Is It Time for a Large, Collaborative Study of Pediatric Stroke?

Darin B. Zahuranec, MD; Devin L. Brown, MD; Lynda D. Lisabeth, PhD; Lewis B. Morgenstern, MD

Background and Purpose—A 2002 report from the National Institute of Neurological Disorders and Stroke cited the critical importance of more childhood stroke studies. We present the incidence rate of pediatric stroke from a biethnic community-based project and calculate the population size required for future prospective studies of pediatric stroke.

Methods—This work is part of the Brain Attack Surveillance in Corpus Christi (BASIC) project. The community of 325 000 is located in southeast Texas and is composed of approximately equal numbers of Mexican Americans (MAs) and non-Hispanic whites (NHWs). Discharge diagnosis codes from all hospitals in the county were used to identify cases of childhood stroke (age >1 month and <20 years) in 2002 and 2003, and stroke cases were validated by source document review. On the basis of the incidence rates, the population size required to complete a case-control study to examine risk factors for pediatric stroke was calculated.

Results—Eight cases of pediatric stroke were identified, yielding an annual incidence rate of 4.3 per 100 000 (95% CI, 1.9 to 8.5). There were 5 cases of intracerebral hemorrhage, 1 subarachnoid hemorrhage, 1 ischemic stroke, and 1 transient ischemic attack. All of the events occurred in MAs. Depending on the prevalence of the risk factors of interest, future studies of pediatric stroke would have to draw from a population of up to 59 million children to complete a case-control study within 4 years.

Conclusions—Given the rarity of pediatric stroke, future studies will require multicenter efforts and possibly a national surveillance system. (Stroke. 2005;36:1825-1829.)

Key Words: child ■ incidence ■ stroke

Childhood stroke, although rare, results in significant mortality and long-term morbidity.1–3 The lack of information about risk factors for childhood stroke recently led an expert panel from the National Institute of Neurological Disorders and Stroke to call for more studies addressing this important issue.4 Prospective, population-based studies, which reduce the possibility of referral bias, are an ideal way to study the impact of disease on a real-world population.

The Brain Attack Surveillance in Corpus Christi (BASIC) project is an ongoing stroke surveillance study in Nueces County, Texas. Our goal was to assess the feasibility of conducting community-based studies to assess risk factors for pediatric stroke. To this end, we calculated the incidence rate of childhood stroke and examined stroke type in this large biethnic community. On the basis of the stroke incidence rate and the estimated prevalence of various risk factors, we calculated the sample size required to investigate potential risk factors for childhood stroke in a hypothetical case-control study.

As a secondary goal, we sought to investigate ethnic differences in childhood stroke incidence rates in this population. Previous studies have suggested that gender and ethnicity may be independent risk factors for stroke in children, but this has not been well studied in Mexican Americans (MAs).5,6 Hispanics are the largest minority group in the United States, and MAs are the largest subgroup of Hispanics.7 Previous research has demonstrated differences in stroke incidence in adult MAs compared with non-Hispanic whites (NHWs).8

Methods

Description of the Community

Nueces County, Texas, has a population of 325 000 and is composed of an approximately equal distribution of MAs and NHWs. It is urban and geographically isolated in southeast Texas, and it does not have a university medical center. Major referral facilities in San Antonio or Houston are >150 miles away, making complete case capture for first presentation of acute neurological disease highly likely. Although pediatric cases may be seen at any of the 7 hospitals in the county, the majority of children requiring hospitalization are admitted to Driscoll Children’s Hospital. This facility is a 200-bed, free-standing pediatric hospital with a 20-bed intensive care unit and a 52-bed neonatal intensive care unit.

Identification of Cases

The methods of the BASIC project were reported previously.8 Briefly, BASIC is a community-based study of cerebrovascular

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1825
disease in Nueces County, Texas. Discharge diagnosis codes from all hospitals in the county were used to identify cases of childhood stroke (age >1 month and <20 years) in 2002 and 2003. Given the geographic isolation of the community, direct transfer to other centers outside of the county from a Nueces County emergency department is unlikely. However, to account for the possibility of children being sent to other centers outside of the community, emergency department discharge codes were also searched for Driscoll Children’s Hospital, which is the likely site of care for critically ill children. The upper limit of age was chosen as <20 years to provide comparison with other studies because a variety of age limits have been used previously ranging from <15 years to <20 years. Children <1 month of age were excluded because perinatal stroke has distinct pathogenesis and clinical features. International Classification of Disease, Ninth Revision (ICD-9) codes searched included all stroke-related codes 430 to 438 and all subcodes. Cases related to trauma and perinatal stroke were excluded.

