Cerebral vasculopathy in patients with sickle cell disease and stroke: now you see it, now you don't

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Strokes are one of the most devastating complications of sickle cell disease (SCD). Until recently SCD was the main cause of ischemic strokes in children in the USA and many other countries. After the development of an ischemic stroke children have to be placed on chronic transfusions to prevent a recurrence although the risk may be lower if the stroke occurred during another acute event.[1] The incidence of ischemic strokes was significantly reduced after the advent of transcranial Doppler (TCD) screening and the institution of transfusion therapy for primary prevention in children found to be at high risk. More recently hydroxyurea treatment was shown to be equally effective in primary stroke prevention in children with abnormal TCD both in the setting of high-income countries as well as in low income countries in sub-Saharan Africa.[2] Stem cell transplantation is also effective in secondary prevention in children who have already had a stroke as well as primary prevention in children with abnormal TCD. The epidemiology of ischemic strokes was defined in a seminal study of a large number of patients which showed that ischemic strokes were more prevalent in the first decade of life and the vast majority of patients had either homozygous sickle cell anemia (HbSS) or heterozygous HbSβ^0 thalassemia, with few, if any, strokes occurring in patients with HbSC.[3] As a result, most studies have since focused on the first two genotypes, and little is published about strokes in other genotypes. The pathophysiology of cerebral ischemic strokes remains somewhat of a mystery. Originally thought to be caused by small vessel vasculopathy these events were demonstrated to be due to large arterial vasculopathy in the anterior cerebral circulation and the vessels of the circle of Willis by Stockman *et al*.[4] and others. It remains unknown why the posterior circulation is relatively spared and what are the etiological drivers for stroke risk. Furthermore, recent studies, using techniques such as magnetic resonance angiography demonstrate that 30-40% of children with ischemic strokes do not have demonstrable cerebral arterial stenosis.[5]

In a study published in the current issue of *Haematologica*, Linguet and colleagues describe strokes that occurred over a period of 13 years in a group of more than 1,500 children with SCD at a comprehensive care center in France.[6] Relatively few strokes were reported in this group, who had access to TCD screening. Of a total of 25 affected children, 12 had what the authors refer to as atypical strokes without evidence of cerebral arteriopathy. These patients were older and 25% had a HbSC genotype. Despite the small number of patients important themes emerged from this study.

The first theme is that these atypical strokes occurred in the setting of other complications of SCD. These included fat embolism syndrome, a complication that seems to be more common in patients with HbSC,[7] sepsis and acute chest syndrome as well as admission to an Intensive Care Unit. The inability of the cerebral circulation to adapt to changing needs of oxygen has been reported in SCD but this has not been studied in the context of exacerbated responses and vasoconstriction secondary to other insults and acute complications. This issue is worthy of further investigation. With increased accessibility of TCD a higher proportion of strokes are likely to occur in the setting of acute events in patients with normal TCD at screening. While these strokes may not require long-term transfusion for secondary prevention as shown in the current study, prevention may be possible by prompt management of the initial event, for example by initiating exchange transfusion followed by therapeutic plasma exchange early for fat embolism.[7]

The second theme is that the posterior circulation was involved in several patients. While typically spared in ischemic strokes the posterior circulation is not normal in SCD. The fact that the cerebral blood flow is increased in SCD to keep up with oxygen demand may render many segments of the brain relatively ischemic and liable to damage during acute events. The posterior circulation has been shown to have increased cerebral blood velocities and cerebral

blood flow in patients with SCD;[8,9] the significance of this should be explored in more depth. Furthermore, SCD is a known risk for posterior reversible encephalopathy syndrome (PRES) and several factors have been invoked to explain the failed cerebral autoregulation and endothelial dysfunction in this setting.[10]

The third theme concerns the deleterious impacts of certain treatment modalities used in SCD. First among these are corticosteroids, the use of which has been associated with multiple complications of sickling in SCD, including the precipitation of painful crises, hemorrhagic strokes, and now ischemic strokes. Thus, caution is urged when these agents must be used and patients should be adequately prepared, otherwise alternative therapies should be considered, for example rituximab and intravenous immunoglobulins in delayed hemolytic transfusion reactions. Attention should also be paid to the role of hyperviscosity in SCD. This is often ignored and the consequences, as demonstrated by Linguet *et al.*, may be dire. While it is unclear how to mitigate the risk of hyperviscosity in acute settings, judicious use of transfusions, preferential use of exchange transfusions and in some cases, phlebotomy is recommended to prevent hyperviscosity from developing.

Finally, as described in a recent editorial to an issue of Frontiers in Physiology, in SCD there is "evidence of local ischemia despite global hyperemia" in the brain. Arteriopathy may, however, only be seen after its deleterious effects become manifest or by using appropriate techniques that are still not well developed for clinical use. The pathology is always there but, as in the magician's adage, "now you see it, now you don't".

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