Neurological problems in children with Sickle Cell Disease

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Neurological Symptoms/presentation in Sickle Cell Disease – A spectrum

- Symptomatic (stroke) or asymptomatic (silent) infarction
- Transient ischaemic attack
- Seizures
- Coma and 'reversible neurological syndrome'
- Insidious - neurological 'soft' signs
- Poor school progress
- Headaches - Acute severe
  - Chronic = migraine type and non migraine type (in both exclude sleep disordered breathing)

Cerebrovascular Disease in SCD

- Large vessel disease: Stenosis or occlusion
- 'Small vessel disease'
- Moya- Moya + collaterals
- Venous sinus thrombosis

Stroke in Childhood (excluding perinatal)

- 2 – 5/100 000 children/year
- Stroke with SCD (probably) regarded as second most common cause in UK. Most common cause in London area
- 200x more common than in a child without a haemoglobinopathy

'Setting the scene' – not a unusual problem in SCD

- 25% of HbSS – some form of CVA by age 45
- 10% of HbSC
- 10 – 11% a clinically evident effect of ischaemic damage
- 17 – 25% (estimates) – covert 'silent' ischaemic damage – most are anterior or posterior vascular 'border zone' lesions

Limitations of using the term 'stroke'

Ischaemic Stroke

- Arterial – 50-80% definable cerebrovascular pathology
- Venous sinus thrombosis –
  - Under recognised esp. deep posterior and superficial cortical lesions

Haemorrhagic Stroke (higher mortality) → 40-60% significant residual disability

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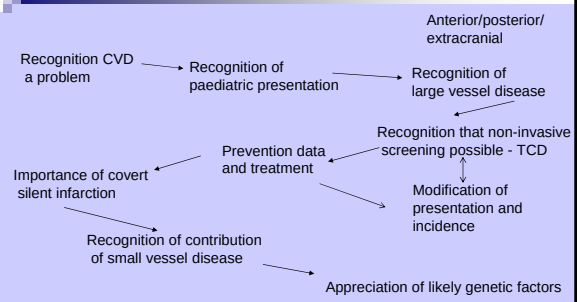
In SCD

- Peak age presentation for a clinically overt ischaemic event = 2-5 years of age
- Peak age for haemorrhage 20-30 years (aneurysms)

- Haemorrhagic stroke much less common in childhood

HISTORICAL PERSPECTIVE

Cerebrovascular pathology in SCD



All this against a background of:

- Improvements in Brain imaging – anatomy, angiography, perfusion
- Changes care provided for paediatric population
- Introduction screening programmes
- Increasing advances in understanding of clinical genetics

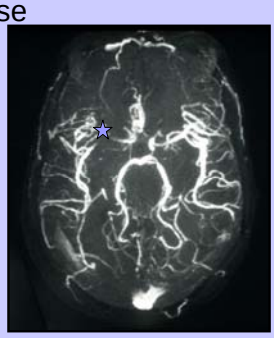
The various types of SCD cerebrovascular pathology

Overt Paediatric clinical stroke (focal signs lasting >24hours)

- Usually due to *large vessel occlusion* – hemiparesis, monoparesis, hemianaesthesia, visual field defects, aphasia, C.N. palsies, acute change of behaviour
- Can be 'stroke in progression' – stuttering course, gradual worsening of deficit, new focal abnormalities appear
- Occasionally recovery 'complete' over longer period of time. More typically – 'completed stroke' with *permanent sequalae*
- Although there are factors which make it more likely to happen – ***commonly 'out of the blue',* previously well child, no previous complications of SCD – 1st presentation of any overt medical problem**
- Still patients, not born in UK, where their 1st presentation and recognition of SCD, is a neurological event

Large vessel disease

- Around 80% of those with SCD and overt stroke have progressive large vessel vasculopathy determined by imaging
- Often additional pruning and loss of smaller distal vessels



