Stroke Prevention and Management in Sickle Cell Disease

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Intended Audience

This document contains information and clinical guidelines for management of children attending the Sheffield Childrens Hospital Haematology department. It is to be used by staff within the Trust whenever they are caring for children with Sickle Cell Disease (SCD).

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1 Background

Stroke is a common complication of sickle cell disease. It is caused by the combined effects of small and large vessel damage and chronic anaemia. Small vessels in the arterial border zones are thought to be lost early in the process and this leads to deep white matter 'silent' infarcts and changes in perfusion in apparently asymptomatic SCD patients.

Overt stroke is typified by stenosis and occlusion of large cerebral arteries, particularly those of the circle of Willis. There is intimal hyperplasia that may be severe enough to occlude the vessel or there may be embolisation of a thrombus formed in a damaged vessel. These vessels also show increased formation of aneurysms and Moya Moya (formation of a mass of friable blood vessels). Rupture of the aneurysms or the friable vessels in Moya Moya is the usual cause of haemorrhagic stroke in SCD. The bleeding can be subarachnoid, intraventricular, or parenchymal.

Stroke is seen in all the common SCD genotypes but is more frequent in SS. The annual incidence of first stroke is 0.6/100 patient years. The highest incidence is in children of 2 – 5 years with Hb SS.

Cumulative risk of stroke increases with age, reaching 11% by age 20 years.

2 Risk Factors for Infarctive Stroke in SCD

Prior transient ischaemic attack
History of meningitis
Increased systolic blood pressure
Nocturnal hypoxaemia
SCD sibling who has had a stroke
Low steady state haemoglobin
Increased cerebral blood flow velocity
The 2 week period following acute chest syndrome

Alpha thalassaemia (of any degree) is protective from stroke through its positive effect on steady state haemoglobin.

3 Clinical Presentation

Typical presentations of infarctive stroke include hemiparesis, aphasia, monoparesis and seizure. In young children subtle motor changes may be missed as a sign of stroke (e.g. painless limp)

Haemorrhagic stroke often presents with severe headache, rarely the presentation is with coma.
4 Visual Disturbances

Sickle cell vaso occlusive events can affect every part of the eye and may have serious and permanent visual consequences. Sometimes it is difficult to know whether the symptom the child describes is related locally to the eye, or to cerebrovascular disease. If a child reports visual symptoms (reduced acuity, blurring, loss of vision, flashing lights) they should be referred for an urgent ophthalmic opinion. They may also need further neurological investigation.

Detectable retinal disease is rare in childhood, occurring commonly between 15-30yrs in patients with HbSC and HbS/βthal rather than in Hb SS.

There is currently no evidence for routine childhood ophthalmology screening, but this should be replaced by prompt action in response to reported symptoms

5 Immediate Management of Acute Stroke Symptoms (including TIA) in a Patient with SCD

There are no clinical trials to guide optimal acute management.

a) Initial assessment and care

i) History and examination. Distinguish between symptoms due to pain and those due to weakness. Consider if meningitis is a possibility.

ii) Support. Monitor vital signs, maintain euthermia, ensure good oxygenation and give IV fluids at maintenance or less.

b) Laboratory

i) FBC and reticulocyte count

ii) Clotting screen

iii) Crossmatch (phenotypic match if possible for D, C, E and Kell antigens). Known patients should have had a red cell phenotype determined at a previous visit.

iv) U+Es and LFTs

c) Neuro Imaging

i) CT scan as soon as possible to rule out haemorrhage. The CT may be unremarkable in the first few hours following infarctive stroke.

ii) MRI/MRA. To demonstrate parenchymal and large vessel disease.
d) Red cell transfusion

i) Initial transfusion can be a simple top up transfusion to raise the haemoglobin to 100g/L (NO HIGHER). Do not exceed 15ml/kg of packed cells in a single transfusion. Allow 2 – 3 hours after the end of the transfusion then check the haemoglobin. Give further transfusion if necessary to achieve 100g/L.

ii) Exchange transfusion (manual or automated). The final haemoglobin should be 100-120g/L and the HbS% <30. There is a separate guideline covering automated exchange transfusion in sickle cell disease CG 1465

Do not delay the initial transfusion if an exchange transfusion is not readily available

The aim of the above acute management is to lessen anaemia, reduce tissue hypoxia and reduce HbS% thus increasing oxygen carrying capacity and removing sickle cells. Hypotension should be avoided and hydration maintained. Fever is associated with worse outcome in non SCD related ischaemic stroke (no data in SCD stroke). Use of fibrinolytic agents such as t-PA has not been studied in SCD.

