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Profile and Predictors of new onset acute symptomatic seizures following community acquired acute bacterial meningitis

[1]S Sinha, [1]SL Rao, [2]S Nagarathna, [3]V Ravi

Departments of [1]Neurology, [2]Neuromicrobiology and [3]Neurovirology, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India

Abstract

Introduction: Studies regarding acute symptomatic seizures in patients with acute bacterial meningitis are few. We analyzed the incidence and details of new-onset acute symptomatic seizures in patients with 'etiology proven acute bacterial meningitis'. *Methods:* This retrospective cross-sectional study involved 47 patients with community-acquired confirmed acute bacterial meningitis who manifested with new-onset acute symptomatic seizures among 191 patients with acute bacterial meningitis evaluated from 1999 to 2008 at NIMHANS, Bangalore. The clinical, CT scan and laboratory data patient groups with and without seizures were compared using appropriate statistical tool. *Results:* Forty-seven patients (24.4%; M:F=36:10) with mean age of 20.32±19.48 years had new-onset acute symptomatic seizures. Status epilepticus was noted in 8 while cluster attacks were present in 7 patients. The causative agents included pneumococcal - 28 (59.6%), meningococcal - 3 (6.4%), *H. influenzae* b -10 (21.3%) and others - 5 (12.8%). CT scan (brain) was abnormal in 72.3% and included diffuse edema (23.4%), and focal hypodensities (14.9%). Patients with seizures were significantly younger (<0.05), more often had abnormal brain imaging (p<0.005), and pneumococcal meningitis and H. influenzae type b meningitis (P<0.001) as compared to those without seizures. There was no other significant difference in clinical and laboratory parameters between the two groups. Treatment with adjunctive steroid was not associated with any reduction in acute symptomatic seizures. Majority received parenteral phenytoin (n=40) followed by sodium valproate (n=4) and phenobarbitone (n=3).
Conclusions: New-onset acute symptomatic seizures were noted in 24.4% of patients with etiologically proven community acquired acute bacterial meningitis. The occurrence of remote symptomatic seizures in these patients with acute bacterial meningitis needs to be studied.

INTRODUCTION

Acute symptomatic seizures are defined as seizures occurring in close temporal relation to any central nervous system (CNS) insult secondary to varying etiologies and are associated with an increased risk for subsequent epilepsy.[1-3] Cerebral infections may account for higher incidence of epilepsy in the developing countries.[3] Sequelae following childhood bacterial meningitis include hearing loss, vision loss, cognitive delay, speech/ language disorder, behavioral problems, motor delay/impairment, and seizures.[4]

Acute symptomatic seizures in bacterial meningitis are usually observed in the first 24 hours of presentation. Wang *et al* reported seizures as the third most common feature of acute bacterial meningitis.[5] Seizures are a common complication of bacterial meningitis in the acute phase of illness occurring in 15-23% of cases, and is an individual predictor of poor outcome.[6,7] Though classically cortical inflammation has been described as the main mechanism of seizures in bacterial meningitis, Zoons et al (2008) identified additional CSF and systemic factors like higher ESR, low CSF leukocyte count, and those infected with S. pneumoniae to be associated with increased risk for seizures.[7] In population-based cohorts of survivors of CNS infections, the reported risk of developing unprovoked seizures is between 6.8% and 8.3%.[8,9] In developed countries, 1 to 5% of incident cases of epilepsy are presumed to be due to prior CNS infections.[10,11]

We studied the prevalence of acute symptomatic seizures in patients with 'etiology proven acute bacterial meningitis' and identified the risk factors for acute symptomatic seizures in the same cohort.

Address correspondence to: Dr. Sanjib Sinha, MD, DM, Additional Professor of Neurology, National Institute of Mental Health & Neurosciences (NIMHANS), Hosur Road, Bangalore – 560029, India. Fax: +91 80 26564830, Phone: +91 80 26995150, E-mail: sanjib_sinha2004@yahoo.co.in

METHODS

This retrospective hospital based cross-sectional study involved confirmed patients with community acquired acute bacterial meningitis (n=191; M:F=151:40; mean age: 32.23±20.72 years) who were evaluated from January'1999 to December'2008 at NIMHANS, Bangalore, a university teaching hospital and major tertiary care referral centre in south India for neuropsychiatric disorders. On an average, the number of patients evaluated each year at the neurological outpatient, emergency and inpatient services at our centre are 69281; 12241; and 3066 respectively. This study was approved by the institutional ethics committee. Information regarding patients' details was retrieved from the medical case records section of our institute.

