

Male Predominance in Childhood Ischemic Stroke

Findings From the International Pediatric Stroke Study

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Background and Purpose—Previous studies suggested a male predominance in childhood ischemic stroke, mirroring gender differences in adults but were limited by small sample sizes or unconfirmed diagnoses. We sought to study gender within a large international series of confirmed cases of pediatric ischemic stroke.

Methods—From January 2003 to July 2007, the International Pediatric Stroke Study enrolled children (0 up to 19 years) with arterial ischemic stroke or cerebral sinovenous thrombosis at 30 centers in 10 countries. Neonates were those <29 days of age. We calculated the “expected” gender ratio for our study as the weighted average of population-based childhood gender ratios in enrolling countries weighted by the number of subjects enrolled in each country. χ^2 tests were used to compare the observed gender ratios in our series with this expected ratio (51.7%).

Results—Among 1187 children with confirmed ischemic stroke, 710 were boys (60%, $P<0.0001$). Male predominance persisted after stratification by age (61% for neonates, $P=0.011$; 59% for later childhood, $P=0.002$) and stroke subtype (58% for arterial ischemic stroke, $P=0.004$; 65% for cerebral sinovenous thrombosis, $P=0.002$). The greatest proportion of males occurred among children with arterial ischemic stroke and a history of trauma (75%, $P=0.008$), although boys were also overrepresented among those with arterial ischemic stroke and no trauma (57%; $P=0.07$). There were no gender differences in case fatality or deficits at discharge.

Conclusions—Childhood ischemic stroke appears to be more common in boys regardless of age, stroke subtype, or history of trauma. Further exploration of this gender difference could shed light on stroke mechanisms in both children and adults. (*Stroke*. 2009;40:52-57.)

Key Words: child ■ sex distribution ■ stroke

Among adults, ischemic stroke occurs more commonly in men up to 80 years of age.¹ This gender disparity has often been attributed to lifestyle differences such as increased levels of smoking and alcohol intake in men.^{2,3} Because these factors are unimportant in the pathogenesis of childhood ischemic stroke, gender differences in childhood stroke risk are of interest.

The International Pediatric Stroke Study (IPSS) is a multinational registry that began identifying pediatric ischemic stroke cases in January 2003 and has now enrolled 1187 children from 30 hospitals in 10 countries. With consent of the participating centers, we examined this large series to determine whether a male predominance exists in pediatric arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT), and whether this gender difference varies by age, stroke subtype, or etiology.

Methods

IPSS Study Overview

With pilot funding from the Child Neurology Society and Foundation, the IPSS was established in 2003 by 11 original coinvestigators (pediatric neurologists, hematologists, and epidemiologists) as an international registry with the long-term goal of developing multinational clinical trials in pediatric ischemic stroke. Since 2003, the number of enrolling centers has increased to 30 located in 10 countries (Figure 1): Australia, Canada, Chile, China, Georgia, Germany, Malaysia, Thailand, the United Kingdom, and the United States. A central IPSS office at the Hospital for Sick Children in Toronto, Canada, was established to manage the IPSS web site and database. IPSS investigators established consensus-based diagnostic definitions for stroke subtypes, etiologic investigations, study outcomes, and treatment approaches during quarterly or triannual meetings (ongoing).

IPSS Patient Population

Patients were prospectively or retrospectively enrolled in the IPSS if they were diagnosed with an acute AIS or CSVT between birth

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Figure 1. Centers participating in the IPSS group as of July 1, 2007.

(gestational age ≥ 37 weeks) and 19 years of age from January 1, 2003, to July 1, /2007, at a participating IPSS center and provided consent (Figure 2). The IPSS defined ischemic stroke as focal ischemic brain injury due to obstruction of either arterial or venous blood flow, and hence included both AIS and CSVT. Patients with CSVT were included whether or not there was parenchymal injury. Data on children who presented after the perinatal period with infarctions that were presumed to occur in the perinatal period⁴ were collected but not included in this analysis because the exact time of infarction could not be confirmed. Other childhood cerebrovascular disorders excluded from the IPSS were transient ischemic attacks without infarction, primary intracranial hemorrhage, metabolic infarction in a nonvascular territory (eg, MELAS), hypotensive watershed injury, periventricular leukomalacia, or reversible hypertensive leukoencephalopathy.

