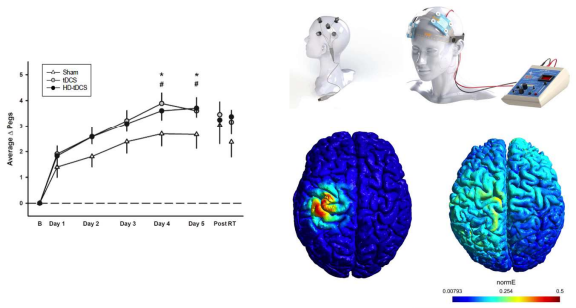
Transcranial direct-current stimulation can enhance motor learning in children



80

Ciechanski and Kirton, *Cereb Cortex.* 2017;**27**(5):2758-2767

Accelerated Motor Learning in PEDiatrics (AMPED)

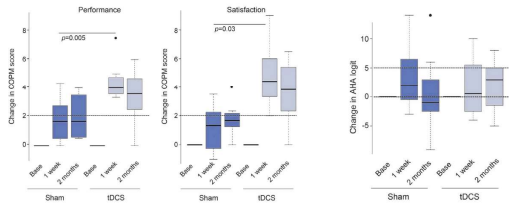


81

Cole, Giuffre *et al.*, ICCN Washington, 2018
Ciechanski *et al.*, submitted

Prof. Adam Kirton – University of Calgary, Canada

Phase II trial in children with perinatal stroke and hemiparesis



Higher achievement with tDCS

No effect on AHA

82

Kirton *et al.*, Neurology. 2016;88(3):259-267

SPORT trial

Stimulation for Perinatal stroke: Optimizing Recovery Trajectories

CHILD-BRIGHT Network

SPOR

CIHR IRSC

83

SPORT trial

Stimulation for Perinatal stroke: Optimizing Recovery Trajectories

Prof. Adam Kirton – University of Calgary, Canada

Different goals for different patients

MEDICAL TREATMENT

Camp offers real results for infant victims of stroke

ANNE MCILROY — SCIENCE REPORTER

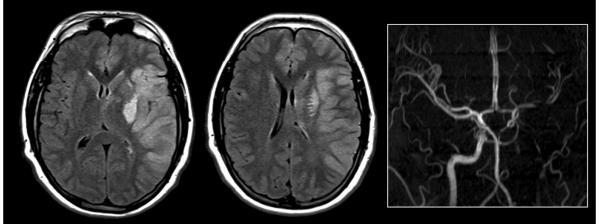
HEART & STROKE FOUNDATION

Camp helps kids overcome stroke

84

Example: 14-year-old footballer

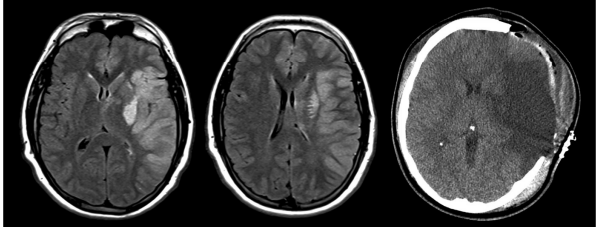
- 14-year-old high school footballer, huge left MCA stroke



85

Example: 14-year-old footballer

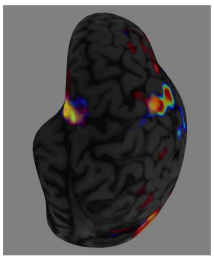
- 14-year-old high school footballer, huge left MCA stroke
- His goal - he wanted to speak

