EUROPEAN HEMATOLOGY ASSOCIATION

Update on hemoglobinophaties - Section 3

Neurological complications of sickle cell disease

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Take-home messages

- Pathologies underlying acute neurological events in sickle cell disease include (1) arteriopathy: cervical carotid and vertebral and intracranial arterial stenosis, dissection, occlusion and aneurysm, (2) venous sinus thrombosis (3) posterior reversible encephalopathy syndrome (4) shunting at pulmonary and cardiac level
- While emergency transfusion is the mainstay of management of acute neurological problems, consultation with intensive care and the stroke unit enables appropriate supportive management, while thrombolysis is not contraindicated in adults with SCD and stroke within the 4.5 hour window from onset and if hemorrhage has been excluded by CT scan
- Velocities >200 cm/sec on transcranial Doppler ultrasound (TCD) predict stroke in children; indefinite transfusion or 1 year of transfusion followed by Hydroxyurea in those with normal magnetic resonance angiography prevents stroke.

Abstract

Children with sickle cell disease may have a wide variety of neurological syndromes, including ischemic and hemorrhagic stroke, anterior and posterior territory transient ischemic attacks (TIAs), seizures, headache, coma, visual loss, altered mental status, 'silent' cerebral infarction (SCI) on neuroimaging and cognitive difficulties. Those with clinical ischemic stroke usually have stenosis or occlusion of the cervical and intracranial arteries. Venous sinus thrombosis may cause coma with or without ischemic or hemorrhagic stroke. Seizures are associated with cerebrovascular disease and SCI but may also occur secondary to posterior reversible encephalopathy syndrome (PRES). For hemorrhagic stroke, aneurysms are common in adults but children may present with hypertension secondary to transfusion or corticosteroids, possibly PRES. Long term transfusion prevents recurrent infarction in those with SCI but does not appear to improve intelligence quotient. Velocities >200 cm/sec ontranscranial Doppler ultrasound (TCD) predict stroke in children; indefinite transfusion or 1 year of transfusion followed by Hydroxyurea in those with normal magnetic resonance angiography prevents stroke. The interaction between genetic and modifiable environmental effects should be investigated. As hemoglobin oxygen desaturation and airway obstruction appear to be risk factors, randomised trials of overnight respiratory support in older children and adults, and of Montelukast in preschool children, are underway.

Introduction

There is a broad spectrum of acute presentation with CVA and other neurological complications in patients with SCD.[1] Without preventative strategies, clinical stroke, with focal signs lasting >24 hours (Table 1), is 250 times more common in children with SCD than in the general pediatric population, and commonly presents 'out-of-the-blue' in an apparently well child. Patients with SCD also have transient ischemic attacks (TIAs) with symptoms and signs resolving within 24 hours, although many of these individuals are found to have recent cerebral infarction or atrophy on imaging (Table 1). In addition, seizures, headache[2] and coma are common in patients with SCD. Altered mental status can occur in numerous contexts, including acute chest syndrome (ACS),[3] acute anemia e.g. aplastic secondary to parvovirus,[4] after surgery, transfusion[5] or immunosuppression, and apparently spontaneously. These patients may have had an ischemic or hemorrhagic cerebrovascular accident (Table 1), although there is a wide differential of alternative focal and generalized vascular and non-vascular pathologies, including posterior reversible encephalopathy syndrome (Table 1),[6] and shunting at pulmonary or cardiac level.[7]

As well as those with obvious acute neurological events, patients with SCD accumulate 'silent' cerebral infarction (SCI) on MRI from infancy through to adulthood,[8-10] characteristically in the anterior and/or posterior borderzones (Table 1), without having had a clinical stroke, although they may have had subtle TIAs, headaches or seizures. Cognitive diffi-

culties affect processing speed, attention and executive function,[11] as well as intelligence.[12]

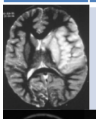
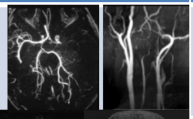
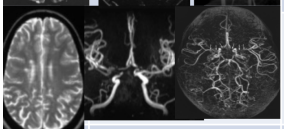
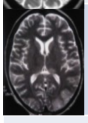
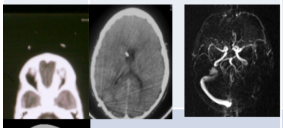
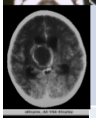
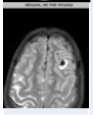
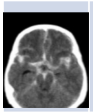
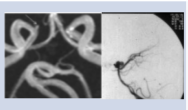
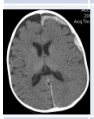
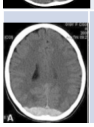
Current state of the art

Acute neurological problems

When a patient with SCD presents with acute neurological problems, the priority is to transfuse to improve brain tissue oxygenation. Attention to fluid balance, blood pressure and oxygenation is also likely to improve neurological outcome and there should be consultation with Intensive Care and with the local Stroke Unit, as in adults, in the absence of hemorrhage on emergency CT scan, thrombolysis is not contraindicated within a 4.5-hour window.[13]

As these patients are often admitted to a peripheral hospital without facilities for emergency imaging under general anesthesia, acute imaging is often not performed. Except in hemorrhage (Table 1), CT may not show abnormalities within the

Table 1. Neurological complications in sickle cell disease.

