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Original Article

Stroke in Pediatric Bacterial Meningitis: Population-Based Epidemiology

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ABSTRACT

BACKGROUND: Bacterial meningitis is a severe infection of the nervous system with a high complication rate including stroke. The purpose of this study is to assess the incidence, risk factors, patterns, and outcomes in pediatric meningitis complicated by stroke.
METHODS: The study design was a population-based, 10-year retrospective (2002 to 2012) cohort study set in Southern Alberta, Canada. The inclusion criteria were: (1) age from newborn to 18 years, (2) brain magnetic resonance imaging (MRI) including diffusion-weighted imaging during admission, and (3) laboratory confirmed acute bacterial meningitis. The main outcomes were demographics, clinical presentations, risk factors, laboratory findings, radiographic findings, and neurological outcomes.
FINDINGS: Forty-three patients had confirmed bacterial meningitis and diffusion MRI (9 neonates (21%), 89% male; 22 infants aged one month to one year (51%), 50% male; and 12 children older than one year (28%), 58% male, median age four years (interquartile range 7.9 years). Ischemic stroke was confirmed in 16/43 (37%), often multifocal (94%). Patients with stroke were significantly more likely to have seizures ($P = 0.025$), otitis media ($P = 0.029$), and multiple presentations to hospital ($P = 0.013$). Mortality was 25% in children with stroke compared with 4% in those without ($P = 0.067$). Survivors with stroke were more likely to have neurological deficits at follow-up (69% versus 26%, $P = 0.019$).
CONCLUSIONS: More than one-third of children with acute bacterial meningitis and clinically indicated MRI had ischemic stroke. Stroke was associated with clinical factors including duration of illness, seizures, and causative organisms. Stroke was associated with higher mortality and morbidity, warranting consideration of increased MRI screening and new approaches to treatment.

Introduction

Bacterial meningitis is a severe infection with high morbidity and mortality that is most common in the first year of life.[1] Advances in immunization and critical care have reduced the incidence and improved survival,[2] but

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there is still a high rate of adverse outcome which may be attributable to cerebrovascular complications and stroke.

Amongst patients with bacterial meningitis, stroke may complicate 17% to 43% of cases.[3-6] Few data exist in the pediatric population. Only two studies have compared children with and without stroke in bacterial meningitis, both of which were limited by modest, nonpopulation-based samples and lack of routine diffusion-weighted MRI.[3,4] To date, no study has utilized diffusion MRI to identify and characterize cerebral infarction in neonatal and childhood meningitis compared with those without stroke. The utility of diffusion MRI includes improved sensitivity for infarct detection, especially in neonates where clinical examination has limited ability to identify stroke and cerebrovascular complications.[5,7] Although more established in adults,[8] meningitis can lead to both large and small vessel cerebral arteritis, conferring a risk of arterial ischemic stroke.[9]

Adult studies have identified risk factors for cerebral infarction in bacterial meningitis including older age, compromised immunity, lower level of consciousness at admission, increased inflammatory markers, and seizures.[10-13] Although clinical trials do not exist, agents to potentially mitigate this risk including anti-inflammatory (e.g. corticosteroids) and antithrombotic (e.g. aspirin or heparins) medications are readily available and likely safe.[14] An improved understanding of risk factors and imaging biomarkers of meningitis-associated stroke in children is required to advance strategies to improve outcomes.

We conducted a population-based, retrospective cohort study of pediatric patients with bacterial meningitis who underwent acute diffusion MRI to identify risk factors, imaging patterns, and clinical outcome characteristics of bacterial meningitis-associated stroke.

Methods

Study design and populations

This was a population-based, 10-year retrospective, cohort study designed to capture all neonates and children diagnosed with bacterial meningitis in Southern Alberta, Canada (approximately 2.2 million persons). Methods were approved by the Conjoint Health Research Ethics Board of the University of Calgary.

Case ascertainment

Screening began from the year 2002 when diffusion MRI became routinely available and ended in 2012 as an institutional MRI screening protocol for meningitis was introduced in 2013. A rigorous approach defined a population-based sample where a single tertiary care pediatric center, regional laboratory, and universal health care combined to assure near 100% case ascertainment.