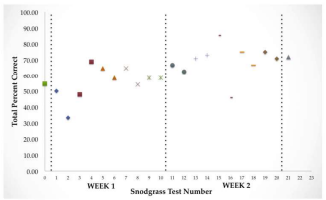


Prof. Adam Kirton – University of Calgary, Canada

Example: 14-year-old footballer

86

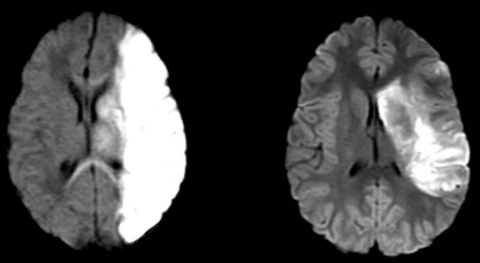




See '**Links**' for a news story about Matt

Carlson *et al.*, *Brain Lang.* 2016;**159**:23-34

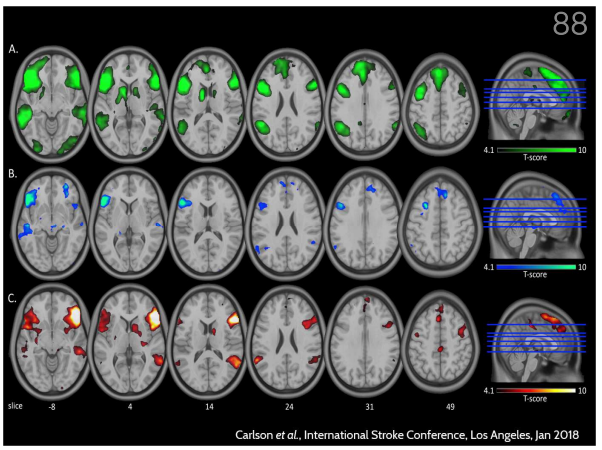
Example of developmental plasticity



1-day-old

12-year-old

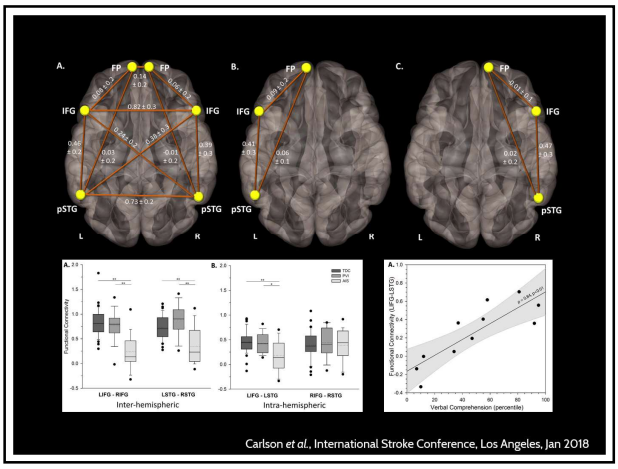
87



88

Carlson *et al.*, International Stroke Conference, Los Angeles, Jan 2018

Prof. Adam Kirton – University of Calgary, Canada



Education and mental health

Grief

Guilt

Blame

Fear

Original Article

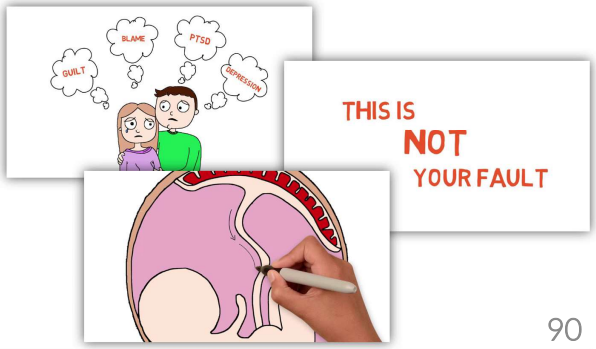
Development, Reliability, and Validity of the Alberta Perinatal Stroke Project Parental Outcome Measure

Taryn B. Bemister MSc[a,b], Brian L. Brooks PhD[b,c,d,e], Adam Kirton MD, MSc[b,d,e,f,*]

Pediatric Neurology 51 (2014) 43–52

89

Parent education



90

Prof. Adam Kirton – University of Calgary, Canada

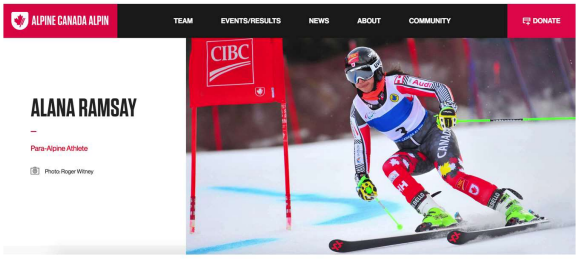
Community support groups

91

Success stories

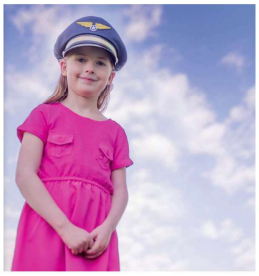
92

Success stories



Prof. Adam Kirton – University of Calgary, Canada

Success stories



Acknowledgements

93

Dr. Aleks Mineyko
Jacquie Hodge
Amalia Floer
Dr. Taryn Bernister
David Czank
Zeanna Jadavji
Dr. Kara Murias
Dr. Colleeen Curtis
Dr. Lisa Smithson

ACH Peds NIBS Lab
Dr. Ephrem Zewdie
Dr. Sultan Nelson
Dr. Liu Shi Gan
Dr. Cherie Kuo
Dr. Patrick Ciechanski
Omar Damji
Jeff Grab
Jack Zhang
Tara Shannon

Calgary Stroke
Dr. Michael Hill
Dr. Sean Dukelow
Dr. Andrea Kucyznski
Megan Meztler
Felix Wei
Lauran Cole
Adrianna Giuffre
Asha Hollis
Brett Paffrath

APSP Edmonton
Dr. Jerome Yager
Dr. John Andersen
Dr. Jaynie Yang
Kathleen O'Grady
ACH
Eva Haspels
Mia Herrero
Lisa Carsolio
Dr. Alberto Nettel

SickKids Stroke
Dr. Gabrielle deVeber

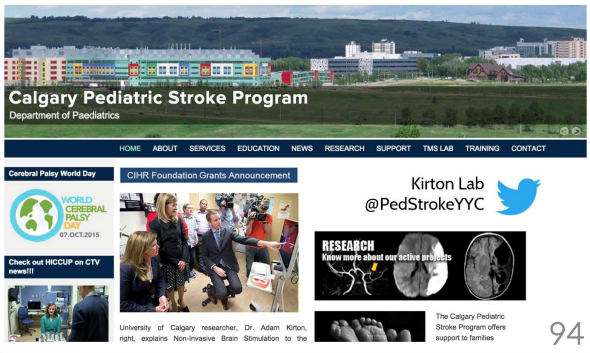
Neuroimaging
Dr. Helen Carlson
Dr. Xing-Chang Wei

Dr. Brad Goodyear
Dr. Bita Vaseghi
Jenny Saunders

Sabrina Yu
Brandon Craig
Kristine Woodward
Kayla Baker

U Toronto
Dr. Robert Chen
Dr. Darcy Fehlings

www.perinatalstroke.ca



94

Prof. Adam Kirton – University of Calgary, Canada