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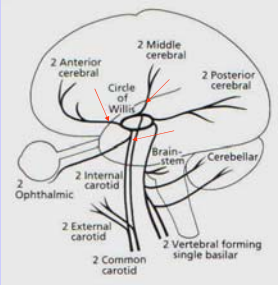
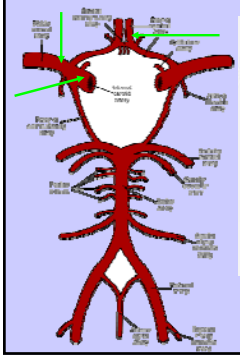
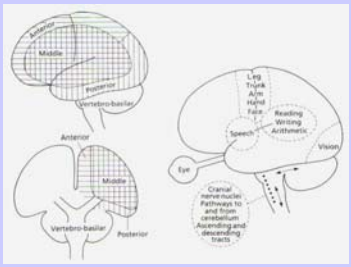
Large vessel arterial vasculopathy – principally located to:

- Distal supraclinoid internal carotid
- Proximal portions middle cerebral
- Anterior cerebral

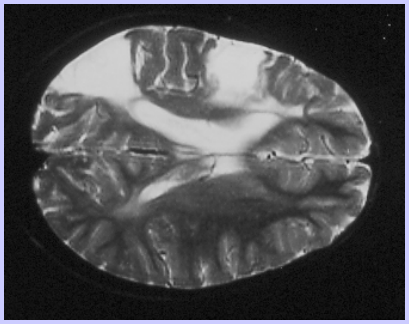


Arteries of the Circle of Willis



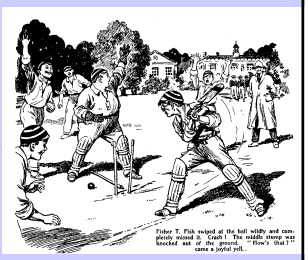


Lesion from MCA disease



Stumped?

- Why these vessels?
- Why anterior more than posterior?
- Why not always a more symmetrical pathology?
- Why does new vessel formation vary in its extent?
- Why only some patients?



Definition of Silent Infarcts

Increased signal on T2 weighted image on MRI with no history of a focal neurologic deficits

Cooperative Study for Sickle Cell Disease Glauser et al.

(J Child Neurol 1995; 10:88-92)

What difference does a small bright lesion on T2W MRI really make?

Prevalence of Silent Cerebral Infarcts at Institutions who Performed Surveillance MRI Examinations

Reference	Number of Silent Cerebral Infarcts	Total Number of Patients	Prevalence	95% Confidence Interval
Pegelow, 2002	58	266	21.8%	16.8-26.8
Bernaudin, 2000	23	155	15%	9.4-20.6
Kirkham, 2000	16	64	25%	14.4-35.6
Total	**97**	**485**	**20%**	**16.4-23.6**

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Morbidity of Silent Cerebral Infarcts

- Global IQ and specific cognitive domains scores are lower than children with SCA and normal MRIs
- The rate of “grade” failure is twice that of children with normal MRIs and five times higher than sibling control
- Lesion size influences the magnitude of global IQ loss in silent cerebral infarcts

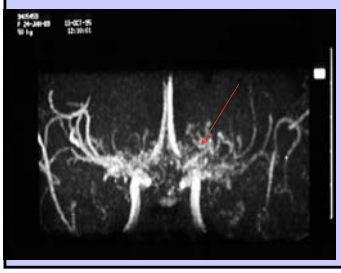
J of Child Neurology 2002; 17:891-895

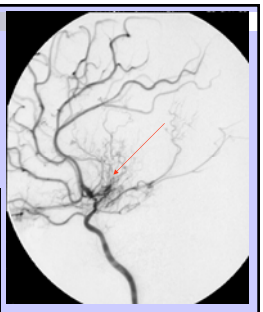
Cases with abnormal performance on neuropyschological evaluation
(< 1.5 SD below age expected value in at least two domains)

Domain	Silent Infarcts (n=19)	SCD with no Infarcts (n=45)	Sibling (n=18)
Attention/ Executive	53%	13%	0%
Viso-Spatial/ motor	30%	33%	0%
Memory	13%	10%	6%
Language	20%	23%	6%
Any domain	79%	36%	11%

Moya-Moya

- Secondary new vessel formation
- Angiogenesis upregulated by hypoxia
- Tiny collateral vessels
- Underestimated on conventional MRA





Problems:
Haemorrhage easily
Occlude easily
Vasoconstriction – CO_2 responsive

(beware TIA type symptoms)

Transient ischaemic attack (TIA) in SCD

- Can be ‘stroke in progression’
- TIA definitions vary – deficit lasts < 24hours
  (? < 48 hours for vertebral or basilar symptoms – dizzy, ataxia, diplopia, visual disturbance)
- Often a ‘warning’ of subsequent stroke
  Thus assess, investigate and consider transfusion with some urgency

Mechanisms?

