Title

Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke.

Journal

Annals of Neurology, 72(6)

Authors

Hills, Nancy
Sidney, Stephen
Zielinski, Brandon
et al.

Publication Date

2012-12-01

DOI

10.1002/ana.23688

Peer reviewed

Published in final edited form as:
Ann Neurol. 2012 December ; 72(6): 850–858. doi:10.1002/ana.23688.

Recent Trauma and Acute Infection as Risk Factors for Childhood Arterial Ischemic Stroke

Nancy K. Hills, PhD[1], **S. Claiborne Johnston, MD, PhD**[1,3], **Stephen Sidney, MD, MPH**[4], **Brandon A. Zielinski, MD, PhD**[5], and **Heather J. Fullerton, MD MAS**[1,2]

[1]Department of Neurology, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143

[2]Department of Pediatrics, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143

[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143

[4]Division of Research, Kaiser Permanente-Northern California, 2000 Broadway, Oakland, CA 94612

[5]Department of Pediatrics, University of Utah, Primary Children's Medical Center, 100 N Mario Capecchi Drive, Salt Lake City, UT 84113

Abstract

Objective—Trauma and acute infection have been associated with stroke in adults, and are prevalent exposures in children. We hypothesized that these environmental factors are independently associated with childhood arterial ischemic stroke (AIS).

Methods—In a case-control study nested within a cohort of 2.5 million children (≤ 19 years old) enrolled in an integrated health care plan (1993–2007), childhood AIS cases (n=126) were identified from electronic records and confirmed through chart review. Age- and facility-matched controls (n=378) were randomly selected from the cohort. Exposures were determined from review of medical records prior to the stroke diagnosis, or the same date for the paired controls; time windows were defined a priori.

Results—A medical encounter for head or neck trauma within the prior 12 weeks was an independent risk factor for childhood AIS (odds ratio [OR] 7.5, 95% confidence interval [CI] 2.9, 19.3), present in 12% of cases (1.6% of controls). Median time from trauma to stroke was 0.5 days (interquartile range 0, 2 days); post-hoc redefinition of trauma exposure (prior 1 week) was more

Corresponding Author: Heather J. Fullerton, MD, MAS, Department of Neurology, Box 0114, University of California, San Francisco, 513 Parnassus Ave.; S-784, San Francisco, CA 94143-0114, FullertonH@neuropeds.ucsf.edu, Phone: (415) 353-3681, Fax: (415) 476-2500.

Dr. Hills drafted the manuscript and performed all data analyses, including statistical analyses, and contributed to the interpretation of these data.

Dr. Johnston contributed to the conception and design of the study, and the analysis and interpretation of the data, critically revised the manuscript for important intellectual content, and assisted with the statistical analyses.

Dr. Sidney contributed to the conception and design of the study, and the analysis and interpretation of the data, critically revised the manuscript for important intellectual content, and supervised the research staff that performed primary data collection.

Dr. Zielinski contributed acquisition of data, critically revised the manuscript for important intellectual content, and assisted with statistical analysis. He has no disclosures.

Dr. Fullerton conceived of and designed the study, obtained funding, contributed to data acquisition and analysis and interpretation of the data, drafted the comments section of the manuscript, critically revised the manuscript for important intellectual content, and supervised the overall study.

Barbara Rowe, RN, performed the bulk of the primary data collection for this study.

strongly associated with AIS: OR 39 (95% CI 5.1, 298). A medical encounter for a minor acute infection (prior 4 weeks) was also an independent risk factor (OR 4.6, 95% CI 2.6, 8.2), present in 33% of cases (13% of controls). No single infection type predominated. Only two cases had exposure to trauma and infection.

Interpretation—Trauma and acute infection are common independent risk factors for childhood AIS, and may be targets for stroke prevention strategies.

INTRODUCTION

At least 2,400 U.S. children suffer an arterial ischemic stroke (AIS) each year,[1] with a mean 5-year direct cost of $130,000,[2] yet their pathogenesis remains poorly understood. While adult AIS is largely attributable to atherosclerotic risk factors, childhood AIS has been linked to a variety of chronic conditions: congenital heart disease, hematological disorders, and autoimmune diseases.[3, 4] However, the majority of children are healthy at the time of their first AIS, suggesting other potential risk factors.[3] Two environmental exposures are of particular interest given their prevalence among children and association with adult stroke: head/neck trauma and minor acute infections.[5, 6] Studies have demonstrated that minor infections increase the risk of AIS in adults,[5, 7–12] particularly young adults, while influenza vaccination reduces that risk.[13, 14] Blunt injury to cervical or cerebral vessels can predispose to AIS by causing arterial dissection; screening paradigms are being established to detect such injury in adult trauma patients[15–21] and prevent stroke with antithrombotic therapy.[22–26] If these environmental factors play a role in childhood AIS, opportunities for primary stroke prevention in children may exist.

We hypothesized that recent head/neck trauma and acute infection are risk factors for childhood AIS, independent of the conditions traditionally linked to this disease. We tested this hypothesis with a population-based case-control study in a large Northern Californian integrated health care plan with a well-defined population, high level of retention in the system, and linkable electronic medical records.

METHODS

This case-control study was nested within a retrospective population-based cohort previously identified as part of the Kaiser Pediatric Stroke Study (KPSS). KPSS identified all ischemic and hemorrhagic stroke cases within the cohort of children (≤19 years of age)[27] enrolled in Kaiser Permanente Medical Care Program (KPMCP), 1/1993 through 12/2003.[1, 28] For the current study, we added 29 non-neonatal AIS cases by extending the study period through 12/2007; the final study cohort included 2.5 million children (Figure 1). We also identified matched controls. All study procedures were approved by the institutional review boards at the KPMCP Division of Research and University of California, San Francisco.