IPSS Case Identification and Confirmation

Investigators at each enrolling center advertised the IPSS study locally and identified potential cases in both inpatient and outpatient settings. Cases were confirmed by the enrolling investigator (a pediatric neurologist or hematologist) using consensus-based, published clinical and radiographic criteria.⁵ Criteria for AIS included (1) neurological deficit of acute onset, or seizure alone in neonates;

and (2) radiographic image(s) (MRI or CT) showing cerebral parenchymal infarct(s) conforming to known arterial territory(ies) and corresponding to clinical manifestations. Criteria for CSVT were (1) headache, seizure, lethargy, or focal neurological deficit; and (2) radiological (MRI, MR venography, CT venography, or cerebral angiography) image(s) showing thrombus or flow interruption within cerebral veins or dural sinuses with or without venous infarction.

IPSS Data Abstraction and Database Management

Investigators abstracted the following health record data onto standardized IPSS data collection forms: patient demographics (age, gender), stroke subtype, clinical and radiographic features at presentation, results of evaluation for underlying clinical conditions, treatment (antithrombotic and other), outcome at discharge (normal, death, neurological deficit), and discharge destination (home, rehabilitation hospital, other hospital) at hospital discharge. Ethnicity was added to a later version of the data collection form and therefore was not collected for the majority of subjects.

Stroke etiologies were classified by the enrolling investigator using IPSS definitions into the following categories (not mutually exclusive): cardiac, vasculopathy, other underlying chronic disease (such as connective tissue disease, sickle cell, or prothrombotic state), head and neck pathology (such as sinusitis or meningitis), or

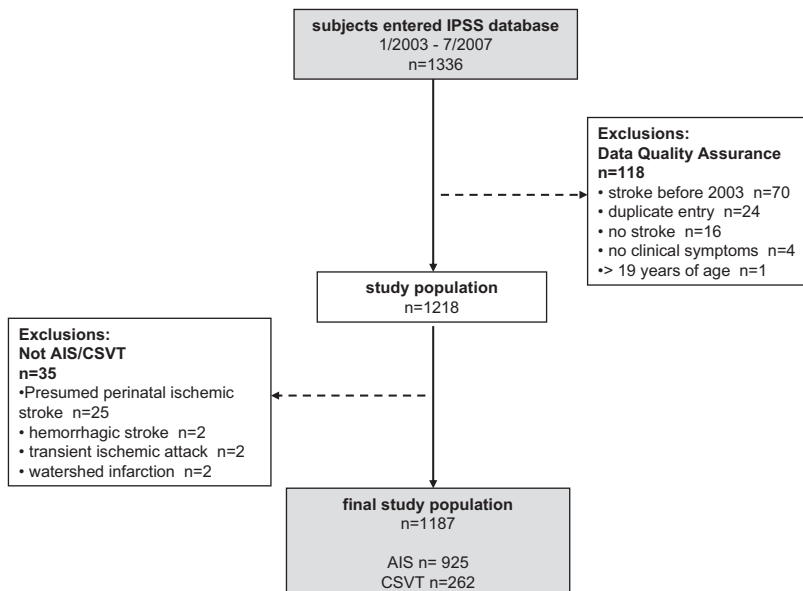


Figure 2. Flowchart demonstrating patient enrollment with numbers of excluded patients.

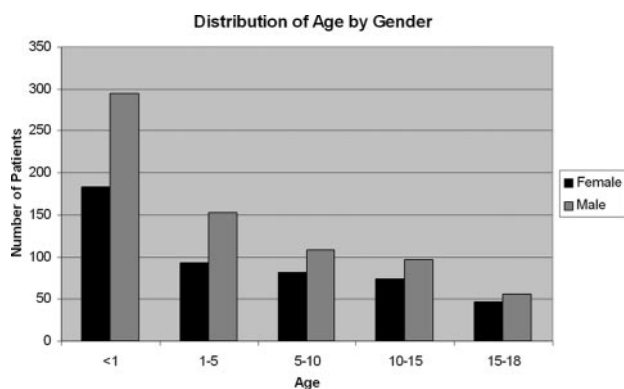


Figure 3. Age at stroke onset stratified by gender.

other associated acute illness (such as dehydration, fever >48 hours, sepsis, acidosis). For neonates, additional data were abstracted regarding maternal and perinatal history (maternal age, infertility, gestational age, birth order, prolonged rupture of membranes, mode of delivery, instrument assistance, birth weight, Apgar scores, meconium staining, need for resuscitation) and maternal or neonatal disorders (maternal hypertension or fever, oligohydramnios, cord abnormalities). Cardiac disease was further classified into congenital versus acquired heart disease. Vasculopathies were further classified by applying previously published consensus definitions for arterial dissection, moyamoya, postvaricella angiopathy, transient cerebral angiopathy, and vasculitis.⁵ Treatment data included antithrombotic therapies (heparin, low-molecular-weight heparin, warfarin, aspirin, tissue plasminogen activator, other), antibiotics, anticonvulsants, and other treatments. Outcomes and destination at discharge were assessed by study coinvestigators based on clinical data from their care of the patient or health records data. Causes of death were noted.

