Laboratory associations with transcranial Doppler categories in sickle cell disease

[1]Dipty Jain and [2,3]Fenella J Kirkham

[1]Government medical College, Nagpur, India; [2]Developmental Neurosciences Section, UCL Great Ormond Street Institute of Child Health, London, UK; [3]Clinical and Experimental Sciences, University of Southampton, Southampton, UK

Correspondence to:

Fenella Kirkham,

Developmental Neurosciences Section,

UCL Great Ormond Street Institute of Child Health,

London, UK

fenella.kirkham@ucl.ac.uk

The manuscript by Mahmoud et al (1) provides insight into the pathophysiology of cerebrovascular pathology in children with homozygous sickle cell disease (SCD), compound heterozygotes with haemoglobin Sβ-thalassaemia and controls. They found that platelet-derived growth factor (PDGF-AA) and homocysteine levels were higher in patients with SCD than controls in line with previous data (2), particularly in studies from the Middle East and India, perhaps related to a higher prevalence of vitamin deficiencies (3). High homocysteine levels have long been recognised as a risk factor for vascular disease and the thermolabile variant of the methylene tetrahydrofolate reductase gene is associated with ischaemic stroke in adults with SCD (3)and predicted recurrence in children with stroke(4). PDGF-AA is associated with vascular remodelling in response to challenges including infection, e.g. with Cytomegalovirus (5;6), and increased shear stress related to high flow. Non-imaging and imaging transcranial Doppler (TCD) may be used to measure cerebral blood flow velocity (CBFV) in the intracranial vessels, including the middle cerebral and distal internal carotid arteries. High CBFV may be secondary to high cerebral blood flow (CBF) or to narrowing (stenosis) of the blood vessel; magnetic resonance imaging, including arteriography (MRA) and measurement of CBF, may allow the distinction. However, the non-imaging TCD categories defined by Adams based on prediction of stroke over several years in children with SCD (Normal velocity <170 cm/sec, Conditional ≥170<200 cm/sec, Abnormal ≥200 cm/sec)(7) have proved practical, as treatment with blood transfusion (8) and/or hydroxyurea (9;10) reduces CBFV and prevents the majority of strokes. These categories were used to explore associations with PDGF-AA and homocysteine and the former, in particular, appeared to be a sensitive and specific marker of non-normal TCD in this (1) and a previous (2) study. Blood transfusion appears to reduce PDGF-AA, potentially

preventing stroke by preventing vascular remodelling (11) but there are few data on the effect of hydroxyurea. Despite the evidence for an association with recent infection(12;13), here are few data in paediatric or adult (14;15) ischaemic or haemorrhagic (16) stroke other than that associated with SCD but there is some evidence for an association with moyamoya (17) and arteriovenous malformation (16) . Further studies in SCD might look at whether there is a tighter association of PDGF-AA levels with vasculopathy defined on MRA (18), which is associated with abnormal white matter integrity even if mild, (19) at any association with haemoglobin in other anaemias, which are common in children with stroke (20), and at the accuracy and cost-effectiveness of serum biomarkers compared with TCD in predicting stroke risk.

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