Setting

KPMCP is the largest nonprofit managed care organization in the country; its 16 hospitals and 36 out-patient facilities provide care to approximately 30% of the population of Northern California. Its members are demographically similar to the overall population of California, except for underrepresentation of socioeconomic extremes.[29] Study investigators had access to all paper and electronic medical records, as well as electronic databases with extensive, linkable data including demographics, inpatient and outpatient diagnoses, and radiology reports. Because KPMCP functions as the insurer, care provided outside the system is captured within both the electronic databases and traditional medical records as part of the claims process.

Case Ascertainment and Confirmation

KPSS case ascertainment methods have been published.[1, 28] This report includes only children with AIS aged 29 days through 19 years. In brief, potential cases were identified through electronic searches of inpatient and outpatient databases for diagnoses suggestive of stroke, and text string searches of radiology databases for brain imaging reports suggestive of infarction.[1] Cases were confirmed through independent chart review by two neurologists using pre-established clinical and radiographic criteria, with arbitration of disputes by a third.[28]

Control Selection

For each case, three population-based controls were randomly selected from the remaining cohort of 2.5 million stroke-free children (Figure 1), with pair-wise matching for birth year and year of enrollment in the KPMCP system (to remove any potential cohort effect of time), and primary care facility (to control for potential variability across KPMCP hospitals).

Data Abstraction

A single pediatric RN-trained medical records analyst used a standardized protocol to abstract data from all paper and electronic records. To prevent recall bias, all exposure variables were restricted to those documented in the medical records *prior* to the stroke diagnosis, or, for the controls, the "index date," defined as the date of the stroke for that control's matched case. All exposure variables were defined a priori, unless otherwise indicated. Risk factors were treated as absent (rather than missing) if the condition was not documented.

Recent environmental exposures—"Recent minor infection" was a documented outpatient medical encounter for infectious illness within four weeks preceding the stroke/index date; time windows for infectious exposure in adult stroke studies have varied from one week to 20 months, but most were within four weeks.[5, 8, 11, 12] Minor infectious illnesses included acute fever attributed to infection by the treating physician, upper respiratory tract infection, pneumonia, acute otitis media, pharyngitis, urinary tract infection, and acute gastroenteritis. "Recent major infection" was a documented diagnosis of meningitis or encephalitis within the prior four weeks or bacteremia/sepsis within the prior one week; in the absence of data to define the time window at risk, these were defined a priori by consensus opinion of the stroke neurologists on our team regarding the period during which a stroke might be attributable to the infection. "Chicken pox" was a documented primary varicella virus infection within one year prior.[30, 31]

"Head/neck trauma" was defined a priori as any medical encounter for head or neck trauma that occurred within the prior 12 weeks; a broad time window was chosen because the period of highest risk is not well defined in the literature. After analyzing the time from trauma to stroke ictus among our cases, we created a post-hoc definition of trauma exposure that narrowed the at-risk period to 1 week. We abstracted data on trauma mechanism, loss of consciousness, and skull fractures. In some cases, trauma and stroke occurred on the same day. In order to rule out the possibility of reverse causality (i.e., trauma caused by the stroke), we examined the details of each trauma event to determine the likely direction of causality.

Traditional pediatric stroke risk factors—We abstracted data on any past history of the following disease categories that have been traditionally linked to pediatric AIS, and created composite variables for each: "cardiac disease," including congenital heart disease, endocarditis, cardiomyopathy, and arrhythmia (excluding patent ductus arteriosus and patent

foramen ovale); “hematologic disease,” primarily sickle cell disease and hematologic malignancies (thrombophilias could not be assessed due to lack of data in the controls); and “autoimmune disease.”

Data Analysis

To assess predictors of AIS, we calculated ORs and 95% CIs using conditional logistic regression to account for pair-wise matching. We used univariate screening, with a p-value cutoff of 0.20, to select variables for the multivariable model, and included sex since prior literature suggests an association between gender and childhood AIS.[32, 33] For collinear variables, such as head/neck trauma and skull fracture, we included the more general variable (e.g., head/neck trauma). For risk factors which could not be included in regression models because they did not occur in controls, we used Cochran’s Q-test, a special case of the Friedman test for use with binary data, in order to account for matching. We used the a priori definition of head/neck trauma (12 week time window) in our primary analysis, and the post hoc definition (1 week time window) in a sensitivity analysis.

To graphically display the temporal relationship between head/neck trauma and AIS, we created a plot demonstrating the proportion of cases versus the entire (unmatched) cohort of controls that had no trauma encounters in the 12 weeks preceding the AIS, or the index date in the matched controls. For illustrative purposes only, we designed this plot to be analogous to a Kaplan-Meier curve; “time 0” was defined as the date of stroke and duration as the time measured from stroke (retrospectively) to preceding trauma. When a stroke and trauma occurred on the same day, we set duration for the event at 0.5 days.

All analyses were conducted using Stata, v11 (College Station, TX).

RESULTS

We identified 126 incident cases of childhood AIS and 378 pair-matched controls (Figure 1). The strokes occurred at all ages (Figure 2A), with a median of 10.5 (IQR: 2.0, 17.1) years. The cohort was ethnically diverse; 56% were boys (Table 1). Matching on facility had the effect of matching on race (data not shown); hence, the relationship between race and stroke could not be assessed.