Study identification numbers were assigned at the time of enrollment. Data were deidentified and entered either directly from the collaborating site into a password-protected, web-based data entry system (<https://app3.ccb.sickkids.ca/cstrokestudy/>) or faxed to the central IPSS office for manual entry by research staff.

Data Analysis

Proportions of boys and girls were calculated for the group as a whole and after stratification by age, stroke subtype, and etiology (as defined previously). Ninety-five percent CIs were calculated using the method of Armitage and Berry.⁶ Neonatal strokes were defined as those occurring in the first 28 days of life; all others were considered later childhood strokes. Preadolescent strokes were classified as occurring in children 0 to 12 years of age, whereas adolescent strokes were classified as occurring in children 13 to 18 years of age.

The null hypothesis was that there is no gender difference in incident childhood stroke (ie, the proportion of boys within a stroke cohort equals the proportion of boys in the general population). We used χ^2 tests to compare the observed proportion of boys in this study (not population-based) with the expected (population-based) proportion of boys. We calculated the "expected" ratio of boys to girls as a weighted average of gender ratios from enrolling countries weighted by the number of subjects enrolled from each country. For the country-specific gender ratios, we used United Nations estimates of the ratio of male to female children (ages 0 to 19 years) in 2005 (the only year during our study period for which such data were available).⁷ Slightly more boys than girls are born⁸⁻¹⁰; most countries had a ratio at or near 1.05:1 boys:girls (51.2% boys). For our study, the expected proportion of boys (weighted average) was 51.7% (ratio of boys to girls, 1.07:1).

We used univariate logistic regression techniques to analyze the association between stroke type (AIS versus CSVT, the dependent variable) and gender (the independent variable). We used multivariate logistic regression to adjust for potential confounders such as age and underlying etiologies. After demonstrating the absence of a

Table 1. Proportion of Boys in an International Cohort of 1187 Children With Ischemic Stroke, Stratified by Age and Stroke Type

Age Group	Stroke Type	No. of Boys/Total	Percent (95% CI)	<i>P</i> *
All	All	710/1187	60 (57–63)	<0.0001
	AIS	540/925	58 (55–62)	0.004
	CSVT	170/262	65 (59–71)	0.002
Neonatal	All	209/341	61 (56–66)	0.011
	AIS	141/249	57 (50–63)	0.280
	CSVT	68/92	74 (64–82)	0.002
Childhood	All	501/846	59 (56–63)	0.002
	AIS	399/676	59 (55–63)	0.006
	CSVT	102/170	60 (52–67)	0.126

* χ^2 compared with expected proportion of 51.7%.

significant association between gender and stroke type, we combined these 2 stroke types for the majority of the analyses.

We performed stratified analyses by stroke subtype, age group, and etiology to determine whether the gender ratio varied in different subgroups. Furthermore, because trauma can be a risk factor for stroke (eg, by triggering arterial dissection), and boys are often thought to be more prone to trauma, we specifically examined the effect of a history of trauma. Enrolling investigators coded whether a subject had preceding head or neck trauma; the timeframe of the trauma with respect to the stroke ictus was not specified. We performed a stratified analysis to determine the gender ratios in children with AIS with and without a history of head or neck trauma. Because sex hormones could also play a role in the pathogenesis of stroke, analyses were conducted separately in the adolescents.

All data analyses were performed using Stata 9 (College Station, Texas). Alpha was set at 0.05.

Results

Our study cohort included 1187 cases of childhood ischemic stroke and sinovenous thrombosis enrolled in Asia (2%, China, Malaysia, and Thailand), Australia (6%), Canada (18%), Chile (7%), Georgia (1%), Germany (10%), the United Kingdom (2%), and the United States (54%). A total of 925 cases had AIS, 246 had CSVT, and 16 had both stroke types, but were combined with CSVT for the remainder of the analysis. The stroke was identified in the neonatal period for 341 subjects (29%). Among later childhood cases, mean age at stroke was 6.8 years for boys (median, 5.5 years; SD, 5.5), and 7.4 years (median, 6.4 years; SD, 5.6) for girls (Figure 3).

