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Review

Cerebrovascular Event and Stroke Rates in Pediatric Patients with Sickle Cell Disease and Moyamoya Syndrome: a Systematic Review

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Review

Abstract

Introduction: Although children with sickle cell disease (SCD) are at increased risk for cerebrovascular events (CVEs), the added risk due to severe cerebral vasculopathy is understudied. This lack of data regarding the benefits of treating vasculopathy in the context of SCD contributes to uncertainty regarding optimal care of these patients. We sought to review the extent that severe vasculopathy, specifically moyamoya syndrome (MMS), contributes to the occurrence of CVEs in children with SCD.

Methods: A systematic review was conducted following PRISMA guidelines. 904 full-text articles were screened; 13 were included.

Results: Of those receiving chronic transfusion therapy, we found that children with SCD and MMS had an elevated CVE occurrence and risk [48.3% (29/60) and 11.15 CVEs/100 patient-years, respectively]; those selected for cerebral revascularization surgery (CRS) had the highest [76.9% (10/13), 29.50 CVEs/100 patient-years]. Following CRS, CVE occurrence and rate decreased to 23.7% (14/59) and 6.37 CVEs/100 patient-years.

Conclusions: Pediatric patients with SCD further complicated with MMS have considerably elevated rates of CVE occurrence and risk. Further studies are needed to help guide physicians treating this complicated patient population.

Key Words: sickle cell disease, moyamoya, transfusion, surgery, vasculopathy, stroke

Review

Main Text

Introduction

Sickle cell disease (SCD) is the most common inherited blood disorder and affects up to 100,000 people of African descent in the U.S.[1] Stroke is a devastating complication of SCD, with SCD as the most common co-existing risk factor for stroke in African-American children.[1] If left untreated, 10% of those with subtype HbSS will suffer ischemic stroke, with an additional 22% experiencing asymptomatic or silent cerebral infarcts before adulthood.[2,3]

In 1998, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated that use of chronic transfusion therapy (CTT) to reduce hemoglobin S content and raise hemoglobin levels could decrease the stroke risk 10-fold in children without previous strokes or cerebrovascular disease and with abnormal transcranial doppler (TCD) velocities, from 10% per year to 1% per year.[4] This was further demonstrated by Fullerton et al. with a rate of first stroke as 0.88 per 100 patient-years prior to the STOP trial, which decreased to 0.17 first strokes per 100 patient-years by year 2000.[5] In 2014, CTT was also found to reduce the incidence of recurrent silent cerebral infarcts in children with SCD at risk for infarct, from 4.8 to 2.0 cerebrovascular events (CVEs) per 100 patient-years.[6] In 2016, the TCD With Transfusions Changing to Hydroxyurea (TWiTCH) trial

Pediatr Stroke. 2024;8: 33-85
www.pediatricstrokejournal.com

demonstrated that hydroxyurea was non-inferior to CTT in maintaining TCD velocities and preventing primary stroke for those without severe vasculopathy and after four years of CTT.[7]

Despite best medical management, some children with SCD are still at significant stroke risk, especially those with cerebral vasculopathy. Moyamoya syndrome (MMS) is a severe form of cerebral steno-occlusive vasculopathy with varied manifestations that is characterized by progressive narrowing of intracranial arteries followed by collateral vessel formation.[8] Forty-one percent of those with SCD and MMS suffered additional strokes or transient ischemic attacks (TIAs) while on CTT.[9] Progressive cerebral vasculopathy has also been associated with new cerebral infarctions.[8,10] Indeed, many have perceived the presence of severe cerebral vasculopathy to predict a worse course of ischemic disease in SCD patients, yet the treatment options for stroke prevention are limited as the trials evaluating the efficacy of CTT and hydroxyurea excluded those with severe vasculopathy.[4,6,7] This treatment gap has stimulated research in additional treatments to decrease stroke risk, including cerebral revascularization surgery (CRS) or hematopoietic stem cell transplant (HSCT). Few studies have focused on determining the rates of these strokes and TIAs in children with SCD and MMS (a severe form of vasculopathy), and less have examined the effects of additional surgical treatments.

Through a systematic review, we examined the burden of cerebral ischemic disease in children with MMS in SCD who are receiving established forms of stroke-reducing therapy - CTT and hydroxyurea as well as newer forms of therapy – cerebral revascularization surgery and HSCT.

Methods

Literature Search and Screening

A systematic review of studies reporting stroke rates in pediatric patients with SCD and MMS was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] The search was designed for maximal inclusion of articles dealing with cerebral vasculopathy and not only moyamoya. The databases used were PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) and the following terms were employed in the search: pediatric, sickle cell disease, cerebral vasculopathy, moyamoya, medical treatment, transfusion, hydroxyurea, surgical treatment, bone marrow transplant, aspirin, stroke, and transient ischemic attack (TIA). Search strategy is described in Supplementary Table 1.

Selection Criteria

Articles were imported into EndNote (Clarivate 2013), duplicates were removed, and remaining articles were uploaded onto Rayyan, a Cochrane-recommended Web application, to ensure blinded screening.[12] Titles and abstracts were independently screened by four reviewers (S.H.H., R.P., A.H., A.R.) using predefined inclusion and exclusion criteria. Disagreement was resolved through inter-reviewer discussion and consultation with a fifth reviewer (P.R.A.).

Inclusion criteria for eligible studies were: 1) pediatric patients with SCD (HbSS subtype) and MMS; 2) reported intervention of CTT, hydroxyurea, HSCT, or cerebral revascularization surgery; 3) reported CVEs (consisting of strokes, or TIAs, or silent infarcts); and 4) a minimum of 12 months of follow up. Conference abstracts and presentations, editorials, commentaries, reviews, and non-English studies were excluded.