Recent infection and head/neck trauma were risk factors for childhood AIS, and were more prevalent in our cohort than the traditional pediatric AIS risk factors (Table 1). An out-patient medical encounter for a minor acute infection increased a child’s risk of AIS more than 4-fold. The most common infectious diagnoses among the cases were upper respiratory tract infections (33%), other viral syndromes (26%), acute otitis media (19%), and acute gastroenteritis (17%); no single type of infection predominated. Parents of children with chronic diseases that are associated with AIS (i.e., autoimmune, hematologic, and cardiac diseases) may have a lower threshold for seeking medical care for a minor infection. However, after adjustment for these, minor acute infection remained an independent predictor of childhood AIS (Table 2).

Ten percent of cases, versus 0% of controls, had a recent major acute infection: bacteremia/sepsis (n=6) or meningitis/encephalitis (n=9). Of the meningitis/encephalitis diagnoses, four were bacterial (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus milleri*, *Escherichia coli*); five had inflammatory cerebrospinal fluid profiles but no organism identified. We saw no association between chicken pox and AIS; however, we likely under-detected this exposure because clinics discourage children with suspected chicken pox from coming to clinic and exposing other patients.

Recent acute infection (major or minor) was present in AIS cases of all ages, although this risk factor was particularly common in children under the age of 3 years (Figure 2A). As a sensitivity analysis, we examined the effect of environmental risk factors for childhood stroke by age, dichotomizing young (0–9 years) versus older (10–19 years) subjects. In multivariable analysis adjusted OR for minor acute infection was 3.3 (95% CI 1.5, 7 · 1) for younger and 8.8 (2.4, 32.7) for older children (p=0.17, test for interaction). The strokes in our cohort occurred in all seasons (Figure 2B).

An encounter for head/neck trauma in the prior 12 weeks was documented in 12% of cases versus 2% of controls (Table 1), with no clear seasonal predilection (data not shown). In multivariable analysis, it remained a strong independent predictor of AIS: OR 9.0 (95% CI 3.2, 25.1; Table 2). The trauma occurred within a median of 0.5 days prior to stroke (Figure 3). In the sensitivity analysis, using the post-hoc definition of trauma exposure as a documented encounter within the prior 1 week, the adjusted OR was 36.2 (95% CI 4.7, 281; P=0.001). Stratifying by age, the adjusted OR for head/neck trauma (prior 12 weeks) was 7.2 (1.6, 31.4) for younger and 12.4 (2.7, 56) for older children (p=0.62, test for interaction).

Markers of greater trauma severity—loss of consciousness and admission to the hospital—were strongly associated with AIS. Among the 15 cases, the mechanism included penetrating (n=3) and blunt trauma (n=12): severe motor vehicle accidents (n=6); minor falls (n=2); minor sports-associated injuries (n=2); crush injury (n=1; television set on the head); and non-accidental trauma (n=1). The mechanism among the seven controls included only blunt trauma: minor falls (n=4), minor blows to the head (n=2), and a motor vehicle accident (n=1). Seven out of 15 cases experienced trauma and stroke on the same day. Two were passengers in motor vehicle accidents, 2 received sports-related blows to the head, 1 suffered a gunshot wound, 1 had delayed focal deficit after a blow to the head from jumping on the bed, and the last was involved in a motor vehicle accident, although it was unclear whether as a passenger or driver. In all cases, we concluded that the trauma had preceded the stroke; however, as a sensitivity analysis, we excluded the last two cases (which could be viewed as non-conclusive in terms of direction of causality) from the analysis; our adjusted OR decreased from 9.0 to 7.7, and remained highly significant (p=0.001).

DISCUSSION

Association studies of childhood ischemic stroke have largely been limited to hematologic studies of genetic pro-thrombotic conditions; summarized in a recent meta-analysis, these conditions are modest stroke risk factors.[34] A small case-control study suggested an association between varicella zoster infection and childhood AIS.[30] Population-based cohort studies, limited by either few incident cases or reliance on administrative data, have shown that male gender and black race modestly increase risk of childhood stroke, while sickle cell disease has a strong effect, but have not assessed other risk factors.[32, 35, 36] In this case-control study nested within a population-based cohort, we confirmed the importance of diseases traditionally considered risk factors for childhood AIS: autoimmune, hematologic, and cardiac diseases. In addition, we found that environmental exposures—documented medical encounters for head/neck trauma, and acute infections—were the most common independent risk factors.

Although traumatic cervical or cerebral arterial dissection has long been recognized as a cause of childhood AIS,[37] recent exposure to trauma has never been formally evaluated as a risk factor. In our cohort, a head/neck trauma in the prior 12 weeks was both prevalent (present in 12% of cases) and strongly associated with AIS (OR= 9.0 in adjusted analysis). Because we could only measure trauma that resulted in a medical encounter, the true prevalence of preceding trauma among children with AIS is likely higher. (The true

prevalence of trauma would also be higher among control children, which could impact the estimate of relative risk.) The time between trauma exposure and AIS ictus was short (median of 0.5 days); when we narrowed the time window for the trauma exposure to 1 week, the adjusted OR increased to 36. Loss of consciousness and admission for trauma were particularly associated with childhood AIS, suggesting that more severe head/neck trauma might indicate a subgroup of trauma victims at particularly high risk.