Vessel pathology in large vessel disease

- Initiating factor is an abnormal interaction between erythrocyte and endothelium
- Mechanism unknown
- ? Amount of free haemoglobin
- Laminar flow (of blood) shear forces suppress vascular leucocyte adhesion molecules V-CAM1 expressed in intima (branch points are where disturbance to lamina flow)
- Laminar flow also augments NO release = local anti inflammatory effect
- Limited vasa vasorum anterior cerebral circulation – less bidirectional arterial wall oxygenation in this area

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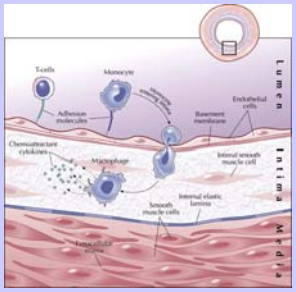
Vessel pathology process

- Abnormal interaction results in intimal proliferation and disconuity of internal elastic lamina
- With intimal proliferation get increased amounts of smooth muscle cell, fibroblasts and fibrous tissue
- A concomitent thrombus formation at site of intimal damage – perpetuates the cycle of intimal damage
- Actual acute event due to narrowing, thrombus, distal embolic effect of dislodged thrombus and vessel spasm



Libby, P. et al. J Am Coll Cardiol 2006;48:A33-A46

Nutritional factors?

- Role of supplementation to improve 'endothelial function'?
- Antioxidants?
- Exclude pernicious anaemia
- Role of homocysteine levels?

Prevention

Identified Risk factors for cerebrovascular disease in SCD

Overt ischaemic stroke:
Low HB
High WCC
Previous TIA
Hypertension
History of chest crisis

Haemorrhagic stroke:
?low Hb
?high WCC
Recent Tx.
Corticosteroids

Transcranial Doppler studies – distal ICA & MCA:
Increased velocity, reliable indicator that patient at risk of stroke

Predict increased TCD value (and hence risk) from age related index incorporating Hb & Aspartate transaminase value

Nocturnal Hypoxemia: ?sustained ?intermittent
Low 'sats' increase platelet and leukocyte activation
? Additional effect of nocturnal bronchospasm – Asthma cohort
current practice – Over night O/N 'sat' study
If abnormal consider adenotonsillectomy
(beware may persist after surgery)
? CPAP O/N respiratory support

The Case for Preventing First Stroke in SCD

- Damage unpredictable
- Outcome in advanced vessel disease is poor
- SCD good target for a prevention strategy
  - Newborn identification of disease – pre CV disease
  - Excellent prediction of stroke and CVD with non invasive, low risk procedure -TCD
  - Once risk identified - effective preventive treatment is available

Prevention of ischaemic stroke in SCD

- 1992 – 20 years ago - Adams group recognised transcranial doppler ultrasonography to measure blood flow velocity in large vessels of the anterior cerebral circulation predict stroke in the paediatric population (TCD abnormality can be found before MRA changes)
  - high velocity - stenosis
  - low velocity/absent flow – occlusion
- 1998 – 14 years ago STOP trial – Stroke prevention trial in SC anaemia – clear benefit for prophylactic transfusions where blood flow velocity > 200cm/sec. Not eliminate stroke risk completely
- STOP II – 2005 – 7 years ago – essential to Tx. Long term, even if TCD values return to normal

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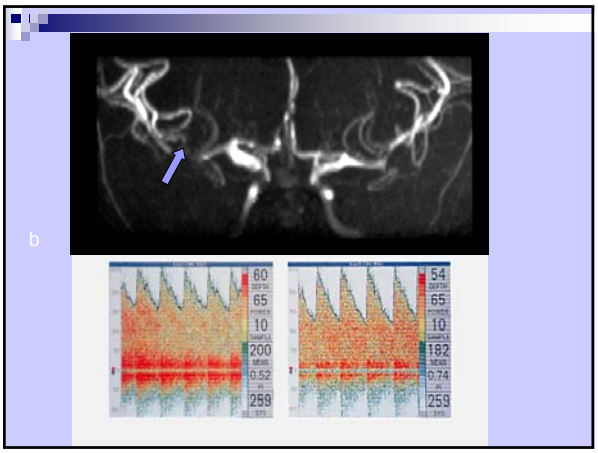
TCD Risk Stratification