Inclusion criteria were: (1) age at diagnosis from newborn (including prematurity) to 18 years, (2) brain MRI including diffusion imaging during admission, and (3) confirmed acute bacterial meningitis. Definitive diagnosis required a clinical diagnosis of bacterial meningitis AND either (1) cerebrospinal fluid (CSF) culture positive for a pathogenic organism OR the combination of CSF pleocytosis (white blood cell count greater than 50×10^6 cells/L) with concomitant positive blood culture for a pathogenic organism. Excluded were cases with: viral, fungal or tuberculous meningitis, clinically or microbiologically suspected contaminant in CSF culture, shunt infection without evidence of clinical meningitis, wound infection related to myelomeningocele or trauma, or incomplete clinical or imaging data. It is possible that the requirement for MRI with diffusion-weighted imaging (DWI) may cause some of the most acutely unwell patients to be omitted, as they may have only received a CT.

Potential cases were first identified from the Calgary Lab Services database where all positive CSF cultures from the population-base were reviewed. Next, systematic screening of International Classification of Disease 9 and 10 (ICD) codes consistent with bacterial meningitis were applied by skilled coding experts to the Alberta Children's Hospital records as described previously,[15] enabling capture of patients transferred after CSF was collected outside the regional laboratory catchment area.

Chart review

Using standardized data capture forms, clinical history, physical examination findings, and laboratory values were extracted. All follow-up records were reviewed to estimate neurological outcomes which were extrapolated to the pediatric stroke outcome measure (PSOM). The PSOM is the standard measure in this population and has been validated across all childhood stroke age groups.[16] For analysis, PSOM scores were dichotomized into good (PSOM < 1) versus poor outcome (PSOM ≥ 1).

Imaging

All neuroimaging was obtained on a clinical basis on Siemens 1.5T MRI scanners (Magnetom Sonata before or Avanto after September 2006) in accordance with institutional protocols that included diffusion-weighted imaging (b = 0, 500, 1000) and apparent diffusion coefficient maps. Image analysis was performed by two neuroimaging experts (AK, XW) who were not aware of clinical variables. The primary imaging outcome was the presence of acute ischemic stroke, defined as one or more areas of restricted diffusion (hyperintense on DWI, hypointense on apparent diffusion coefficient) in a focal vascular territory. Arterial lesions were classified as arterial ischemic strokes and infarcts in conjunction with cerebral sinovenous thrombosis were classified as venous. Additional imaging outcomes collected were stroke location, structures affected, anterior or posterior circulation, vascular territory (small, large), and laterality based on reported criteria.[17] MR venography and arteriography were evaluated. Imaging diagnosis of other complications of meningitis was also recorded: abscess, empyema, extra-axial collections, and hydrocephalus.

Analysis

Categorization of patterns and their association with organism, and categorical comparisons of stroke (yes/no), organisms, and proportions were evaluated using Chi-Square or Fisher's exact test. Ordinal data and continuous variables were represented with medians and interquartile ranges (IQR) and significance tested with Wilcoxon rank sum tests due to non-normal distribution of data and low numbers of subjects. Correlation between variables was determined by calculating the coefficient of correlation. Correction for multiple comparisons was not performed.

Results

Population

There were 487 positive CSF cultures evaluated, 62 of which were included. Reasons for exclusion of positive CSF cultures included contamination, patients with shunts

without evidence of meningitis, many of whom had multiple samples drawn. ICD-10 codes identified 469 potential patients, of whom 66 were confirmed. Finally, 21 patients had positive blood cultures and CSF leukocytosis, of which 19 were included. There were a total of 93 unique cases of confirmed bacterial meningitis (Fig 1). This included 25 neonates (26%, 64% male), 37 infants aged one month to one year (40%, 57% male), and 34 children greater than one year (37%, 50% male, median age 5.7 years, IQR 6.7 years). Government statistics estimated an average pediatric population of Southern Alberta during the study of approximately 390,000.[18] Our 93 cases over 10 years translates into an estimated incidence of bacterial meningitis of 2.37/100,000 children per year.

