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Ischemic stroke in children with critical illness: a poor prognostic sign

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Abstract

A consecutive case series of 55 children (0-17 years old) with arterial ischemic stroke is reported. Twenty of these children were critically ill at the time their stroke occurred. Mortality among these 20 children was 40%, as compared to 3% in non-critically ill children with arterial ischemic stroke; overall mortality in this case series was 16%. Mortality resulted primarily from the underlying illness. Prognosis after stroke is markedly worsened in children with premorbid critical illness.

Introduction

Cerebrovascular disorders are among the top 10 causes of death in children [1]. Strokes in children also result in significant morbidity as > 50% of survivors will have cognitive or motor disabilities [2,3]. Little attention has been paid to strokes that occur in children who are already critically ill. Serious systemic illnesses, such as meningitis and underlying malignancy, are well-known risk factors for stroke in childhood [4,5]. We hypothesized that mortality among pediatric stroke patients increases when critical illness precedes stroke. We report a consecutive case series of 55 children with arterial ischemic stroke (AIS), of whom 20 were critically ill prior to stroke onset.

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Methods

Medical records were searched at a single urban tertiary academic medical center using International Classification of Diseases (ICD)-9 codes to identify all patients younger than 18 years diagnosed with acute AIS from 1999 to 2003. AIS was defined as the sudden onset of a neurological deficit, localized to the brain, that lasted more than 24 hours, with accompanying CT or MRI studies showing changes consistent with brain infarction in an arterial distribution. Trauma, meningitis, and AIS related to brain tumor were all included; children with hemorrhage or venous infarction were excluded. Critical illness was defined as a non-elective admission to the ICU. A Pediatric Risk of Mortality Score (PRISM) III at 12 hours is routinely calculated for all patients admitted to the pediatric ICU and so was available to assess severity of illness in critically ill children.[6] PRISM-III is a validated scale that has 17 physiologic variables (maximum score 74). Each medical record was reviewed by two of the authors (LCJ, JVB). The Institutional Review Board approved this protocol.

Relationships between ICU stay, death, age, sex, race, and location of stroke (i.e., single versus multi-focal lesions) between critically ill and non-critically ill patients with AIS were evaluated by multiple logistic regression (Stata 9®, College Station, Texas). Means were tested by a two-tailed t-test for continuous variables and by Fisher's exact test for categorical variables. The significance level for all tests was $p < 0.05$.

Results

Patient Characteristics and Mortality

We identified 55 children with acute AIS (Table 1), of whom 20 (36%) were critically ill (already in the ICU or presented in extremis with a systemic illness such as meningitis or endocarditis, requiring blood pressure or respiratory support) when their stroke occurred. None of these children were admitted to the ICU because they had had a stroke. Critically ill children with stroke were 60 times more likely to die (OR=60, 95% CI=4 – 840, p=0.002) than non-critically ill children with stroke after adjusting for age and single versus multiple infarcts (crude OR=23). Of the 20 critically children with AIS, 8 (40%) died, compared to 1 child of 35 (3%) who was not critically ill at the time of stroke. This non-critically ill child with stroke had complex congenital heart disease and died of a fatal arrhythmia. Not surprisingly, cause of death was most often related to the underlying medical illness, rather than to stroke (Table 2).

The overall mortality in our cohort of children with AIS was 16%. Compared to other critically ill children, mortality was higher in children with stroke: for the 6,099 non-elective pediatric ICU admissions at our institution during the study period, mortality was 4% (n= 271), versus 40% for pediatric ICU patients with stroke ($\chi 2=40$, $p<0.0001$). Children with stroke who died were significantly younger than survivors, mean age 2.7 versus 7.5 years (p=0.03). The presence of multiple cerebral infarctions was also highly associated with critical illness; multiple infarcts were 2.4 times more common in ICU patients than non-ICU patients ($p = 0.02$), but were not significantly associated with a higher mortality. The mean PRISM score in critically ill stroke patients was 16 (range 4-35, SD 7.8) while the mean PRISM score for all ICU admissions during this time was 5 (range 0-46, SD 6), and the mean PRISM score for ICU patients without stroke who died was 14.8 (range 0-43, SD 10).

Stroke Presentation

Seizure was the initial presentation of stroke in fifteen patients (27%); these patients were significantly younger than those without seizures (mean 2.0 vs. 8.4 years). Other presenting features associated with AIS were hemiparesis (48%), aphasia (11%), altered mental status

(6%), and unresponsiveness (6%). Seizures were seen in 45% of critically ill patients, compared to 19% of non-ICU patients.