Manuscripts were reviewed for clinical and radiographic findings pertinent to stroke. Each study reviewed utilized its own definitions for these findings which may have varied between studies. The following are general definitions for the pertinent clinical and radiographic findings that

were tracked in this review. Cerebral vasculopathy was defined as imaging evidence of cerebral arterial anatomic pathology as detected by computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction catheter angiogram, as indicated in the study reviewed. Studies that defined cerebral vasculopathy solely by elevated transcranial doppler (TCD) velocities (> 200 cm/s) were excluded. While TCD has been validated and demonstrated to identify SCD patients at high risk for stroke with high sensitivity and is largely inferred as "vasculopathy" in a patient, its specificity and positive predictive value are low for cerebral arterial anatomic pathology when compared to CTA, MRA, digital subtraction catheter angiogram.[13] MMS is defined as a chronic occlusive arterial cerebrovascular disorder characterized by progressive stenosis of the bilateral supraclinoid internal carotid arteries followed by formation of tortuous arterial collaterals at the base of the brain due to an associated underlying disease, such as SCD.[14] CVE is defined as any stroke, silent infarct, or TIA. Stroke is defined as persistent neurologic abnormalities or transient symptoms accompanied by a new cerebral lesion consistent with the patient's clinical presentation. Silent infarct is defined as a magnetic resonance imaging (MRI) signal abnormality, at least 3 mm, with either a normal neurologic examination or an abnormality on examination that could not be explained by the

location of the brain lesion(s).[6] TIA is defined as a motor or sensory deficit lasting less than 24 hours without a corresponding acute cerebral infarct on MRI.

When study data allowed CVE rate calculations, the following formula was used: CVE rate = (total # of CVEs in the study) ÷ (total # of follow up years) x 100 patient-years.

Statistical Analysis

A meta-analysis was not performed. The differences across the studies, including poor reporting quality, protocol diversity, lack of control group, and inconsistent outcome reporting precluded statistical synthesis of the included studies other than basic descriptive statistics.

Results

Search Strategy

904 references were identified. After exclusion of non-English, duplicate, and non-relevant references, 72 potentially relevant articles were assessed by full-text evaluation. A final 13 studies met inclusion criteria with 10 reporting individual patient data for further data

extraction (Figure 1). The remaining 3 reported grouped summary data that could not be consolidated but were included. All 13 studies included subjects with MMS.

Cerebrovascular Events on Medical Therapy

Three studies reported summary data on groups of patients with SCD and MMS who were treated with CTT and later went on to receive cerebral revascularization surgery and/or HSCT. 54.1% (20/37) of patients experienced a CVE while on CTT preoperatively (Table 1).[15-17] Four studies (Table 2[A]) reported on detailed outcomes of 40 patients on CTT as the sole treatment for stroke prevention (without cerebral revascularization surgery).[8,18-20] 40.4% (19/47) of patients had a CVE while on treatment with a rate of 8.60 CVEs/100 patient-years. 19.1% (9/47) had a stroke and 27.7% (13/47) had a TIA, with rates of 3.23 strokes/100 patient-years and 4.73 TIAs/100 patient-years.

In two surgical studies (Table 2[B]), 76.9% (10/13) of patients had a CVE while on CTT, prior to cerebral revascularization surgery.[18,20] 30.8% (4/13) had a stroke and 46.2% (6/13) had a TIA.

These patients had the highest observed rates with 29.50 CVEs/100 patient-years, 7.76 strokes/100 patient-years, and 15.53 TIAs/100 patient-years.

These two subsets of patients with MMS treated with CTT had a collective 60 patients (Table 2[A+B]).[8,18-20] 48.3% (29/60) had a CVE, 21.7% (13/60) had a stroke, and 31.7% (19/60) had a TIA. Event rates calculated to 11.15 CVEs/100 patient-years, 3.78 strokes/100 patient-years, and 6.05 TIAs/100 patient-years.

Cerebrovascular Events in Patients Undergoing Cerebral Revascularization Surgery

All patients treated with cerebral revascularization surgery were treated with CTT initially. There were three studies with group level data, all had small sample sizes (12 or less) (Table 3).[15-17] Two studies reported 50.0% (12/24) of patients had CVEs prior to surgery.[16,17] After surgery, three studies showed an aggregate decrease in CVE occurrence to 15.2% (5/33).[15-17]

Eight studies provided detailed individual patient data on 59 patients following cerebral revascularization surgery.[19-26] All patients had MMS and were managed with CTT prior to surgery (Table 4). 23.7% (14/59) of patients had a CVE after the procedure, with a rate of 6.37 CVEs/100

patient-years (Table 4). 10.2% (6/59) had a stroke and 13.6% (8/59) had a TIA, with rates of 2.39 strokes/100 patient-years and 3.98 TIAs/100 patient-years.

Two of these studies allowed comparison of the same patient group on CTT before and after cerebral revascularization surgery.[19,21] CVE occurrence decreased 2-fold [from 76.9% (10/13) to 38.5% (5/13)], stroke occurrence decreased 4-fold [30.8% (4/13) to 7.7% (1/13)], and TIA occurrence decreased from 46.2% (6/13) to 30.8% (4/13). The overall CVE rate decreased from 29.50 CVEs/100 patient-years while on CTT to 11.90 CVEs/100 patient-years after surgery. The stroke and TIA rates/100 patient-years also decreased from 7.76 and 15.53 to 1.70 and 10.20, respectively. The Alamri et al. study did not note CTT utilization but did allow for a comparison of pre- and post-surgical CVE rates. Pre-surgically, the CVE rate was 10.75 CVEs/100 patient-years (7.53 strokes/100 patient-years and 2.15 TIAs/100 patient-years). The post-surgical CVE rate dropped to 3.75 CVEs/100 patient-years (3.75 strokes/100 patient-years and 0.0 TIAs/100 patient-years).[22]

Cerebrovascular Events Following Bone Marrow Transplantation/Hematopoietic Stem Cell Transplant

Two studies reported on CVE occurrence after HSCT.[15,19] Four out of 8 (50%) patients had CVEs after HSCT. There were no studies with sufficiently detailed data to extract individual patient data.

Discussion

In our systematic review, we found that children with SCD and MMS receiving CTT for history of CVEs had significant CVE occurrence and rates [40.4% (19/47) and 8.60 CVEs/100 patient-years, respectively], and even worse disease courses in those who later underwent surgery [76.9% (10/13) and 29.50 CVEs/100 patient-years, respectively]. Following cerebral revascularization surgery, CVEs decreased to 23.7% (14/59) and 6.37 CVEs/100 patient-years, respectively.