Published estimates of the association between trauma and adult AIS are, to our knowledge, lacking; however, there is a large body of literature on "blunt cerebrovascular injury (BCVI)" referring to non-penetrating traumatic injury of cervical or cerebral vessels (namely arterial dissection). Among patients presenting to trauma centers, approximately 1.5% have evidence of BCVI on vascular imaging,[38–41] and 12% of those with BCVI will go on to have a stroke.[42] A variety of screening paradigms for BCVI have been published; patients meeting certain clinical or radiologic criteria are screened with cerebrovascular imaging, most often CT angiography (CTA).[38–41] Although the efficacy of antithrombotic therapy for stroke prevention in this setting has yet to be established, trauma patients found to have BCVI are typically treated prophylactically with aspirin or heparin.[22–26] A better understanding of the association between trauma and AIS in children—specifically, what trauma characteristics confer a higher risk of AIS—is needed to develop strategies for primary stroke prevention in pediatric trauma victims.

Major infections, like bacterial meningitis and sepsis, have long been considered etiologies of childhood AIS: meningitis can cause a vasculitis of the circle of Willis,[43] and sepsis can lead to embolic strokes due to systemic thrombosis or endocarditis.[44, 45] Fortunately, vaccines against *Haemophilus influenzae*, type B, *Neisseria meningitidis*, and *Streptococcus pneumonia* are now widely available, and we observed only four AIS cases with preceding bacterial meningitis. Minor infections, however, remain common among children, and have been linked to AIS in adults.[5, 7–12] In our cohort, a medical encounter for a minor acute infection was the most frequently observed childhood AIS risk factor, present in a 33% of cases. Because our definition of recent infection required a documented medical encounter, the true prevalence of this risk factor is higher, as many minor infections do not result in a medical visit. However, hospital series and an international prospective registry study have reported preceding minor infections (by parental report) in 24 to 34% of cases.[3, 4, 46] The strength of the association between recent infection and AIS observed in our study (adjusted OR 3.9) was similar to that reported in the adult studies, ranging from 2.9 (95% CI 1.6,5.3) for an infection in the prior 2 months,[12] to 4.5 (95% CI 2.1,9.7) for an infection in the prior week.[5]

As in adults, the association between recent infection and AIS does not appear to be specific to any particular type of infection; a variety of infectious illnesses were observed in our cases, with none predominating. We did not observe a clear seasonal predilection to stroke associated with either infection or trauma in our cohort; however, the relatively temperate climate in Northern California may minimize seasonal variation in infection. We saw no association between chicken pox and AIS; however, we likely under-detected this exposure because clinics discourage parents from bringing children with suspected chicken pox to clinic and exposing other patients.

Minor infections could predispose to AIS by promoting thrombosis through systemic inflammation, or by causing endothelial injury to a cervical or cerebral artery.[47, 48] Supporting the latter mechanism, in an international prospective registry of childhood AIS, recent minor infection was significantly associated with cerebral arteriopathy.[49] Among previously healthy children presenting with a first AIS, a cerebral arteriopathy is found in the majority,[3] and is the strongest predictor of recurrent childhood AIS.[28, 50] Hence, a better

understanding of the role of infection, the focus of the on-going NIH-funded Vascular effects of Infection in Pediatric Stroke (VIPS) study,[51] is crucial for stroke prevention in children. The influenza vaccine has been shown to decrease stroke risk in adults;[13, 14] influenza vaccination programs may similarly act as primary stroke prevention in children.

The retrospective nature of our study was a limitation. Missing data led to potential misclassification of exposure variables. However, because we abstracted exposure variables only if that exposure was documented prior to the stroke diagnosis, or the index date in the paired controls, misclassification likely would be non-differential and should therefore bias our results towards the null hypothesis. Hereditary thrombophilias have been shown to be risk factors for childhood AIS,[34] yet could not be evaluated in this study, and we were underpowered to examine interactions between risk factors. Underrepresentation of socioeconomic extremes reduces the generalizability of our findings. Strengths of the study, however, included the availability of unbiased controls and longitudinal clinical data in a population-based setting; this allowed for novel observations regarding environmental exposures as risk factors for childhood AIS.

Acknowledgments

This study was funded by an NINDS Independent Scientist Award (K02 NS053883; PI Heather Fullerton). Dr. Zielinski's effort on this project was funded by a UCSF Clinical and Translational Science Institute (CTSI) Resident Research Award.

References

1. Agrawal N, Johnston SC, Wu YW, et al. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. Stroke. 2009; 40(11):3415–21. [PubMed: 19762687]
2. Gardner MA, Hills NK, Sidney S, et al. The 5-year direct medical cost of neonatal and childhood stroke in a population-based cohort. Neurology. 2010; 74(5):372–8. [PubMed: 20054007]
3. Ganesan V, Prengler M, McShane MA, et al. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol. 2003; 53(2):167–73. [PubMed: 12557282]
4. Mackay MT, Wiznitzer M, Benedict SL, et al. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Ann Neurol. 2011; 69(1):130–40. [PubMed: 21280083]
5. Grau AJ, Buggle F, Heindl S, et al. Recent infection as a risk factor for cerebrovascular ischemia. Stroke. 1995; 26(3):373–9. [PubMed: 7886709]
6. Biffl WL, Ray CE Jr, Moore EE, et al. Treatment-related outcomes from blunt cerebrovascular injuries: importance of routine follow-up arteriography. Ann Surg. 2002; 235(5):699–706. discussion -7. [PubMed: 11981216]
7. Grau AJ, Buggle F, Becher H, et al. The association of leukocyte count, fibrinogen and C-reactive protein with vascular risk factors and ischemic vascular diseases. Thromb Res. 1996; 82(3):245–55. [PubMed: 8732628]
8. Grau AJ, Buggle F, Becher H, et al. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: clinical and biochemical studies. Neurology. 1998; 50(1):196–203. [PubMed: 9443480]
9. Syrjanen J. Infection as a risk factor for cerebral infarction. Eur Heart J. 1993; 14(Suppl K):17–9. [PubMed: 8131782]
10. Syrjanen J, Valtonen VV, Livanainen M, et al. Preceding infection as an important risk factor for ischaemic brain infarction in young and middle aged patients. Br Med J (Clin Res Ed). 1988; 296(6630):1156–60.
11. Becher H, Grau A, Steindorf K, et al. Previous infection and other risk factors for acute cerebrovascular ischaemia: attributable risks and the characterisation of high risk groups. J Epidemiol Biostat. 2000; 5(5):277–83. [PubMed: 11142603]
12. Bova IY, Bornstein NM, Korczyn AD. Acute infection as a risk factor for ischemic stroke. Stroke. 1996; 27(12):2204–6. [PubMed: 8969781]