Cerebral imaging of any kind was performed on 71 of 93 patients (76%) (Fig 1). The final study population consisted of 43 patients with diffusion MRI (Fig 1). The age and sex of the study population are summarized in Table 1. The median age of children was 4.0 years, IQR 7.9 years. The entire age range was 26 weeks gestational age to 13.3 years. The proportion of males in the neonatal group was higher than expected (p = 0.023) (Fig 2).[19] Sixteen patients had diffusion MRI confirmation of ischemic stroke (37%) of the 43 with DWI imaging. The demographics of those with and without stroke were not significantly different (Table 2).

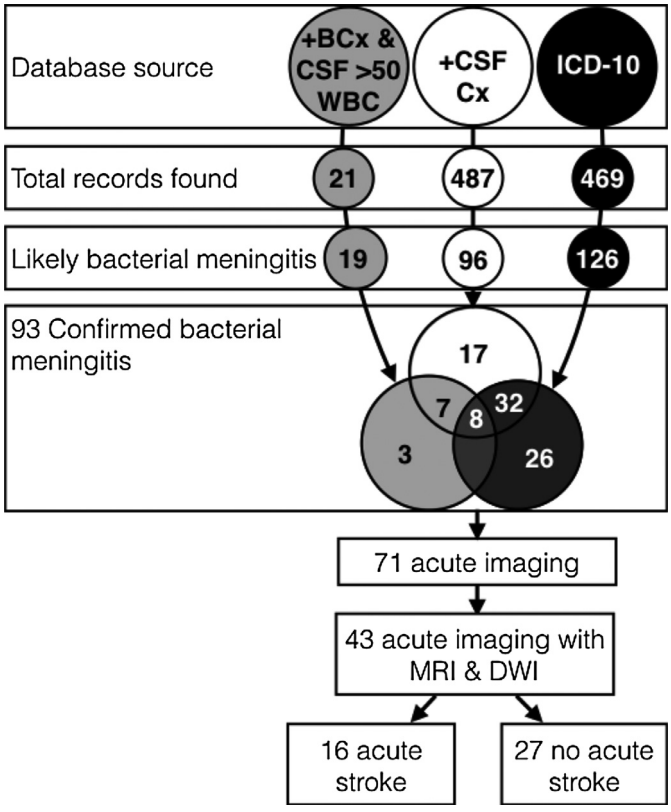

FIGURE 1. Selection criteria. Patients were identified based on positive cerebrospinal fluid cultures (+CSF Cx), ICD-10 discharge codes (ICD-10), and positive blood cultures with at least 50 CSF WBC (+BCx + CSF > 50 WBC). The Venn diagram illustrates the overlap of patients found by each method.

Table 1. Age and Sex. Sex and Age Distribution of the 43 Patients With Bacterial Meningitis and MRI With DWI

	Number (% of total)	% Male
Neonates (< 28 days)	9 (21%)	89%
Infants (28 days-1 year)	22 (51%)	50%
Children (> 1 year)	12 (28%	58%

Clinical presentation

More stroke patients had fever for more than 48 hours at presentation compared with those without stroke (60% versus 26%, $P = 0.049$). The median number of presentations to the hospital for a patient with stroke was two (IQR 2) and significantly more than one (IQR 0) for those without ($P = 0.013$). Seizure before or during admission was more common in stroke patients (81% versus 44%, OR 5.5 (1.3 to 24.3), $P = 0.025$). The proportion of patients with decreased level of consciousness, meningismus, hyponatremia, and new focal neurological signs during admission all appeared higher in the stroke group but did not reach significance.

Microbiology

Group B Streptococcus (GBS) and *Escherichia coli* were associated with neonates and infants under 90 days old while *Streptococcus pneumoniae* accounted for 53% of the children older than one month, of whom 44% had stroke. GBS was the responsible organism in three (33%) of the neonatal cases, but also affected an additional three infants with late presentation. One neonate and two older infants with GBS had stroke (50%). There were five individuals with *Haemophilus influenza*, one of whom had stroke (20%), and four cases of *E. coli*, one of whom had stroke (25%) (Supplementary Fig 1).