Validation of Stroke Diagnosis
Hospital medical records for individual cases were reviewed independently by 2 of the authors (D.Z. and L.M.) blinded to ethnicity. Actual brain computed tomography and MRI films were not available for review. Imaging findings were interpreted on the basis of the report of the neuroradiologist or consulting neuroradiologist. Definition of stroke was based on previously published criteria from the World Health Organization.

Statistical Analysis
The incidence rate of stroke was calculated with 95% CIs on the basis of the Poisson distribution. Census data for Nueces County, Texas, for 2000 was used as the population denominator for the incidence rate. The incidence rate was not age adjusted because of the small sample size. Ethnic classification was determined from the medical records for the cases. Because of the small number of individuals of other races in the community, only MAs and NHWs were included in the analysis.

Calculations were performed to determine the sample size needed to study various potential risk factors for pediatric stroke assuming a case-control design. A case-control study design was chosen because this is an appropriate design for studying rare diseases such as childhood stroke. Sample size calculations were performed assuming a 4:1 ratio of controls to cases based on the expected low incidence rate of stroke and therefore small number of available cases. Based on the sample size calculations and the incidence rate of pediatric stroke, the population size needed to complete a study of pediatric stroke within 4 years was calculated. A study period of 4 years was chosen because this is the standard ascertainment time for a 5-year National Institutes of Health grant, assuming a 6-month start-up period and a 6-month period at the end of the study to finish data abstraction and analysis and manuscript preparation. The institutional review board of the University of Michigan and the review boards of the individual hospitals approved the study protocol.

Results
There were 15 cases of childhood acute cerebrovascular events identified during the 2 years of the study using ICD-9 codes. There were 4 cases of subarachnoid hemorrhage (SAH), 3 cases of intracerebral hemorrhage (ICH), 3 cases of transient ischemic attack (TIA), 2 cases of ischemic stroke (IS), 2 cases of subdural hematoma, and 1 case of hypertensive encephalopathy. After review of the medical records, 7 cases were excluded because no other stroke diagnosis was found after chart review. Two of the cases of TIA were determined to be conversion disorders, and 1 case each of ICH and IS were remote events in children admitted for seizures. All validated cases were in MAs. Three of the cases coded as SAH were validated as ICH, for a total of 5 cases of ICH, 1 case of SAH, 1 IS, and 1 TIA. A summary of the clinical features of each case is included in Table 1. None of the deceased cases had an autopsy.

The total 2000 population of Nueces County, Texas, for MA and NHW children <20 years of age was 92,418. Annual stroke incidence rate per 100 000 children was 4.3 (95% CI, 1.9 to 8.5). To provide comparison with other studies, the calculation was also repeated for children <16 years of age for a total of 4 cases and an annual overall incidence rate of 2.7 per 100 000 (95% CI, 0.7 to 7.0). Examining individual stroke subtypes, the rate of ICH was 2.7 per 100 000 (95% CI, 0.9 to 6.3), the rate of IS/TIA was 1.1 per 100 000 (95% CI, 0.1 to 3.9), and the rate of SAH was 0.5 per 100 000 (95% CI, 0.01 to 3.0 per 100 000).

We were interested in the feasibility of studying stroke risk factors in children. Ethnicity is an example of such a risk factor. Because there were no cases of stroke discovered in NHWs, we could not calculate a rate ratio for stroke incidence comparing rates of stroke by ethnicity. Assuming that the true rate ratio for stroke in MAs compared with NHWs ranges between 1.3 and 4.0, we calculated the sample size needed to complete a case-control study with a risk factor prevalence of 50% (as would be the case for gender or ethnicity in this community). This range of rate ratios was chosen on the basis of previously reported ratios for stroke rate by ethnicity in children and adults. For a rate ratio of 2.0 (indicating a 2-fold increased risk of stroke), 86 childhood stroke cases would need to be identified, assuming 80% power and a 4:1 ratio of controls to cases. Based on the population size of Nueces County and incidence rate of 4.3 per 100 000, it would take >20 years to complete such a study in this single community. Assuming the true rate of stroke to be 8.5 per 100 000 (upper limit of 95% CI), it would still take ≈10 years to complete a study in this single community.