In ICU patients, 16 (80%) were critically ill at the time of presentation to the hospital and were admitted directly to the ICU. Five patients were diagnosed with stroke on the day of admission, but the average time from hospital admission to stroke diagnosis in critically ill patients was 13 days (range 0 – 117, SD 27). Of the 8 critically ill patients who died, the median time between stroke diagnosis and death was 5 days; however, the data are bimodal. Four patients died in less than 5 days, while 4 patients survived 6 to 118 days.

Stroke Risk Factors

Stroke risk factors could be identified in 93% of patients. The most common risk factors were cardiac disease, infection, vasculopathy, trauma, and hematological disorders. Vasculopathy included cerebral arterial abnormalities due to moyamoya, HIV, arterial dissection, and transient cerebral arteriopathy. Thirty-three out of fifty-five patients (60%) were investigated with vascular imaging. ICU patients had slightly more stroke risk factors (mean=1.8) than non-ICU patients (mean=1.5) but the difference was not significant (p=0.77). Risk factors found in patients who died were: cardiac disorders (n= 4), infections (n= 2), trauma (n= 1), oncologic disease (n= 2), and extracorporeal membrane oxygenation (ECMO) (n= 2).

Infections, ranging from an upper respiratory infection to fulminate sepsis, were diagnosed before stroke onset in 40% of the ICU patients compared with 17% of non-ICU patients. Two risk factors, ECMO and endocarditis, were only seen in critically ill patients. Cardiovascular disorders were more frequently seen in ICU patients than in non-ICU patients, 40% compared with 17%. Stroke recurred in 7 patients (13%), and only 2 of these recurrences occurred in critically ill patients.

Discussion

The most noteworthy finding in this study was that children who had a stroke in the setting of critical illness were 60 times more likely to die than children who were not critically ill at the time their stroke occurred. The overall AIS mortality of 16% during the 5-year study period is similar to that in other reports [7,8]; however, when stroke occurred in the ICU, mortality was 40% and in non-critically ill children, stroke mortality was 3%. In most cases, death was related to the underlying medical illness rather than to the stroke (Table 2). A number of studies have reported mortality of 16% -23% in childhood stroke however, causes of death are rarely provided. Lanthier et al. have reported that the coexistence of multiple stroke risk factors in children predicts poor outcome [9]; it would be interesting to know how many of these children were critically ill at time of stroke onset. In our series, only one child died of clearly neurologic causes i.e. stroke and head trauma leading to cerebral edema and uncal herniation. The others died of non-neurologic causes. Using a California-wide hospital discharge database there was a 16.5% case fatality rate for all first admissions for childhood ischemic stroke [8]. Severity of illness and cause of death were not mentioned and presumably these data were not available. We suspect that this 16.5% case fatality rate may be a combination of two groups of patients, those that are critically ill and those that are not.

The fact that the mean PRISM score in critically ill stroke patients was similar to the mean PRISM score for ICU patients without stroke who died, 16 and 14.8, respectively, and quite different than the mean PRISM score of 5 for all ICU admissions is telling. This information suggests that critically ill children with stroke were more ill than the general population of children admitted to the ICU, and were similar to other critically ill patients who died.

Children with stroke who died were significantly younger than stroke survivors. Seizures were also a more common presenting symptom in young children and in critically ill children regardless of age. Thus, a young child in the ICU with new-onset seizures should be carefully evaluated. There are many etiologies for seizure in critically ill children, but stroke should be considered.

Our study has several important limitations. It is likely that our case ascertainment via ICD-9 codes did not identify all patients with AIS [11]. Since these data were collected retrospectively, standardized measures of neurological outcome were available on very few surviving patients. Furthermore, the study population, patients at a tertiary children's hospital, may not be representative of all pediatric populations. This bias is minimized, however, by the fact that most children with acute stroke, with or without critical illness, are transferred to a pediatric referral center.

This study provides an important first look at stroke presenting in children in the pediatric ICU. Further prospective, multi-center studies are necessary to better define specific risk factors for stroke in critically ill children as well as predictors of outcome. Future childhood stroke studies should report not only the mortality rate, but also the causes of death. Our results suggest that when stroke occurs in a child who is already critically ill, it is a marker of severe illness from which the child may not recover.