Pathophysiology of cerebral vasculopathy in SCD and significance of MMS

Stroke in children with SCD can occur due to progressive stenosis of blood vessels, leading to reduction in cerebral blood flow and infarction. Pathologic examination reveals endothelial damage to mid- to large-sized arteries of the brain. Damage is mediated by multiple

mechanisms including red blood cell adhesion and viscosity, intravascular hemolysis, arterial wall dissection, endothelial activation, inflammatory responses, and procoagulant factors.[27-29] The degree of arterial stenosis and its vascular distribution impacts the extent and severity of the stroke.[29] Distal arteries can be affected resulting in subcortical, clinically silent infarcts.[30-32]

In moyamoya disease, the most common site of stenosis is the terminal bifurcation of the internal carotid artery and the proximal middle cerebral artery and anterior cerebral artery. With decreased intracranial perfusion, compensatory mechanisms stimulate the formation of collateral arteries. Arterioles from the circle of Willis can present with a characteristic angiographic appearance resembling a “puff of smoke”, or “moyamoya”, the term given by the Japanese investigators that first described it.[33-36]

The progression of cerebral arterial pathology in moyamoya disease has been described in detail.[37] Initially there is progressive arterial stenosis of the large intracranial arteries which can cause ischemic strokes. This is followed by collateral vessel formation (including the moyamoya collaterals found at the base of the brain) with eventual occlusion of the large intracranial arteries and collateral vessels taking over major cerebral blood supply. If the progressive cerebral arterial pathology is secondary to a disease (e.g., sickle cell disease) or agent (e.g.,

ionizing radiation) resulting in the changes described, the term moyamoya *syndrome* is used. If there is no known etiology to the vascular pathology, then it is called moyamoya *disease*. Recently, a gene mutation in RNF213 has been linked to some forms of primary moyamoya disease.[38,39]

Patients with primary moyamoya disease are known to have high rates of stroke.[40,41] To decrease the risk of stroke, cerebral revascularization surgery has been an established treatment – first reported for moyamoya disease in 1967 and for moyamoya syndrome with sickle cell disease in 1996.[21,42] The surgery involves increasing cerebral blood flow by implanting arteries from the extracranial circulation to the intracranial compartment.[43-45] In both children and adults, the procedure has been shown to reduce stroke risk.[46-52] The results of these studies led pediatric hematology centers to utilize cerebral revascularization surgery to reduce stroke risk in MMS due to SCD when able.

CVEs in the absence of MMS while on conservative treatment

The STOP trial in 1998 studied the effects of transfusion therapy for the prevention of primary CVEs in those of the pediatric SCD population with abnormal TCD velocities.[4] In this trial, 11 children (16.4%) in the standard care group (without blood transfusions) had a stroke, while one

child (1.6%) in the transfusion group had a stroke. The impact of this treatment later demonstrated a decline in admission rates for stroke in pediatric SCD patients with an observed first stroke rate of 0.17 strokes/100 patient-years.[5] The SIT study in 2014 investigated the effect of CTT in preventing recurrent silent infarcts in those with at least one infarct detected on MRI in those with normal TCD velocities.[6] In this study, 16 children (16.5%) in the observation group had a CVE while only 6 children (6.1%) in the transfusion group had a CVE. CVE rates in the observation and transfusion groups were 5.6 and 2.0 CVEs/100 patient-years, respectively. Majumdar et al. reported an even lower recurrent stroke rate of 0.66 strokes/100 patient-years amongst 27 patients receiving CTT.[53] In the TWiTCH trial in 2016 (comparing non-inferiority of hydroxyurea to CTT), the majority of patients did not have vasculopathy findings (10 of the 110 had mild-moderate vasculopathy, none with MMS).[7] In this study, 6 patients (5.4%) had TIAs, equally distributed between treatment groups, demonstrating non-inferiority of hydroxyurea (after one year of CTT) to CTT. Ware et al. additionally reported a rate of 3.6 strokes/100 patient-years for patients treated with hydroxyurea.[54]

It is important to recognize that the STOP, SIT, and TWiTCH trials[4,6,7] are not ideal comparators to the smaller, less standardized studies reported in our results, as each focused on a different

patient sub-population in those with SCD, as well as different endpoints. The studies included in this review were all retrospective and did not distinguish between primary or secondary stroke prevention. The STOP trial investigated patients treated for primary stroke prevention with abnormal TCDs and did not screen for arterial stenosis with angiograms. The TWiTCH trial investigated the non-inferiority of hydroxyurea in similar patients who had been on CTT without evidence of vasculopathy, while the SIT study investigated those treated for secondary silent infarct prevention with normal TCDs and no vasculopathy.[4,6,7] This lack of data from comparable studies highlights the need to conduct prospective studies that focus on the effect of severe cerebral vasculopathy, such as MMS, on stroke in SCD.

CVEs in the presence of MMS while on conservative treatment

Compared to studies that did not include patients with MMS, the proportion of patients who had a CVE on CTT is markedly higher in studies of patients exhibiting MMS.[4] The group level data of patients with MMS managed on CTT showed that 54.1% (20/37) had a CVE while on treatment (Table 1). The studies with MMS patients on CTT (Table 2[A+B]) had 30x greater stroke occurrence compared to the STOP trial [48.3% (29/60) versus 1.6%, respectively].[4] The CVE rate of the MMS population was over 5x greater than those in the SIT study (11.15 CVEs/100

patients-years and 2.0 CVEs/100 patient-years, respectively).[6] Likewise, the stroke rate was also 5x greater at 3.78 strokes/100 patient-years, compared to 0.77 strokes/100 patient-years in the Fullerton study.[5]

Our findings are consistent with others that showed the presence of MMS, has been associated with a worse course of CVEs when compared to patients without any form of vasculopathy.[8,10,30,55] While the results demonstrated that CTT can reduce the proportion and rate of CVE occurrence in the presence of MMS, these patients still experience a markedly elevated CVE incidence compared to those without MMS despite continued treatment. It is speculated that the vascular changes found in MMS signify a late stage in the progression of vascular stenosis where the structural vessel wall changes are irreversible and result in a permanent increase in the risk of stroke. Future studies can characterize the progression of and development of MMS in SCD and measure the efficacy of CTT in halting or reversing the development of this type of vasculopathy. If the point at which this vasculopathy becomes irreversible is known, it may help guide the treatment of these patients and shift them to alternative therapies earlier in addition to CTT to decrease their stroke risk.

CVEs following Cerebral Revascularization Surgery and HSCT

In our review, we found that patients who were treated with either cerebral revascularization surgery or HSCT in addition to CTT had worse CVE history than those that were not. The series available for review were all limited by their small sample size and retrospective nature.