Overall, there was a male predominance of 60% (95% CI, 57% to 63%), which persisted after stratification by stroke type (AIS versus CSVT) and age group (neonatal versus later childhood; Table 1). The male predominance was greater for CSVT compared with AIS, particularly among neonates. We used logistic regression techniques to further explore whether male gender was associated more with one stroke type than another. In an unadjusted logistic regression analysis including all 1187 subjects, there was a trend toward an overall association between male gender and CSVT (versus AIS; OR, 1.32; 95% CI, 0.99 to 1.75; *P*=0.058); this association was significant among the 341 neonates (OR, 2.17; 95% CI, 1.28 to 3.68; *P*=0.004). However, after adjusting for age (as a continuous variable) and underlying etiologies (as defined previously), there was no significant association between male gender and stroke type (OR, 1.17; 95% CI, 0.83 to 1.64;

Table 2. Proportion of Boys in an International Cohort of 1187 Children With Ischemic Stroke, Stratified by Etiology*

Etiology	No. of Boys/Total	Percent (95% CI)	<i>P</i> †
Vasculopathy	176/299	59 (53–64)	0.084
Stenosis	82/145	57 (48–65)	0.409
Dissection	43/58	74 (61–85)	0.013
Moyamoya	34/77	44 (33–56)	0.333
Vasculitis	24/33	73 (54–77)	0.076
Transient cerebral arteriopathy	8/16	50 (25–75)	1.000
Postvaricella arteriopathy	14/25	56 (35–76)	0.777
Cardiac disease	167/293	57 (51–63)	0.185
Congenital	110/189	58 (51–65)	0.215
Acquired	27/43	63 (47–77)	0.276
Other chronic disease	208/379	55 (50–60)	0.382
Acute head and neck illness	173/267	65 (59–71)	0.002
Head and neck trauma	57/83	69 (58–78)	0.026
Other acute illness	238/363	66 (60–70)	0.0002

*Categories are not mutually exclusive.

† χ^2 compared with expected proportion of 51.7%.

$P=0.372$). Hence, we combined these 2 stroke types for the majority of the analyses.

The male predominance was true of most etiologies (Table 2), although the study was underpowered to show a significant difference between the observed and expected proportions for most subgroups. The greatest observed proportion of boys was among cases with an underlying arterial dissection (74%; 95% CI, 61% to 85%) or history of head or neck trauma (69%; 95% CI, 58% to 78%); these categories were not mutually exclusive.

We performed additional stratified analyses to determine to what extent trauma explains the male predominance for childhood AIS. This analysis included 648 subjects past the neonatal period with data on recent head or neck trauma. Among 60 subjects with AIS and a positive history of trauma, 75% were boys (95% CI, 62% to 85%; $P=0.008$ for the comparison to the “expected” proportion of boys). However, even after excluding the cases with a history of trauma, there was a trend toward male predominance: 57% of 588 cases of childhood AIS with no reported history of trauma were boys (95% CI, 53 to 61; $P=0.07$ for the comparison to the “expected” proportion of boys).

To determine whether the gender ratios differed for adolescent compared with preadolescent subjects, we performed further stratified analyses by age group. Of the 1009 preadolescent subjects (aged 0 to 12 years), 60% were boys (95% CI, 57% to 63%; $P=0.0001$ for the comparison to the “expected” proportion of boys). Of the 178 adolescent subjects (aged 13 to 18 years), 58% were boys (95% CI, 50% to 65%; $P=0.242$ for the comparison to the “expected” proportion of boys; $P=0.565$ for the comparison to the preadolescent group).

There were no gender differences in outcome. The case fatality rate was 3.2% for girls and 3.4% for boys ($P=0.637$). The majority of both girls (57%) and boys (59%) had a neurological deficit at discharge, whereas 35% of girls and 32% of boys were normal at discharge, and outcome was unknown in 5% of girls and 6% of boys ($P=0.637$ for the overall comparison in outcome between boys and girls). Similarly, there was no significant gender difference in discharge location with 74% of boys and 75% of girls being discharged to home.

Discussion

Multiple studies have suggested that pediatric stroke may be more common in boys than in girls. Canadian¹¹ and Saudi Arabian¹² studies found a male:female ratio of 1.6:1 for neonatal arterial ischemic stroke, and a Canadian study¹¹ found a 3.6:1 male:female ratio for neonatal CSVT. A population-based Californian study relying on administrative data found that boys had a higher incidence of childhood (nonneonatal) stroke than girls for both ischemic and hemorrhagic stroke subtypes with a relative risk of 1.25 (95% CI, 1.11 to 1.40) for ischemic stroke.¹³ Data from studies of childhood AIS and CSVT from Europe, Israel, Argentina, and Turkey also showed a male predominance, although it was not always statistically significant.^{14–19} In our multinational cohort, there was also a predominance of boys in the group as a whole and for most subtypes.

