Strokes in Children
A Systematic Review

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Context: Pediatric strokes lead to significant morbidity and mortality. To date, no systematic review has been available to guide the initial diagnostic approach to pediatric stroke.

Objective: The objective of this review was to elucidate the current data regarding etiologies of stroke in children and then develop an initial diagnostic evaluation for the pediatric patient presenting to the emergency department with a stroke.

Data Source: Using the PubMed engine, the MEDLINE database was searched using the Preferred Reporting Items in Systematic Reviews and Meta-Analyses guidelines.

Study Selection: The inclusion and exclusion criteria were established a priori. Studies must have extractable data regarding first strokes in pediatric patients with clear diagnostic categories.

Data Extraction: A standardized tool was developed to extract demographic data and stroke etiologies.

Results: Twelve studies were found that met the inclusion criteria. From these studies, a total of 1455 children aged between 21 days and 20 years were available to assess the etiologies of stroke.

Conclusions: In pediatric patients, the etiologies of stroke are varied and differ for children with ischemic stroke versus hemorrhagic stroke. With the present systematic review, a guide to the initial evaluation of stroke is presented.

Key Words: stroke, etiology, evaluation

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Pediatric stroke is an acute neurologic deficit that results from an ischemic or hemorrhagic cerebral vascular event, which occurs among individuals aged 28 days to 18 years, persists for at least 24 hours, and results from a disturbance of the cerebral circulation.[1] The incidence of pediatric stroke is low, affecting 2 to 8 per 100,000 children[2]; however, neurologic deficits and seizures occur in 75% of cases, recurrences occur in 20% of cases, and death is the result in up to 10% of those affected.[2]

Given the dire outcomes, children with acute strokes require expedited medical care and an intensive diagnostic evaluation to identify etiology, often begun in the emergency department. Unlike adults whose strokes typically follow long-standing acquired cardiovascular disease, the etiologies of pediatric strokes are myriad and include infectious, hematologic, neoplastic, vascular, and toxic etiologies.[3] Most studies addressing the etiologies of stroke in children are case reports or short case series, making it difficult to determine the relative prevalence rates of the different etiologies. As a result, it is difficult to develop an organized, systematic diagnostic approach to these children. Large, narrative reviews of stroke are available but do not lend themselves to the use in the pediatric emergency department. This systematic review was undertaken to address the issue of etiology of stroke by using a large pooled sample of patients and, from that pool, determine the proportion of patients with specific diagnosis and then use these data to provide an initial diagnostic approach to the pediatric patient presenting with a stroke.

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METHODS

The Preferred Reporting Items in Systematic Reviews and Meta-Analyses guidelines were followed.[4]

Literature Search

Using the PubMed search engine, the MEDLINE database was searched using the following key words: "stroke," "Case series" or "cohort," "etiology," "NOT sickle," "NOT neonatal," and "NOT perinatal." The filters used were "all children" and "humans." The references of each selected study were reviewed for additional studies that may have been missed by the computer search.

Study Protocol

To be included in the review, studies needed to meet all of the following requirements:

1. Participants needed to present immediately with clinical signs and symptoms suggestive of first stroke. Studies including only patients with sickle cell disease were excluded.
2. All participants were between 28 days and 20 years or defined as *pediatric*. Although the usual definition for pediatric stoke includes up to 18 years, some authors used younger than 21 years; thus, the age used for this review was increased to 20 years. In cases where the population included adults, the children needed to be reported as a separate group.
3. Studies needed to include at least 4 participants. This was done to eliminate case reports as opposed to systematic studies.
4. Evidence of an extensive diagnostic evaluation or a systematic evaluation was required.
5. Results of the study were expressed in summary or individually and included sufficient information to determine
   a. if the strokes were hemorrhagic or ischemic and
   b. the etiology of the stroke.

Data Analysis

Composite age, ethnicity, and sex data were recorded for each study. Strokes were classified as hemorrhagic or ischemic on the basis of computed tomography or magnetic resonance imaging as reported in each study.

The etiologies of ischemic strokes were defined by the scheme developed by Wraige et al[5] in 2005. Patients with ischemic strokes were broken down into 8 etiological subtypes including (1) sickle cell disease; (2) cardioembolic phenomena; (3) *Moyamoya syndrome* defined as an occlusion or stenosis of intracranial arteries eventually leading to the occlusion of the internal carotids with lenticulostriate collaterals and identified by angiography[6]; (4) cervical arterial dissection; (5) steno-occlusive cerebral arteriopathy that included irregularity, stenosis, or occlusion of a large intracranial artery; (6) other determined etiologies such as

mitochondrial encephalomyopathy, lactic acidosis, or strokelike episodes; (7) multiple probable/possible etiologies, such as cerebral angiitis, fibromuscular dysplasia, cerebral involvement in systemic vasculitis, bacterial meningitis, hypertension, prothrombotic disorders, clinical chicken pox within the past year without cerebral arterial abnormalities, and hyperhomocysteinemia; and (8) undetermined etiology. An additional category, sinovenous thrombosis, was included by the authors.