Laboratory

Serum and CSF white blood cell counts did not differ significantly between groups with and without stroke (Table 2). Twenty patients had CSF glucose that was

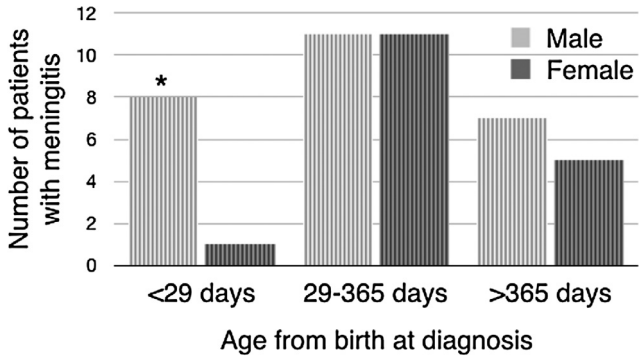

FIGURE 2. Meningitis demographics. Sex of study population divided by age from birth at presentation. Star = P value < 0.05 for test of proportion of male patients = 0.512.

Table 2. Population Demographics. Patient Populations of Those With and Without Stroke in Bacterial Meningitis. n = Number of Patients with Positive Result/ Number of Patients With Available Information. *P* Values Determined by Fisher's Exact Test or Wilcoxon Rank-Sum Test

	Stroke		No Stroke		*P* Value
	n	%	n	%	
Demographics					
Total number	16		27		
Male	11/16	68.8%	15/27	55.6%	0.52
<35 weeks post conceptual age at diagnosis	1/15	6.7%	2/26	7.7%	1
<28 days old at diagnosis	3/16	18.8%	6/27	22.2%	1
1 month 1 year at diagnosis	6/16	40.0%	7/26	26.9%	0.51
>1 year at diagnosis	4/15	26.7%	8/26	30.8/%	1
History of prematurity (<35 weeks GA)	3/15	20.0%	7/26	26.9%	0.72
Shunt predating presentation	1/16	6.3%	1/27	3.7%	1
Pre-existing medical condition	3/16	18.8%	6/25	24.0%	1
Presented from community	15/16	93.8%	23/27	85.2%	0.64
Presented from NICU	1/16	6.3%	4/27	14.8%	0.64
Presentation					
Duration of symptoms (median days, IQR)	3.5	(5)	2	(1)	0.086
Number of presentations (median, IQR)	2	(2)	1	(0)	0.013
Triage to first antibiotics (median min, IQR)	124	(182)	273	(398)	0.35
Decreased LOC at admission	10/15	66.7%	9/24	37.5%	0.19
Fever >48 hours at admission	9/15	60.0%	6/23	26.1%	0.049
Meningismus	10/11	90.9%	6/13	46.2%	0.11
Seizures before or during admission	13/16	81.3%	11/25	44.0%	0.025
New focal signs during admission	4/16	25.0%	3/26	11.5%	0.40
Hyponatremia	6/15	40%	5/21	23.8%	0.27
Laboratory values					
Serum WBC on admission (median, IQR)	7.8	(11.1)	6.5	(8.1)	0.75
Serum Hb on admission (median, IQR)	105	(38)	112	(34)	0.82
CSF WBC on admission (median, IQR)	261	(474)	784	(2261)	0.14
CRP at admission (median, IQR)	237	(232.9)	155.5	(63.3)	0.11
Number of patients with CSF glucose <0.5	9/14	64.3%	11/20	55.0%	0.73
MRI findings					
Time between MRI and CSF (median days, IQR)	3.65	(4.35)	1.75	(4.8)	0.09
Changes consistent with sinusitis	1/16	6.3%	5/24	20.8%	0.37
Changes consistent with otitis	5/16	31.3%	1/24	4.2%	0.029
Changes consistent with mastoiditis	5/16	31.3%	2/24	8.3%	0.077
Course and treatment					
PICU admission	10/16	62.5%	15/26	57.7%	1
PICU admission duration (median days, IQR)	3	(28.5)	4	(4)	0.34
Hospital admission duration (median days, IQR)	29.9	(73.5)	13.89	(11)	0.013
ASA	5/15	33.3%	0/14		0.042
Heparin	4/15	26.7%	1/22	4.5%	0.14
Steroids	3/12	25%	1/21	4.8%	0.13
Need for vasopressors	2/14	14.3%	3/8	37.5%	0.33
Outcome					
Death	4/16	25%	1/25	4%	0.067
Follow-up duration (median years, IQR)	6.7	(7.9)	4.8	(4.9)	0.67
Epilepsy at follow-up	3/13	23.1%	3/18	16.7%	0.68
Normal neurological exam	5/16	31.3%	14/19	73.7%	0.019
Motor deficit	7/15	46.7%	4/15	26.7%	0.45
Cognitive deficit	5/12	41.7%	2/9	22.2%	0.64
Behavioral deficit	1/11	9.1%	1/12	8.3%	1
Speech deficit	4/12	33.3%	1/13	7.7%	0.16
Hearing loss	2/10	20.0%	3/17	17.6%	1