Neonatal Stroke

We found an overall male predominance of 61% (male:female ratio of 1.6:1) for neonatal ischemic stroke and sino-venous thrombosis, which was significantly greater than the expected ratio of 1.07:1. After stratification by stroke subtype, however, the male predominance in neonatal AIS (57%, male:female ratio of 1.3:1) was not significantly different than the overall expected ratio of 1.07:1. Because we may have been underpowered to detect a difference, we will re-examine this issue when the cohort is larger.

Later Childhood Stroke

We observed a similar male predominance for later childhood stroke (59%; male:female ratio of 1.5:1). Although we cannot specifically address the role of gender differences in behavior, we did find a particularly high male predominance in cases of arterial dissection and cases with a history of trauma. This may suggest that risk-taking behaviors partly explain a gender disparity in childhood stroke. Alternatively, allowing for the possibility that boys and girls display similar behavior, boys may be more susceptible to traumatic dissection, perhaps related to as yet undiagnosed X-linked disorders. However, there was still a trend toward male predominance (57%) even after excluding cases with a history of trauma. Another study of childhood arterial dissection similarly found a predominance of males, which persisted when cases due to trauma were excluded.²⁰ The Californian study of stroke in children, which looked at all stroke subtypes, also found a predominance of boys, which persisted when cases of trauma were excluded.¹³ However, this study was based on administrative data, and trauma was likely incompletely coded. We

found a male predominance in cases of vasculitis (73%), which contrasts with the gender distribution in adults, in whom autoimmune diseases are more common among women.²¹ Although this may be due to chance (this was not significantly different from the expected ratio), this may reflect a difference in pathophysiology or a difference in the use of this label in children versus adults.

The overall male predominance in adult stroke has been attributed to neuroprotective effects of estrogen.²² It is possible that endocrine factors play a role in pediatric stroke. However, we found no difference in the gender ratio between preadolescent compared with adolescent children, making it more difficult to ascribe this gender difference to sex hormones.

Outcome

A study of stroke mortality in US children using death certificate data from the National Center for Health Statistics found that boys had a higher risk of death from hemorrhagic stroke but not ischemic stroke.¹³ We similarly found no gender difference in case fatality nor any difference in neurological outcome or discharge location.

Our study uses "ischemic stroke" as an umbrella term to include both AIS and CSVT. We did this (1) out of convention; (2) because both entities can result in focal infarction and can at times be difficult to distinguish or even coincident (as was the case for 16 subjects in this study); and (3) because we found no significant association between gender and stroke type, thereby justifying the combination of these entities for the purpose of this gender analysis. However, it is worth noting that the classification of CSVT as a form of ischemic stroke is imperfect. Symptomatic CSVT may occur without parenchymal changes, and parenchymal changes in this setting may not represent irreversible ischemic injury (ie, infarction). Furthermore, the mechanisms of venous infarction and arterial infarction likely differ. Future IPSS articles will further address AIS and CSVT as separate entities.

Our study has several limitations. Although the IPSS is a large international study, it is not necessarily a consecutive series and we cannot assess the completeness of case ascertainment from the various participating centers. Because informed consent was an inclusion criteria, our series may be enriched with subjects with good outcomes if investigators were reluctant to approach the families of children with grave prognoses. Furthermore, IPSS data are not population-based. Hence, the major limitation of our data analysis is that by comparing gender ratios in referral populations with population-based gender ratios, we may have introduced selection or referral bias. However, it seems unlikely that gender influences decisions regarding whether to refer a child to a tertiary care center. In addition, it is not likely that enrollment would have been biased toward male or female patients, so we believe the IPSS database accurately reflects gender distribution at participating centers. The numbers of years of data available from participating centers varies; some centers joined in 2002, whereas others joined as recently as 2006. However, this also seems unlikely to lead to a selection bias that could affect our analysis of gender.

With careful investigation, over 90% of children with stroke are found to have associated risk factors.²³ However, many of these risk factors (such as anemia, infection, and homozygosity for the thermolabile variant of the methylenetetrahydrofolate reductase gene) are relatively common in the pediatric population and cannot fully explain why strokes occur relatively rarely. Understanding the role of gender in pediatric stroke may lead to a better understanding of its underlying pathogenesis.

Appendix

International Pediatric Stroke Study Group

Original Investigators

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Disclosures

None.

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