Of the surgical series, up to 76.9% (10/13) of these patients had CVEs prior to surgery, higher than the non-surgical series of MMS patients [40.4% (19/47)] and again, much higher than even the highest of the non-vasculopathy studies (6.1%).[6] Following surgery, 23.7% (14/59) had a CVE, less than half of the preoperative proportion (Table 4). There is a relative lack of thorough investigation, as only two studies of the surgical series directly reported on CVE rates before and after cerebral revascularization surgery; however, when pooled, they showed a considerable 2.5x decrease in the post-surgical CVE rate (29.50 CVEs to 11.90 CVEs/100 patient-years), and an even greater 4.5x decrease in stroke rate (7.76 strokes to 1.70 strokes/100 patient-years).[19,21] Although there are substantial decreases in CVE proportion and rate following cerebral revascularization surgery in patients with MMS, these are still significantly higher than the CVE rates seen in patients without vasculopathy. The pooled post-operative CVE rate of 6.37 CVEs/100 patient-years (Table 4) and the stroke rate of 2.39 strokes/100 patient-years both remain 3x higher than that reported in the SIT trial[6] and the Fullerton study.[5]

The reduction in CVEs following surgery needs further study to determine the magnitude of the effect of surgery versus the natural history of the disease (where there is an observed decrease in ischemic stroke risk over time). Rigorous prospective studies are needed to evaluate the efficacy and risk of cerebral revascularization surgery in order to determine its role in stroke prevention in children with SCD. In the absence of such studies and other effective treatments, careful consideration of surgical intervention by an experienced team of hematologists and neurosurgeons can be made in the setting of MMS in SCD in for secondary stroke prevention, as recommended in recent guidelines on the management of stroke in sickle cell disease.[56]

Even fewer studies have explored the effects of HSCT on CVE rates in those without vasculopathy. As found in our review, 4 out of 8 patients with MMS had a CVE after HSCT (Table 5). Since this review's database retrieval, a new retrospective study has been published on post-HSCT CVE rates in a cohort of 44 children, of which 52% had vasculopathy. It found that in the post-HSCT cohort overall, the rate of subsequent stroke was 1.6 events/100 patient-years and the rate of SCIs was 2.2 events/100 patient-years. In those with history of symptomatic infarcts, the rate decreased from 13.7 CVEs/100 patient-years to 4.4 CVEs/100 patient-years, nearly 3x the rate of the cohort overall.[57] Furthermore, of patients who presented with a

pre-treatment symptomatic infarct, only those with moderate/severe vasculopathy experienced a CVE after HSCT. In addition, those with mild-moderate arterial stenosis did not progress; however, those with severe vasculopathy did not improve, adding evidence that these vessel wall changes may be irreversible. Several prospective studies are underway on HSCT in patients with severe SCD and this will hopefully shed light on its effect on stroke risk reduction.[58-61]

Limitations

The limitations are due largely to the heterogeneous nature of our source material. Our review included studies which focused primarily on hematological or neurosurgical objectives, making it difficult to standardize them for comparison. The comparator non-vasculopathy study results were large prospective trials, while the results pulled in our review are from small single-center studies without standardization. The varied detail of reporting of outcomes was one of the largest hurdles in comparing outcomes between studies. Additionally, the included studies were conducted throughout a wide period in which there were several advancements in sickle cell disease care and treatment (i.e., STOP trial, TWiTCH trial, etc.), yielding outcome differences that may modulate the interpretation. Further, many did not report on CVEs other than strokes,

potentially lowering CVE rates. Another limitation stems from the natural history of stroke and its effects on the resulting data of patients who progress to receive cerebral revascularization surgery or HSCT. As such, there may also be a bias of surgery candidate selection, which could not be ascertained. The risk of ischemic stroke decreases as the patients age, and patients undergoing these more invasive treatments could have an inherent decrease in risk. Studies that consider additional adjustments for time after stroke in this patient population are lacking.

Conclusions

Children with SCD and MMS experience a much higher CVE occurrence and rate compared to those without vasculopathy, despite treatment for stroke prevention. We found that these patients have a CVE rate up to 11.15 CVEs/100 patient years and a stroke rate up to 3.78 strokes/100 patient-years, both 5x greater, compared to patients without vasculopathy. Additional treatment with cerebral revascularization surgery or HSCT in those with MMS decreases CVE rates and occurrences; however, these outcomes remain elevated compared to those without vasculopathy. More research needs to be conducted on alternative treatments to decrease stroke risk in patients with SCD and MMS.

Conflict of Interest Statement

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Pediatr Stroke. 2024;8: 33-85
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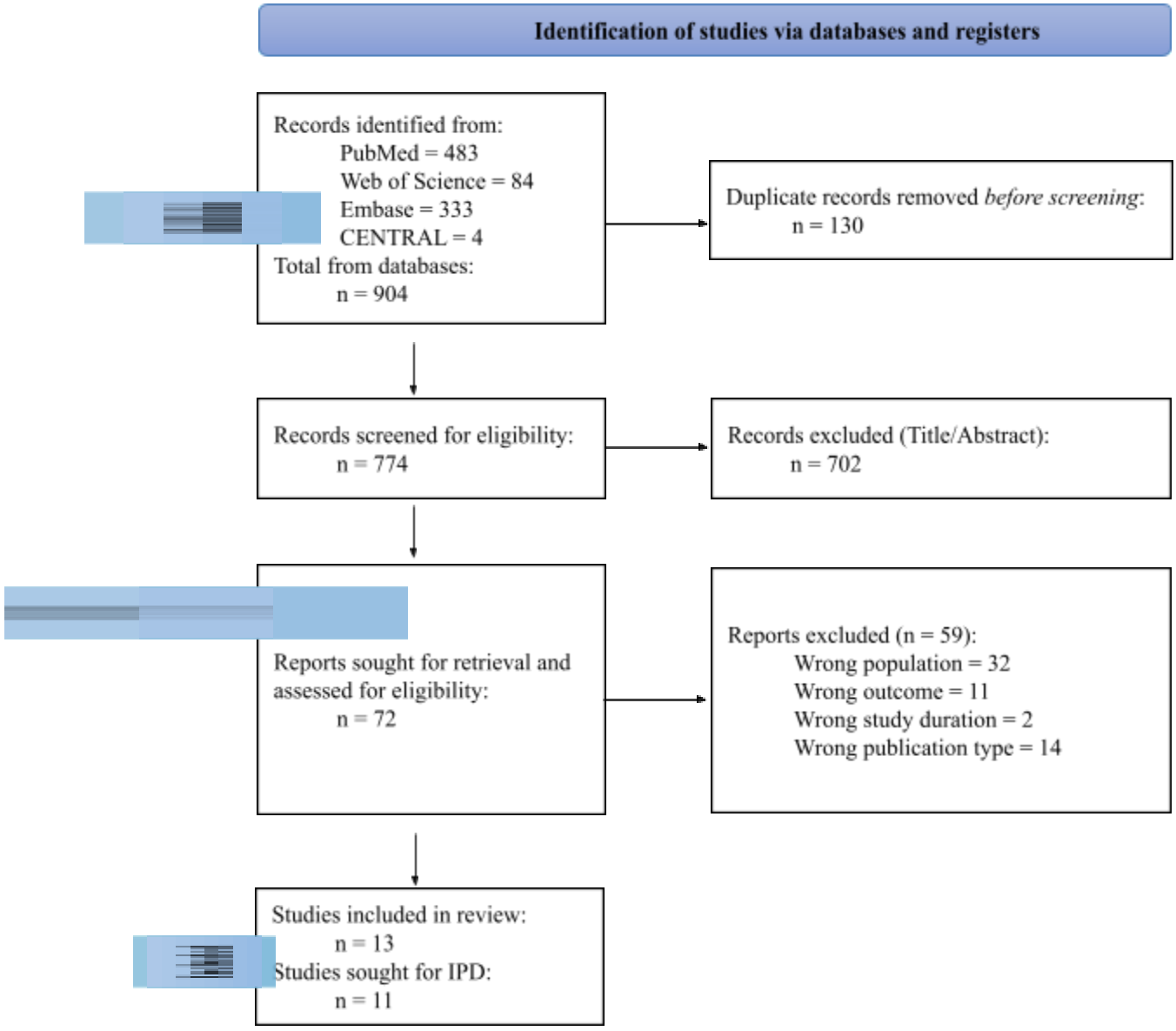
Figure 1. PRISMA diagram depicting the literature search strategy.



