Published in final edited form as:

Pediatr Neurol. 2017 April ; 69: 49–57. doi:10.1016/j.pediatrneurol.2016.11.005.

Large Vessel Vasculopathy in Children with Sickle Cell Disease: an MRI 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 (SCD) 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 (MRI) and angiography (MRA) scans of 66 children with SCD 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 borderzone region in both LVV and non-LVV hemispheres, but with greater infarct density and larger infarct volumes in LVV hemispheres (2.2 mL vs 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 to non-LVV hemispheres.

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Authorship:

K.P.G., and A.L.F. designed the study, collected data, interpreted data, and wrote the manuscript. J.M.L. designed the study, interpreted data, and wrote the manuscript. D.K.R. and Y.C. collected, analyzed, and interpreted data. M.E.F. and J.N.R. collected data. M.M.B. performed statistical analysis. C.E., H.A., M.L.H., interpreted data. K.V., R.C.M., J.S.S. interpreted clinical images. All authors critically reviewed and approved the manuscript.

Conflict of Interest Disclosures:

The authors have no conflicts of interest to disclose.

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Conclusion—LVV in SCD appears to increase ischemic vulnerability in the borderzone region, as demonstrated by the increased frequency and extent of infarction within deep white matter, and increase risk of focal atrophy. Scattered infarctions across the LVV-affected hemispheres suggest additional stroke etiologies of vasculopathy (i.e. thrombo-embolism) in addition to chronic hypoxia-ischemia.

Introduction

Stroke is a well-recognized, but devastating consequence of sickle cell disease (SCD).¹ Approximately 1 in 3 children have radiographic evidence of ischemic strokes prior to adulthood.² In a minority of patients, strokes are accompanied by acute symptoms and focal deficits, termed “overt” strokes, while a much larger proportion of children are affected by non-localizable ischemic brain injury, termed “silent” strokes.

Beyond ischemic brain injury, recent attention has focused on progressive cognitive decline and failure of 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. identified reduced gray matter volume with increasing age in SCD compared to healthy children, suggesting early onset of generalized atrophy in SCD.⁷ Baldeweg et al. noted a reduction in gray and white matter density in children with SCD—with and without infarcts—suggesting ongoing neuronal and axonal loss.⁸ The Cooperative Study of Sickle Cell Disease followed young sickle cell children with serial MRIs 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 steno-occlusive 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 (MCA) and anterior cerebral arteries,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 to 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 to 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 MRAs clinically obtained on children with SCD attending the Sickle Cell Disease Clinic at St. Louis Children's Hospital between 2004–2014. In 2006, it became clinical practice to obtain a screening MRI and MRA on all children with SCD at age 6 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 either 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 utilized 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 symptomology (i.e. overt vs. silent stroke).⁹ Regions of infarction within each hemisphere were manually delineated on the FLAIR images using publically 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) co-registered 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 co-registered to a symmetric human brain atlas defined by the International Consortium for Brain Mapping (<http://nist.mni.mcgill.ca/?p=904>) using ANTS non-linear co-registration (<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 to 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 co-registration. This, 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 non-linear co-registration, 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 non-linear 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 contraction. Thus, brain regions with smaller volumes (i.e. more atrophy) would have Jacobian determinants less than 1. Methods for quantifying global and focal atrophy in adult neurodegenerative disease suggest calculation of Jacobian determinants outperforms other methods of atrophy analysis, having been used effectively with both cross-sectional and longitudinal data.^{23,24} Hemispheres were also visually inspected for focal atrophy.

