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Original Article

# Cerebral Blood Flow Abnormalities in Children With Sickle Cell Disease: A Systematic Review

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ABSTRACT

A systematic review was performed to assess whether cerebral blood flow with different imaging modalities could identify brain abnormalities in children with sickle cell disease where structural magnetic resonance imaging and transcranial Doppler velocity appeared normal. A total of 11 studies were identified which reported cerebral blood flow abnormalities alongside structural magnetic resonance imaging or transcranial Doppler velocity abnormalities in patients with sickle cell disease. Potential for bias was assessed with the quality assessment of diagnostic accuracy studies scale in addition to treatment bias. Subjects of each study were categorized into patients with and without stroke. The prevalence of abnormalities for each modality was then separately calculated in each group. The included studies had mostly moderate degrees of bias. The prevalence of blood flow abnormalities compared with structural magnetic resonance imaging abnormalities was equal to or lower in patients with stroke and equal to or greater in patients without stroke. Blood flow abnormalities were more prevalent than transcranial Doppler abnormalities in four studies of patients without stroke and in one study of patients with stroke. The studies suggest that the assessment of cerebral blood flow in sickle cell disease can be of potential value in addressing brain abnormalities at the tissue level; however, further studies are warranted.



## Introduction

Sickle cell disease is a spectrum of disorders of the red blood cell, in which the sickle β globin gene is inherited. It is characterized by rigid and sickle-shaped-red blood cells, which can be destroyed during the passage through the vasculature, leading to intravascular hemolysis and anemia. In addition, adhesion of the sickled red blood cells to the vascular endothelium causes occlusion and subsequent tissue ischemia. Cerebral ischemic events, particularly overt stroke, are among the most devastating complications in children with sickle cell disease. Strokes affect 7% to 11% of children with sickle cell disease [1,2], a prevalence that is 250 times higher than in the general pediatric population [3]. Overt stroke is diagnosed as a focal neurologic deficit resulting from cerebrovascular compromise that persists for more than 24 hours and has neuroimaging evidence of a cerebral infarct corresponding to the focal deficit. Interestingly, an even higher number of patients exhibit silent infarcts, defined as increased signal intensity on multiple $T_2$-weighted or fluid-attenuated inversion recovery magnetic resonance images in the brain with no history or physical findings. Silent strokes occur in approximately 22% of children with sickle cell disease [4] and can herald subsequent overt stroke [4-6]. Mechanisms responsible for cerebral ischemic events in sickle cell disease are complex and seem to be related to

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impaired blood flow. Blood flow abnormalities can be caused as a result of narrowing or occlusion of cerebral vessels, increased viscosity, adherence of red blood cells to the vascular endothelium, and exhaustion of autoregulatory vasodilation. Given the high susceptibility to cerebral ischemic events in children with sickle cell disease, early screening with advanced neuroimaging tools is important, particularly assessment of modalities that can detect evolving changes in cerebral blood flow. Detection of abnormalities of blood flow before clinical progression to stroke could be important information that can help or halt progression.

Standard transcranial Doppler ultrasonography is a low-cost method to identify patients with sickle cell disease at increased risk for development of a stroke. The Stroke Prevention Trial in Sickle Cell Anemia demonstrated that periodic red blood cell transfusion therapy in patients with transcranial Doppler velocities above 200 cm/s in the middle cerebral artery or terminal portion of the internal carotid artery can prevent overt strokes [7]. However, a large number of children (60%) with high velocities (>200 cm/s) do not develop a stroke [8,9], whereas others with velocities below 200 cm/s may still be at risk for overt stroke [10] or silent infarct [11]. Furthermore, transcranial Doppler assessment is dependent on operator skill, the need for an ultrasonic window ability to detect distal branches of intracranial vessels, the dependence of the velocity measurement on the angle, and depth of insonation [12].

Advanced modalities for cerebral blood flow (CBF) measurements include stable Xenon-enhanced computed tomography, positron emission tomography, and single photon emission tomography. Although nuclear medicine techniques such as positron emission tomography and single photon emission tomography can provide accurate regional measures of CBF, they require inhalation, injection, or exposure to ionizing radiation. Further disadvantages include low spatial resolution and, in the case of Xenon-enhanced computed tomography, a concomitant increase in CBF as a result of stable xenon inhalation [13]. Another disadvantage, specific to positron emission tomography, is limited availability and high cost. More recently, perfusion magnetic resonance imaging (MRI) techniques including dynamic susceptibility contrast MRI and arterial spin labeling have gained popularity as tools for imaging brain physiology, including CBF. MRI is