Inclusion criteria

All patients with community acquired acute bacterial meningitis were included. Community acquired acute bacterial meningitis was defined as those developing features of meningitis namely fever, meningism and alteration in conscious levels with CSF showing polymorphic pleocytosis, elevated protein (>45 mg/dl) and glucose <40mg/dl and evidence of bacterial infection in Gram stain, antigen studies, latex agglutination or by culture.

Exclusion criteria

Patients with pyogenic meningitis but not meeting the inclusion criteria (no microbiological evidence of the infective agent), sub-acute / chronic central nervous infections like tubercular, fungal or cysticercal meningitis, nosocomial meningitis, immunocompromised state; living with epilepsy, history of head injury, VP shunt, granuloma / tumour in the brain were excluded. TB meningitis was excluded reasonably by clinical, CSF and imaging features. The CSF ELISA test for anti-mycobacterial antibody was also negative. The patients were closely monitored for other illnesses. If doubts existed in the data during audit, such patients were excluded from the study.

Definitions

1. Acute symptomatic seizures[12] in patients with ABM defined as seizures occurring in close temporal relation to any central nervous system (CNS) insult of varying aetiology.
2. Epilepsy as defined by the ILAE 1989 – Commission on Epidemiology and Prognosis - criteria: A condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24-h period are considered a single event. An episode of status epilepticus is considered a single event. Individuals who have had only febrile seizures or only neonatal seizures as herein defined are excluded from this category.
3. Status epilepticus is defined as a single epileptic seizure of >30-min duration or a series of epileptic seizures during which function is not regained between ictal events in a >30-min period.[13]
4. Cluster seizures are defined as 3 attacks of seizures per 24 hours.[14]

Medical case records were retrieved from the Medical Records Department, NIMHANS after obtaining the hospital numbers of those patients who met the inclusion criteria from the department of Neuromicrobiology. The demographic profile, clinical features, seizure details, details of brain imaging of brain, CSF profile, therapeutic details, clinical and seizure outcome at discharge were recorded in a pre-designed proforma and then in MS excel sheet. CSF sampling was carried out at variable time from the onset of illness, depending on the evaluation of the patient by the neurological services. Axial cranial CT scan (plain and contrast) was carried out in all using standard procedures. The prevalence of unprovoked seizures could not be analyzed as there was no follow up and an attempt to contact them by surface mail was not successful.

The clinical data, including gender, and clinical manifestations between two patient groups (with and without seizures) during the acute symptomatic phase were analyzed by Chi-square test or Fisher's exact test (parametric test) to find association between categorical variables. The mean ages between the two groups and the mean CSF cell count and mean CSF sugar and protein were analyzed by Student's t test (parametric test) for continuous variables. A p-value of less than 0.05 was considered significant

RESULTS

The clinical and demographic details of 191 patients with acute bacterial meningitis are shown in Table 1. Among the 191 patients, 44 patients were children of less than 18 years and 17 were elderly patients more than 64 years. Fever,

Table 1: Demographic and clinical features in patients with acute bacterial meningitis

Parameters	N (%)
Age (mean)	33.23±20.72
Male	151 (78.8%)
Female	40 (21.2%)
Fever	189 (97.9%)
Headache	165 (85.5%)
Vomiting	128 (66.3%)
Otitis media	15 (7.8%)
Seizures	47 (24.6%)
Altered sensorium	147 (76.2%)
Tachycardia	90 (46.6%)
Weakness	11 (5.7%)
Anemia	62 (32.1%)
Restricted extra-ocular eye movements	7 (3.6%)
Steroid	25 (13.0%)
Abnormal brain imaging	118 (61.1%)
Mean CSF cell count <1000 cells/cu.mm	7345.61 ±14328 84 (43.5%)
CSF sugar	29.85 ±102.93
CSF protein	518.44 ±700.94
CSF Gram stain +	56 (29%)
CSF culture +	136 (70.5%)
Pneumococcal meningitis	144 (74.6%)
Meningococcal meningitis	21 (10.9%)
H. infleunza type b meningitis	13 (6.7%)
Others	13 (7.3%)
Altered renal parameters	29 (15%)
Elevated liver enzymes/	25 (13%)
Raised bilirubin	19 (9.8%)
Hyponatremia	22 (11.4%)
In hospital mortality	54 (28%)

headache, vomiting and altered sensorium was the commonest symptoms. Forty-seven patients (24.4%) had seizures during the acute phase of the illness i.e. acute symptomatic seizures. Status epilepticus was a presenting phenomenon in 8 (4.14%) of the patients with acute symptomatic seizures in bacterial meningitis. Cluster attacks were noted in 4.66% of patients with acute bacterial meningitis. Focal neurological deficits in the form of mono- or hemi paresis and extra-ocular nerve palsies were noted in 69 patients (35.7%). CT scan of brain, carried out in all, was abnormal in 118 (61.1%) and it included diffuse cerebral edema (20.2%), hydrocephalus (14.5%) and focal hypodensities (10.9%). Parenteral cephalosporins either ceftriaxone or cefotaxime were initially administered in the recommended dosages empirically till the Gram stain/culture reports were available. Treatment with antibacterial agents was modified as per the culture-sensitivity pattern. Adjunctive steroid, dexamethasone (16 to 32 mg/day in divided dosages for 3 to 4 days), was