MRI	Vascular: MRA/MRV	Clinical and pathological findings	Treatment
		Sudden onset **stroke** with arterial territory infarct: stenosis, occlusion, dissection ICA, MCA. Exclude shunting	Transfuse, O2, Intensive care Stroke Unit -TL
		**Silent cerebral infarction**: no stroke but may have had seizures. Stenosis, occlusion, moyamoya ICA,MCA. Shunt	?Transfuse; ?Hydroxyurea
		**PRES: Posterior reversible encephalopathy syndrome** after rapid transfusion, acute chest, hypertension	Treat seizures, hypertension, hypoxia
		**Venous sinus thrombosis**: presents c hemiplegia, seizures, coma. CT : empty delta, thrombus, CTV /MRV	?Transfuse; rehydrate, anticoagulate
		**Abscess:** seizures, headaches, coma, raised intracranial pressure, fever	Antibiotics Neurosurgeon Intensive care
		**Intracerebral haemorrhage:** sudden onset very severe headache, coma. Venous , hypertension, aneurysm	Neurosurgeon Intensive care
		**Subarachnoid haemorrhage:** sudden onset very severe headache, coma . Aneurysm, venous , hypertension	Neurosurgeon Intensive care
		**Subdural haemorrhage:** headache, coma, raised intracranial pressure, skull infarction. Exclude trauma /NAI	Neurosurgeon Intensive care
		**Extradural haemorrhage:** headache, coma, raised intracranial pressure, skull infarction. Exclude trauma /NAI	Neurosurgeon Intensive care

first 24 hours after the onset of neurological symptoms. Diffusion-weighted MRI (DWI) can show ischemic regions within minutes, i.e. before irreversible infarction has occurred, and can also help to distinguish between alternative pathologies, while T2-weighted MRI is usually abnormal within a few hours. There is therefore a case for emergency MRI (Table 1), which might reveal:

- acute infarct (detected on DWI) in the distribution of an artery (cervical or intracranial stenosis, occlusion or dissection; shunting)
- abnormality in the basal ganglia, or deep white or grey matter of the border zones (old 'SCI' secondary to cervical or intracranial stenosis, occlusion or dissection; shunting)
- occipito-parietal or thalamic involvement (sinovenous thrombosis)
- posterior reversible encephalopathy syndrome
- subarachnoid or intracerebral hemorrhage[14] (acute hypertension/sinovenous thrombosis/aneurysm or moyamoya collateral rupture)

Between 60% and 90% of patients with SCD and acute stroke in an arterial distribution have abnormal findings on magnetic resonance (MRA) angiography (Table1). Typical abnormalities include

- stenosis or occlusion of the cervical or intracranial carotid or middle cerebral arteries
- vertebral or carotid dissection[15]
- moyamoya (bilateral severe stenosis or occlusion of the internal carotid arteries with collateral formation)
- small vessel vasculitis
- aneurysm[10,14]

Venous sinus thrombosis (Table 1)[16] is probably underdiagnosed; if emergency MRA is normal, MR or CT venography should be considered.

Secondary prevention

Clinical stroke

Despite a lack of high quality evidence,[17] blood transfusion, ideally erythrocytapheresis because of the lower rate of iron accumulation, has been the mainstay for secondary stroke prevention. Moyamoya syndrome is associated with an increased risk of stroke recurrence which appears to be reduced by revascularisation.[18] The majority of patients have stable findings on neuroimaging after hematopoietic stem cell transplant but although some improve, around 1 in 6 deteriorate.[19]

Silent cerebral infarction

The Silent Cerebral Infarct Transfusion was conducted to determine whether blood transfusion therapy for 36 months prevents progression of infarct recurrence (stroke or SCI) in children with SCA (5 to 15 years of age) and pre-existing SCI. In participants receiving regular blood transfusion, there was 58%relative risk reduction in cerebral infarct recurrence (stroke or new or progressive silent cerebral infarcts) when compared to the children in the observation arm.[20] The evidence is of moderately good quality,[17] but the number of children with SCA and SCI who need to be transfused to prevent one recurrent infarct is 13.8 and there is no evidence of benefit on intelligence so the high burden of regular blood transfusion may decrease enthusiasm for this management strategy.

Primary prevention of stroke

Time-averaged maximum velocity on transcranial Doppler ultrasound (TCD) >200 cm/sec predicts clinical stroke in children with SCD not receiving regular blood transfusion therapy (3-6weekly to hemoglobin S level<30%). The number needing indefinite transfusion to prevent one stroke is 7 but the strategy has dramatically reduced the stroke rate.

The Transfusions Switching to Hydroxyurea (TWiTCH) trial,[21] was a primary stroke prevention trial for SCD children who had received at least 12 months of blood transfusion for TCD velocities >200 cm/sec. Standard therapy was continuation with blood transfusion therapy and chelation and experimental therapy was hydroxyurea therapy and phlebotomy, although there was a median overlap of 6 months. The primary outcome was TCD velocity; after the first interim analysis, the trial was ended early because non-inferiority was demonstrated. Trial design limitations included the short period of time on hydroxyurea therapy at maximum tolerated dose, approximately 18 months, and the exclusion of c.10% of children with abnormal TCD *and* MRA, meaning that management for this group cannot be determined from the TWiTCH trial, but it does appear that hydroxyurea is effective in maintaining a lower TCD in those with normal MRA.

Future perspectives

Genetic and environmental risk factors for stroke in sickle cell disease

There appears to be a familial predisposition to stroke and to high blood flow velocities in SCD, indicating that genetic fac-

tors probably play a role. Siblings might, however, also share adverse environmental conditions, including poverty, air pollution and poor nutrition. Difficulties in sleeping are well-recognized in SCD and the prevalence of sleep-disordered breathing, including snoring, arousals, obstructive sleep apnea (OSA) and nocturnal desaturation, is higher in SCD than in the general population and is associated with cerebral vasculopathy[22] and cognitive dysfunction. These may be useful biomarkers alongside quantitative MRI for randomised controlled trials of treatment, e.g. of overnight respiratory support in older children and adults, and of Montelukast in preschool children.

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