References

1. National center for health statistics. Deaths, percentage of total deaths, and death rates for the 10 leading causes of death in selected age groups, by race and sex: United States, 2002. In: National Vital Statistics Reports Vol. 53, No. 17, March 7, 2005, CDC website [online]. Available at: www.cdc.gov/nchs/data/nvsr/nvsr53/nvsr53_17.pdf , pages 17-18. Accessed June 16, 2006.
2. Hogan AM, Kirkham FJ, Isaacs EB. Intelligence after stroke in childhood: review of the literature and suggestions for future research. J Child Neurol 2000;15:325–332. [PubMed: 10830199]
3. Steinlin M, Roellin K, Schroth G. Long-term follow-up after stroke in childhood. Eur J Pediatr 2004;163:245–250. [PubMed: 14986120]
4. Chang CJ, Chang WN, Huang LT, Chang YC, Huang SC, Hung PL, Ho HH, Chang CS, Wang KW, Cheng BC, Lui CC, Chang HW, Lu CH. Cerebral infarctions in perinatal and childhood bacterial meningitis. QJM 2003;96(10):755–762. [PubMed: 14500862]
5. Santoro N, Giordano P, Del Vecchio GC, Guido C, Rizzari C, Varotto S, Masera G, Mattia D. Ischemic stroke in children treated for acute lymphoblastic leukemia: a retrospective study. J Pediatr Hematol Oncol 2005;27:153–157. [PubMed: 15750448]
6. Pollack MM, Patel KM, RUttimann UW. Prism III: an updated pediatric risk of mortality score. Crit Care Med 1996;24:743–752. [PubMed: 8706448]
7. Deveber G. Arterial ischemic strokes in infants and children: an overview of current approaches. Semin Thromb Hemost 2003;29:567–573. [PubMed: 14719173]
8. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. Neurology 2003;61:189–194. [PubMed: 12874397]
9. Lanthier S, Carmant L, David M, Larbrisseau A, deVeber G. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. Neurology 2000;54:371–378. [PubMed: 10668698]
10. Esmon CT. The impact of the inflammatory response on coagulation. Thromb Res 2004;114:321–327. [PubMed: 15507261]
11. Benesch C, Witter DM Jr, Wilder AL, Duncan PW, Samsa GP, Matchar DB. Inaccuracy of the International Classification of Diseases (ICD-9-CM) in identifying the diagnosis of ischemic cerebrovascular disease. Neurology 1997;49:660–664. [PubMed: 9305319]

Table 1

Patient Characteristics

	ICU (n=20) Number of patients (%)	Non-ICU (n=35) Number of patients (%)	p-value
Sex			
Male	10 (50)	18 (51)	1.000
Mean Age	5.3 years	7.6 years	0.189
Race			0.068
African American	5 (25)	17 (48)	0.086
Caucasian	13 (65)	18 (51)	0.329
Other	2 (10)	0 (0)	0.057
Location/Type of Stroke			0.202
Anterior Circulation	14 (70)	31(89)	0.086
Posterior Circulation	4 (20)	2 (6)	0.102
Anterior and Posterior Circulation	2 (10)	2 (6)	0.556
Lacunar Infarct	1 (5)	2 (6)	1.000
Watershed Infarct	3 (15)	4 (11)	0.696
Multiple Infarcts	11 (55)	8 (23)	**0.021**
Seizure at Presentation	9 (45)	6 (17)	**0.033**
Death	8 (40)	1 (3)	**0.001**

Table 2

Critical Illness in Children with AIS

Critical Illness at Time of Stroke	Death	Cause of death
Cardiac Surgery	Yes	Multiorgan failure
Heart Failure, awaiting transplant	Yes	Cardiac Arrest
Head Trauma	Yes	Cerebral edema
Congenital Heart Disease, heart failure, sepsis	Yes	Multiorgan failure*
Leukemia, disseminated toxoplasmosis	Yes	Cardiac arrest
Opiate ingestion, respiratory distress	Yes	Cardiac arrest
Congenital Heart disease, on ECMO*, multi-organ failure	Yes	Care withdrawn, no return of cardiac function
Pulmonary hypoplasia and ventilator dependence	Yes	Care withdrawn, no improvement in respiratory function
Bacterial sepsis, meningitis	No	NA
Bacterial meningitis	No	NA
Staph Aureus endocarditis	No	NA
Congenital Heart Disease, Staph Aureus pneumonia, ARDS*, ECMO	No	NA
Aneurysm clipped, vasospasm	No	NA
Bacterial pneumonia, ARDS	No	NA
Head Trauma	No	NA
Head Trauma	No	NA
Congenital Heart Disease, Cardiac Surgery	No	NA
Congenital Heart Disease, Cardiac Surgery	No	NA
Congenital Heart Disease, Cardiac Surgery, Cardiac arrest, post-op	No	NA
Severe combined immunodeficiency, Bone marrow transplant, warm IgM antibody Causing thrombosis	No	NA

*ECMO (extra corporeal membrane oxygenation), **ARDS (acute respiratory distress syndrome)