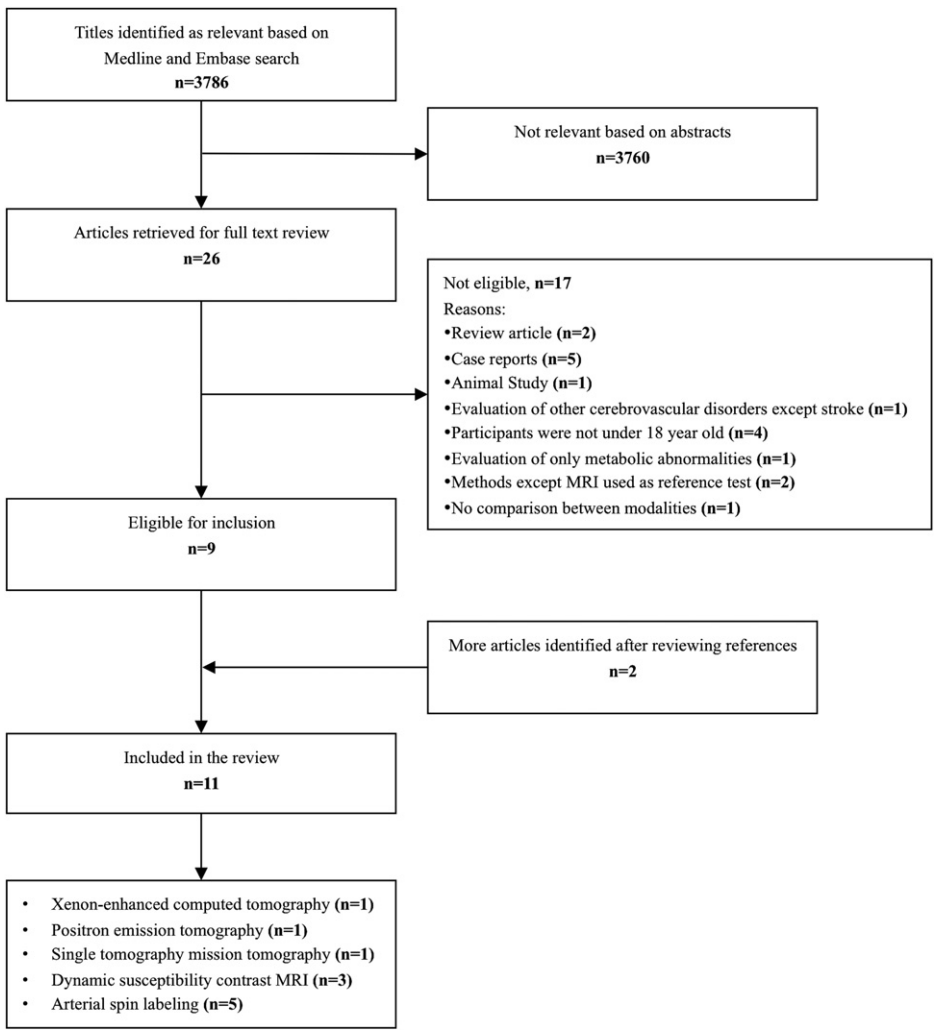


**Figure 1.** Flow diagram for study selection.

**Table 1. Baseline characteristics of included studies**

| Author, Year | Patient Characteristics | | | |
|---|---|---|---|---|
| | Mean Age, y (range) | Total No. M/F | Scanned No. | Inclusion Criteria (No. in Each Group) |
| Numaguchi et al., 1990 [15] | NR (1-16) | 25<br>19/6 | 25 (structural MRI)<br>25 (Xe-CT) | History of stroke (12)<br>History of CNS symptoms including, headache seizures, seizure-like episodes except stroke (13) |
| Powars et al., 1999 [16] | NR (3-19)* | 49<br>26/23 | 49 (structural MRI)<br>49 (PET) | History of stroke (19)<br>Prior hypoxic illness requiring hospitalization or soft neurologic signs (20)<br>Neurological normal (10) |
| AL- Kandari et al., 2007 [17] | 17 (8-45)* | 21<br>12/9 | 19 (structural MRI)<br>21 (SPECT) | Normal neurological assessment with no history of previous stroke or TIA or abnormal CT or MRI (21) |
| Tzika et al., 1993 [18] | NR (3-20)* | 33<br>NR | 33 (structural MRI)<br>33 (DSC MRI) | History of stroke (13)<br>Absence of any clinical indication of stroke with normal MRI (20) |
| Kirkham et al., 2001 [19] | 13 (4-34)* | 48<br>24/24 | 48 (structural MRI)<br>44 (TCD)<br>48 (DSC MRI) | History of stroke (8), TIA (8), RIND (6), seizure (6), severe headache /coma (1)<br>No acute Neurological events (22) |
| Grueneich et al., 2004 [20] | 11.9 (9-16) | 31<br>12/19 | 22 (structural MRI)<br>22 (DSC MRI) | No history of stroke or other neurological disorders (31) |
| Helton et al., 2009 [21] | 12 (5-17) | 21 NR† | 21 (structural MRI)<br>21 (TCD)<br>21 (PASL) | No history of stroke or TIA (30) |
| Oguz et al., 2003 [22] | 8.7 (6-12) | 18<br>12/6 | 18 (structural MRI)<br>16 (CASL) | No history of stroke, TIA, seizure and chronic transfusion or any drugs may affect CBF (18) |
| Strouse et al., 2006 [23] | 8.5 (6-12) | 24 NR | 24 (structural MRI)<br>24 (CASL) | No history of stroke, transfusion, seizure, previous traumatic brain injury and cognitive impairment with TCD less than 200 cm/sec (24) |
| Tweel et al., 2009 [24] | 13.4 (12-18) | 24 NR | 24 (structural MRI)<br>24 (TCD)<br>24 (CASL) | No history of neurological events with normal TCD (24) |
| Hijmans et al., 2011 [25] | 11.8 (6-18) | 37<br>18/16 | 21 (structural MRI)<br>34 (TCD)<br>21 (CASL) | No prior overt stroke or cerebral bleeding receiving treatment for a severe SCD |

Abbreviations:

| | | | |
|---|---|---|---|
| $^{99m}$Tc HMPAO | = 99m Tc-D, L-hexamethylene-propyleneamine oxime | PASL | = Pulsed arterial spin labeling |
| CASL | = Continuous arterial spin labeling | PET | = Positron emission tomography |
| CBF | = Cerebral blood flow | RIND | = Reversible ischemic neurologic deficit |
| CBV | = Cerebral blood volume | SC | = Sickle-hemoglobin C disease |
| CNS | = Central nervous system | SCD | = Sickle cell disease |
| DSC | = Dynamic susceptibility contrast | S$\beta^0$Thal | = Sickle beta-null thalassemia |
| CT | = Computed tomography | S$\beta^+$Thal | = Sickle beta-plus thalassemia |
| ECMO | = Extra corporeal membrane oxygenation | sMRI | = Structural magnetic resonance imaging |
| F | = Female | SPECT | = Single photon emission tomography |
| FDG | = Fluorodeoxyglucose | SS | = Sickle cell anemia |
| M | = Male | TCD | = Transcranial Doppler ultrasonography |
| MRI | = Magnetic resonance imaging | TIA | = Transient ischemic attack |
| MTT | = Mean transit time | Xe-CT | = Xenon-enhanced computed tomography |
| NR | = Not reported | Y | = years old |

* Median was under age 18.
† Fifteen of 21 scanned subjects were male.
‡ One patient without sickle cell disease who had undergone extracorporeal membrane oxygenation after cardiac surgery was also included.
§ Six patients had more than 2 transfusions before cerebral blood flow study.

particularly well suited for pediatric studies because it is noninvasive and does not require ionizing radiation.