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Review

CVE Rates in Pediatric SCD and Moyamoya

Pediatr Stroke. 2024;8: 33-85
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Abbreviations	
SCD	Sickle Cell Disease
CVE	Cerebrovascular Event
MMS	Moyamoya Syndrome
CTT	Chronic Transfusion Therapy
TIA	Transient Ischemic Attack
CRS	Cerebral Revascularization Surgery
HSCT	Hematopoietic Stem Cell Transplant
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TCD	Transcranial Doppler
CTA	Computed Tomography Angiography
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
STOP	Stroke Prevention Trial in Sickle Cell Anemia

Pediatr Stroke. 2024;8: 33-85
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TWiTCH	TCD With Transfusions Changing to Hydroxyurea
SIT	Silent Cerebral Infarct Transfusion

References

1. Baker C, Grant AM, George MG, Grosse SD, Adamkiewicz TV. Contribution of Sickle Cell Disease to the Pediatric Stroke Burden Among Hospital Discharges of African-Americans-United States, 1997-2012. *Pediatr Blood Cancer*. Dec 2015;62(12):2076-81. doi:10.1002/pbc.25655
2. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. Apr 2010;38(4 Suppl):S512-21. doi:10.1016/j.amepre.2009.12.022
3. Estcourt LJ, Fortin PM, Hopewell S, Trivella M, Doree C, Abboud MR. Interventions for preventing silent cerebral infarcts in people with sickle cell disease. *Cochrane Database Syst Rev*. 05 13 2017;5:CD012389. doi:10.1002/14651858.CD012389.pub2
4. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. Jul 02 1998;339(1):5-11. doi:10.1056/NEJM199807023390102
5. Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. *Blood*. Jul 15 2004;104(2):336-9. doi:10.1182/blood-2004-02-0636

6. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. Aug 21 2014;371(8):699-710. doi:10.1056/NEJMoa1401731
7. Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet*. Feb 13 2016;387(10019):661-670. doi:10.1016/S0140-6736(15)01041-7
8. Guilliams KP, Fields ME, Dowling MM. Advances in Understanding Ischemic Stroke Physiology and the Impact of Vasculopathy in Children With Sickle Cell Disease. *Stroke*. 2019;50(2):266-273. doi:10.1161/STROKEAHA.118.020482
9. Dobson SR, Holden KR, Nietert PJ, et al. Moyamoya syndrome in childhood sickle cell disease: a predictive factor for recurrent cerebrovascular events. *Blood*. May 01 2002;99(9):3144-50. doi:10.1182/blood.v99.9.3144
10. Hulbert ML, McKinstry RC, Lacey JL, et al. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. *Blood*. Jan 20 2011;117(3):772-9. doi:10.1182/blood-2010-01-261123

11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 03 29 2021;372:n71. doi:10.1136/bmj.n71
12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 12 05 2016;5(1):210. doi:10.1186/s13643-016-0384-4
13. Seibert JJ, Glasier CM, Kirby RS, et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8-year study. *Pediatr Radiol*. Mar 1998;28(3):138-42. doi:10.1007/s002470050314
14. Willis RCotPaToSOotCo, Diseases HLSRGfRoMfI. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)*. 2012;52(5):245-66. doi:10.2176/nmc.52.245
15. Gatti JR, Torriente AG, Sun LR. Clinical Presentation and Stroke Incidence Differ by Moyamoya Etiology. *J Child Neurol*. 03 2021;36(4):272-280. doi:10.1177/0883073820967160
16. Hankinson TC, Bohman LE, Heyer G, et al. Surgical treatment of moyamoya syndrome in patients with sickle cell anemia: outcome following encephaloduroarteriosynangiosis. *J Neurosurg Pediatr*. Mar 2008;1(3):211-6. doi:10.3171/PED/2008/1/3/211