13. Lavallee P, Perchaud V, Gautier-Bertrand M, et al. Association between influenza vaccination and reduced risk of brain infarction. Stroke. 2002; 33(2):513–8. [PubMed: 11823662]
14. Nichol KL, Nordin J, Mullooly J, et al. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med. 2003; 348(14):1322–32. [PubMed: 12672859]
15. Berne JD, Norwood SH, McAuley CE, et al. The high morbidity of blunt cerebrovascular injury in an unscreened population: more evidence of the need for mandatory screening protocols. J Am Coll Surg. 2001; 192(3):314–21. [PubMed: 11245373]
16. Berne JD, Norwood SH, McAuley CE, et al. Helical computed tomographic angiography: an excellent screening test for blunt cerebrovascular injury. J Trauma. 2004; 57(1):11–7. discussion 7–9. [PubMed: 15284541]
17. Biffl WL, Egglin T, Benedetto B, et al. Sixteen-slice computed tomographic angiography is a reliable noninvasive screening test for clinically significant blunt cerebrovascular injuries. J Trauma. 2006; 60(4):745–51. discussion 51–2. [PubMed: 16612293]
18. Biffl WL, Moore EE, Offner PJ, et al. Blunt carotid arterial injuries: implications of a new grading scale. J Trauma. 1999; 47(5):845–53. [PubMed: 10568710]
19. Biffl WL, Moore EE, Offner PJ, et al. Optimizing screening for blunt cerebrovascular injuries. Am J Surg. 1999; 178(6):517–22. [PubMed: 10670864]
20. Bok AP, Peter JC. Carotid and vertebral artery occlusion after blunt cervical injury: the role of MR angiography in early diagnosis. J Trauma. 1996; 40(6):968–72. [PubMed: 8656485]
21. Bub LD, Hollingworth W, Jarvik JG, et al. Screening for blunt cerebrovascular injury: evaluating the accuracy of multidetector computed tomographic angiography. J Trauma. 2005; 59(3):691–7. [PubMed: 16361914]
22. Colella JJ, Diamond DL. Blunt carotid injury: reassessing the role of anticoagulation. Am Surg. 1996; 62(3):212–7. [PubMed: 8607581]
23. Cothren CC, Biffl WL, Moore EE, et al. Treatment for blunt cerebrovascular injuries: equivalence of anticoagulation and antiplatelet agents. Arch Surg. 2009; 144(7):685–90. [PubMed: 19620551]
24. Cothren CC, Moore EE, Biffl WL, et al. Anticoagulation is the gold standard therapy for blunt carotid injuries to reduce stroke rate. Arch Surg. 2004; 139(5):540–5. discussion 5–6. [PubMed: 15136355]
25. Davis JW, Holbrook TL, Hoyt DB, et al. Blunt carotid artery dissection: incidence, associated injuries, screening, and treatment. J Trauma. 1990; 30(12):1514–7. [PubMed: 2258964]
26. Wahl WL, Brandt MM, Thompson BG, et al. Antiplatelet therapy: an alternative to heparin for blunt carotid injury. J Trauma. 2002; 52(5):896–901. [PubMed: 11988655]
27. Fullerton HJ, Chetkovich DM, Wu YW, et al. Deaths from stroke in US children, 1979 to 1998. Neurology. 2002; 59(1):34–9. [PubMed: 12105304]
28. Fullerton HJ, Wu YW, Sidney S, et al. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007; 119(3): 495–501. [PubMed: 17332202]
29. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992; 82(5):703–10. [PubMed: 1566949]
30. Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. Ann Neurol. 1999; 45(5):679–80. [PubMed: 10319896]
31. Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke. 2001; 32:1257–62. [PubMed: 11387484]
32. Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: Ethnic and gender disparities. Neurology. 2003; 61(2):189–94. [PubMed: 12874397]
33. Golomb MR, Fullerton HJ, Nowak-Gottl U, et al. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke. 2009; 40(1):52–7. [PubMed: 18787197]
34. Kenet G, Lutkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation. 2010; 121(16):1838–47. [PubMed: 20385928]