*Purpose of the study*

The purpose of this review is to systematically review the prevalence of neuroimaging abnormalities in children with sickle cell disease identified on Xenon-enhanced computed tomography, positron emission tomography, single photon emission tomography, and perfusion MRI techniques (dynamic susceptibility contrast MRI and arterial spin labeling) to those abnormalities obtained with structural MRI and transcranial Doppler velocity. Identification of abnormalities in blood flow at an earlier stage of progression may lead to intervention, which can prevent further deterioration of flow and halt clinical progression to overt ischemia.

## Materials and Methods

*Criteria used for including studies in this review*

*Types of studies and participants*

Cohort studies that assessed children aged 0 to 18 years with a diagnosis of sickle cell disease were included. For completeness of the

| Patient Characteristics | | Reference Test | Index Test | |
|---|---|---|---|---|
| Type of SCD (No.) | Treatment History | | Method | Parameter |
| NR | Transfusion (12)<br>No treatment (13) | structural MRI | Xe-CT | Baseline TCD |
| SS (49) | Transfusion (17)<br>No treatment (32) | structural MRI | PET (using $H_2O$ and FDG) | Baseline CBF and glucose metabolism |
| SS (13),<br>$S\beta^0$Thal (8) | NR[§] | structural MRI | SPECT (using $^{99m}$Tc HMPAO) | Baseline CBF |
| SS (32)[‡] | NR | structural MRI | DSC MRI | Baseline CBF, CBV, MTT |
| SS (45), SC(1),<br>$S\beta^0$Thal (2) | Transfusion (21)<br>Hydroxyurea (1)<br>No treatment (26) | structural MRI, TCD | DSC MRI | Baseline CBF, CBV, MTT |
| SS (15), SC(9),<br>$S\beta^+$Thal (6),<br>$S\beta^0$Thal (1) | NR | structural MRI | DSC MRI | Baseline CBF, CBV, MTT |
| SS (30) | Hydroxyurea (18)<br>No treatment (3) | structural MRI, TCD | PASL | Baseline CBF |
| SS (18) | No treatment (18) | structural MRI | CASL | Baseline CBF |
| SS (24) | Hydroxyurea (22)<br>No treatment (2) | structural MRI | CASL | Baseline CBF |
| SS or $S\beta^0$Thal (24) | No treatment (24) | structural MRI, TCD | CASL | Baseline CBF |
| SS (30),<br>$S\beta^0$Thal (4) | No treatment (34)<br>Transfusion (3) | structural MRI, TCD | CASL | Baseline CBF |

relevant evidence, we included studies in which median age of population was <18 years, recognizing that some patients may be older than 18 years.

*Target condition and reference test*

Studies were included in this review if cerebral ischemic stroke was considered one of the outcomes of interest. Studies reporting only on seizures were excluded. Furthermore, we only included studies that used either structural MRI or transcranial Doppler scanning or both as reference test(s).

*Index tests*

Studies that have used any test methods of assessment of CBF including Xenon-enhanced computed tomography, positron emission tomography, single photon emission tomography, and perfusion MRI techniques (dynamic susceptibility contrast MRI and arterial spin labeling) were included.

*Search strategy*

We performed a comprehensive search of the Ovid/Medline and Embase databases (1980 to July 2012) to identify eligible studies. We used the following keywords and MeSH terminology: sickle cell, cerebrovascular disorder, hemodynamic, cerebral blood flow, magnetic resonance imaging, and transcranial Doppler ultrasonography. Articles were assessed irrespective of language of publication. Bibliographies of acquired articles were then reviewed to complete the search. We also searched the first 200 hits of Google Scholar to identify any articles published in grey literature.

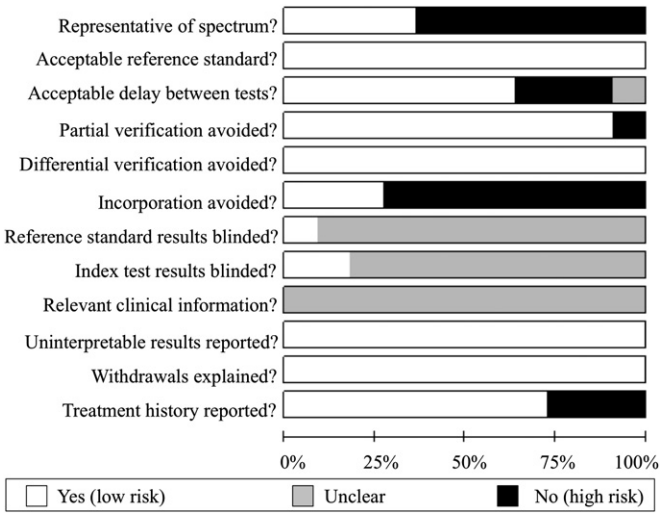


**Figure 2.** Risk of bias assessment in each category.

*Study Selection*

We included peer-reviewed studies that reported CBF measurements along with structural MRI or transcranial Doppler velocity findings in children with sickle cell disease. Case reports and review studies were not included but were read to identify additional eligible articles. Two independent reviewers (A.B., A.K.) assessed the title and abstract of each article as the first step. The same reviewers manually reviewed the full text for potentially relevant publications as the next step. Regular consensus meetings were organized between the two reviewers at both steps, and any disagreement was discussed and resolved by engaging a third reviewer (P.S.).

Two reviewers (A.B., A.K.) extracted the data independently from eligible articles, and discrepancies were resolved by consensus. Data on number and mean age of included patients, number of scanned patients with CBF imaging modalities, inclusion criteria, type of sickle cell disease, treatment history, type of reference test, type of CBF imaging modality, and different parameters used in the CBF study were collected.

*Risk of bias assessment*

To analyze the potential for bias, 11 criteria of the quality assessment of diagnostic accuracy studies (QUADAS) scale [14] were used. In addition, to evaluate the effect of treatment as confounding factor in included studies, we added another criterion as "treatment bias." These 12 criteria (Appendix) were scored separately in each study as either "low risk" (the study is free of evidence of bias or at very minimal risk of bias), "high risk" (the study assessment reveal evidence of bias) or "unclear" (the assessment indicated uncertainty around potential bias). Two authors (A.B., A.K.) assessed all articles independently. Discrepancies were checked, and consensus was achieved by discussion. If needed, a third author reviewed the data to reach a consensus (P.S.).