Region of interest (ROI) Jacobian Determinant Analysis

To investigate specific regions of focal atrophy in LVV compared to non-LVV hemispheres, we applied an anatomically segmented lobar atlas to each hemisphere.^{21,25} We applied eight regions of interest (ROIs) to each hemisphere: gray and white matter for frontal, parietal, temporal, and occipital lobes. The average Jacobian determinant value for each of the eight ROIs was the outcome variable of interest for this analysis with vasculopathy status (LVV present/absent) and normalized hemispheric infarct volume as the predictors. Infarct volumes were delineated as described above. A normalized infarct volume was calculated as hemispheric infarct volume divided by the hemispheric intracranial volume to ensure that infarct volume was normalized to head size in children of different ages. Focal atrophy as defined by the average Jacobian determinant was modeled using a generalized mixed linear

model with the repeated effect of each subject contributing two hemispheres and the random effect of intra-subject hemispheres. Both vasculopathy status and infarct volume were modeled as main effects to evaluate the contribution of each variable on prediction of focal atrophy. Age at time of scan was not included as a covariate as all hemispheres were aligned to a common atlas for normalization of variable brain and head size across ages. The functional forms of the residuals were checked to ensure normality of a linear outcome variable. Results of regression coefficient (beta) and standard error (SE) were reported with a p-value less than 0.05 required for significance of either vasculopathy status or infarct volume predicting atrophy within an ROI.

Results

Two-hundred seventy-two children with SCD had clinically obtained MRIs during the study period. Of these, 84 children had evidence of infarct on MRI. Two children had evidence of LVV on MRA, but did not have any infarcts.. Eighteen children were excluded from analysis due to history of hemorrhagic stroke, cyanotic heart disease, brain tumor with associated hydrocephalus or insufficient imaging data (i.e. missing sequences necessary for analysis or motion artifact). Sixty-six had evidence of stroke with sufficient MPRAGE image quality to allow for accurate alignment to the atlas as well as adequate FLAIR image quality for delineation of infarction as described above (Figure 1). Of these 66 children, 23 had LVV. Twenty-one children had a history of an overt stroke. Forty-five children did not have any documentation of overt stroke and had silent strokes only. Table 1 provides demographics of included subjects.

To identify the unique contribution of vasculopathy to imaging characteristics of infarct distribution and focal atrophy, we performed a hemispheric analysis instead of subject-based analysis for the remainder of the study. Twenty-nine LVV hemispheres from 23 subjects (six subjects had bilateral LVV) were compared to 105 non-LVV hemispheres.

Infarction Patterns in LVV and non-LVV Hemispheres

Figure 2 shows the LVV and non-LVV hemispheric infarct density maps. Both LVV and non-LVV hemispheres demonstrated infarct hot-spots within the deep white matter internal borderzone distribution, but the LVV heatmap showed a larger extent and greater density of borderzone region infarction. The peak infarct density within the LVV hemispheres was 32% vs. 10% within non-LVV hemispheres ($p=0.04$). The median infarct volume in LVV hemispheres was 2.2 vs 0.25 mL in non-LVV hemispheres ($p < 0.001$). The non-LVV hemispheres had a low frequency of cortical involvement, with a few cortical infarcts within the cortical borderzone region. In the LVV heatmap, infarcts extended out to the cortex in the anterior and posterior borderzone regions with higher frequency, in addition to other wedge-like regions within the MCA and ACA distribution. LVV hemispheres demonstrated significantly higher gray and white matter infarct volume compared to non-LVV hemispheres ($p < 0.001$) (Table 2). The common infarct region map overlaying LVV and non-LVV heatmaps (thresholded at 3% to exclude the contribution of less than two subjects) confirmed that the deep white matter internal borderzone infarcts occurred in both cohorts.

This common region encompasses 96.5% of the non-LVV heatmap infarct volume, but only 4% of the LVV heatmap infarct volume ($p < 0.0001$).