undetectably low (<0.5 mmol/L), nine of whom had stroke ($P = 0.728$).

Neuroimaging

Of the 71 patients with acute imaging, 15 underwent a CT, six an ultrasound, two a CT and an ultrasound, four an MRI without DWI, and one an MRI on a separate admission. The remaining 43 comprise the study population with MRI and DWI. Of the 28 patients with acute imaging excluded from the study due to lack of MRI with DWI, one (4%) was found to have stroke (venous sinus thrombosis and brainstem infarction), the remainder had no evidence of stroke. Thus there does not seem to have been significant selection bias introduced by the requirement for MRI with DWI. The median duration between presentation and MRI for patients with stroke was 1.75 days (IQR 4.8, range 0 to 17 days) compared with 3.65 days (IQR 4.35, range 0 to 80 days) for patients without stroke ($P = 0.09$).

Fourteen of the sixteen stroke patients had arterial ischemic infarction, most (75%) in the bilateral anterior circulation in small-to-medium sized, perforating arterial territories (Fig 3). Seven patients had associated hemorrhage though all were petechial transformation with no hematoma formation. The median number of infarcted

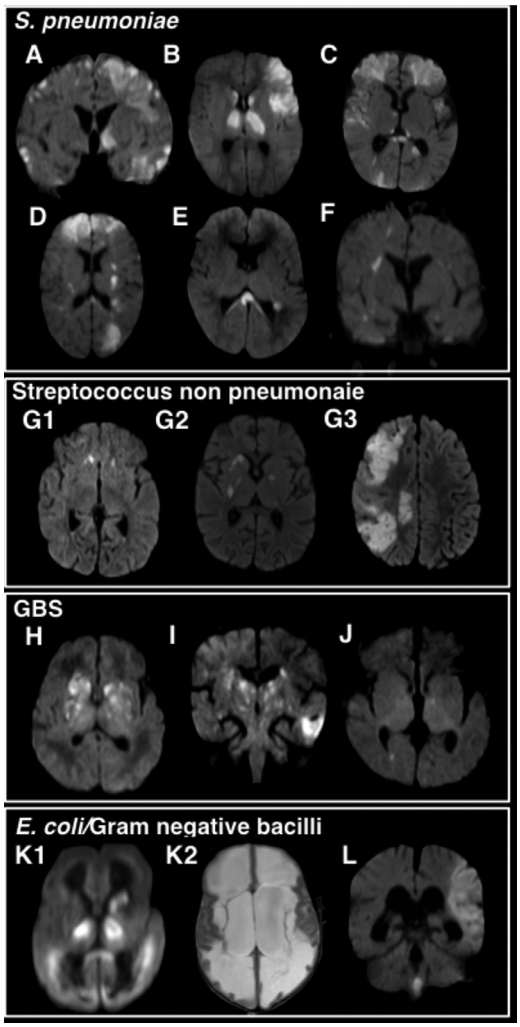

FIGURE 3. Stroke Imaging. Images are axial MRI diffusion-weighted images (b = 1000) unless otherwise stated. Areas of acute infarction appear "bright". A-I; *Streptococcus pneumonia* with multifocal, deep and superficial multiple areas of infarction. A = patient 27 coronal, B = patient 36, C = patient 22, D = patient 21, E = patient 10, F = patient 19, G: Streptococcus, not pneumonia, patient 33, sequence demonstrates progressive infarction over 19 days. G2: 4 days after initial imaging, G3: 19 days after initial imaging. H-J: Group B Streptococcus. H = patient 4, I = patient 14 coronal, J = patient 16. K: *E. coli*, patient 2. K2: axial T2-weighted MRI demonstrating diffuse encephalomalacia due to extensive infarction. L = gram negative bacilli, patient 25.

areas per patient was six (range one to 15). *S. pneumoniae* was typically associated with frontal infarction and deeper perforating areas including the basal ganglia and splenium of the corpus callosum (Fig 3A-F). GBS affected predominantly deep perforating arteries in the basal ganglia (Fig 3H-J). Gram negative infections were associated with severe, bilateral thalamic or brainstem infarction, both of which were fatal (Fig 3K and L).

Eleven patients (26%) had MR angiography, seven of whom had stroke. Four (9%) demonstrated signs of large vessel arteriopathy consisting of irregular stenosis of major branches of the circle of Willis. One patient demonstrated progression of both arteriopathy and stroke recurrence over three MRI assessments across 19 days (Fig 3G). In another patient, there was progression of arterial stenosis but no new infarcts. MR venography was completed in 15 subjects (35%). Cerebral sinovenous thrombosis was diagnosed in four, two of which had venous infarction.

