



Original Article

Large-Vessel Vasculopathy in Children With Sickle Cell Disease: A Magnetic Resonance Imaging Study of Infarct Topography and Focal Atrophy



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ABSTRACT

BACKGROUND: Large-vessel vasculopathy (LVV) increases stroke risk in pediatric sickle cell disease beyond the baseline elevated stroke risk in this vulnerable population. The mechanisms underlying this added risk and its unique impact on the developing brain are not established. **METHODS:** We analyzed magnetic resonance imaging and angiography scans of 66 children with sickle cell disease and infarcts by infarct density heatmaps and Jacobian determinants, a metric utilized to delineate focal volume change, to investigate if infarct location, volume, frequency, and cerebral atrophy differed among hemispheres with and without LVV. **RESULTS:** Infarct density heatmaps demonstrated infarct “hot spots” within the deep white matter internal border zone region in both LVV and non-LVV hemispheres, but with greater infarct density and larger infarct volumes in LVV hemispheres (2.2 mL versus 0.25 mL, $P < 0.001$). Additional scattered cortical infarcts in the internal carotid artery territory occurred in LVV hemispheres, but were rare in non-LVV hemispheres. Jacobian determinants revealed greater atrophy in gray and white matter of the parietal lobes of LVV compared with non-LVV hemispheres. **CONCLUSION:** Large-vessel vasculopathy in sickle cell disease appears to increase ischemic vulnerability in the borderzone region, as demonstrated by the increased frequency and extent of infarction within deep white matter, and increased risk of focal atrophy. Scattered infarctions across the LVV-affected hemispheres suggest additional stroke etiologies of vasculopathy (i.e., thromboembolism) in addition to chronic hypoxia-ischemia.

Keywords: sickle cell, stroke, vasculopathy, infarction, atrophy, MRI, heatmap

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Introduction

Stroke is a well-recognized, sometimes devastating, consequence of sickle cell disease (SCD).¹ Approximately one in three affected children has radiographic evidence of ischemic strokes before adulthood.² In a minority of

patients, strokes are accompanied by acute symptoms and focal deficits, termed “overt” strokes, whereas a much larger proportion of children are affected by nonlocalizable ischemic brain injury, termed “silent” strokes.

Beyond ischemic brain injury, recent attention has focused on progressive cognitive decline and failure of

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normal brain development in children with SCD, even in the absence of stroke.^{3,4} Outside of SCD, multiple studies across ages and diseases have found a correlation between reduced brain tissue volumes and lower cognitive performance.^{5,6} In a prospective longitudinal morphometry study of children with SCD, Chen et al.⁷ identified reduced gray matter volume with increasing age in SCD compared with healthy children, suggesting early onset of generalized atrophy in SCD. Baldeweg et al.⁸ noted a reduction in gray and white matter density in children with SCD—with and without infarcts—suggesting ongoing neuronal and axonal loss. The Cooperative Study of Sickle Cell Disease followed young children with SCD with serial magnetic resonance imaging (MRI) to identify the spectrum of brain abnormalities.⁹ In addition to ischemia, atrophy was a major contributor to brain injury, occurring in 19% of the population. Of those with atrophy, 35% demonstrated generalized atrophy and 74% demonstrated focal regions of atrophy. Nearly 50% of the children with focal atrophy had no sign of stroke, suggesting that focal brain regions are susceptible to injury even in the absence of stroke.

Large-vessel vasculopathy (LVV), including stenocclusive disease and moyamoya syndrome, occurs in 12% to 23% of children with SCD, and substantially increases stroke risk.^{2,10} Autopsies of children with SCD and LVV demonstrate intimal hyperplasia of the distal internal carotid artery (ICA) and proximal arteries of the circle of Willis, most commonly the middle cerebral artery (MCA) and anterior cerebral artery (ACA),¹¹ similar to intimal thickening described in other non-SCD moyamoya disease cases.^{12,13} LVV is a known risk factor for both overt¹⁴ and silent¹⁵ stroke incidence and recurrence. In a cohort study of 40 children with SCD on chronic transfusion therapy for secondary stroke prevention, children with progressive LVV were found to have a particularly high risk of recurrent stroke (relative risk = 12.7) compared with children without progressive LVV.¹⁵

To further our understanding of brain injury in children with SCD and LVV, we evaluated (1) the extent and pattern of infarction and (2) focal atrophy within hemispheres affected by LVV compared with hemispheres unaffected by LVV. We hypothesized that infarct distributions would be more extensive with multiple infarction patterns in LVV-affected hemispheres and that focal atrophy would be more prevalent in LVV hemispheres, even after adjustment for infarct volume.