17. Smith ER, McClain CD, Heeney M, Scott RM. Pial synangiosis in patients with moyamoya syndrome and sickle cell anemia: perioperative management and surgical outcome. *Neurosurg Focus*. Apr 2009;26(4):E10. doi:10.3171/2009.01.FOCUS08307
18. Gyang E, Yeom K, Hoppe C, Partap S, Jeng M. Effect of chronic red cell transfusion therapy on vasculopathies and silent infarcts in patients with sickle cell disease. *Am J Hematol*. Jan 2011;86(1):104-6. doi:10.1002/ajh.21901
19. Hall EM, Leonard J, Smith JL, et al. Reduction in Overt and Silent Stroke Recurrence Rate Following Cerebral Revascularization Surgery in Children with Sickle Cell Disease and Severe Cerebral Vasculopathy. *Pediatr Blood Cancer*. 08 2016;63(8):1431-7. doi:10.1002/pbc.26022
20. Yang W, Xu R, Porras JL, et al. Effectiveness of surgical revascularization for stroke prevention in pediatric patients with sickle cell disease and moyamoya syndrome. *J Neurosurg Pediatr*. Sep 2017;20(3):232-238. doi:10.3171/2017.1.PEDS16576
21. Vernet O, Montes JL, O'Gorman AM, Baruchel S, Farmer JP. Encephaloduroarterio-synangiosis in a child with sickle cell anemia and moyamoya disease. *Pediatr Neurol*. Apr 1996;14(3):226-30. doi:10.1016/0887-8994(96)00045-8

22. Alamri A, Hever P, Cheserem J, Gradil C, Bassi S, Tolias CM. Encephaloduroateriosynangiosis (EDAS) in the management of Moyamoya syndrome in children with sickle cell disease. *Br J Neurosurg*. Apr 2019;33(2):161-164. doi:10.1080/02688697.2017.1339227
23. Fryer RH, Anderson RC, Chiriboga CA, Feldstein NA. Sickle cell anemia with moyamoya disease: outcomes after EDAS procedure. *Pediatr Neurol*. Aug 2003;29(2):124-30. doi:10.1016/s0887-8994(03)00047-x
24. Griessenauer CJ, Lebensburger JD, Chua MH, et al. Encephaloduroarteriosynangiosis and encephalomyoarteriosynangiosis for treatment of moyamoya syndrome in pediatric patients with sickle cell disease. *J Neurosurg Pediatr*. Jul 2015;16(1):64-73. doi:10.3171/2014.12.PEDS14522
25. Kennedy BC, McDowell MM, Yang PH, et al. Pial synangiosis for moyamoya syndrome in children with sickle cell anemia: a comprehensive review of reported cases. *Neurosurg Focus*. Jan 2014;36(1):E12. doi:10.3171/2013.10.FOCUS13405
26. Winstead M, Sun PP, Martin K, et al. Encephaloduroarteriosynangiosis (EDAS) in young patients with cerebrovascular complications of sickle cell disease: Single-institution

experience. *Pediatr Hematol Oncol*. Mar 2017;34(2):100-106. doi:10.1080/08880018.2017.1313917

27. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: Biology, pathophysiology, genetics, translational medicine, and new research directions. *Am J Hematol*. Sep 2009;84(9):618-25. doi:10.1002/ajh.21475
28. Kassim AA, DeBaun MR. Sickle cell disease, vasculopathy, and therapeutics. *Annu Rev Med*. 2013;64:451-66. doi:10.1146/annurev-med-120611-143127
29. Fasano RM, Meier ER, Hulbert ML. Cerebral vasculopathy in children with sickle cell anemia. *Blood Cells Mol Dis*. Jan 2015;54(1):17-25. doi:10.1016/j.bcmd.2014.08.007
30. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. *Br J Haematol*. Aug 2009;146(3):300-5. doi:10.1111/j.1365-2141.2009.07753.x
31. Pavlakis SG, Bello J, Prohovnik I, et al. Brain infarction in sickle cell anemia: magnetic resonance imaging correlates. *Ann Neurol*. Feb 1988;23(2):125-30. doi:10.1002/ana.410230204

32. Tewari S, Renney G, Brewin J, et al. Proteomic analysis of plasma from children with sickle cell anemia and silent cerebral infarction. *Haematologica*. 07 2018;103(7):1136-1142. doi:10.3324/haematol.2018.187815

33. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol*. Mar 1969;20(3):288-99. doi:10.1001/archneur.1969.00480090076012

34. Maki Y, Enomoto T. Moyamoya disease. *Childs Nerv Syst*. Aug 1988;4(4):204-12. doi:10.1007/BF00270916

35. Suzuki J, Kodama N. Moyamoya disease--a review. *Stroke*. 1983 Jan-Feb 1983;14(1):104-9. doi:10.1161/01.str.14.1.104

36. Oshima H, Katayama Y. Discovery of cerebrovascular moyamoya disease: research during the late 1950s and early 1960s. *Childs Nerv Syst*. Apr 2012;28(4):497-500. doi:10.1007/s00381-012-1708-x

37. Burke GM, Burke AM, Sherma AK, Hurley MC, Batjer HH, Bendok BR. Moyamoya disease: a summary. *Neurosurg Focus*. Apr 2009;26(4):E11. doi:10.3171/2009.1.FOCUS08310

38. Liu W, Morito D, Takashima S, et al. Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. *PLoS One*. 2011;6(7):e22542. doi:10.1371/journal.pone.0022542

39. Kamada F, Aoki Y, Narisawa A, et al. A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. *J Hum Genet*. Jan 2011;56(1):34-40. doi:10.1038/jhg.2010.132

40. Kim T, Oh CW, Bang JS, Kim JE, Cho WS. Moyamoya Disease: Treatment and Outcomes. *J Stroke*. Jan 2016;18(1):21-30. doi:10.5853/jos.2015.01739

41. Lee S, Rivkin MJ, Kirton A, deVeber G, Elbers J, Study IPS. Moyamoya Disease in Children: Results From the International Pediatric Stroke Study. *J Child Neurol*. Oct 2017;32(11):924-929. doi:10.1177/0883073817718730

42. Vilela MD, Newell DW. Superficial temporal artery to middle cerebral artery bypass: past, present, and future. *Neurosurg Focus*. 2008;24(2):E2. doi:10.3171/FOC/2008/24/2/E2

43. Karasawa J, Kikuchi H, Furuse S, Kawamura J, Sakaki T. Treatment of moyamoya disease with STA-MCA anastomosis. *J Neurosurg*. Nov 1978;49(5):679-88. doi:10.3171/jns.1978.49.5.0679

44. Patel NN, Mangano FT, Klimo P. Indirect revascularization techniques for treating moyamoya disease. *Neurosurg Clin N Am*. Jul 2010;21(3):553-63. doi:10.1016/j.nec.2010.03.008

45. Olds MV, Griebel RW, Hoffman HJ, Craven M, Chuang S, Schutz H. The surgical treatment of childhood moyamoya disease. *J Neurosurg*. May 1987;66(5):675-80. doi:10.3171/jns.1987.66.5.0675