The images of the 71 patients with cerebral imaging of any kind during their admission were reviewed for additional nonstroke complications. Two had definitive abscess while another was considered probable (4%). Seven (10%) were suspected to have empyema, 28 (40%) had extra-axial collections, and 13 (19%) developed early hydrocephalus.

Course in hospital

The majority of children in both groups (63% stroke, 58% without) were admitted to intensive care. Median length of hospital stay was 29.9 days (IQR 73.5) for stroke patients, significantly longer than 13.9 days (IQR 11) for those without ($P = 0.013$) (Table 2). Five of the children with stroke (31%) were treated with ASA for stroke prevention. Heparin was given to one patient with cerebral venous sinus thrombosis, and three patients for femoral clot. Steroids were given to four children, three with stroke and one without.

Outcomes

Follow-up information was available for all 16 stroke patients (Supplementary Table 1) and 24 of 27 without stroke. The mean duration of follow-up was 6.7 years (range four months to 10.5 years) and 4.8 years (range one month to 12 years) respectively. Four stroke patients died (25%) compared with one in the nonstroke group (4%) ($P = 0.067$). Children with stroke were less likely to have a normal neurological examination at discharge (21% versus 76%, $P = 0.002$) and at follow-up (31% versus 74%, $P = 0.019$). Type of deficits did not differ between groups. Epilepsy was present at follow-up for three of 13 stroke patients for whom information was available (23.1%), compared with three of 18 without stroke (16.7%) ($P = 0.66$).

PSOM scores were available for 40 patients (93%) (Table 2). There was a strong correlation between PSOM score and the number of areas infarcted (coefficient of correlation 0.78, $P = 0.007$). Patients with a good outcome (PSOM < 1) had fewer areas of infarct (median 4, IQR 5.5) compared with those with poor outcome (PSOM ≥ 1) (median 11, IQR 7) ($P = 0.0061$). All subjects with bilateral thalamic or bilateral brainstem infarcts had a severe outcome or death. Among patients with stroke, no additional clinical factors were associated with outcome.

Discussion

We provide population-based data describing the clinical, imaging, and microbiologic factors associated with bacterial meningitis and stroke in children. Our results confirm that stroke is common and serious complication with increased morbidity and mortality.