Methods

The institutional review board at Washington University reviewed and approved this study. A waiver of consent was provided. This was a retrospective analysis of MRIs and magnetic resonance angiograms (MRAs) clinically obtained on children with SCD attending the Sickle Cell Disease Clinic at St. Louis Children's Hospital between 2004 and 2014. In 2006, it became clinical practice to obtain a screening MRI and MRA on all children with SCD at age six years, or when developmentally able to tolerate a scan without sedation. Children undergo additional neuroimaging if they present with new neurological signs or symptoms, severe or recurrent headaches, or school difficulties. MRI/MRA studies were performed on a 1.5T Siemens Sonata, 1.5T Siemens Avanto, or 3T Siemens Trio MRI scanners (Siemens Healthcare, Malvern, PA), with standard sequences including T1 magnetization-prepared pulse and rapid acquisition gradient echo (MPRAGE), T2 turbo spin echo, axial and coronal fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted

imaging, diffusion-weighted imaging, and time-of-flight head MRA. We defined LVV as any vascular narrowing within the distal ICA or proximal MCA or ACA near the circle of Willis, regardless of severity to ensure that any potential ischemic consequence of vasculopathy was captured and due to challenges of absolute quantification of vascular stenosis on MRA. Imaging diagnosis of ischemic stroke and LVV was determined by a board-certified neuroradiologist. A board-certified pediatric neurologist reviewed charts to categorize subjects as having any history of overt stroke or silent stroke only. Children who had both overt and silent strokes were classified as overt stroke. The history of overt and silent stroke was obtained to give a description of stroke in this population, but was not a distinction made for the heatmap analysis described below. SAS 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses. Categorical values were compared with χ -square or Fisher's exact test, and continuous variables with a Mann-Whitney U test.

Infarct heatmaps

The most recent MRI and MRA images were used for analysis if a participant had multiple scans over the 10-year period. Age at the time of scan was recorded. As some individuals had vasculopathy present in one hemisphere while absent in the other, each cerebral hemisphere was individually categorized as "LVV" (vasculopathy present) or "non-LVV" (vasculopathy absent), based on the corresponding MRA. Infarcts were defined as an area of abnormally increased signal on T2 FLAIR images, without regard to clinical symptomatology (i.e., overt versus silent stroke).⁹ Regions of infarction within each hemisphere were manually delineated on the FLAIR images using publicly available Medical Image Processing, Analysis and Visualization (MIPAV) software (mipav.cit.nih.gov) to form an infarct mask for each subject. FMRIB's (<https://fsl.fmrib.ox.ac.uk>) Linear Image Registration Tool (FLIRT) coregistered FLAIR images to the subject's T1 MPRAGE map with rigid body registration.¹⁶ Brain tissue was segmented into gray and white matter using FMRIB's Automated Segmentation Tool (FAST).¹⁷ Hemispheres were separated and sorted according to LVV status. Right hemispheres were flipped to orient as left hemispheres. Hemispheres were coregistered to a symmetric human brain atlas defined by the International Consortium for Brain Mapping (<http://nist.mni.mcgill.ca/?p=904>) using ANTS nonlinear coregistration (<http://stnava.github.io/ANTs/>).^{18,19} Using this approach, two infarct density heatmaps were obtained: (1) hemispheres with LVV and (2) hemispheres without LVV. Infarct volumes from individual hemispheres were calculated using Python (www.python.org).²⁰

The LVV and non-LVV density heatmaps were thresholded at 3% infarct density to include areas of infarction occurring in two or more subjects. The LVV and non-LVV density heatmaps were overlaid to form a common infarct map. The overlapping infarct volume between LVV and non-LVV heatmaps was calculated and compared with infarct volume for LVV and non-LVV maps.

Atrophy analysis

In this study, the term "atrophy" is used to describe a smaller tissue volume, but without ability to determine if it is due to impaired brain growth (delayed/stunted development) or tissue volume loss (true atrophy). Jacobian determinants were obtained to quantify atrophy. Individual MRIs were registered voxel-wise to a bilaterally symmetric atlas of 152 young adult brains.²¹ As we expected differences in head and brain size due to the younger ages of our subjects, images were first aligned to the template with rigid-body linear coregistration. This method allows for intracranial volume normalization due to difference in head size and shape between the individual and the template, as may be expected by age variation. Next, we performed nonlinear coregistration, leading to local brain deformation to account for shifts in local brain volume. During this step, a Jacobian matrix of the deformation vectors is calculated for each voxel as it expands or contracts to align with the template during the nonlinear registration process. The determinant of this matrix provides a quantitative measure of the local volume adjustment.²² A determinant less than 1 denotes expansion of the original voxel into the template space, and a determinant greater than 1 denotes

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