Category	t-ICA/MCA TAMV (cm/s)	Stroke Risk
Normal	< 170 cm/s	0.25 - 1%/yr
Conditional	170 - 199	1 - 3%/yr
Abnormal	≥ 200 cm/s	10%/yr
Inadequate	Unable to obtain	1 - 3%/yr

Adams et al. *Blood.* 2004;103:3689-3694.



UK childhood stroke guidelines 2004 (RCP)

- Primary prevention – HbSS or Hb Sthal
  TCD screen yearly from 12 months (debated), using appropriately trained personnel (from 3 years of age NHS standards and guidelines document 2006)
- Children with ICA or MCA velocity > 200cm/sec on TCD study should be offered long term blood transfusions

Practicality:
Concern in technical difficulty age 1-3 years. Many start age 3
Appropriately trained personnel not universally available

Debate about how often to screen What is optimal re-screening frequency?

- Not all children with stroke have had documented abnormal TCD
  - Interval too long between screening?
  - Different pathophysiology for some?
  - TCD technique missed small stenotic lesion?

When plan consider:
- Younger age more likely to become pathological
- If initial value conditional or pathological
- Monitor more closely within a family group if pathology recognised in any member

Summary: TCD Screening Intervals

- Factor in age, prior TCD results
  <10 years, high conditional: repeat within 6 wks, if unchanged then 3 mth
  <10 years, low conditional: repeat within 4 mth if unchanged then 6 mth
  >10 years, high conditional: repeat within 3 mth if unchanged then 6 mth
  >10 years, low conditional: repeat within 6 mth if unchanged then 1 yr
- If other stroke risk factors, such as sibling with abnormal TCD or stroke, child should be screened more frequently

(JL Kwaitkowski – Philadelphia)

Secondary Prevention

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Secondary prevention

Once first stroke – risk of recurrence high

Range 20 – 92%

2004 Childhood stroke guidelines:

- In children with SCD, regular blood transfusion (every 3-6 weeks) should be undertaken to maintain HbS at <25% and Haemoglobin at 10-12.5g/dl (decreases recurrence risk to 10-20%).
  After 3 years, a less intensive regime maintaining HbS at <50% might be sufficient for stroke prevention
- Children with SCD who cannot receive regular blood transfusions because of alloimmunization, autoantibody formation or non-compliance with transfusion or chelation might be considered for treatment with hydroxyurea
- Children with Moya-Moya appearances should be referred for evaluation to a centre with expertise in evaluating patients for surgical revascularisation
- Advice should be offered regarding preventable risk factors for arterial disease in adult life (smoking, exercise and diet)
- Blood pressure should be measured annually to screen for hypertension

Hydroxyurea

- Subject of current multi-centre trial
- Role still uncertain
- Inhibits polymerization of HbS, increases % HbF, improves RBC deformability, improves RBC survival
- Can cause general myelosuppresion and induce chromosomal changes

Aspirin

- Variable response to Aspirin in population – high group of none responders
- Not a drug without risk in children - 'Reyes'
- Risk of haemorrhage from underappreciated new vessel formation

Current randomised trial START

(Rochester USA)

How do you manage progression despite transfusion regime? – i.e.

New clinical event or just vessel or perfusion changes on MR

1. 'Optimise' transfusion regime
   - ensure tight compliance
   - Target lower HbS ?%
2. Exclude additional complications
   emergence of hypoxaemia, lifestyle and diet changes
3. Consider hydroxyurea, BMTx.
4. Consider revascularisation

Surgical revascularisation – provide some intracerebral supply from external circulation

- Role in patients with SCA unknown
  - anecdotal benefits documented
  - Classical non-sickle Moya-Moya (Japanese) see 80% improvement in extent of vascular compromise and symptoms
- Currently offered to patients with
  - Proximal occlusive arterial disease, usually with progressive changes and Moya-Moya
  - Hypoperfusion affecting uninfarcted tissue
  - Clinical symptoms despite blood transfusion (i.e. adjunct to long-term transfusion)