*Outcomes*

The outcome of interest in this review was evidence of neuroimaging abnormalities identified by any of the studied modalities. Patients in each study were categorized into two different groups: the stroke group, which involved patients with sickle cell disease and evidence of stroke, versus the nonstroke group, which involved either neurologically normal patients with sickle cell disease or patients who had a neurologic disorder that could not be attributed to ischemic stroke.

*Statistical analysis*

The prevalence of neuroimaging abnormalities was calculated for each imaging method (test) as a percentage by dividing the number of patients with abnormal scanning results by the total number of patients scanned in each group. The calculated prevalence of neuroimaging abnormalities was then separately compared with structural MRI and transcranial Doppler velocity findings (reference), within and between the two groups (stroke vs nonstroke) for each study. With prior knowledge of clinical and methodologic heterogeneity between studies, we did not plan any meta-analysis in this review.

## Results

*Search strategy and study selection*

The database search retrieved 3786 peer-reviewed articles. After reviewing the title and abstract, 26 reports were found potentially relevant for our review. The full texts of potentially relevant articles were then retrieved in the next step, with nine articles meeting the criteria for this review. In addition, references of these nine articles were checked, and two additional articles were included, for a total of 11 eligible articles. A flowchart of the article selection process is summarized in Figure 1. The baseline characteristics of the identified articles are reported in Table 1. All 11 included studies [15-25] were prospective cohort studies, which used different CBF imaging modalities in children with sickle cell disease to identify neuroimaging abnormalities. Seven [15-18,20,22,23] of 11 studies used structural MRI as a reference test, and the remaining four used both structural MRI and transcranial Doppler scanning as a reference test [19,21,24,25]. The CBF modalities used in these studies included one article with Xenon-enhanced computed tomography [15], one article with positron emission tomography [16], one article with single photon emission tomography [17], and eight articles with perfusion MRI

**Table 2. Risk of bias assessment**

| Criteria for Assessment | Numaguchi et al., 1990 [15] | Powars et al., 1999 [16] | AL-Kandari et al., 2007 [17] | Tzika et al., 1993 [18] | Kirkham et al., 2001 [19] |
|---|---|---|---|---|---|
| 1. Representative of spectrum | Low risk | Low risk | High risk | Low risk | Low risk |
| 2. Acceptable reference standard | Low risk | Low risk | Low risk | Low risk | Low risk |
| 3. Acceptable delay between tests | High risk | Unclear | High risk | Low risk | Low risk |
| 4. Partial verification avoided | Low risk | Low risk | Low risk | High risk | Low risk |
| 5. Differential verification avoided | Low risk | Low risk | Low risk | Low risk | Low risk |
| 6. Incorporation avoided | Low risk | Low risk | Low risk | High risk | High risk |
| 7. Reference standard results blinded | Unclear | Low risk | Unclear | Unclear | Unclear |
| 8. Index test results blinded | Low risk | Unclear | Unclear | Unclear | Unclear |
| 9. Relevant clinical information | Unclear | Unclear | Unclear | Unclear | Unclear |
| 10. Uninterpretable results reported | Low risk | Low risk | Low risk | Low risk | Low risk |
| 11. Withdrawals explained | Low risk | Low risk | Low risk | Low risk | Low risk |
| 12. Treatment history reported | Low risk | Low risk | High risk | Low risk | Low risk |

techniques, either dynamic susceptibility contrast MRI (three studies) [18-20] or arterial spin labeling (five studies) [21-25].

*Study analysis*

The risk of bias in the included studies is summarized in Figure 2 and Table 2. The overall included studies had moderate risk of bias. Four criteria (differential verification bias, acceptable reference test bias, study examination bias, and withdrawal bias) had low risk of bias for all studies. In general, studies scored poorly on diagnostic and test review biases and were susceptible to relevant clinical information bias. Only four publications [15,16,18,19] had low risk of spectrum bias, indicating that subjects with different clinical history of stroke were included.

*Outcomes*

To compare the prevalence of CBF abnormalities (index test) to structural MRI and transcranial Doppler velocity abnormalities (reference tests); hemispheric asymmetry of CBF regardless of the type of CBF imaging modality was identified as the common criteria of CBF abnormality (index test) in ten studies [15-22,24,25]. Hemispheric asymmetry was defined qualitatively on the basis of visual inspection for most studies or defined as decreased CBF in gray matter relative to the contralateral side. In addition, four studies included a more quantitative approach by comparing absolute CBF measurements in different vascular territories between two hemispheres [21,22,24,25]. One study [23] was excluded from our analysis because of the lack of individual CBF measurements and reference test data. For the reference test, tissue with increased $T_2$ signal on structural MRI and a transcranial Doppler velocity greater than 200 cm/s or lower than 70 cm/s was defined as abnormal. In addition, stroke and nonstroke groups were found in four [15,16,18,19] and ten [15-22,24,25] studies respectively. We therefore compared the prevalence of neuroimaging abnormalities to those of structural MRI abnormalities within stroke groups in four studies [15,16,18,19], within non-stroke groups in 10 studies [15-22,24,25], and between groups (stroke versus non-stroke) in four studies [15,16,18,19]. Prevalence of neuroimaging abnormalities were also compared with those of transcranial Doppler velocity abnormalities in nonstroke groups of four studies [19,21,24,25] and stroke groups of one study [19] (Table 3).

*CBF abnormalities versus structural MRI abnormalities*

Comparison within nonstroke groups in nine studies showed that the prevalence of CBF abnormalities defined with Xenon-enhanced computed tomography [15], positron emission tomography [16], single photon emission tomography [17], dynamic susceptibility contrast MRI [19,20], and arterial spin labeling [21,22,24,25] was higher than those of structural MRI abnormalities. One remaining study with dynamic susceptibility contrast MRI [18] demonstrated the identical prevalence for CBF and structural MRI abnormalities. Comparison within stroke groups showed that two studies with Xenon-enhanced computed tomography [15] and dynamic susceptibility contrast MRI [19] identified similar prevalence, and, in two other studies with positron emission tomography [16] and dynamic susceptibility contrast MRI [18], the prevalence of structural MRI abnormalities was greater than those of CBF abnormalities. Comparison between groups showed that all four studies [15,16,18,19] demonstrated higher prevalence of CBF and structural MRI abnormalities in stroke groups than nonstroke groups.