Focal atrophy in LVV and non-LVV hemispheres

Nineteen of 29 LVV hemispheres (66%) and 30 of 103 non-LVV hemispheres (29%) had focal atrophy on qualitative inspection ($p=0.003$). Figure 3 shows an example of focal atrophy identified qualitatively in the frontal and parietal regions of an individual subject and average Jacobian determinants maps from the LVV and non-LVV hemispheric cohorts. We hypothesized LVV may be associated with chronic ischemia from reduced blood flow within the tissue distal to the stenosis or occlusion as well as focally reduced brain volume because of acute ischemia causing infarction and subsequent atrophy and encephalomalacia. As we found LVV hemispheres to have larger infarct volumes, we modelled both LVV status and infarct volume as independent predictors of atrophy in a generalized mixed linear model. Using the Jacobian determinant within each ROI as the dependent variable within the model allowed us to examine whether or not LVV status was an independent predictor of atrophy. LVV-status had a small, but significant contribution of predicting a smaller Jacobian determinant (i.e. reduced local brain volume or atrophy) within the parietal gray and white matter ROIs. Infarct volume also was a significant predictor of the Jacobian determinants in frontal white matter ROI. These findings suggest that while infarction and subsequent encephalomalacia do contribute to brain atrophy in this population, LVV status is an independent predictor of atrophy even after adjusting for effects of prior infarction (Table 3).

Discussion

Vasculopathy has long been recognized as a risk factor for stroke in pediatric SCD. In this study, we demonstrated the impact of LVV on infarct density and distribution, as well as its impact on the young brain as manifested by focal atrophy. The presence of LVV increased the burden of hemispheric brain injury compared to hemispheres without LVV as evidenced by both greater infarct volume in a wider distribution and greater focal atrophy. We demonstrated high infarct frequency and overlap within the deep white matter of the internal borderzone region, present in children with and without LVV. In LVV hemispheres, the burden and frequency of infarction within this borderzone region was further increased. Wedge-like infarctions extending towards the cortex outside of the borderzone region in several LVV hemispheres suggested additional mechanisms, such as thrombo-embolism, which may place distal territories at heightened stroke risk. This may explain the higher incidence of overt strokes noted within the subjects with LVV. Furthermore, even with adjustment for infarct volume, LVV is a significant predictor of focal atrophy, particularly within the parietal lobe.

The internal borderzone region is highly vulnerable to ischemia with and without LVV

Strokes in SCD can occur in diverse spatial distributions, but have been qualitatively noted to frequently occur within the borderzone and deep white matter.^{11,26–29} The borderzone, also referred to as the “watershed region”, consists of the area supplied by the terminal collaterals of two adjacent large vessels, such as the anterior cerebral artery and middle cerebral artery. The borderzone is suspected to have lower cerebral blood flow (CBF)

relative to other areas of the brain and be uniquely sensitive to states of hypoperfusion, such as in adults with ipsilateral internal carotid artery occlusion.³⁰ We noted both LVV and non-LVV hemispheres demonstrate highest infarct density within this region.

Ischemic strokes occur when oxygen delivery is insufficient to meet the brain's metabolic demands. The cerebral metabolic rate of oxygen utilization (CMRO₂) is the product of: 1) oxygen available in the blood [arterial oxygen content (CaO₂)], 2) rate of blood delivery [cerebral blood flow (CBF)], and 3) the percentage of oxygen taken up by the tissue [oxygen extraction fraction (OEF)]. In SCD, arterial oxygen content (CaO₂) is chronically low due to ongoing hemolytic anemia. Recent demonstration that OEF is globally increased in SCD, likely reflects ongoing compensation for oxygen metabolic stress.³¹ Furthermore, acute ischemic lesions have been identified on brain MRIs in children with SCD experiencing an acute decrease in oxygen delivery, such as in splenic sequestration or aplastic crisis.³²

CBF increases globally in children with SCD via cerebral autoregulation (dilation of the cerebral arterioles) to increase oxygen delivery to the tissues^{33,34} and by increased cardiac output in the setting of anemia.³⁵ However, as the deep borderzone has limited vascular supply relative to the rest of the brain, this region is likely vulnerable to hypoxia/ischemia despite the global increase in CBF, as demonstrated by the infarct hotspots within the borderzone region, regardless of LVV status.