Etiologies of hemorrhagic strokes were classified as vascular malformations, trauma or vascular dissections, underlying medical disorders, and brain tumors. Vascular malformations were subdivided into arterial venous malformations (AVM), cavernous hemangiomas, bleeding of venous origin, aneurysms, and subarachnoid hemorrhage (SAH). The overall proportion of the various etiologies for ischemic and hemorrhagic stroke was determined from the pooled data.

RESULTS

The results of the literature search are shown in Figure 1. The MEDLINE search returned 568 abstracts and titles for review. Related articles identified by PubMed and review of the reference lists of selected studies meeting inclusion criteria yielded an additional 18 studies for a total of 586. Five hundred thirty-seven studies were excluded by title or abstract review. Thirty-seven studies were excluded because they included only sickle cell or other prothrombotic diseases (6 studies), focused on recurrences (4 studies), failed to define etiology (13 studies), did not contain published or available raw data (7 studies), focused on neuroimaging (3 studies), or focused on other medical disorders (4 studies).

The 12 studies[7–18] that comprised this report include 1455 children aged between 21 days and 20 years (2 patients had both hemorrhagic and ischemic components, so the total number of patients used for discussion is 1457); 1262 (86%) children had ischemic strokes. A summary of the characteristics of these patients is shown in Table 1. Most patients with pediatric stroke were non-Hispanic white, followed by Afro-Caribbean/Black, Hispanic, and Asian. Seven of the 12 studies did not publish the ethnicities of their patient populations. Of the 11 studies that published the sex of the patients, males were more likely to experience a form of stroke (male/female ratio, 1.3:1.0). The average of the published median ages was 8.2 years at the time of illness. Eight of the studies used in this review described patients with ischemic strokes, 1 study described patients with hemorrhagic stroke only, and 3 studies described children with both ischemic and hemorrhagic strokes.

The etiologies of ischemic stroke are shown in Table 2. Twenty-four percent (301/1262 children) of pediatric ischemic strokes resulted from an irregular, stenotic, or occluded large intracranial artery. Twelve percent (146/1262 children) had possible/probable etiologies that were not further defined. Eleven percent (141/1262 children) of the children had strokes from Moyamoya syndrome, 9% (110/1262 children) of the children had arterial dissections, 6% (75/1262 children) of the children had cardioembolic phenomena, 6% (75/1262 children) of the children had "other" etiologies, 5% (63/1262 children) of the strokes occurred in children with sickle cell disease, and 1% (16/1262 children) of the strokes resulted from sinovenous thrombosis. Twenty-six percent (335/1262 children) of the patients failed to have an identified etiology.

The etiologies of hemorrhagic stroke in 195 children are shown in Table 3. Hemorrhagic vascular malformations accounted for 54% (106/195 children) of hemorrhagic strokes; AVMs were the most common form of vascular malformation and accounted for 30% (58/195 children) of the hemorrhagic strokes and 55% (58/106 children) of all vascular malformations. Cavernous hemangiomas made up 12% (23/195 children) of the hemorrhagic strokes and 22% (23/106 children) of the vascular malformations; aneurysms were 10% (20/195 children) overall