46. Jeon JP, Kim JE, Cho WS, Bang JS, Son YJ, Oh CW. Meta-analysis of the surgical outcomes of symptomatic moyamoya disease in adults. *J Neurosurg*. 03 2018;128(3):793-799. doi:10.3171/2016.11.JNS161688

47. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. *J Neurosurg*. Feb 2004;100(2 Suppl Pediatrics):142-9. doi:10.3171/ped.2004.100.2.0142

48. Ishikawa T, Houkin K, Kamiyama H, Abe H. Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. *Stroke*. Jun 1997;28(6):1170-3. doi:10.1161/01.str.28.6.1170

49. Golby AJ, Marks MP, Thompson RC, Steinberg GK. Direct and combined revascularization in pediatric moyamoya disease. *Neurosurgery*. Jul 1999;45(1):50-8; discussion 58-60. doi:10.1097/00006123-199907000-00013

50. Guzman R, Lee M, Achrol A, et al. Clinical outcome after 450 revascularization procedures for moyamoya disease. *J Neurosurg*. Nov 2009;111(5):927-35. doi:10.3171/2009.4.JNS081649

51. Dusick JR, Gonzalez NR, Martin NA. Clinical and angiographic outcomes from indirect revascularization surgery for Moyamoya disease in adults and children: a review of 63 procedures. *Neurosurgery*. Jan 2011;68(1):34-43; discussion 43. doi:10.1227/NEU.0b013e3181fc5ec2

52. Houkin K, Kuroda S, Nakayama N. Cerebral revascularization for moyamoya disease in children. *Neurosurg Clin N Am*. Jul 2001;12(3):575-84, ix.

53. Majumdar S, Miller M, Khan M, et al. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. *Br J Haematol*. Jun 2014;165(5):707-13. doi:10.1111/bjh.12795

54. Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using

hydroxyurea and phlebotomy. *J Pediatr.* Sep 2004;145(3):346-52. doi:10.1016/j.jpeds.2004.04.058

55. Arkuszewski M, Krejza J, Chen R, et al. Sickle cell anemia: intracranial stenosis and silent cerebral infarcts in children with low risk of stroke. *Adv Med Sci*. Mar 2014;59(1):108-13. doi:10.1016/j.advms.2013.09.001
56. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv*. 04 28 2020;4(8):1554-1588. doi:10.1182/bloodadvances.2019001142
57. Carpenter JL, Nickel RS, Webb J, et al. Low Rates of Cerebral Infarction after Hematopoietic Stem Cell Transplantation in Patients with Sickle Cell Disease at High Risk for Stroke. *Transplant Cell Ther*. 12 2021;27(12):1018.e1-1018.e9. doi:10.1016/j.jtct.2021.08.026
58. HLA Haploidentical Bone Marrow Transplant in Patients With Severe Sickle Cell Disease (DREPHAPLO). ClinicalTrials.gov Identifier: NCT03240731, https://clinicaltrials.gov/ct2/show/NCT03240731

59. Haploidentical Bone Marrow Transplantation in Sickle Cell Patients (BMTCTN1507). ClinicalTrials.gov Identifier: NCT03263559, https://clinicaltrials.gov/ct2/show/NCT03263559

60. Bone Marrow Transplantation vs Standard of Care in Patients With Severe Sickle Cell Disease (BMT CTN 1503) (STRIDE2). ClinicalTrials.gov Identifier: NCT02766465, https://clinicaltrials.gov/ct2/show/NCT02766465

61. Haploidentical Transplantation With Pre-Transplant Immunosuppressive Therapy for Patients With Sickle Cell Disease. ClinicalTrials.gov Identifier: NCT03279094, https://clinicaltrials.gov/ct2/show/NCT03279094

Legends

FIGURE 1. PRISMA diagram depicting the literature search strategy.

TABLE 1. ***CVE proportions in patients with MMS on chronic transfusion therapy, grouped summary data***

Study	**Total # patients**	**Intervention (%)**	**# patients with CVE prior to CTT (%)**	**# patients with CVE while on CTT (%)**
Gatti et al. (2021)[15]	18	CTT/Pre-Surg (50.0) or HSCT (16.7)	NA	8 (44.4)
Hankinson et al.* (2008)[16]	7*	CTT/Pre-Surg (100)	NA	5 (71.4)
Smith et al. (2009)[17]	12	CTT/Pre-Surg (100)	NA	7 (58.3)
All MMS Totals	**37**			**20 (54.1)**

These studies presented data that allowed group level extraction but was insufficient to pull patient-level data.

CTT = chronic transfusion therapy, CVE = cerebrovascular event, MMS = moyamoya syndrome, HSCT = hematopoietic stem cell transplant

* Only patients receiving CTT included in this table.

TABLE 2. ***CVE rates in patients with MMS on chronic transfusion therapy, individual pooled data***

Study	# CVEs	# strokes	# TIAs	# silent	# patient w CVE (%)	Total # patients	Total FU (years)
Dobson et al. (2002)[9]	21	6	15	Unknown	11 (57.9)	19	127
Gyang et al. (2011)[18]	0	0	0	0	0	5	16.75
Hall et al. (2016)[19]	18	8	7	3	7 (46.7)	15	146.5
Yang et al. (2017)[20]	1	1	0	0	1 (12.5)	8	174.6
CTT Only – All MMS Total[A]	**40**	**15**	**22**	**3**	**19 (40.4)**	**47**	**464.85**
Rate / 100 patient years	**8.60**	**3.23**	**4.73**	**0.65**			
Hall et al. (2016)[19]	18	4	10	4	9 (75.0)	12	59.63

Vernet et al. (1996)[21]	1	1	0	0	1 (100)	1	4.8
Pre-Operative – All MMS Total[B]	**19**	**5**	**10**	**4**	**10 (76.9)**	**13 (100)**	**64.4**
Rate / 100 patient years	**29.50**	**7.76**	**15.53**	**6.21**			
All MMS Total[A+B]	**59**	**20**	**32**	**7**	**29 (48.3)**	**60**	**529.25**
Rate / 100 patient years	**11.15**	**3.78**	**6.05**	**1.32**			

These studies presented data that was sufficiently detailed to pull individual patient data.
CVE = cerebrovascular event, TIAs = transient ischemic attacks, silent = silent infarcts, CTT = chronic transfusion therapy, MMS = moyamoya syndrome, FU = follow up
[A] Patients of Dobson et al.[9], Gyang et al.[18], Hall et al.[19], and Yang et al.[20] receiving CTT only.
[B] Pre-operative patients of Hall et al.[19] and Vernet et al.[21] studies receiving CTT.

