Review Article

The Genetic Landscape of Cerebral Steno-Occlusive Arteriopathy and Stroke in Sickle Cell Anemia

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Sickle cell disease (SCD) is one of the most common autosomal recessive diseases in humans, occurring at a frequency of 1 in 365 African-American and 1 in 50 sub-Saharan African births. Despite progress in managing complications of SCD, these remain a major health burden worldwide. Stroke is a common and serious complication of SCD, most often associated with steno-occlusive cerebral arteriopathy, but little is known about its pathogenesis. Transcranial Doppler ultrasonography is currently the only predictive test for future development of stroke in patients with sickle cell anemia and is used to guide preventative treatment. However, transcranial Doppler ultrasonography does not identify all patients at increased risk for stroke, and progressive arteriopathy may occur despite preventative treatment. While sibling studies have shown a strong genetic contribution to the development of steno-occlusive arteriopathy (SOA) in SCD, the only genome-wide association study compared a relatively small cohort of 177 patients with stroke to 335 patients with no history of stroke. This single study detected variants in only 2 genes, *ENPP1* and *GOLGB1*, and only one of these was confirmed in a subsequent independent study. Thus, the underlying genes and pathogenesis of SOA in SCD remain poorly understood, greatly limiting the ability to develop more effective preventive therapies. Dissecting the molecular causes of stroke in SCD will provide valuable information that can be used to better prevent stroke, stratify risk of SOA, and optimize personalized medicine approaches.

Key Words: Stroke—moyamoya disease—sickle cell disease—sickle cell anemia—steno-occlusive arteriopathy.

Introduction

Sickle cell disease (SCD) is among the most common autosomal recessive diseases in humans, occurring at a frequency of 1 in 365 African-American and 1 in 50 sub-Saharan African births. Sickle cell anemia (SCA) is a subclass of SCD defined as having a homozygous Glu7Val mutation in the beta-globin gene (HbSS) or compound heterozygous sickle beta zero thalassemia (HbSβ^0). More than 300,000 infants with SCD are born worldwide every year, and estimated 100,000 individuals in the USA and 20-25 million worldwide live with SCD, with about 80% living in sub-Saharan Africa.[1-5] Both ischemic and hemorrhagic strokes are common and devastating complications of SCA.

Patients with SCA are at risk for an increasing number of neurocognitive complications with age. Notably, cognitive impairment increases with age in children with SCA,

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even in the presence of normal brain imaging.[6] Neuropsychological testing in neurologically asymptomatic adults has demonstrated diminished cognitive function compared to controls that worsen with advancing age.[7]

Treatment with chronic red blood cell (RBC) transfusion or hydroxyurea significantly reduces morbidity and mortality but does not cure the disease and is not readily available to most of the millions of people living with SCA. While hematopoietic cell transplantation can successfully cure SCA, this resource-intensive therapy is associated with treatment risks of its own and is not feasible for the vast majority of individuals living with SCA due to limited donor availability and/or cost.[8]

Addressing the ongoing morbidity and mortality from SCA worldwide will require improved access to medical care and preventative treatments, and the development of new, biologically relevant and less costly therapies directed at the underlying pathogenesis. Genetic predictors of disease outcome can be used to direct high risk and resource-intensive therapies to those at the highest risk, avoid use of unneeded and burdensome therapies to those at low risk, and facilitate the development of new treatment strategies through improved understanding of underlying pathogenesis.

Stroke and Cerebral Steno-Occlusive Arteriopathy in SCA

Patients with SCA produce defective hemoglobin that damages and deforms RBC membranes, causing hemolysis which, in combination with leukocytosis, triggers a cascade of pathologic events including inflammation, hypercoagulability, endothelial dysfunction, and vaso-occlusion.[9] Without treatment, 7%-12% of individuals with SCA will have an overt stroke by 20 years, and 24% by 45 years.[10-12]