35. Broderick J, Talbot GT, Prenger E, et al. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. J Child Neurol. 1993; 8(3):250–5. [PubMed: 8409267]
36. Earley CJ, Kittner SJ, Feeser BR, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. Neurology. 1998; 51(1):169–76. [PubMed: 9674798]
37. Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. Neurology. 2001; 57(7):1155–60. [PubMed: 11601431]
38. Utter GH, Hollingworth W, Hallam DK, et al. Sixteen-slice CT angiography in patients with suspected blunt carotid and vertebral artery injuries. J Am Coll Surg. 2006; 203(6):838–48. [PubMed: 17116552]
39. Langner S, Fleck S, Kirsch M, et al. Whole-body CT trauma imaging with adapted and optimized CT angiography of the craniocervical vessels: do we need an extra screening examination? AJNR Am J Neuroradiol. 2008; 29(10):1902–7. [PubMed: 18784210]
40. Cothren CC, Moore EE. Blunt cerebrovascular injuries. Clinics (Sao Paulo). 2005; 60(6):489–96. [PubMed: 16358140]
41. Schneidereit NP, Simons R, Nicolaou S, et al. Utility of screening for blunt vascular neck injuries with computed tomographic angiography. J Trauma. 2006; 60(1):209–15. discussion 15–6. [PubMed: 16456458]
42. Stein DM, Boswell S, Sliker CW, et al. Blunt cerebrovascular injuries: does treatment always matter? J Trauma. 2009; 66(1):132–43. discussion 43–4. [PubMed: 19131816]
43. Snyder RD, Stovring J, Cushing AH, et al. Cerebral infarction in childhood bacterial meningitis. J Neurol Neurosurg Psychiatry. 1981; 44(7):581–5. [PubMed: 7026737]
44. Richardson SG, Matthews KB, Cruickshank JK, et al. Coagulation activation and hyperviscosity in infection. Br J Haematol. 1979; 42(3):469–80. [PubMed: 476000]
45. Ogata K, Yagawa K, Hayashi S, et al. Thrombosis-inducing activity in plasma of patients with acute respiratory tract infection disappears after treatment. Respiration. 1991; 58(3–4):176–80. [PubMed: 1745851]
46. Riikonen R, Santavuori P. Hereditary and acquired risk factors for childhood stroke. Neuropediatrics. 1994; 25(5):227–33. [PubMed: 7885530]
47. Elkind MS, Cole JW. Do common infections cause stroke? Semin Neurol. 2006; 26(1):88–99. [PubMed: 16479447]
48. Grau AJ. Infection, inflammation, and cerebrovascular ischemia. Neurology. 1997; 49(5 Suppl 4):S47–51. [PubMed: 9371150]
49. Amlie-Lefond C, Bernard TJ, Sebire G, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation. 2009; 119(10):1417–23. [PubMed: 19255344]
50. Prengler VM, Wade A, et al. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation. 2006; 114(20):2170–7. [PubMed: 17075014]
51. Fullerton HJ, Elkind MS, Barkovich AJ, et al. The Vascular Effects of Infection in Pediatric Stroke (VIPS) Study. J Child Neurol. 2011; 26(9):1101–10. [PubMed: 21616922]

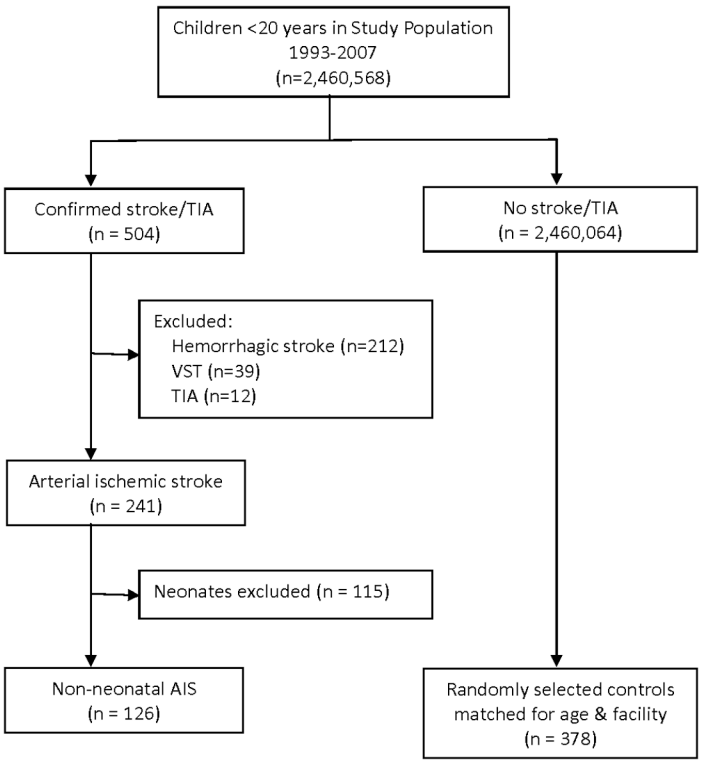

Figure 1.
Selection of study cases and controls. Abbreviations: AIS, arterial ischemic stroke; VST, venous sinus thrombosis; TIA, transient ischemic attack.