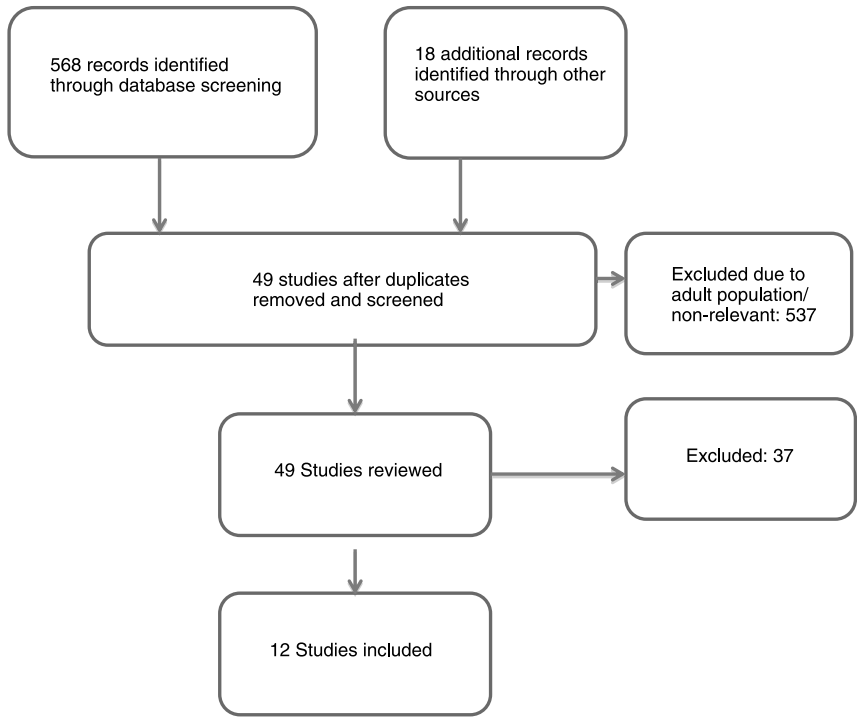


FIGURE 1. Results of literature search.

TABLE 1. Demographics of 12 Articles

Article	Study's Time Span	Age of Study Participants	n	Ethnicity, n (%)	Male/female Ratio	Median/Mean Age, y	Ischemic Stroke/Hemorrhagic Stroke Ratio
Christerson and Strömberg[7]	January 1, 2000–December 31, 2006	28 d, 18 y	51	White, 49 (96); Asian, 2 (4)	23:28	Median, 13	26 (51%):25 (49%)
Mancin et al[8]	January 1985–February 1995	2 mo, 17 y 8 mo	35	Not published	19:16	Median, 7.7	35 (100%):0 (0%)
Cheng et al[9]	January 1996–June 2000	Pediatrics not defined	5	Not published	3:2	Median, 8	5 (100%):0 (0%)
Lanthier et al[10]	1991–1997	1 mo, 18 y	72	White, 61 (85); Black, 4 (6); Asian, 2 (3)	1.5:1	Mean ischemic, 6.1; sinovenous thrombosis, 9.1; hemorrhagic, 7.9	51 (71%):21 (29%)
Ganesan et al[11]	1978–2000	21 d, 19.7 y	212	White, 151 (71); Afro-Caribbean, 42 (20); Black Asian, 17 (8); Far East, 2 (1)	114:98	Median, 5	212 (100%):0 (0%)
Chabrier et al[12]	January 1985–June 1998	3 mo, 16.5 y	59	Not published	33:26	Median, 6.11	59 (100%):0 (0%)
Yock-Corrales et al[13]	January 2003–December 2008	1 mo, 18 y	81	Not published	41:40	Mean ischemic, 7; hemorrhagic, 11	50 (62%):31 (38%)
Perkins and Butler[14]	September 1999–May 2003	12, 17	4	Not published	3:1	Median, 16	4 (100%):0 (0%)
Bernard et al[15]	January 1, 2005–May 1, 2006	29 d, 18 y	50	Non-Hispanic white, 29 (58); Hispanic, 16 (32); Asian, 2 (4); American Indian/Alaskan native, 1 (2); other, 2 (4)	32:18	Median, 9	50 (100%):0 (0%)
Jordan et al[16]	January 1993–December 2003	Younger children (28 d, 19.9 y)	116	Not published	Not published	Median, 12.1	0:116 (100%)
Amlie-Lefond et al[17]	January 2003–July 2007	29 d, 19 y	676	White, 64 (68); black, 23 (24); other, 7 (7)*	59:41	Median, 5.7	676 (100%):0 (0%)
Lee et al[18]	January 1996–July 2006	30 d, 18 y	94	Not published†	58:36	Median, 7.8	94 (100%):0 (0%)

Total number of patients (N) is 1455; 2 patients had both hemorrhagic and ischemic components, so the total number of patients used for discussion is 1457.

*Race data were available for 94 patients.

†The authors noted that the patients were exclusively from Taiwan.

TABLE 2. Etiologies of Ischemic Stroke in 1262 Children

Etiology	n (%)
Steno-occlusive arteriopathy	301 (24)
Moyamoya syndrome	141 (11)
Probable/possible*	146 (12)
Arterial dissection	110 (9)
Cardioembolic and other phenomena	75 (6)
Other	75 (6)
Sickle cell disease	63 (5)
Sinovenous thrombosis	16 (1)
Undetermined	335 (26)

*Cerebral angiitis, fibromuscular dysplasia, cerebral involvement in systemic vasculitis, bacterial meningitis, hypertension, prothrombotic disorders, clinical chicken pox within the past year without cerebral arterial abnormalities, and hyperhomocysteinemia.

and 19% (20/106 children) of the vascular malformations; SAH accounted for 2% (4/195 children) overall and 4% (4/106 children) of the vascular malformations, with venous bleeds accounting for 0.5% (1/195 children) overall and 0.9% (1/106 children) of the vascular malformations. Other medical etiologies accounted for 9% (18/195 children) of the hemorrhagic strokes, whereas brain tumors accounted for 2.5% (5/195 children) and trauma/dissection made up an additional 1% (2/195 children). The etiology of the 33% (64/195 children) of the hemorrhagic strokes was not determined.