Surgical procedural options

- *Indirect bypass surgery*
  Encephalo-duro-arterio-synangiosis EDAS
  Encephalo-myo-synangiosis EMS
  Encephalo-myo-arterio-synangiosis EMAS
  Encephalo-duro-arterio-myo-synangiosis EDAMS

  Multiple Burr hole approach (France)
- *Direct bypass surgery*
  Superficial temporal artery to Middle cerebral
  STA-MCA
- *Combination of indirect and direct procedures*

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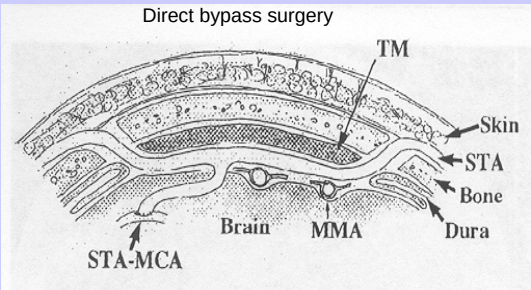
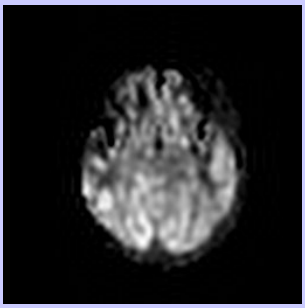
Direct bypass surgery



Improved perfusion Right side- post revascularisation procedure



Genetics of stroke

- Highly penetrant single gene disorder where additional multiple genes (polygenic) each exert a small influence on risk to the phenotype
- Each genetic influence may have a small but key effect
- Incomplete penetrance of genetic expression
- Thus individuals show different combinations of genetic and environmental influences

Stroke in SCD - Familial Predisposition

- Cases of stroke in multiple family members with SCD (link between TCD values)
- Sib-pair analysis
  Increased risk vs. general SCD population
- HLA type and stroke risk
  Certain HLA-B, DR, DQ alleles associated with increased or decreased risk

No evidence to link genetically determined prothrombotic disorder

Driscoll, et al. *Blood* 2003;101:2401-2404
Styles, et al. *Blood.* 2000;95:3562-7

Areas of interest:

- Non sickle large vessel disease – polymorphisms found in gene for phosphodiesterase 4D (PDE4D) – controls level of smooth muscle proliferation and immune function in vessels
- Polymorphisms of angiotensin gene (blood pressure effect)
- Vascular cell adhesion molecule V-CAM1 gene = high frequency of single nucleotide polymorphisms (SNP) in Afro-Caribbean pop. One of the variant alleles Gly1238Cys associates with protection from stroke in the Jamaican population
- SNP studies in candidate genes – identified a group of genes which, where present together, when considering HbF level in addition, find a high correlation with patients who have suffered stroke

Acardi Goutiers syndrome 4 types
- Intracranial Calcification – looks like congenital infection
- Older child 'regressive' form
- 'Lupus like' syndrome
- Intracerebral large artery disease

- TREX1 intracellular alarm system – normally triggered by viral nucleic acids
- Here triggered by persons own nucleic acids, given right circumstances

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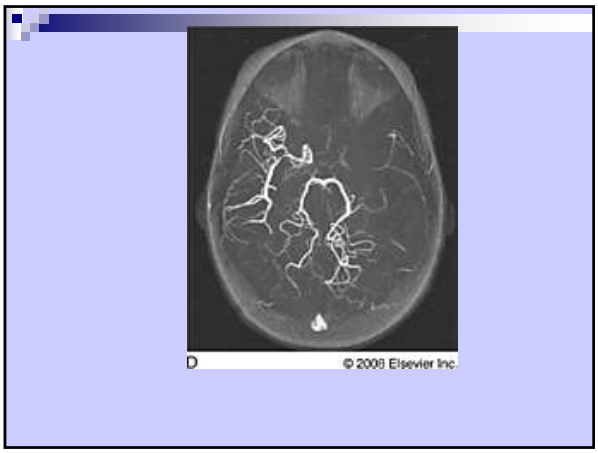

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