*CBF abnormalities versus transcranial Doppler velocity abnormalities*

CBF abnormalities were more prevalent than transcranial Doppler velocity abnormalities in nonstroke groups of the three arterial spin labeling studies [21,24,25] and one dynamic susceptibility contrast MRI study [19]. Comparison within the stroke groups in the same dynamic susceptibility contrast MRI [19] study also showed a higher prevalence of CBF abnormalities than those of transcranial Doppler velocity abnormalities.

## Discussion

In this review, we included 11 studies, which assessed CBF abnormalities in pediatric patients with sickle cell disease and compared them with transcranial Doppler velocity and structural MRI abnormalities. We identified that CBF and structural MRI abnormalities were more prevalent in patients who previously had a stroke compared with those who did not. In the stroke groups, the prevalence of CBF abnormalities was equal to or lower than those of MRI abnormalities. In the nonstroke groups, the prevalence of CBF abnormalities was equal to or greater than those of structural MRI abnormalities. In addition, CBF abnormalities were more prevalent than transcranial Doppler velocity

| Grueneich et al., 2004 [20] | Helton et al., 2009 [21] | Oguz et al., 2003 [22] | Strouse et al., 2006 [23] | Tweel et al., 2009 [24] | Hijmans et al., 2011 [25] |
|---|---|---|---|---|---|
| High risk | High risk | High risk | High risk | High risk | High risk |
| Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| High risk | High risk | High risk | High risk | High risk | High risk |
| Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Unclear | Low risk | Unclear | Unclear | Unclear | Unclear |
| Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| High risk | Low risk | Low risk | Low risk | Low risk | Low risk |

**Table 3. Results**

| Study, Year | Type of CBF Imaging Modality | Criteria of Abnormality | |
|---|---|---|---|
| | | CBF Measurement | Structural MRI |
| Numaguchi et al., 1990 [15] | Xe-CT | (1) Definite: obvious decreased flow areas in more than two contiguous slices relative to the normally perfused cortex of the comparable opposite hemisphere. (2) Possible: extensive areas of decreased flow in a single slice area or multiple small areas of decreased flow in a single slice area, or in multiple noncontiguous slices areas | High signal intensity on T2-w images |
| Powars et al., 1999 [16] | PET | Decrease of blood perfusion in the gray matter regions | High signal intensity on T2-w images |
| Al-Kandari et al., 2007 [17] | SPECT | The perfusion deficit: mild (10%–25%), moderate (25%-50%), severe (more than 50%): The contralateral side of each slice was used as the control for each patient with hypoperfusion. | Evidence of infarction on T1-w, T2-w and PD images |
| Tzika et al., 1993 [18] | DSC-MRI | Asymmetry in reduction of signal intensity between right and left | High signal intensity on T2-w images |
| Kirkham et al., 2001 [19] | DSC-MRI | Focal reduction in CBF, increase in MTT, reduction or increase in CBV, or increase in TTP | Changes in signal intensity on T2-w High ADC on DWI |
| Grueneich et al., 2004 [20] | DSC-MRI | Presence of hemispheric asymmetry | High signal intensity on T2-w images |
| Helton et al., 2009 [21] | PASL | rCBF asymmetry of CBF within ACA, ACAP, MCA, MCAP, PCA, PCAP defined as: if a statistically significant ($P$ values $< 0.0002$) difference existed between the left and right brain. | High signal intensity areas on T2-w and FLAIR |
| Oguz et al., 2003 [22] | CASL | rCBF asymmetry within ACA, MCA, PCA defined as: $R = f_L\text{-}f_R/\max(f_L, f_R)$ Then ratio $R$ with a central reduced normal variable K(R) were associated, defined as: $K(R) = (R\text{-}ì_R)/ó_{Rõ}$ | High signal intensity areas on T2-w and FLAIR Acute infarction on isotropic DWI |
| Strouse et al., 2006 [23] | CASL | NR | High signal intensity area ≥3 mm in diameter on T2-w or FLAIR consistent with ischemia and seen in two planes |
| Tweel et al., 2009 [24] | CASL | rCBF asymmetry within ACA, MCA, PCA defined as: difference in rCBF lower than11.7 mL/100 g/min between right and left. | High signal intensity on T2-w images |
| Hijmans et al., 2011 [25] | CASL | A difference in blood flow between both hemispheres >11.7 mL/100 g/min | Evidence of silent infarct on MRI |

Abbreviations:

$f_L$, $f_R$ = Cerebral blood flow in the left and right territories
$ì_R$ and $ó_R$ = Nonbiased estimators of the mean and SD of R over a normal population calculated with data from the group of volunteers
ACA = Anterior cerebral artery
ACAP = Anterior cerebral artery perforator
ADC = Apparent diffusion coefficient
CASL = Continuous arterial spin labeling
CBF = Cerebral blood flow
CBV = Cerebral blood volume
CI = Confidence interval
DSC = Dynamic susceptibility contrast
DWI = Diffusion weighted imaging
FLAIR = Fluid-attenuated inversion recovery
MCA = Middle cerebral artery
MCAP = Middle cerebral artery perforator
MTT = Mean transit time
MCAP = Middle cerebral artery perforator
MTT = Mean transit time
MRI = Magnetic resonance imaging
NR = Data are not reported
PASL = Pulsed arterial spin labeling
PCA = Posterior cerebral artery
PCAP = Posterior cerebral artery perforator
PD = Proton density
PET = Positron emission tomography
pMCA = Proximal middle cerebral artery
rCBF = Regional cerebral blood flow
SPECT = Single photon emission tomography
T1-w = $T_1$ weighted
T2-w = $T_2$ weighted
TCD = Transcranial Doppler ultrasonography
Xe-CT = Xenon-enhanced computed tomography

abnormalities in four studies of patients without stroke, as well as in one study of patients with stroke.