At least 85% individuals with SCA presenting with overt stroke—whether ischemic or hemorrhagic—will have stenosis or occlusion of large cerebral blood vessels on neuroimaging.[13-15] Progressive narrowing of the intraluminal diameter of the internal carotid arteries (ICAs) and middle cerebral arteries (MCAs) reduces blood flow to the cerebral hemispheres, resulting in downstream vasodilatation of cortical vessels and recruitment of collateral vascular pathways.[16] Cerebral catheter angiogram (CCA; Fig 1) shows progressive arterial narrowing of the distal ICA, proximal MCA, and often anterior cerebral arteries with moyamoya ("puff of smoke") collaterals at the base of the brain.[13] Moyamoya can rarely involve the proximal branches of the posterior cerebral arteries as well.[15] Brain magnetic resonance imaging and magnetic resonance angiography (MRA) are increasingly used in place of CCA to diagnose moyamoya, which is particularly important in patients with SCA who are at increased risk of thrombotic complications.[17,18] In addition, magnetic resonance imaging and MRA can show evidence of slow blood flow, impaired perfusion, and ischemic injury, typically in a watershed distribution, associated with moyamoya.

In the literature, various terms are used to describe the cerebral arteriopathy of SCA including stenosis, occlusion, or stenotic vasculopathy of the circle of Willis, large vessels, or carotid circulation.[13,14,19] We propose the term "steno-occlusive arteriopathy" (SOA) to encompass the spectrum of SCA-associated arteriopathy, from elevated Transcranial Doppler (TCD) velocities that likely represent reversible MCA narrowing to the most severe arteriopathy characterized by moyamoya syndrome.

SOA has been identified as a risk factor for stroke as 80%-90% of children with SCA who have SOA on vascular imaging have a history of stroke[19-23] and are at high

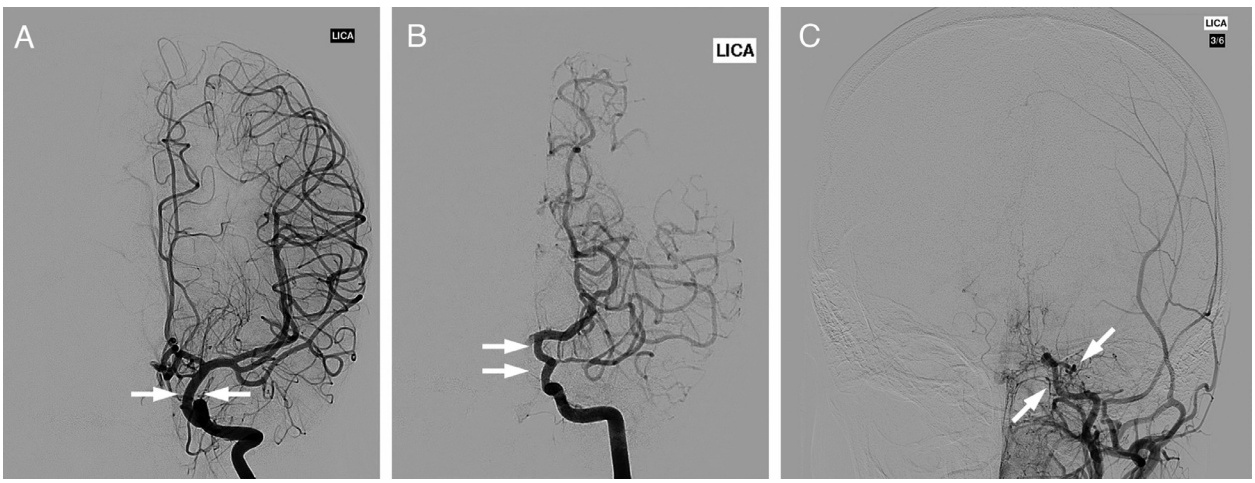

Figure 1. *Frontal views of cerebral catheter angiograms from 3 different individuals showing (A) normal left ICA, with robust filling of MCA (arrow) and MCA distribution arteries in a patient without SCA for comparison; (B) severe stenosis of the origin of the left MCA (arrow) with decreased filling of MCA distribution arteries in a patient with SCA; and (C) complete occlusion of the distal ICA (arrow) with no filling of MCA distribution arteries in another patient with SCA. Abbreviations: ICA, internal carotid artery; MCA, middle cerebral artery; SCA, sickle cell anemia.*