TABLE 3. ***CVE proportions in patients with MMS after cerebral revascularization surgery, grouped summary data***

Study	Total # patients	Intervention	# patients with CVE pre-surgery (%)	# patients with CVE post-surgery (%)
Gatti et al. (2021)[15]	9	CTT/CRS	NA	2 (22.2)
Hankinson et al.* (2008)[16]	12*	CRS	5 (41.6)	2 (16.6)
Smith et al. (2009)[17]	12	CRS	7 (58.3)	1 (8.3)
Study Total	**33**		**12 (50.0)†**	**5 (15.2)**

These studies presented data that allowed group level extraction but was insufficient to pull patient-level data.
CRS = cerebral revascularization surgery, CTT = chronic transfusion therapy, CVE = cerebrovascular event, MMS = moyamoya syndrome
* Includes patients receiving and not receiving CTT.
† Gatti et al.[15] were excluded from % calculation.

TABLE 4. ***CVE rates in patients with MMS after cerebral revascularization surgery (with medical management on CTT), individual pooled data***

Study	# CVEs	# strokes	# TIAs	# silent	# patients w CVE (%)	Total # patients	Total FU (years)
Alamri et al. (2019)[22]	1	1	0	0	1 (12.5)	8	26.7
Fryer et al. (2003)[23]	1	1	Unknown	Unknown	1 (16.7)	6	16.5
Griessenauer et al. (2015)[24]	1	1	0	0	1 (12.5)	8	18.3
Hall et al. (2016)[19]	6	0	6	0	4 (33.3)	12	57.0
Kennedy et al. * (2014)[25]	2	1	1	0	2 (20.0)	10	43.6
Vernet et al. (1996)[21]	1	1	0	0	1 (100)	1	1.8

Winstead et al. (2017)[26]	1	1	0	0	1 (14.3)	7	20.2
Yang et al. (2017)[20]	3	0	3	Unknown	3 (42.9)	7	66.9
Study Total	**16**	**6**	**10**	**0**	**14 (23.7)**	**59**	**251.0**
Rates / 100 patient years	**6.37**	**2.39**	**3.98**	**0.00**			

These studies presented data that was sufficiently detailed to pull individual patient data.
CVE = cerebrovascular event, TIAs = transient ischemic attacks, silent = silent infarcts, CTT = chronic transfusion therapy, MMS = moyamoya syndrome, FU = follow up
* Only patients on CTT included.

TABLE 5. ***CVE proportions in patients with MMS after HSCT, grouped summary data***

Study	Total # patients	Intervention	# patients with CVE pre-HSCT (%)	# patients with CVE post-HSCT (%)
Gatti et al. (2021)[15]	3	CTT + HSCT	NA	2 (66.7)
Hall et al. (2016)[19]	5	CTT + HSCT +/- CRS	5 (100) *	2 (40.0)
Study Total	**8**			**4 (50)**

These studies presented data that allowed group level extraction but was insufficient to pull patient-level data.

CRS = cerebral revascularization surgery, CTT = chronic transfusion therapy, CVE = cerebrovascular event, HSCT = hematopoietic stem cell transplant

* Includes patients who had CVEs while on CTT, and before surgery or HSCT.

Supplementary Table 1. Search Engines and Queries, all conducted on July 19, 2021

PubMed	(pediatrics[MeSH Terms] OR child[MeSH Terms] OR adolescent[MeSH Terms] OR infant[MeSH Terms] OR child, preschool[MeSH Terms] OR pediatric) AND (anemia, sickle cell[MeSH Terms]) AND ("Cerebrovascular Disorders"[Mesh] OR attack, transient ischemic[MeSH Terms] OR cerebrovascular OR microvascular OR stroke* OR infarct* OR ischem* OR ischaem* OR hemorrhag* OR haemorrhag* OR "cerebral vascular accident" OR "cerebral vascular accidents" OR CVA OR CVAs OR TIA OR TIAS) AND (arterial occlusive diseases[MeSH Terms] OR moyamoya OR “moya moya” OR vasculopathy) AND (“standard care” OR “medical treatment” OR hydroxyurea[MeSH Terms] OR hydroxyurea OR transfusion OR "exchange transfusion, whole blood"[MeSH Terms] OR “platelet aggregation inhibitors”[MeSH Terms] OR antiplatelet OR neurosurgery[MeSH Terms] OR neurosurg* OR “direct bypass” OR “indirect bypass” OR EDAS)
Embase	('cerebrovascular disease'/exp OR 'cerebrovascular accident'/exp) AND 'sickle cell anemia'/exp AND ('pediatrics'/exp OR 'child'/exp OR 'adolescent'/exp OR 'infant'/exp) AND ('moyamoya disease'/exp OR moyamoya OR vasculopathy) AND ('medical treatment'/exp OR 'medical treatment' OR (medical AND ('treatment'/exp OR treatment)) OR 'surgical treatment'/exp OR 'surgical treatment' OR (surgical AND ('treatment'/exp OR treatment)) OR 'surgery'/exp OR surgery OR 'hydroxyurea'/exp OR 'transfusion'/exp OR 'antithrombocytic agent'/exp OR aspirin OR neurosurgery OR ‘direct bypass’ OR ‘indirect bypass’ OR EDAS)
Web of Science	ALL FIELDS: ((pediatric) AND (sickle cell) AND ((CVE) OR (stroke) OR (ischemic) OR (hemorrhagic) OR (tia)) AND ((moyamoya) OR (vasculopathy)) AND ((medical treatment) OR (standard care) OR (hydroxyurea) OR (transfusion) OR (surgical treatment) OR (neurosurgery) OR (indirect bypass) OR (direct bypass) OR (EDAS) OR (antiplatelet) OR (aspirin)))
CENTRAL	(pediatric) AND (sickle cell) AND ((CVE) OR (stroke) OR (ischemic) OR (hemorrhagic) OR (tia)) AND ((moyamoya) OR (vasculopathy)) AND ((medical treatment) OR (standard care) OR (hydroxyurea) OR (transfusion)

	OR (surgical treatment) OR (neurosurgery) OR (indirect bypass) OR (direct bypass) OR (EDAS) OR (antiplatelet) OR (aspirin))