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Original Article

Epidemiology and Outcomes of Arterial Ischemic Stroke in Children: The Canadian Pediatric Ischemic Stroke Registry

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ABSTRACT

BACKGROUND: Pediatric arterial ischemic stroke remains incompletely understood. Population-based epidemiological data inform clinical trial design but are scant in this condition. We aimed to determine age-specific epidemiological characteristics of arterial ischemic stroke in neonates (birth to 28 days) and older children (29 days to 18 years). **METHODS:** We conducted a 16-year, prospective, national population-based study, the Canadian Pediatric Ischemic Stroke Registry, across all 16 Canadian acute care children's hospitals. We prospectively enrolled children with arterial ischemic stroke from January 1992 to December 2001 and documented disease incidence, presentations, risk factors, and treatments. Study outcomes were assessed throughout 2008, including abnormal clinical outcomes (stroke-related death or neurological deficit) and recurrent arterial ischemic stroke or transient ischemic attack. **RESULTS:** Among 1129 children enrolled with arterial ischemic stroke, stroke incidence was 1.72/100,000/year, (neonates 10.2/100,000 live births). Detailed clinical and radiological information were available for 933 children (232 neonates and 701 older children, 55% male). The predominant clinical presentations were seizures in neonates (88%), focal deficits in older children (77%), and diffuse neurological signs (54%) in both. Among neonates, 44% had no discernible risk factors. In older children, arteriopathy (49% of patients with vascular imaging), cardiac disorders (28%), and prothrombotic disorders (35% of patients tested) predominated. Antithrombotic treatment increased during the study period ($P < 0.001$). Stroke-specific mortality was 5%.

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Outcomes included neurological deficits in 60% of neonates and 70% of older children. Among neonates, deficits emerged during follow-up in 39%. Overall, an initially decreased level of consciousness, a nonspecific systemic presentation, and the presence of stroke risk factors predicted abnormal outcomes. For neonates, predictors were decreased level of consciousness, nonspecific systemic presentation, and basal ganglia infarcts. For older children, predictors were initial seizures, nonspecific systemic presentation, risk factors, and lack of antithrombotic treatment. Recurrent arterial ischemic stroke or transient ischemic attack developed in 12% of older children and was predicted by arteriopathy, presentation without seizures, and lack of antithrombotic treatment. Emerging deficit was predicted by neonatal age at stroke and by cardiac disease. **CONCLUSIONS:** This national data set provides a population-based disease incidence rate and demonstrates the protective effect of antithrombotic treatment in older children, and frequent long-term emerging deficits in neonates and in children with cardiac disorders. Further clinical trials are required to develop effective age-appropriate treatments for children with acute arterial ischemic stroke.

Keywords: pediatric, ischemic, stroke, incidence, epidemiology

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Introduction

Arterial ischemic stroke (AIS) has emerged as an important cause of neurological disability in children. The reported annual incidence ranges from 1.2 to 8 per 100,000 for children[1-3] and one per 2500 to 4000 live births for neonates.[2] A child with a neurological disability from stroke exerts a disproportionate burden of illness over many decades. The causes of stroke in children differ markedly from those in adults, in whom atherosclerosis is the predominant cause. Important age-related differences in the coagulation, cerebrovascular, and neurological systems also exist[4] that limit the extrapolation of adult stroke studies to children. Baseline age-specific epidemiological data are important in informing the design and execution of clinical treatment trials for childhood stroke.

National surveillance systems provide a valuable means of charting the changes in disease incidence, treatment, and outcomes over time. In pediatric stroke, a relatively recently studied condition, there are only a limited number of national registry or population-based studies.[1,3,5] Global studies of children from 1990 to 2005 indicate that stroke is among the top 20 causes of death globally; however, Canada was excluded due to lack of epidemiologic data.[6] In a recent focused global study of pediatric stroke data, specific pediatric data were included only from the United Kingdom and France.[7]

We initiated the Canadian Pediatric Ischemic Stroke Registry (CPISR) in 1992 as a nationwide, prospective, population-based study of validated cases of childhood stroke at all 16 institutions. Canada presented a unique opportunity to develop a national registry on this relatively rare condition. Sixteen acute care children's hospitals provided specialized health care for all of Canada's pediatric population. Universal health care ensured consistent referral of children with serious diagnoses, including stroke, to these hospitals. The incidence and disease characteristics of 160 children in the CPISR with cerebral sinovenous thrombosis (CSVT) were previously published.[8] We now report the incidence, disease characteristics, and outcomes of neonates and children with AIS. The study objective was to determine age-specific characteristics of AIS in neonates and older children including incidence, presentations, risk factors, treatments, outcomes, and outcome predictors.

Materials and Methods

Participants and data collection

The registry enrolled children from birth until their eighteenth birthday. Children were classified as neonates if their clinical presentation occurred within the first 28 days of life following a full-term pregnancy (≥36 weeks' gestation). For older children, presentation occurred from 29 days of life to 18 years. Individuals with AIS were included if they were diagnosed from January 1, 1992, to December 31, 2001, at any of 16 Canadian acute care pediatric hospitals. The diagnostic criteria for AIS included acute neurological deficit (or isolated seizures in infants less than six months) and corresponding acute infarct(s) conforming to an established arterial territory on brain computed tomography (CT) or magnetic resonance imaging (MRI). The exception to this was children with presumed perinatal ischemic stroke (PPIS), a nonacute AIS subtype presenting in late infancy with remote AIS on neuroimaging,[9] which we included exclusively for calculating the incidence rate. We excluded isolated transient ischemic attack (TIA), global/watershed ischemia, CSVT, primary hemorrhage, neurometabolic infarcts, hemiplegic migraine, and cerebrovascular disease without AIS.

Patients were enrolled by two methods: (1) at diagnosis when co-investigators either faxed notification to the CPISR coordinating center in Toronto or called in notification to the principal investigator (G.D.) via 1-800-NOCLOTS[10] or (2) identified through annual health record searches applying International Classification of Diseases-9 stroke codes (eTable 1)[2] from 1992 to 2001. Registry staff visited the sites annually or biannually and reviewed patient charts to validate AIS diagnosis and collect standardized data. Radiographic features were abstracted from clinical CT/MRI reports. During site visits through 2008, outcomes were updated on previously enrolled patients. Data were entered into a central database with double data entry employed in 50% to ensure accuracy. This study was approved by the Research Ethics Boards at the Hospital for Sick Children (REB # 0019920593) and each enrolling institution. Patient or parental consent was obtained when required.

Incidence

National population estimates were obtained through Statistics Canada.[11] Pediatric incidence values were calculated per 100,000 children per year, and neonatal incidence, per 100,000 live births. Pediatric incidence was calculated for birth to age 15 years. Patients between the ages 16 and 18 years were excluded for incidence calculation as many of them were managed at adult stroke centers.[12]

Presentation and diagnosis

Clinical presentations included focal neurological deficits, diffuse neurological deficits (with subcategories, e.g., decreased level of