We additionally calculated the population size required to study childhood stroke either in a larger community or using a multicenter design. Assuming a risk factor prevalence of 50%, true rate ratios ranging from 1.3 to 4.0, and an annual stroke incidence rate of 4.3 per 100 000, the population size required to complete a study of childhood stroke within 4 years ranged from 139,535 to just >3.3 million. These population size estimates are based on the incidence rate for all stroke types combined, and any investigation into stroke risk factors would more reasonably examine risk factors for a particular type of stroke. Therefore, we calculated population size estimates on the basis of our observed rates of ICH (2.7 per 100 000), IS/TIA (1.1 per 100 000), and total stroke (4.3 per 100 000). Additional population size estimates for these incidence rates are presented in Table 2, examining the effect of varying rate ratios from 1.3 to 4.0.

As an example of the population size needed to study stroke risk factors other than ethnicity, we repeated the sample size calculations assuming a risk factor prevalence of 5% (as may be expected for pediatric hypertension or factor V Leiden heterozygosity and 20% (eg, obesity). These results are presented in Table 2.
calculations are presented in Tables 3 and 4. A population size of up to 59 million would be required to study risk factors of lower prevalence in relation to risk of IS/TIA.

TABLE 1. Summary of Cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex, Ethnicity</th>
<th>Discharge Diagnosis</th>
<th>Validated Diagnosis</th>
<th>Clinical Presentation</th>
<th>Imaging</th>
<th>Cause or Associated Conditions</th>
<th>Discharge Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 months, M, H</td>
<td>ICH</td>
<td>ICH</td>
<td>Multiple cardiorespiratory arrests in a former 33-week premature infant</td>
<td>Right cerebellar hemorrhage</td>
<td>VSD, ECMO</td>
<td>Home</td>
</tr>
<tr>
<td>2</td>
<td>8 years, M, H</td>
<td>SAH</td>
<td>ICH</td>
<td>Severe headache, followed by altered consciousness</td>
<td>Right frontoparietal hemorrhage</td>
<td>AVM</td>
<td>Inpatient rehabilitation, then home ambulating with minimal assistance</td>
</tr>
<tr>
<td>3</td>
<td>10 years, F, H</td>
<td>SAH</td>
<td>ICH</td>
<td>Sudden loss of consciousness</td>
<td>Left parietal ICH with midline shift</td>
<td>None, other than recent sinus infection</td>
<td>Deceased</td>
</tr>
<tr>
<td>4</td>
<td>14 years, F, H</td>
<td>SAH</td>
<td>ICH</td>
<td>Sudden loss of consciousness, asymmetric pupils</td>
<td>Left frontoparietal ICH with midline shift</td>
<td>Unknown, presumed AVM per chart</td>
<td>Deceased</td>
</tr>
<tr>
<td>5</td>
<td>17 years, F, H</td>
<td>ICH</td>
<td>ICH</td>
<td>Sudden severe headache, exam otherwise normal</td>
<td>Left occipital ICH, angiogram revealed a distal left PCA aneurysm</td>
<td>Suspected mycotic aneurysm, Echocardiogram showed known VSD, but no endocarditis</td>
<td>Home with no disability</td>
</tr>
<tr>
<td>6</td>
<td>18 years, F, H</td>
<td>SAH</td>
<td>SAH</td>
<td>Progressive headache over 3 days, CSF with 12 000 red blood cells</td>
<td>Frontal SAH in interhemispheric fissure</td>
<td>Cocaine and crystal methamphetamine use</td>
<td>Home with no disability</td>
</tr>
<tr>
<td>7</td>
<td>17 years, M, H</td>
<td>IS</td>
<td>IS</td>
<td>Dysarthria, gait ataxia, left hemiparesis, facial diplegia</td>
<td>MRI showed pontine infarction with basilar occlusion</td>
<td>Schizophrenia, no other cause found</td>
<td>Inpatient rehabilitation</td>
</tr>
<tr>
<td>8</td>
<td>19 years, M, H</td>
<td>TIA</td>
<td>TIA</td>
<td>Transient right hemiparesis. Patient arrested during cardiac catheterization unrelated to TIA</td>
<td>Head CT normal</td>
<td>Congenital heart disease with right to left shunt</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

M indicates male; F, female; H, Hispanic; VSD, ventricular septal defect; ECMO, extra corporeal membrane oxygenation; AVM, arteriovenous malformation; PCA, posterior cerebral artery; CSF, cerebrospinal fluid; CT, computed tomography.