Our estimate of the incidence of pediatric bacterial meningitis in Southern Alberta was 2.37/100,000 children/year, slightly lower than previous estimates in Canada of 3.5/100,000.[20] This may relate to our strict inclusion criteria and exclusion of patients with other forms of meningitis such as shunt infections. The incidence of stroke in those with DWI was 37%. A less precise estimate based on the 71 children who received cerebral imaging of any kind is 24%, and if it is assumed that none of the 22 children without cerebral imaging had stroke, the rate of stroke in our cohort of 93 patients with meningitis was 18%. Studies of stroke in infant bacterial meningitis have estimated an incidence ranging from 24%[21] to 43%[22] while in children with *S. pneumoniae* meningitis, rates of 45% have been reported.[3] Similar to our study, these earlier studies were affected by some degree of selection bias with regard to which patients underwent imaging.

Stroke has been consistently reported in neonatal meningitis,[23] mostly in small cases series, with rates ranging widely from 2.3% to 75%[24-26] as compared with our population-based rate of 33%. Half of our neonates with GBS meningitis had stroke in keeping with a series of 14 infants with late onset GBS meningitis and cerebrovascular complications, 11 of which included acute stroke (78%).[27]

Males were over-represented in the 93 patients with confirmed meningitis, but only during the first four months of life (67% of cases birth to four months). A male preponderance in meningitis has been reported in some studies[28] but not others.[29] Male neonates may also have an increased incidence of complications due to meningitis[30] and higher mortality from infections in general.[31,32] Male sex is a risk factor for childhood stroke of all etiologies,[31,32] including neonatal arterial strokes,[32,33] though mechanisms are unclear.[34]

The most common pathogen in non-neonates was *S. pneumoniae* (53%) where the stroke rate was high at 48%. This rate appears comparable to a prospective Danish study in adults that found *S. pneumoniae* responsible for 51% of bacterial meningitis with a stroke rate of 36%.[10] Arteriopathy is also prominent in adults with *S. pneumoniae* meningitis imaged prospectively.[35] The marked progress in immunization strategies against this organism[36] may represent an important public health advance toward the prevention of stroke in the young. Routine immunizations were also recently shown to be protective against childhood stroke,[37] further highlighting the complexity of relationships between infections, immunity, and stroke. In addition, the advent of vaccines to prevent meningitis decreased the overall incidence of meningitis over the course of the study period.[38]

The pathophysiology of cerebral infarction in bacterial meningitis is not well established. In four of our patients, cerebral arteriopathy was observed, one of which was associated with progressive infarction. In adults with meningitis undergoing systematic transcranial Doppler, cerebral arteriopathy is suggested in 50% to 80%.[39,40] Arterial irregularity and stenosis in neonatal bacterial meningitis is demonstrable by MR angiography and has been correlated with pathologic evidence of vasculitis.[5] In contrast, other series have shown imaging evidence of vessel narrowing but no vasculitis on pathology, suggesting alternative mechanisms such as vasospasm,[41,42] which may also underlie “delayed” stroke in meningitis.[43] Arterial clots have also been described in the absence of vasculitis in *S. pneumoniae* meningitis,[44] the mechanisms of which are likely to be multifactorial, with recent *in vivo* evidence that neutrophil extracellular traps contribute to intravascular coagulation in mouse models of bacteremia.[45] There is evidence that greater host immune reactions may be associated with higher stroke likelihood.[10,11] The interaction between organism and host immunity may in part explain why rates of stroke differ between organisms. There is growing evidence that recent herpesvirus infection is associated with pediatric stroke, further suggesting an immune-host response that results in vasculopathy.[46]

Most patients had multiple areas of infarction, often involving both the basal ganglia and cortex. An Australian study of MRI patterns by organism determined that the majority of patients with streptococcal meningitis had multiple infarcts that were often confluent over multiple vascular territories and involved the basal ganglia.[7] This appears similar to patterns in neonatal GBS infarction where combined deep and superficial injuries are described.[47] In contrast, *E. coli* meningitis may be more likely to demonstrate diffusion restriction in extra-axial collections and ventriculomegaly.[7] Such imaging patterns may be useful biomarkers of organism identification (when cultures are not available) or help identify pathophysiological mechanisms that might be targeted with new therapies.