In this cohort, the burden of infarction along the internal borderzone was much greater in LVV hemispheres compared to non-LVV hemispheres, with both larger infarct hotspots in this region and with infarct frequencies peaking at over 30% of the LVV hemispheres compared to 10% in the non-LVV cohort. LVV is likely to further impede CBF in the internal carotid artery vascular territory and may also impair the brain's autoregulatory responses.³⁶ Children without SCD, but with moyamoya vasculopathy, demonstrate a propensity for infarctions within the borderzone regions,³⁷ indicating that LVV alone causes hemodynamic stress via inadequate blood flow to this region. Children with SCD and LVV have two compounding risk factors for infarction: (1) chronically low CaO₂ (hypoxia), and (2) a progressive restriction of CBF (ischemia), leading to both metabolic and hemodynamic stress. This may explain the greater extent and higher frequency of deep white matter borderzone infarctions in LVV hemispheres compared to the non-LVV hemispheres. In non-SCD adults with internal carotid artery occlusion, hemispheric OEF is a strong predictor of ipsilateral stroke, reflecting an increase in OEF to compensate for restricted CBF as a means to maintain CMRO₂. In adults with progressive MCA stenosis, increased hemispheric OEF was detectable prior to detectable differences in CBF, thus marking early hemodynamic stress.³⁸ Prospective investigation into global and deep borderzone CBF and OEF may further elucidate mechanisms of ischemic vulnerability.

Vasculopathy is associated with cortical strokes in vascular branch territories

In addition to a larger area of infarction within the borderzone region, children with SCD and LVV also demonstrated infarcts extending out to the cortical gray matter, which were rare in the non-LVV cohort. These cortical strokes often had a wedge-like distribution, suggestive of a thrombo-embolic mechanism. Patients with SCD have evidence of coagulation activation, marked by elevated tissue factor and platelet activation.^{39,40} In SCD,

the vascular endothelium is activated, leading to abnormal adherence of red and white blood cells and coagulation activation. In addition, hemolytic anemia, which increases levels of free hemoglobin and inactivates nitric oxide, may cause vasoconstriction.⁴¹ A lower flow state in the artery distal to the stenosis may provoke sickling of red blood cells, which may further provoke and propagate thrombus formation. This theory is supported by autopsies of patients with SCD that revealed intra-arterial thrombi distal to the occlusion or stenosis.¹¹ Our findings of differing stroke patterns between the two cohorts suggest multiple etiologies may contribute to stroke risk in children with SCD.

Focal atrophy occurs in LVV hemispheres

Beyond strokes, additional brain injury was noted in the LVV hemispheres as demonstrated by increased focal atrophy within the gray and white matter of the parietal lobe. The quantitative Jacobian determinant analyses were consistent with focal atrophy identified qualitatively in a previous study and within our cohort.⁹ The Jacobian determinants are based on comparison to a non-SCD adult template (age range 18–90), but we adjusted for potential age-confounding effects both within our cohort (age range 6–21) and to the non-SCD adult template by the initial linear registration to normalize volumes prior to obtaining the determinants. The areas identified as having the greatest volume reduction encompass the areas we noted to have greatest infarct density, notably the borderzone region of the frontal and parietal lobes. In this retrospective study, the location or number of the ROIs with either vasculopathy or infarct volume as a significant predictor of atrophy is likely less clinically relevant than the finding that the presence of LVV remained a significant, independent predictor of cerebral atrophy even after controlling for volume of infarction. This suggests the chronic restriction of blood flow due to LVV may lead to both acute ischemic events as well as chronic hypoxia/ischemia that may focally disrupt development of the young brain or cause gradual brain tissue loss.