TABLE 2. Sample Size and Population Required Assuming 50% Risk Factor Prevalence (eg, gender or ethnicity)

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>No. of Cases</th>
<th>Incidence per 100 000</th>
<th>Childhood Population Size Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>574</td>
<td>1.1</td>
<td>13 045 455</td>
</tr>
<tr>
<td>1.5</td>
<td>243</td>
<td>1.1</td>
<td>5 222 727</td>
</tr>
<tr>
<td>2.0</td>
<td>86</td>
<td>1.1</td>
<td>1 954 545</td>
</tr>
<tr>
<td>4.0</td>
<td>24</td>
<td>1.1</td>
<td>545 455</td>
</tr>
</tbody>
</table>

Sample size calculations were based on a case-control study design assuming 80% power, a 4:1 ratio of controls to cases, and a 4-year study.

TABLE 3. Sample Size and Population Required Assuming 5% Risk Factor Prevalence (eg, factor V Leiden heterozygosity)

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>No. of Cases</th>
<th>Incidence per 100 000</th>
<th>Childhood Population Size Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>2599</td>
<td>1.1</td>
<td>59 068 182</td>
</tr>
<tr>
<td>1.5</td>
<td>1008</td>
<td>1.1</td>
<td>22 909 091</td>
</tr>
<tr>
<td>2.0</td>
<td>297</td>
<td>1.1</td>
<td>6 750 000</td>
</tr>
<tr>
<td>4.0</td>
<td>54</td>
<td>1.1</td>
<td>1 227 273</td>
</tr>
</tbody>
</table>

Sample size calculations were based on a case-control study design assuming 80% power, a 4:1 ratio of controls to cases, and a 4-year study.

Discussion

Pediatric stroke is a rare disease. In this biethnic community, the annual incidence rate of childhood stroke was 4.3 per 100 000, comparable to the incidence of childhood central nervous system malignant tumors. The fact that all validated stroke cases in our study occurred in MAs may suggest an increased stroke risk relative to NHWs, although the small number of cases identified precludes definitive conclusions. The sample size calculations in this analysis can be applied to any potential risk factor for pediatric stroke, such as gender, race, or ethnic differences.
ethnicity, hypertension, obesity, prothrombotic states, or other risk factors yet to be identified. Our sample size estimates suggest the need for large populations ranging from 127,907 up to 59 million children/20 years of age to complete adequate prospective studies of risk factors for pediatric stroke. The US population/20 years of age was 80 million in 2000, suggesting that multicenter approaches may be necessary to attain these large sample sizes.7

A summary of the few previously published population-based studies of childhood stroke is presented in Table 5. Previous single-center studies have drawn from a population ranging from 15,834 to 295,557.5 Fullerton et al had the largest population size at just <10 million, using a California statewide administrative database.6 Although administrative databases can provide estimates of disease incidence and mortality, more detailed analyses are not possible given the limited data available.

Stroke registries can also be informative. The Canadian Pediatric Ischemic Stroke Registry has provided valuable information about stroke and cerebral venous thrombosis in Canadian children.16 Although they have included an impressive number of cases, this registry has several limitations. Because this study is based at tertiary care centers, it relies on case referral and may be subject to referral bias. Additionally, this registry excludes cases of ICH and SAH. Although this registry is quite valuable, additional efforts will be required for adequate study of pediatric stroke.

Hemorrhagic stroke was more common than IS in our population, consistent with previous childhood stroke studies.2,5,10 We cannot exclude the possibility that some of the hemorrhagic strokes in our series were actually hemorrhagic transformations of ISs or venous infarctions. It is also possible that some IS cases may have been missed based on case identification solely through discharge ICD-9 codes. In fact, the inaccuracies we identified call into question the validity of using only ICD-9 codes for case identification in childhood stroke without verification by review of hospital

### Table 4. Sample Size and Population Required Assuming 20% Risk Factor Prevalence (eg, obesity)

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>No. of Cases</th>
<th>Incidence per 100 000</th>
<th>Childhood Population Size Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>812</td>
<td>1.1</td>
<td>18,454,545</td>
</tr>
<tr>
<td>1.5</td>
<td>325</td>
<td>1.1</td>
<td>7,386,364</td>
</tr>
<tr>
<td>2.0</td>
<td>102</td>
<td>1.1</td>
<td>2,318,182</td>
</tr>
<tr>
<td>4.0</td>
<td>22</td>
<td>1.1</td>
<td>500,000</td>
</tr>
</tbody>
</table>

Sample size calculations were based on a case-control study design assuming 80% power, a 4:1 ratio of controls to cases, and a 4-year study.