To our knowledge, this review is the first to systematically compare a range of CBF imaging modalities with structural MRI and transcranial Doppler velocity measurements in children with sickle cell disease. In previous reviews the role of CBF imaging modalities in children with sickle cell disease was only partly discussed [26-28]. Furthermore, additional CBF studies, particularly arterial spin labeling studies, were not included in these reviews. In 2000, a review by Powars et al [26] discussed the management of cerebral vasculopathy in children with sickle cell disease and briefly reviewed Xenon-enhanced computed tomography, positron emission tomography, and single photon emission tomography CBF studies. However, perfusion MRI methods examining CBF were not considered. In 2003, Winrow et al [27] evaluated utility and accuracy of clinical, as well as neuroimaging examinations

| Criteria of Abnormality | Prevalence of Abnormalities %, (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | Stroke Group | | | Non-stroke Group | | |
| TCD | Structural MRI | TCD | CBF | Structural MRI | TCD | CBF |
| – | 100 (76-100) | – | 100 (76-100) | 15 (4-42) | – | 31 (13-58) |
| – | 90 (69-97) | – | 84 (62-95) | 43 (27-60) | – | 47 (30-64) |
| – | – | – | – | 11 (3-31) | – | 33 (17-55) |
| – | 100 (77-100) | – | 77 (50-92) | 0 (0-16) | – | 0 (0-16) |
| MCA velocity: <70 or >200 cm/s | 100 (68-100) | 86 (49-97) | 100 (68-100) | 35 (22-50) | 24 (13-40) | 43 (29-58) |
| – | – | – | – | 23 (10-43) | – | 36 (20-57) |
| MCA velocity: >200 cm/s | – | – | – | 14 (5-35) | 0 (0-16) | 100 (85-100) |
| – | – | – | – | 6 (1-28) | – | 25 (10-50) |
| – | – | – | – | – | – | – |
| ACA, pMCA, dICA velocities: <40 or >200 cm/s | – | – | – | 50 (31-69) | 0 (0-14) | 58 (39-76) |
| Velocity: >200 cm/s | – | – | – | 57 (37-76) | 0 (0-10) | 64 (41-83) |

in children with sickle cell disease. The authors did review CBF measurements with Xenon-enhanced computed tomography, positron emission tomography, dynamic susceptibility contrast MRI studies, as well as one preliminary arterial spin labeling study but omitted a detailed assessment of bias. In 2010, Arkuszewski et al [28] reviewed neuroimaging in assessment of risk of stroke in children with sickle cell disease. The authors discussed a comprehensive array of neuroimaging modalities such as computed tomography, MRI, transcranial Doppler as well as nuclear medicine techniques. However, the discussion on CBF measurements was very minimal, except for two positron emission tomography studies with only one being performed in children with sickle cell disease. Furthermore, the assessment of bias was lacking and advanced CBF methods based on MRI such as dynamic susceptibility

contrast MRI and arterial spin labeling were not included. However, the authors provided a good overview of the use transcranial Doppler scanning and structural MRI in the assessment of children with sickle cell disease. Overall, the listed reviews lacked a comprehensive analysis to draw a reliable conclusion with regard to the utility of CBF assessment in children with sickle cell disease. Although the CBF assessment was recommended in children with sickle cell disease, the recommendations were solely drawn from individual results of the included studies and had no comparison to standard reference tests.

Cerebral blood flow is an important indicator of cerebral function, and impaired CBF seems to be the pathway through which cerebral injury occurs. In vivo, CBF can be assessed in several ways, for example by measuring absolute or relative CBF or by comparing the CBF map of two hemispheres against each other to evaluate CBF asymmetry. In general, measurements of CBF require a tracer whose tissue distribution can be modeled. Different types of tracers (diffusible, intravascular, endogenous or exogenous) are used depending on the type of CBF imaging modality. Almost all CBF imaging modalities use modeling of tracer kinetics (the contrast agent transport in tissue), with either compartment models developed by Kety and Schmidt [29] for example in positron emission tomography, single photon emission tomography, Xenon-enhanced computed tomography, and arterial spin labeling or some version of the indicator dilution theory developed by Meier and Zierler [30] in case of dynamic susceptibility contrast MRI. However, a series of assumptions with these models, as well as complex technical requirements, can lead to variation in absolute CBF values. A simpler alternative is the qualitative assessment of CBF asymmetry. This can be done visually by comparing a CBF map of two hemispheres [31]. CBF asymmetry can also be assessed more quantitatively by comparing absolute CBF measurements of the different vascular territories between both hemispheres. In our review, there was a lack of individual absolute CBF in the evaluated studies, we could therefore only systematically assess CBF asymmetries compared with the reference tests (structural MRI or transcranial Doppler).

The comparison of CBF asymmetries with structural MRI within the included studies identified a considerable percentage of children with no previous history of overt stroke who had CBF asymmetries but a normal structural MRI examination result. Stenosis of large cerebral arteries is probably the main reason for this CBF asymmetry, and in fact progression of stenosis is more often associated with clinically overt stroke [32-34]. However, a number of CBF asymmetries without corresponding stenosis of large cerebral arteries were also reported in four of the included studies [19,21,22,24]. Occlusion of small cerebral arteries caused by abnormal adherence of sickle-shaped blood cells, as well as impaired vasodilatory response, are believed to be responsible for perfusion deficiencies in the absence of large artery stenosis. Asymmetry of CBF in patients with normal structural MRI presumably represents some brain tissue at risk for ischemia [35].

Currently, risk of ischemic stroke in children with sickle cell disease is determined with a threshold transcranial Doppler velocity $>200$ cm/s, correlates with either focal stenosis $\geq 50\%$ in the large cerebral arteries [36], hyperemia, or both. However, abnormal transcranial Doppler velocity in this review was less common compared with CBF asymmetries identified by perfusion MRI techniques (dynamic susceptibility contrast MRI and arterial spin labeling). Transcranial Doppler velocity seems to be less sensitive to perfusion disturbances at tissue level than CBF. Furthermore, concerns about the accuracy of this velocity threshold, as well as operator dependence of transcranial Doppler scanning, may invalidate the interpretation of transcranial Doppler measurements.

