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Original Article

Association Between Prolonged Seizures and Malignant Middle Cerebral Artery Infarction in Children With Acute Ischemic Stroke

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ABSTRACT

BACKGROUND: Malignant middle cerebral artery infarct syndrome is a potentially fatal complication of stroke that is poorly understood in children. We studied the frequency, associated characteristics, and outcomes of this condition in children. **METHODS:** Children, aged two months to 18 years with acute middle cerebral artery infarct diagnosed at our center between January 2005 and December 2012 were studied. Associations with malignant middle cerebral artery infarct syndrome were sought, including age, seizures, neurological deficit severity (Pediatric National Institute of Health Stroke Severity Score), stroke etiology, fever, blood pressure, blood glucose, infarct location, infarct volume (modified pediatric Alberta Stroke Program Early Computed Tomography Score), and arterial occlusion. Death and neurological outcomes were determined. **RESULTS:** Among 66 children with middle cerebral artery stroke, 12 (18%) developed malignant middle cerebral artery infarct syndrome, fatal in three. Prolonged seizures during the first 24 hours (odds ratio, 25.51; 95% confidence interval, 3.10 to 334.81; $P = 0.005$) and a higher Pediatric National Institute of Health Stroke Severity Score (odds ratio, 1.22; 95% confidence interval, 1.08 to 1.45; $P = 0.006$) were independently associated with malignant middle cerebral artery infarct syndrome. All children aged greater than two years with a Pediatric National Institute of Health Stroke Severity Score $\geq$8 and initial seizures $\geq$5 minutes duration developed malignant middle cerebral artery infarct syndrome (100%). **CONCLUSIONS:** Malignant middle cerebral artery infarct syndrome affects nearly one in five children with acute middle cerebral artery stroke. Children with higher Pediatric National Institute of Health Stroke Severity Scores and prolonged initial seizures are at greatly increased risk for malignant middle cerebral artery infarct syndrome.

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Children with middle cerebral artery infarcts warrant intensive neuroprotective management and close monitoring to enable early referral for hemicraniectomy surgery.

Keywords: infarction, middle cerebral artery, children, seizures, hemicraniectomy

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Introduction

Pediatric arterial ischemic stroke (AIS) is a serious neurological condition affecting two to five per 100,000 children per year. Mortality is approximately 5% and more than half of survivors have severe neurological sequelae.[1] Most pediatric AISs involved the middle cerebral artery (MCA) territory, affected in 80% of children.[2] Malignant middle cerebral artery infarction (MMCAI) refers to a rapid neurological deterioration because of the effects of space occupying cerebral edema after MCA territory stroke. In MMCAI, progressive edema and mass effect lead to transtentorial, subfalcine, or uncal herniation. Typically MMCAI occurs within 72 hours of stroke onset.

MMCAI occurs in 10% to 20% of adult MCA stroke patients, usually associated with large infarcts (≥50% of the MCA territory[3]). Medical management alone is associated with an 80% mortality.[4,5] Clinical trials have demonstrated that decompressive hemicraniectomy decreases mortality and improves outcomes in adults.[6] Independent associations for MMCAI in adults include increased initial National Institute of Health Stroke Scale (NIHSS) scores, larger stroke volumes, and combined MCA and internal carotid artery (ICA) occlusion.[4] Knowledge of these associations informs the early selection of at-risk adults who might benefit from timely (i.e., within 48 hours of stroke onset) decompressive hemicraniectomy.

MMCAI is the commonest cause of acute stroke-specific mortality in pediatric AIS. Small case series and a systematic review support the benefit of decompressive hemicraniectomy in children with MMCAI.[7,8] Reported frequencies of MMCAI in pediatric AIS vary widely from 1.3% to 12.5%.[8,9] Clinical and neuroradiological factors associated with childhood MMCAI have yet to be identified. Therefore our study objectives were to describe (1) the frequency of MMCAI, (2) clinical and radiological associations with MMCAI, and (3) clinical outcomes from MMCAI in pediatric stroke patients.

Patients and Methods

Participants and study design

This is a single-center cohort study of patients diagnosed with acute AIS from January 2005 to December 2012 at the Hospital for Sick Children, Toronto, Canada. Patients were identified at diagnosis by referral to the children's stroke consult team, supplemented by International Classification of Diseases-code searches of health records. Written informed consent for enrollment in the database was obtained.

We included patients aged two months to 18 years with AIS located within the MCA territory either alone or in combination with other vascular territory infarcts. The diagnosis of AIS required an acute focal neurological deficit plus imaging studies including computed tomography (CT) or magnetic resonance imaging demonstrating an infarct conforming to an established arterial territory. We excluded children with stroke limited to non-MCA territories, MCA infarcts related to moyamoya or sickle cell disease (because of their complex and multiple mechanisms involved in their pathogenesis), and children with additional intracranial space occupying lesions including tumors.

Clinical data

Clinical variables of interest included age, gender, stroke etiology, initial neurological deficit severity, the occurrence of seizures, fever, abnormal blood glucose level, or abnormal blood pressure within 24 hours of stroke onset. Stroke onset was defined as the time of symptom onset. Stroke etiology was classified as cardiac (acquired or congenital heart disease), vasculopathy (confirmed by vascular imaging), or "other" (other identifiable etiologies or idiopathic). Vasculopathy was defined according to the published criteria as arterial dissection, focal cerebral arteriopathy of childhood, and autoimmune vasculitis.[10,11] Stroke severity at presentation was scored using the Pediatric National Institutes of Health Stroke Scale (PedsNIHSS) by a stroke neurologist either at direct bedside examination or retrospectively based on initial recorded neurological examination.[12] Seizures were clinically diagnosed and classified as brief (less than five minutes) or prolonged (≥5 minutes) based on the international league against epilepsy definitions.[13] Seizure types and electroencephalograph findings were collected. Fever was defined as body temperature greater than 38.3°C. Abnormal blood pressure included hypotension or hypertension based on recorded values less than the fifth percentile or more than the ninety-fifth percentile, respectively, for age and gender. Abnormal blood glucose level was defined as outside the normal range of 2.8 to 6.1 mmol/L.

Standard protocol approvals, registrations, and patient consents

This study was approved by an institutional research ethics board (REB# 0019920593) for studies using human participants. Written informed consent was obtained from study participants for enrollment in the SickKids stroke registry database, from which the current analyses were conducted.

Imaging data

Imaging characteristics were assessed on the initial and follow-up (within seven days after diagnosis) CT, magnetic resonance imaging, computerized tomographic angiography, or magnetic resonance angiography scans. Each patient's original imaging studies were reviewed and classified for the present study by a pediatric neuroradiologist (S.L.). Infarct laterality (right, left, and bilateral), location (anterior, middle, or posterior cerebral artery territories), and tissue involved (cortex, white matter, and basal ganglia) were documented. Arterial occlusion was defined as a hyperdense MCA sign on the initial CT scan or as a "cutoff" of the distal ICA, proximal MCA, both or one of its main branches on magnetic resonance angiography or computerized tomographic angiography. All electronically available scans were further scored with the modified pediatric version of the Alberta Stroke Program Early Computed Tomography Score (modified PedASPECTS, range 0 to 30), a validated method for estimating infarct volume.[14] Evidence of the mass effect including sulcal effacement, ventricular compression, cistern effacement, midline shift, and herniation was also documented, as well as imaging evidence of hemorrhagic transformation. Information was collected regarding the type and timing of antithrombotic treatment based on published institutional protocols.[15]