Table 2: Comparison of Imaging features in ABM with and without seizures

CT head features	With seizures N=47 (%)	Without seizures N=144 (%)	P value
Abnormal	34 (72.3%)	47 (32.6%)	0.001
Diffuse edema	11 (23.4%)	28 (19.4%)	0.3
Focal hypodensity	10 (21.2%)	5 (3.5%)	0.001
Ventricular dilatation	4 (8.5%)	11 (7.6%)	0.9
Subdural fluid collection	4 (8.5%)	5 (3.5%)	0.2
Others	2 (4.2%)	7 (4.8%)	0.7

given in 25 patients (13%). The mean CSF cell count was 7345.61 cells/cu.mm and 84 (43.5%) patients had a CSF cell count of less than 1000 cells/cu.mm. Pneumococcal meningitis was the commonest (74.6%) followed by meningococcal meningitis (10.9%), *H. influenzae* b meningitis (6.7%). Other organisms were streptococcus species (n=6), gram negative bacilli (n=4), *Staphylococcus aureus* (n=1), and enterococcus (n=1). Blood biochemical abnormalities were noted in 63 patients. Sixteen patients had more than one altered parameter.

Imaging in patients with seizures and acute bacterial meningitis

Patients with seizures had abnormal brain CT scans more often when compared to those who did not have seizures (P=0.49). When the various types of abnormalities were compared between the two groups there was no significant difference. Cerebral edema was present in 23.4% of patients with seizures and in 19.2% of the patients without seizures. Focal hypo-densities were detected in 14.9% of the patients with seizures and in 9.6% of patients without seizures while hydrocephalus was noted in 14.9% and 14.4% of the patients respectively. But when only cortical hypodensities when compared between the two groups there is a significant difference between the two groups, 21.27% patients with seizures had cortical hypodensity and 3.4% without seizures had cortical hypodensity detected in a CT scan (P<0.001). (Table 2)

Comparison of patients of acute bacterial meningitis with and without seizures

Patients in the seizure group were significantly younger as compared to those without seizures (P <0.005). Most of them had pre-hospital seizure, as only three of them had their first attack of seizures in hospital. About 53.1% of the seizures occurred within the first 24 hours and 80.8% occurred within the first 48 hours of onset of acute bacterial meningitis. The seizure was focal in onset in nine patients (19.1%). Three patients (6.4%) had status epilepticus while nine had cluster attacks of seizures (19.1%) in the acute phase.

The clinical features in patients with and without acute symptomatic seizures and were not significantly different other than the presence of tachycardia, which was more common in those with seizures as shown in Table 3. Patients with seizures had significantly higher proportion of abnormal brain imaging findings as compared with those without seizures (P = 0.049). There was no significant difference between the two groups with respect to the laboratory parameters, neither the CSF (mean cell count, mean total protein or mean sugar) nor the serum chemistry including kidney or liver function tests and electrolytes. Treatment with adjunctive steroid was not associated with any reduction in acute symptomatic seizures but the number of patients treated with steroids was low and most of the patients had pre-hospital seizures. Acute symptomatic seizures were strongly associated with pneumococcal meningitis and *H. influenzae* type b meningitis (P<0.001).

Out of 47 patients who had acute symptomatic seizures in acute bacterial meningitis, majority of patients (n=40) received parenteral phenytoin. Four patients in addition received sodium valproate and three received phenobarbitone.

DISCUSSION

This study included 47 (24.4%) patients of acute bacterial meningitis with new-onset acute symptomatic seizures. The risk factors for new-

Table 3: Comparison of patients of acute bacterial meningitis with and without seizures