DISCUSSION

Strokes, although an uncommon event in children, carry significant morbidity and mortality.[2] Unlike adults, pediatric strokes have a wide range of etiologies and require detailed investigation that is frequently initiated in the emergency department. This systematic review was undertaken to identify the most common etiologies of ischemic and hemorrhagic strokes in children and to provide a basis for the initial diagnostic investigations in these children.

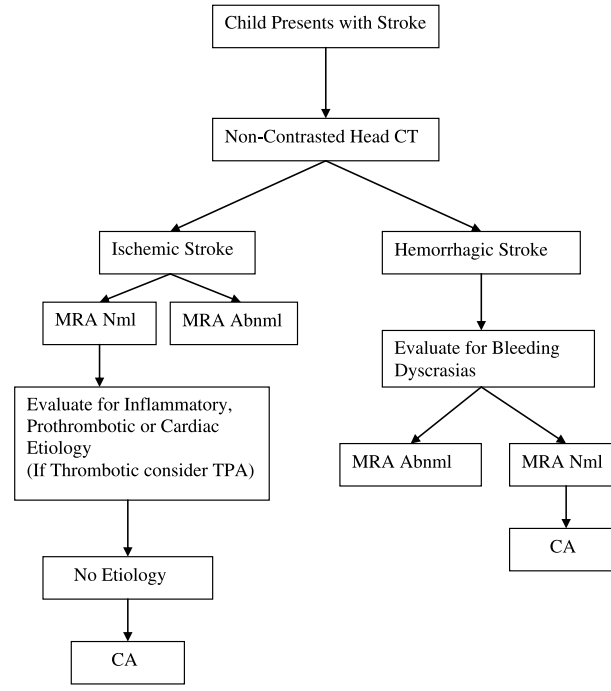
This review suggests that, in children, the etiologies of ischemic strokes and hemorrhagic strokes differ. As a result, neuroimaging should be considered the initial investigation in a child with an acute stroke. Computed tomography without contrast can be performed quickly, often without sedation, and can easily differentiate hemorrhagic from ischemic strokes.[19]

TABLE 3. Etiology of Stroke in 195 Children With Hemorrhagic Stroke

Etiology	n (%)
Vascular malformations	106 (54)
AVM	58 (30)
Cavernous hemangioma	23 (12)
Aneurysm	20 (10)
SAH	4 (2)
Venous malformation	1 (0.5)
Medical etiologies	18 (9)
Brain tumors	5 (2.5)
Trauma/dissection	2 (1)
Undetermined	64 (33)

Given that arteriopathies are the predominate etiology of both ischemic and hemorrhagic strokes, angiography is the next logical step in the evaluation of a child with an acute stroke. Husson et al[20] compared magnetic resonance angiography (MRA) with contrast angiography in 26 episodes of acute stroke in children. All patients had preliminary neuroimaging studies that suggested an infarct occurred in the distribution of an artery. All patients underwent both MRA and contrast angiography. The studies were concordant in cases where the stroke resulted from large vessel disease. In those studies where the findings were discordant, MRA overestimated the degree of stenosis in medium-sized vessels and missed distal occlusion in small vessels. Munot et al[21] identified 40 children with ischemic strokes and normal MRA. Ten of these children carried cardiac or oncologic diagnoses and 14 children had prothrombotic abnormalities. Compared with a control group of children with intravascular lesions, children with normal MRAs were more likely to have infarcts in multiple arterial territories and were more likely to have a nonvascular risk factor. In the present study, 30% of ischemic strokes occurred in children without primary vascular abnormalities. Together, these data suggest that children with ischemic stroke and normal MRA should undergo further evaluation for underlying inflammatory, prothrombotic, or cardiac disease. Although the details are beyond the scope of this article, when a thrombotic cause for a stroke is ascertained, timely therapeutic intervention with tissue plasminogen activator should be considered.

Although the data are limited, MRA or conventional cerebral angiography should be strongly considered in children with hemorrhagic stroke after bleeding dyscrasias and diatheses have been eliminated as the cause of disease. Figure 2 is a flow diagram for the initial evaluation of children who presented with stroke. An



CT: Computed Tomography
MRA: Magnetic Resonance Angiography
CA: Contrast Angiography

FIGURE 2. Flow chart of initial diagnostic evaluation.

exhaustive review of pediatric stroke was undertaken in 2008, but it is of limited usefulness in the emergency department setting.[22]

In summary, we report a systematic review of the etiologies of pediatric strokes. The etiologies are varied and differ for children with hemorrhagic stroke versus ischemic stroke. With the results of our review as a guide, we have outlined a suggested initial diagnostic evaluation of pediatric stroke.

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