Possible predictors of stroke risk in children with meningitis have included seizures, focal neurological signs, fever, decreased level of consciousness, and hydrocephalus.[3,4] Similar risk factors are seen in adults in addition to higher erythrocyte sedimentation rate or C-reactive protein.[10,11] There have been efforts to predict stroke risk based on transcranial Doppler arterial velocity though a recent study found limited correlations with MR angiogram findings.[12] In our study, multiple presentations, presence of seizures, evidence of otitis media, and fever greater than 48 hours were significantly associated with stroke. Seizures are the most common presenting symptom of stroke in neonates with any etiology[48] and are frequently subclinical, suggesting electroencephalogram screening may be useful in this population. There is also evidence that postischemic seizures may be associated with a worse outcome, possibly due to increased excitotoxicity and neuronal death, and thus early detection and treatment may have a positive effect on outcome.[49-51]

Stroke prevention strategies in meningitis are limited. Mechanisms for stroke such as inflammation, vasospasm, and increased coagulation are potential targets for therapy. Inflammation and infection are known risk factors for stroke,[52] and steroids have been shown to improve outcome in certain meningitis populations.[53] A randomized placebo trial of dexamethasone in neonatal meningitis suggested a mortality benefit,[54] however using steroids in meningitis is not generally considered standard of care in children, with the exception of *H. influenzae*.[55] Steroids may also be beneficial in certain childhood stroke populations though this remains unproven.[56] Vasospasm is another potential mechanism however strategies

to treat vasospasm related to other causes (e.g. calcium channel blockers) have not been studied in stroke associated with bacterial meningitis. Finally, hypercoagulability occurs in the setting of meningitis and can possibly be mitigated with heparin, ASA or both. ASA has shown modest benefit in studies of tuberculous meningitis.[57,58] Heparin has not been studied for primary prevention of stroke in meningitis since an adult study in 1977 demonstrated lack of benefit and possible bleeding risk.[59] A more recent retrospective pediatric study suggested safety and possible efficacy when used for secondary prevention.[14] Antithrombotics were used infrequently in our study but there were no apparent adverse effects. There are currently no therapies recommended for primary stroke prevention in meningitis, however, stroke may be a primary mechanism of long-term morbidity and remains an important target where therapeutic approaches need to be advanced.

Outcomes in pediatric meningitis complicated by stroke carry high rates of morbidity and mortality. The largest series of 22 cases of pediatric meningitis and stroke at two Canadian centers demonstrated mortality in two (9%), severe disability in two, moderate disability in two, and minimal disability (PSOM total 1 or 2) in the remainder.[14] Our study found an overall mortality rate of 5/43 (12%), 80% of whom had stroke. There was also significantly more disability in the children with stroke and those with poor outcomes had more areas of infarct. The early recognition of meningitis and effective primary and secondary prevention of stroke remain important clinical goals.

Limitations of our study include its retrospective nature. Not every case of meningitis may have been identified though our population-based methods were exhaustive. Our rigorous inclusion criteria for meningitis may have led to an underestimation of meningitis, and our requirement for MRI may have inadvertently omitted the sickest patients who may have died before undergoing head imaging. One patient of the 28 (4%) excluded from the study due to head imaging with a modality other than MRI with DWI was found to have stroke. Some patients received an MRI later in the course of their illness (after seven days from diagnosis) and thus some diffusion changes may not have been recognized if infarction occurred earlier. Complete clinical information was not available for every patient from the chart review, possibly limiting our risk factors analysis.

In conclusion, more than a third of children with bacterial meningitis warranting MRI have stroke. Risk factors include multiple presentations to hospital, association with otitis media, seizures, and common causative organisms. Stroke was predominantly associated with subtypes of streptococcus in our population and the pattern of infarction frequently involved multiple small-vessel territories and the basal ganglia. Poor outcome was significantly associated with more areas of stroke. Stroke was associated with higher mortality and morbidity, warranting consideration for increased MRI screening and new approaches to treatment.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2018.09.005.

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