It is also important to note that transcranial Doppler scanning cannot distinguish whether high blood flow velocities in sickle cell disease are due to stenosis or hyperemia. Transcranial Doppler scanning does not provide CBF values, because it cannot easily measure the diameter of the large cerebral arteries accurately. Furthermore, previous studies demonstrated poor correlation between transcranial Doppler velocity and perfusion measurements at the tissue level [37,38]. However, it should be noted that transcranial Doppler velocity can be used in children with sickle cell disease to reveal perfusion asymmetry when compared with the contralateral hemisphere [39], but this measure has not been used as a comparison in any of the studies we evaluated. Further studies are needed to investigate whether perfusion asymmetries obtained by transcranial Doppler scanning correlate with other neuroimaging modalities.

This review has several strengths, including a comprehensive search strategy, no language restriction, inclusion of studies limited to pediatric population, inclusion of various CBF imaging modalities such as Xenon-enhanced computed tomography, positron emission tomography, single photon emission tomography, and perfusion MRI techniques, comparison to current clinical standards (structural MRI and transcranial Doppler), and risk of bias assessment. However, our review has some limitations that warrant consideration. Heterogeneity among the CBF imaging modalities prevented meta-analysis. We also were not able to compare the specificity of CBF abnormalities and similarly those obtained with structural MRI and transcranial Doppler velocity. Patient selection can be biased in individual studies; however, bias at article selection was avoided by strict inclusion and exclusion criteria.

On the basis of the findings of this review, we are not in the position to provide clear guidelines for clinical practice. To date, transcranial Doppler scanning and structural MRI have remained the first choice in clinical decision-making in sickle cell disease, at least in part, because of the lack of research with regard to hemodynamic risk factors associated with stroke in sickle cell disease such as CBF abnormalities.

However, the usefulness of CBF measurements in children with sickle cell disease should be further investigated. Perfusion MRI techniques including dynamic susceptibility contrast MRI and arterial spin labeling, because of the lack of radiation exposure, are usually preferred to nuclear medicine techniques in children. Compared with arterial spin labeling, dynamic susceptibility contrast MRI provides higher spatial resolution, requires shorter scanning time, and can measure other hemodynamic parameters such as cerebral blood volume and mean transit time simultaneously. However, dynamic susceptibility contrast MRI

requires the use of gadolinium-based contrast agents, which can potentially increase the risk of vasooclusive crisis. Safety of these contrast agents has not yet been fully established in patients with sickle cell disease [40]. Therefore arterial spin labeling is probably a better choice for CBF assessment in children, because it only uses water as an endogenous contrast agent. Although arterial spin labeling is currently a bit more restricted to the exploration of a limited region of the brain and has an inherently weak signal-to-noise ratio, future developments such as availability of high–field MRI can enhance the role of arterial spin labeling in CBF assessment studies.

Application of other neuroimaging methods may further characterize CBF abnormalities and possibly assist in treating patients with sickle cell disease with such abnormalities. In particular, the need for a high-resolution angiographic assessment is necessary to exclude stenosis of intracranial arteries. Conventional intraarterial subtraction angiography is the most reliable way to infer cerebrovasculature complications such as stenosis and associated collateral vessels, but it is usually risky compared with other techniques such as magnetic resonance angiography. This technique is frequently the angiography of choice in children, which can readily be combined with MRI perfusion techniques.

Other physiological parameters should be considered to thoroughly understand the complex pathophysiological condition of sickle cell disease. For instance, autoregulatory cerebral vasodilation can be assessed to reflect the reserve capacity of the cerebral circulation to increase CBF [41,42]. In addition, the possible role of blood viscosity in regulation of CBF should be examined in patients with sickle cell disease.

In summary, our results suggest that the assessment of CBF in children with sickle cell disease merits further investigation, as CBF abnormalities are potentially associated with risk for ischemia. Longitudinal studies are required to determine the clinical value of CBF.

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## References

[1] Adams RJ. Sickle cell disease and stroke. J Child Neurol 1995;10: 75–6.
[2] Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998; 91:288–94.
[3] Earley CJ, Kittner SJ, Feeser BR, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. Neurology 1998;51:169–76.
[4] Pegelow CH, Macklin EA, Moser FG, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood 2002;99:3014–8.
[5] Kugler S, Anderson B, Cross D, et al. Abnormal cranial magnetic resonance imaging scans in sickle-cell disease. Neurological correlates and clinical implications. Arch Neurol 1993;50: 629–35.
[6] Miller ST, Macklin EA, Pegelow CH, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. J Pediatr 2001; 139:385–90.
[7] Adams RJ, McKie VC, Brambilla D, et al. Stroke prevention trial in sickle cell anemia. Control Clin Trials 1998;19:110–29.
[8] Adams R, McKie V, Nichols F, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med 1992;326:605–10.
[9] 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 1998;339:5–11.
[10] Adams RJ, Brambilla DJ, Granger S, et al. Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study. Blood 2004;103:3689–94.
[11] Wang WC, Gallagher DM, Pegelow CH, et al. Multicenter comparison of magnetic resonance imaging and transcranial Doppler ultrasonography in the evaluation of the central nervous system in children with sickle cell disease. J Pediatr Hematol Oncol 2000;22: 335–9.
[12] Gillams AR, McMahon L, Weinberg G, Carter AP. MRA of the intracranial circulation in asymptomatic patients with sickle cell disease. Pediatr Radiol 1998;28:283–7.
[13] Hartmann A, Dettmers C, Schuier FJ, Wassmann HD, Schumacher HW. Effect of stable xenon on regional cerebral blood flow and the electroencephalogram in normal volunteers. Stroke 1991;22:182–9.
[14] Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25.
[15] Numaguchi Y, Haller JS, Humbert JR, et al. Cerebral blood flow mapping using stable xenon-enhanced CT in sickle cell cerebrovascular disease. Neuroradiology 1990;32:289–95.
[16] Powars DR, Conti PS, Wong WY, et al. Cerebral vasculopathy in sickle cell anemia: diagnostic contribution of positron emission tomography. Blood 1999;93:71–9.
[17] Al-Kandari FA, Owunwanne A, Syed GM, et al. Regional cerebral blood flow in patients with sickle cell disease: study with single photon emission computed tomography. Ann Nucl Med 2007;21:439–45.
[18] Tzika AA, Massoth RJ, Ball WS Jr, Majumdar S, Dunn RS, Kirks DR. Cerebral perfusion in children: detection with dynamic contrast-enhanced T2-weighted MR images. Radiology 1993;187:449–58.
[19] Kirkham FJ, Calamante F, Bynevelt M, et al. Perfusion magnetic resonance abnormalities in patients with sickle cell disease. Ann Neurol 2001;49:477–85.
[20] Grueneich R, Ris MD, Ball W, et al. Relationship of structural magnetic resonance imaging, magnetic resonance perfusion, and other disease factors to neuropsychological outcome in sickle cell disease. J Pediatr Psychol 2004;29:83–92.
[21] Helton KJ, Paydar A, Glass J, et al. Arterial spin-labeled perfusion combined with segmentation techniques to evaluate cerebral blood flow in white and gray matter of children with sickle cell anemia. Pediatr Blood Cancer 2009;52:85–91.
[22] Oguz KK, Golay X, Pizzini FB, et al. Sickle cell disease: continuous arterial spin-labeling perfusion MR imaging in children. Radiology 2003;227:567–74.
[23] Strouse JJ, Cox CS, Melhem ER, et al. Inverse correlation between cerebral blood flow measured by continuous arterial spin-labeling (CASL) MRI and neurocognitive function in children with sickle cell anemia (SCA). Blood 2006;108:379–81.
[24] van den Tweel XW, Nederveen AJ, Majoie CB, et al. Cerebral blood flow measurement in children with sickle cell disease using continuous arterial spin labeling at 3.0-Tesla MRI. Stroke 2009;40: 795–800.
[25] Hijmans CT, Grootenhuis MA, Oosterlaan J, Heijboer H, Peters M, Fijnvandraat K. Neurocognitive deficits in children with sickle cell disease are associated with the severity of anemia. Pediatr Blood Cancer 2011;57:297–302.
[26] Powars DR. Management of cerebral vasculopathy in children with sickle cell anaemia. Br J Haematol 2000;108:666–78.