Atrophy and cortical thinning have been documented in children with SCD population who lack evidence of ischemic injury.^{7,42} Kirk et al. specifically noted the regions of greatest cortical thinning within neurologically intact SCD children to be within the cortical borderzone region, which supports our finding that LVV may exacerbate or accelerate this process. Trajectories of cortical development correlate with intelligence in children,⁴³ therefore interruption (via infarction) or impairment (via chronic tissue hypoxia) of this process may impact cognitive development. In non-SCD adults, progressive atrophy is associated with cognitive decline,⁴⁴ white matter hyperintensities⁴⁵ and sporadic small vessel disease.⁴⁶ Silent infarcts are a subset of white matter lesions which are independently associated with poor cognitive function in children with SCD.⁴⁷ Our finding of additional atrophy after controlling for infarct volume may present an additional imaging biomarker for investigation in future neurocognitive studies.

Study Limitations

The retrospective, cross-sectional study design limits conclusions regarding causality. Longitudinal study design is needed to determine if cerebral atrophy is due to loss of tissue volume from cell death or due to impaired growth. Because we have not included a control group without SCD, we are unable to compare atrophy in the LVV and non-LVV cohorts to

healthy children. Qualitatively we observed focal atrophy in the medial frontal region in LVV hemispheres; however, the Jacobian determinant analysis did not demonstrate a statistical difference within the frontal lobe between LVV and non-LVV hemispheres. This may be due to high infarct volumes overwhelming LVV independent contribution in this region, a smaller proportion of the ROI comprised of borderzone territories, or a relatively small sample size limiting our statistical power. In this cohort, we included all subtypes of SCD. Although there is clinical phenotypic variation among the subtypes of SCD, children with non-Hb SS SCD remain at risk for infarction.^{1,48} We did not distinguish between overt and silent strokes, but included all radiographic evidence of brain injury. The retrospective nature of the study limited the ability to assign clinical symptoms to specific lesions. Additionally, “silent” strokes, are not truly silent, as they are associated with neurocognitive deficits, and cause morbidity within the SCD population. We do not think this minimizes the clinical relevance of our study, however, as vasculopathy has been identified as a risk factor for both overt and silent strokes^{14,15} Technical limitations of this study include the heterogeneity of the MR scanning protocols, as they were performed for clinical care on both 1.5T and 3T MRI scanners over a 10-year period, and the limitations inherent to time-of-flight MRA in SCD.⁴⁹ Although there was not a statistical difference in scanner strength between LVV and non-LVV patients, there may have been small variations in the volumes of strokes noted between the two scanners which would influence results. However, given the robustness of the volume differences of infarcts between LVV and non-LVV hemispheres, we do not think this would alter our overall observations and conclusions. The MRAs were obtained as time-of-flight without contrast, which is not as sensitive or specific as digital subtraction angiography in SCD.⁴⁹ A common challenge in the radiological interpretation of MRA is the appearance of narrowing due to turbulent flow. As we were specifically inclusive of any vascular narrowing within the LVV group, this would have likely introduced more noise, resulting in non-LVV incorrectly assigned as LVV, thereby weakening the differences between the two groups. Given our desire to be inclusive of any vasculopathy, in addition to the technical limitations mentioned above, we did not grade the severity of vasculopathy. Findings from the Stroke with Transfusions Changing to Hydroxyurea (SWITCH) trial also noted an association between presence of vasculopathy and presence of infarction, but did not find an association between grade of vasculopathy and infarct size.⁵⁰

Conclusions

In this cohort of children with SCD, large vessel vasculopathy was associated with increased volumes of infarction and focal atrophy. Further work is needed to prospectively investigate metabolic and hemodynamic stress as risk factors for ischemic stroke in children with SCD as well as how LVV confers additional vulnerability to the young brain. Prospective investigation of the cerebral physiologic responses to commonly prescribed treatments, such as transfusion therapy and cerebral revascularization procedures, aimed at prevention of infarction and neurocognitive decline are warranted.