6 Long Term Management of Stroke in SCD

The goals are to rehabilitate, prevent recurrence, red cell alloimmunisation and iron overload. Without treatment there is a high risk of recurrence (67%) (Powers et al). Chronic transfusion therapy is the most effective known method to reduce stroke recurrence, but does not eliminate the risk entirely (Pegelow et al). There is no data on the efficacy of transfusion in preventing recurrence of haemorrhagic stroke.

The optimal duration of transfusion therapy is unknown. Each child should be assessed individually. It is a consultant decision to stop or reduce transfusion frequency.

There are considerable drawbacks to chronic transfusion: inconvenience, possible infection, possible alloimmunisation and iron overload. The iron overload can be lessened by erythrocytapheresis but the red cell exposure is increased. Hydroxycarbamide is being studied as a possible alternative to chronic transfusion for secondary stroke prevention but studies so far suggest it is not as effective as chronic transfusion. Hydroxycarbamide can be used in a proportion of children for primary stroke prevention after a period of at least 1 year of regular transfusion. This is a consultant decision after discussion with the family.

Stroke is the most common eligibility factor for stem cell transplant in SCD in the USA (Walters et al). However, few children in this situation have a suitable sibling donor. The decision to transplant must be made on an individual basis at consultant level.
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**a) Chronic red cell transfusion therapy**

i) The goal is to maintain a haemoglobin of 100 – 120 g/L and an HbS of <30%. The haemoglobin and HbS% should be checked prior to each transfusion, but a post transfusion check is not usually needed.

As with other conditions requiring chronic transfusions annual review should include Hepatitis and HIV monitoring, and total volume of red cells transfused. Ferritin should be checked 1 - 3 monthly. The child should attend 3 transfusion clinic appointments per year and undergo the annual review as set out in that clinic.

ii) Managing iron overload – either by using automated red cell exchange transfusions or allowing the HbS to rise to 50% after 3-4 years with no stroke complications. Iron overload needs treating with iron chelation therapy. (See the Haematology & Oncology Unit guidelines, section 11, Haematology – Non Malignant 1315 Thalassaemia and Other transfusion dependent conditions (H&O/11/1315)

iii) Managing alloimmunisation. Efforts must be made to prevent this by using closely matched cells. Alloimmunisation may be a reason to stop transfusion. If so this is a consultant decision. Hydroxycarbamide should be considered instead but it is known to be less effective than transfusion.

**b) Neuropsychological evaluation**

i) Obtain the evaluation as soon as possible after the acute event

ii) Institute interventions to improve neurocognitive losses under the guidance of the neurology team

iii) Monitor with re evaluation every 6-12 months.

**c) Physical, occupational, speech and other therapies**

i) Early evaluation

ii) Intervention as appropriate

**d) Neuro imaging**

i) MRI/MRA annually. Assess progression of vascular disease: aneurysms, Moya Moya, lesions amenable to surgery.

ii) TCD 3 – 6 monthly depending on clinical circumstances. This may revert to annually if the TCD normalises
**Haemorrhagic Stroke**
Chronic red cell transfusion has not been shown to be as effective in prevention of recurrent haemorrhagic stroke as it has in infarctive stroke. In fact some patients receiving long term red cell transfusions for infarctive stroke have developed haemorrhagic stroke.

It is important to establish early in the course of evaluating a patient with a new stroke that there is no haemorrhagic component. A bleeding aneurysm may require prompt neurosurgical intervention (e.g. clipping, coil embolisation).

**Silent Cerebral Infarction**
There is some data to support chronic transfusion in the management of ‘silent’ cerebral infarction. However the imaging and treatment requirements are very onerous and educational intervention may be just as effective and less invasive. Historically those patients who have had strokes treated with chronic red cell transfusion have not developed new silent infarcts. (Pegelow and Wang). The use of hydroxy carbamide in this setting is the subject of ongoing research. There is debate on going as to whether those with silent infarcts should be offered chronic transfusion. Currently SCH are not actively seeking silent infarcts in sickle cell anaemia patients with normal TCDs.

7. **Primary Stroke Prevention**

TCD ultrasonography allows non invasive detection of cerebral vasculopathy in children with sickle cell anaemia. Elevated cerebral blood flow velocity in the terminal internal carotid artery and middle cerebral artery predicts an increased risk of stroke. The results of TCD can be divided into stroke risk categories:

- Abnormal (> or = to 200cm/s) (risk of stroke over 3 years, 40%)
- Conditional (170 – 199cm/s)
- Normal (< 170cm/s) (risk of stroke over 3 years, 2%)

(Adams et al)

This classification should be based on the maximal velocity recorded during the examination, with appropriate regard to the settings of the scanning equipment.

However it is important to remember when discussing treatment options with parents that not all children with abnormal TCDs have a stroke (even with no intervention) and that the intervention available is not without risk and inconvenience. Some children with normal TCD can go on to have a stroke.