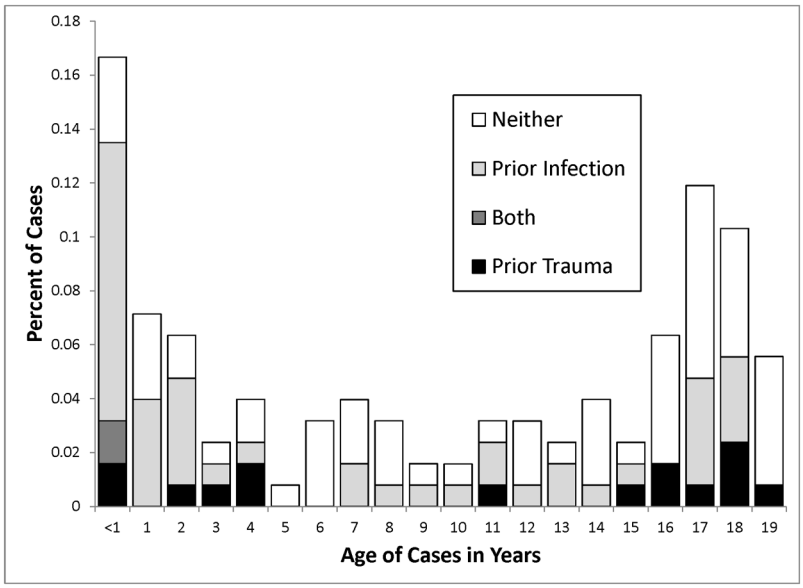

Figure 2B

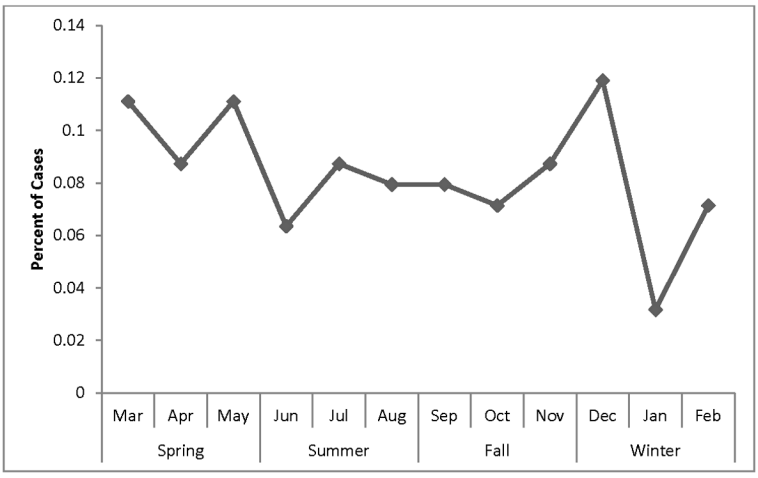

Figure 2.

Demographics of 126 childhood arterial ischemic stroke cases. Age at time of stroke (A). Each bar represents the total percentage of strokes at each age, with shading to indicate the mutually exclusive percentage of all cases with preceding trauma (prior 12 weeks; black), preceding infection (prior 4 weeks; light gray), both (dark gray), or neither (clear). Month/season at time of stroke (B).

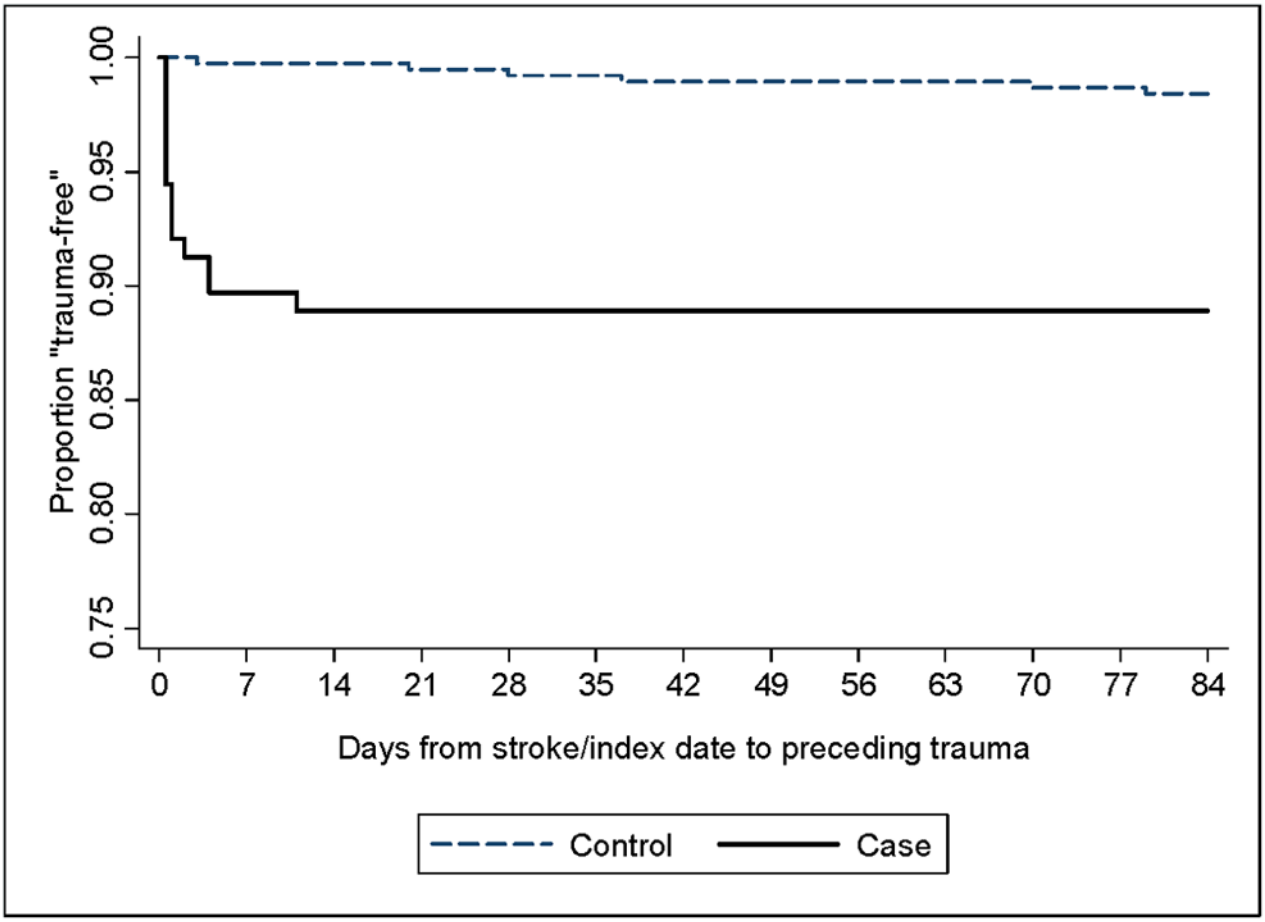

Figure 3.
Plot demonstrating the percentage of cases versus controls that were “trauma-free” (i.e., without a medical encounter for head/neck trauma) during the 12 weeks preceding the stroke/index date. Time is counted backwards in days from stroke/index date to the date of the trauma. (Note that the y-axis begins at 0.75.)