Acknowledgments

Research reported in this publication was supported by the National Institutes of Health [Washington University Institute of Clinical and Translational Sciences grant UL1TR000448 (to K.P.G and M.E.F), K12HD04743913 (to K.P.G.), K12HL087107 (to M.E.F) RO1HL129241 (to A.L.F.) and R01NS085419 (to J.M.L.)] and the Child

Neurology Foundation (CNF). Research reported in this publication was also supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number U54 HD087011 to the Intellectual and Developmental Disabilities Research Center at Washington University. The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH or CNF.

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Figure 1.
Flow chart of hemisphere selection and categorization

Figure 2. Infarct density maps. Infarct density within non-large vessel vasculopathy (non-LVV) [Row A] and large vessel vasculopathy (LVV) [Row B] hemispheres. All infarcts (overt and silent) are included. Row C demonstrates common areas of infarction between the two hemispheric cohorts.

Figure 3. FLAIR image (left) of subject with unilateral LVV. Jacobian maps (right) of averaged Jacobian determinants within LVV (n=30) and non-LVV (n=102) hemispheric cohorts. Arrows denote regions of focal atrophy, corresponding to average jacobian determinants < 1 (gray to red color spectrum).

Table 1

Demographics of children with sickle cell disease and cerebral infarctions included in analysis

	LVV	No LVV	p-value
Total patients	23	43	
Age at time of MRI (Median, range)	15 (7–21)	15 (4–22)	0.20
Male (%)	11 (48%)	11 (26%)	0.07
Hemoglobin SS	22 (96%)	35 (80%)	0.05
Hemoglobin S- β^0	1 (4%)	0	
Hemoglobin S- β^+	0	1 (2%)	
Hemoglobin SC	0	7 (18%)	
Bilateral vasculopathy	6	N/A	N/A
Unilateral vasculopathy	17		
Any overt stroke	14	7	<0.001
Silent stroke only	9	36	
Scanned in 1.5T scanner	12	26	0.71
Scanned in 3T scanner	10	14	
Scanner unknown	1	3	

Table 2

Infarct characteristics according to LVV status

	Hemispheres with LVV N=29	Hemispheres without LVV N=103	p-value
Total infarct volume (mL) **	2.20 [0.29, 7.78]	0.25 [0.03, 1.30]	<0.001 *
Gray matter infarct volume (mL) **	0.94 [0.12, 3.43]	0.04 [0.003, 0.33]	<0.001 *
White matter infarct volume (mL) **	1.53 [0.13, 4.85]	0.19 [0.02, 0.83]	<0.001 *
Peak voxel infarct density	32%	10%	0.04 ⁺

* Wilcoxon

** Median [25th, 75th IQR]⁺ Fisher exact test

Table 3

Vasculopathy and infarct volume as predictors of focal atrophy as measured by mean Jacobian determinant within eight regions of interest (ROI): gray and white matter frontal, parietal, temporal, and occipital lobes

ROI Containing Mean Jacobian Determinant	Vasculopathy Present		Normalized Infarct Volume	
	Beta (SE)	p-value	Beta (SE)	p-value
Frontal Lobe				
Gray matter	0.024 (0.013)	0.06	−1.449 (0.727)	0.05
White matter	0.009 (0.015)	0.57	−2.158 (0.883)	0.02 *
Temporal Lobe				
Gray matter	−0.008 (0.015)	0.60	−1.030 (0.843)	0.22
White matter	0.016 (0.024)	0.50	−0.022 (1.313)	0.99
Parietal Lobe				
Gray Matter	−0.037 (0.016)	0.02 *	0.773 (0.897)	0.39
White Matter	−0.039 (0.019)	0.04 *	−0.160 (1.017)	0.88
Occipital Lobe				
Gray Matter	−0.025 (0.019)	0.19	−0.169 (1.059)	0.87
White Matter	0.040 (0.034)	0.24	−3.708 (1.908)	0.05

*
<0.05 by generalized mixed linear model