This discussion should primarily be at consultant level. Hydroxycarbamide can be offered to those families who refuse transfusion for primary stroke prevention. See the Haematology & Oncology Unit guidelines, section 13, Sickle Cell Disease, 1097 Hydroxycarbamide (Hydroxyurea) use in Paediatric SCD (H&O/13/1097).

TCDi (imaging) using duplex scanners can be used to examine children, although some studies have shown that TCDi velocities can be up to 15% lower than those measured by non imaging TCD. Improved technique and a change in imaging parameters can reduce this difference to 10% or less.
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The action taken following the categorisation of results depends on the age of the child and follows the protocol in the algorithm below. Repeat TCD scans should be undertaken at the time intervals recommended. Because of the long-term consequences of starting chronic transfusions in children at high risk, all available data should be considered prior to beginning treatment. This will include a comprehensive neurological assessment and the results of other imaging studies such as MRI/MRA, although these are not used in the risk classification. Appropriate magnetic resonance or CT imaging studies to assess the extent of the cerebrovascular disease should be considered if the child is placed in the high risk category, requiring blood transfusions, although treatment should not be altered or delayed for this reason. There will be a need for some TCD scans once a child has started on chronic transfusions to ensure that blood velocities have decreased to acceptable levels. The time intervals for performing these scans will depend on individual clinical circumstances and should be considered on a case-by-case basis.

Information for families about TCD, stroke risk and possible intervention is available in Haematology Out Patients (Patient information sheet H&O/13/pis ‘Transcranial Dopplers(TCD) and Sickle Cell Disease)

8. References


http://www.rcplondon.ac.uk/pubs/books/childstroke/childstroke_guidelines.pdf

Transcranial Doppler Scanning for Children with Sickle Cell Disease Standards and Guidance 2nd edition September 2016. UK Forum on Haemoglobin Disorders


Optimizing Hydroxyurea therapy for sickle cell anaemia Russell E Ware ASH 2015
Stroke Prevention and Management in Sickle Cell Disease


Antenatal and Newborn Screening Programmes

Sickle Cell and Thalassaemia Standards and Guidance (March 2009)

Published by the NHS Sickle Cell and Thalassaemia Screening Programme, King’s College London.

ISBN 978-0-9554319-3-7
Appendix I

Protocol for Trans Cranial Doppler (TCD) ultrasonographic screening of children with sickle cell disease.

**SCD - SS or Sβ0thal**

*Age 2 – 16yrs*

This classification should be based on the maximal velocity recorded during the examination, with appropriate regard to the settings of the scanning equipment.

Doppler evaluation of the carotid arteries in the neck prior to the TCD to detect extracranial disease as this is important to diagnose and will influence the TCD findings.

**Initial TCD**

- Normal < 170cm/s
  - Repeat TCD within 1 year*
- Conditional 170 – 199cm/s
  - Repeat TCD between 6 weeks and 3 months*
- Abnormal > = 200cm/s
  - Repeat scan within 1 week.
  - Discuss stroke risk and consider chronic transfusion

**Brain MRI/MRA**

- looking for vessel disease and silent infarcts

*Consider more frequent TCD if young child or sibling with conditional or abnormal TCD.

+ Depends on the age of the child and the blood velocity. Children below 10 years and those with higher velocities are considered to be at higher risk and should be rescanned soon.

Arterial blood velocities must be examined in the distal intracranial carotid artery (dICA), middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA) on both sides of the head.
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The classification should be based on the highest time averaged maximum mean velocity (TAMMV) measured in the distal ICA or MCA during the examination. The risk category is based on the TAMMV cut-offs as identified in the STOP trial.

Inadequate imaging or unusually low MCA TAMMV are also abnormal as follows:

- **Unusual low velocity**: Velocities <70cm/s in MCA
- **Asymmetrical velocities**: Velocity <50% of contralateral MCA
- **Inadequate image**: Incomplete images and measurements from dICA, MCA, ACA or PCA bilaterally

Low velocities or pronounced asymmetry are indicative of possible occlusion and should prompt further investigations and alternative imaging. A TCD scan would be defined as non-diagnostic if for whatever reason unsatisfactory results were obtained. This might be due to causes such as an uncooperative child (in which case a repeat scan should be considered), poor scanning window (in which case an alternative scanning method such as MRI/MRA should be considered) or previous stroke.

The original STOP study did not include a category for abnormal velocities in the ACA. Subsequent analyses indicate a raised risk of stroke in cases of ACA velocities ≥170 cm/s. These findings should prompt early repeat scanning with further clinical and imaging investigation for possible intervention. ACA velocities ≥ 200 cm/s should be considered as high risk.

For inadequate scans Repeat if child is uncooperative, use alternative imaging if poor scan window

Consider further imaging (MRI/MRA) for abnormal findings

**TCD scanning decision tree**

For any particular child, detailed clinical knowledge and judgement might override this guidance.