### Table 5. Summary of Previous Population-Based Studies of Pediatric Stroke Incidence (non-neonates)

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Age, y</th>
<th>Incidence Rate Per 100 000 (95% CI)</th>
<th>Annual Population at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoenberg et al²</td>
<td>1965–1974</td>
<td>&lt;15</td>
<td>IS 0.6 (NR)</td>
<td>15,834</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICH/SAH 1.9 (NR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 2.59 (0.7–6.5)</td>
<td></td>
</tr>
<tr>
<td>Broderick et al⁵</td>
<td>1988–1989</td>
<td>&lt;15</td>
<td>IS 1.2 (0.3–2.0)</td>
<td>295,577</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICH/SAH 1.5 (0.4–2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 2.7 (1.4–4.1)</td>
<td></td>
</tr>
<tr>
<td>Earley et al¹⁰</td>
<td>1988 and 1991</td>
<td>&lt;15</td>
<td>IS 0.58 (0.37–1.34)</td>
<td>773,016</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICH 0.71 (0.28–1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SAH excluded</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 1.29 (0.83–2.11)</td>
<td></td>
</tr>
<tr>
<td>Giroud et al¹⁷</td>
<td>1985–1993</td>
<td>&lt;16</td>
<td>IS 7.9 (2.6–14.6)</td>
<td>23,877</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICH/SAH 5.1 (1.1–12.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 13.0 (8.5–18.8)</td>
<td></td>
</tr>
<tr>
<td>Chung et al⁹</td>
<td>1998–2001</td>
<td>&lt;15</td>
<td>IS 2.1 (NR)</td>
<td>1,158,800</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 2.1 (NR)</td>
<td></td>
</tr>
<tr>
<td>Fullerton et al⁶</td>
<td>1991–2000</td>
<td>&lt;20</td>
<td>IS 1.2</td>
<td>9,907,432</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICH 0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SAH 0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 2.3 (NR)</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>2002–2003</td>
<td>&lt;20</td>
<td>ICH 2.7 (0.9–6.3)</td>
<td>92,418</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SAH 0.5 (0.01–3.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IS/TIA 1.1 (0.1–3.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 4.3 (1.9–8.5)</td>
<td></td>
</tr>
</tbody>
</table>

NR indicates not reported.
charts. Nonetheless, given that hemorrhagic stroke appears to be at least as common as IS in the pediatric population, additional studies of hemorrhagic stroke in children should be pursued.

Our population size estimates varied greatly depending on the assumptions made regarding expected stroke incidence rates, prevalence of the risk factor being studied, and the rate ratio for risk of stroke conferred. The calculated population size estimates are based on a small number of incident cases, and therefore, the required population size presented in the tables may be larger or smaller than noted in the tables. The upper limit of the 95% CI for stroke incidence rate was roughly twice the baseline rate (8.5 versus 4.3 per 100,000). Therefore, one can estimate the population size required if the true rate of stroke is at the upper limit of the 95% CI by dividing the population estimates presented in the tables by a factor of 2. A similar method can be applied to estimate the population size for the lower limit of the 95% CI.

Smaller population sizes may be adequate to determine the effect of factors that confer a large increased risk of stroke; however, thorough investigation of this serious disease will require large populations to avoid missing risk factors that confer small but important risk. We calculated sample size based on detection of a risk factor associated with a ≥30% increase in pediatric stroke risk. The importance and expense of studying risk factors of a lesser magnitude in this rare disease is subject to debate.

The low incidence rate of childhood stroke makes accurate evaluations of risk factors and advocacy for prevention and treatment difficult. The large sample size required to systematically study childhood stroke would require multicenter efforts with many years of case ascertainment. Clinicians, researchers, and policy makers must weigh the relative rarity of this disease against its devastating effect so early in life. Certainly, adequate study of childhood stroke will require a large commitment of financial and personnel resources.

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