Table 1

Univariate Risks for Arterial Ischemic Stroke in Children (29 days to 19 years of age)

	Cases	Controls		
Characteristic	**n/Total (%)**	**n/Total (%)**	**OR (95% CI)**	***P***
Age -- yr, median (IQR)*	10.5	10.5		
Male	70/126 (55.6)	198/378 (52.4)	1.1 (0.8, 1.7)	0.56
Race*				
White	56/126 (44.4)	144/378 (38.1)		
Black	18/126 (14.3)	43/378 (11.4)		
Hispanic	21/126 (16.7)	62/378 (16.4)		
Asian	23/126 (18.3)	39/378 (10.3)		
RECENT ENVIRONMENTAL EXPOSURES				
Head or neck trauma				
Head or neck trauma (past 12 weeks)	15/126 (11.9)	6/378 (1.6)	7.5 (2.9, 19.3)	<0.001
Head or neck trauma (past 1 week)	13/126 (10.3)	1/378 (0.3)	39 (5.1, 298)	<0.001
Days from trauma to stroke/index date, median (IQR)	0.5 (0, 2)	32.5/378 (20, 70)		0.005†
Loss of consciousness	7/126 (5.6)	1/378 (0.3)	21.0 (2.6–170)	0.004
Admission for trauma	11/126 (8.7)	0/378		<0.001‡
Skull fracture	2/126 (1.6)	0/378		0.06‡
Minor or major acute infection	50/126 (39.7)	50/378 (13.2)	6.4 (3.6, 11.4)	<0.001
Minor acute infection (past 4 weeks)	42/126 (33.3)	50/378 (13.2)	4.6 (2.6, 8.2)	<0.001
Major acute infection	12/126 (9.5)	0/378		<0.001‡
Bacteremia/sepsis (past week)	6/126 (4.8)	0/378		<0.001‡
Meningitis (past 4 weeks)	9/126 (7.1)	0/378		<0.001‡
Chicken pox (past year)	2/126 (1.6)	5/378 (1.3)	1.2 (0.2, 6.2)	0.83
TRADITIONAL PEDIATRIC STROKE RISK FACTORS				
Autoimmune disease [composite]	13/126 (10.3)	1/378 (0.3)	39.0 (5.1, 298)	<0.001
Systemic lupus erythematosus	7/126 (5.6)	0/378		<0.001‡
Vasculitis	2/126 (1.6)	0/378		0.01‡
Other autoimmune disease§	9/126 (7.1)	1/378 (0.3)	27 (3.4, 213)	0.002

Characteristic	Cases n/Total (%)	Controls n/Total (%)	OR (95% CI)	*P*
Cardiac disease [composite]	10/126 (7.9)	4/378 (1.1)	7.5 (2.4, 23.9)	0.001
Congenital heart disease	8/126 (6.3)	2/378 (0.5)	12 (2.5, 56.5)	0.002
Arrhythmia	2/126 (1.6)	1/378 (0.3)	6 (0.5, 66.2)	0.14
Endocarditis	1/126 (0.8)	0/378		0.08‡
Cardiomyopathy	1/126 (0.8)	0/378		0.08‡
Other heart disease	2/126 (1.6)	1/378 (0.3)		
Hematologic disease [composite]	7/126 (5.6)	2/378 (0.5)	10.5 (2.2, 50.5)	0.003
Sickle cell disease	2/126 (1.6)	0/378		0.01‡
Leukemia	2/126 (1.6)	0/378		0.01‡
Lymphoma	2/126 (1.6)	0/378		0.01‡
Prior deep venous thrombosis	1/126 (0.8)	0/378		0.08‡
Other hematologic disease//	0/126	2/378 (0.5)		

Abbreviations: CI, confidence interval; IQR, interquartile range

*OR not relevent because of matching on age and facility; matching on facility had the effect of matching on race/ethnicity

†Wilcoxon ranksum test

‡For risk factors which occurred in cases but not controls, p-values were calculated using the Cochran's Q test

§Graves Disease, membranous glomerulonephritis, immune thrombocytopenic purpura (ITP), Wegener granulomatosis, ulcerative colitis, and Crohns disease.

//thalassemia minor and thalassemia β trait

Table 2

Multivariable risks for arterial ischemic stroke in children

Variable*	OR (95% CI)	*P*
Recent environmental exposures		
Head or neck trauma (past 12 weeks)	9.0 (3.2, 25.1)	<0.001
Minor acute infection (past 4 weeks)	3.9 (2.0, 7.4)	<0.001
Traditional pediatric stroke risk factors		
Autoimmune disease	39.5 (4.9, 319)	0.001
Cardiac disease	7.9 (2.1, 29.2)	0.002
Hematologic disease	11.3 (2.2, 58.7)	0.004
Male gender	1.2 (0.7, 1.9)	0.56

*All variables included in the multivariable model are shown.