[27] Winrow N, Melhem ER. Sickle cell disease and stroke in a pediatric population. Evidence-based diagnostic evaluation. Neuroimaging Clin N Am 2003;13:185–96.
[28] Arkuszewski M, Melhem ER, Krejza J. Neuroimaging in assessment of risk of stroke in children with sickle cell disease. Adv Med Sci 2010;55:115–29.
[29] Kety SS, Schmidt CF. The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am J Physiol 1945;143:53–66.
[30] Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume. J Appl Physiol 1954;6: 731–44.
[31] Wintermark M, Sesay M, Barbier E, et al. Comparative overview of brain perfusion imaging techniques. Stroke 2005;36:e83–99.
[32] Stockman JA, Nigro MA, Mishkin MM, Oski FA. Occlusion of large cerebral vessels in sickle-cell anemia. N Engl J Med 1972;287:846–9.
[33] Gerald B, Sebes JI, Langston JW. Cerebral infarction secondary to sickle cell disease: arteriographic findings. AJR Am J Roentgenol 1980;134:1209–12.
[34] Russell MO, Goldberg HI, Hodson A, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood 1984;63:162–9.
[35] Levine RL, Rozental JM, Nickles RJ. Blood flow asymmetry in carotid occlusive disease. Angiology 1992;43:100–9.
[36] Adams RJ. Lessons from the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study. J Child Neurol 2000;15:344–9.
[37] Hartmann A, Ries F, Tsuda Y, Lagreze H, Seiler R, Grolimund P. Correlation of regional cerebral blood flow and blood flow velocity in normal volunteers and patients with cerebro-vascular disease. Neurochirurgia 1991;34:6–13.
[38] Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986;17:913–5.
[39] Arkuszewski M, Krejza J, Chen R, et al. Sickle cell disease: reference values and interhemispheric differences of nonimaging transcranial Doppler blood flow parameters. AJNR Am J Neuroradiol 2011;32:1444–50.
[40] OptiMark. St. Louis, MO: Mallinckrodt Inc.; 2009.
[41] Prohovnik I, Hurlet-Jensen A, Adams R, De Vivo D, Pavlakis SG. Hemodynamic etiology of elevated flow velocity and stroke in sickle-cell disease. J Cereb Blood Flow Metab 2009;29:803–10.
[42] Kedar A, Drane WE, Shaeffer D, Nicole M, Adams C. Measurement of cerebrovascular flow reserve in pediatric patients with sickle cell disease. Pediatr Blood Cancer 2006;46:234–8.

**Appendix. Bias list**

| Item | Bias | Potential Answers to Meet the Bias |
|---|---|---|
| 1 | Spectrum bias | Sickle cell disease patients with different clinical evidence of stroke (patients with and without history of stroke) |
| 2 | Acceptable reference standard | Structural MRI or transcranial Doppler scanning used as reference test |
| 3 | Disease progression bias | No delay occurs between results of index test (CBF imaging) and reference test (structural MRI or transcranial Doppler scanning) |
| 4 | Selection bias | Consecutive selection of patients |
| 5 | Differential verification bias | Patients received verification of their disease status using the same reference test (structural MRI and transcranial Doppler scanning) |
| 6 | Incorporation bias | Index test (CBF imaging) do not form part of the reference test (structural MRI or transcranial Doppler scanning) |
| 7 | Diagnostic review bias | Blind interpretation of index test (CBF imaging) without knowledge of reference test (structural MRI or transcranial Doppler scanning) |
| 8 | Test review bias | Blind interpretation of reference test (structural MRI or transcranial Doppler scanning) without knowledge of index test (CBF imaging) |
| 9 | Observer variability bias | Similar clinical data are available when interpreting reference test (structural MRI or transcranial Doppler scanning) and index test (CBF imaging) |
| 10 | Study examination bias | $<$10% of indeterminate or uninterpretable result |
| 11 | Withdrawal bias | $<$10% of patients withdraw after the index test |
| 12 | Treatment bias | Treatment history of included patients was reported |