Variables	Without seizures	With seizures	P
Male	115 (78.8%)	36 (78.8%)	0.57
Female	30 (21.2%)	10 (21.3%)	
Age	37.39 ± 19.4	20.32±19.48	0.05
Otitis media	12 (8.2%)	3 (6.4%)	0.48
Altered sensorium	111 (76.6%)	36 (78.3%)	0.49
Tachycardia	16 (34%)	74 (50.7%)	0.034
Weakness	6 (4.1%)	5 (10.6%)	0.980
Restricted eye movements	7 (4.8%)	0	0.13
Steroid use	17 (11.6%)	8 (17.0%)	0.23
Abnormal CT head	47 (32.6%)	34 (72.3%)	0.001
Abnormal RFT	19 (13%)	10 (21.3%)	0.13
Hyperbilurubineamia	13 (8.9%)	6 (12.8%)	0.30
Elevated liver enzymes	21 (14.4%)	4 (8.5%)	0.22
Hyponatremia	16 (11%)	6 (12.8%)	0.45
CSF <1000 cells/cu.mm	66 (45.2%)	18 (38.2%)	0.71
Mean CSF cells cells/cu.mm	7235.77 ±14446.03	7686.81 ±14104.94	0.85
CSF sugar- Mean (mg/dl)	30.25 ±117.21	28.64 ±36.501	0.9
CSF protein - Mean (mg/dl)	529.95 ±699.52	485.43 ±711.71	0.71
Pneumococcal meningitis	116 (79.5%)	28 (59.6%)	<0.001
Meningococcal meningitis	18 (12.3%)	3 (6.4%)	0.25
Hib meningitis	3 (2.1%)	10 (21.3%)	<0.001
Other meningitis	8 (6.1%)	5 (12.8%)	0.14
Cephalosporins	23 (57.5%)	59 (56.7%)	0.9
Cepahalosporin + aminoglycoside	8 (20%)	24 (23.07%)	0.7
Cephalosporin + aminoglycoside + metronidazole	7 (17.5%)	18 (17.3%)	0.9
Adjunctive Steroid (n=35)	11 (22.5%)	24 (20.19%)	0.7
Cephalosporins	23 (57.5%)	59 (56.7%)	0.9

onset seizures included young age (p=0.03); abnormal cranial CT scan findings (p=0.001); pneumococcal (p=0.001) and *H. influenzae* (p=0.001) meningitis. Though seizures in acute CNS infection are commonly reported, very few studies have actually analyzed this systematically.[5,7,14,15] Most of the published reports have either studied acute symptomatic seizures of varying etiology as a single cohort or evaluated the various manifestations of different central nervous infective syndromes. Seizures following bacterial meningitis are commonly of the focal-onset type with or without secondary generalization, though generalized seizures and myoclonic seizures may also occur.[6,8,16] There have been a few focused studies from India, which evaluated the risk of seizures in CNS infections like Japanese encephalitis and cerebral malaria,

but not in bacterial meningitis.[17-19] However, while analyzing the etiology of localization related epilepsy, ABM accounted for 0.9% of the cohort in a university hospital in South India.[20]

The clinical features of the patients included in this study were comparable with those studies evaluating a large cohort of patients with acute bacterial meningitis.[21] In the present study, all patients with acute bacterial meningitis were evaluated with a cranial CT, and an abnormal brain imaging was noted in 61.1% of the patients, out of which diffuse cerebral edema was the most common finding. Other significant abnormalities were hydrocephalus in 14.5% and focal hypodensities in 10.9%. Van de Beek *et al* (2004), observed abnormal imaging after a cranial CT in 34% and the most common abnormality was cerebral edema (10%), cerebral infarcts (6%) and hydrocephalus (3%).[21] Hydrocephalus appears to be a common imaging abnormality in these patients as other studies have reported this finding in up to 25%.[5,15]

In this study about one-fourth of the patients had acute symptomatic seizures with acute bacterial meningitis as compared to 15 to 33% in the other retrospective studies from tertiary hospitals.[6,22,23] Seizures were focal in about 19% of the patients while 6.4% patients presented with status epilepticus and 19% had seizures in clusters. In 80% of the patients, seizures occurred within 48 hours of onset of other symptoms of meningitis.

In the Dutch Meningitis Cohort study, seizures were noted in 17% (121/696) of the patients with acute bacterial meningitis.[7] It was reported as focal in onset in about 8% of their patients. A distant focus of infection, immunocompromised state, tachycardia, and low GCS score at admission were associated with a higher risk of seizures. Patient with seizures were more likely to have an abnormal cranial imaging and an unfavorable outcome, with a significant mortality of 41% in those with seizures. Five patients had status epilepticus with 100% mortality. In another study, Wang *et al* (2005) noted seizures in 27% of the 112 cases. Five out of the 31 patients had focal seizures and 10 patients had status epilepticus. About 38% of the patients with seizures had an abnormal cranial imaging but no significant association was present between these two factors. *K. pneumoniae* was causative agent in a large proportion of the patients with seizures. Altered consciousness was significantly associated with seizures. Seizures were significantly associated with a poor outcome.[5] Chang *et al* (2004a), observed seizures in 47% (55/116) of the seizures in children with bacterial meningitis. One-fourth of the seizures were focal and 17 patients progressed to status epilepticus. The EEG was abnormal in 83% and the abnormality was unilateral in 33%.

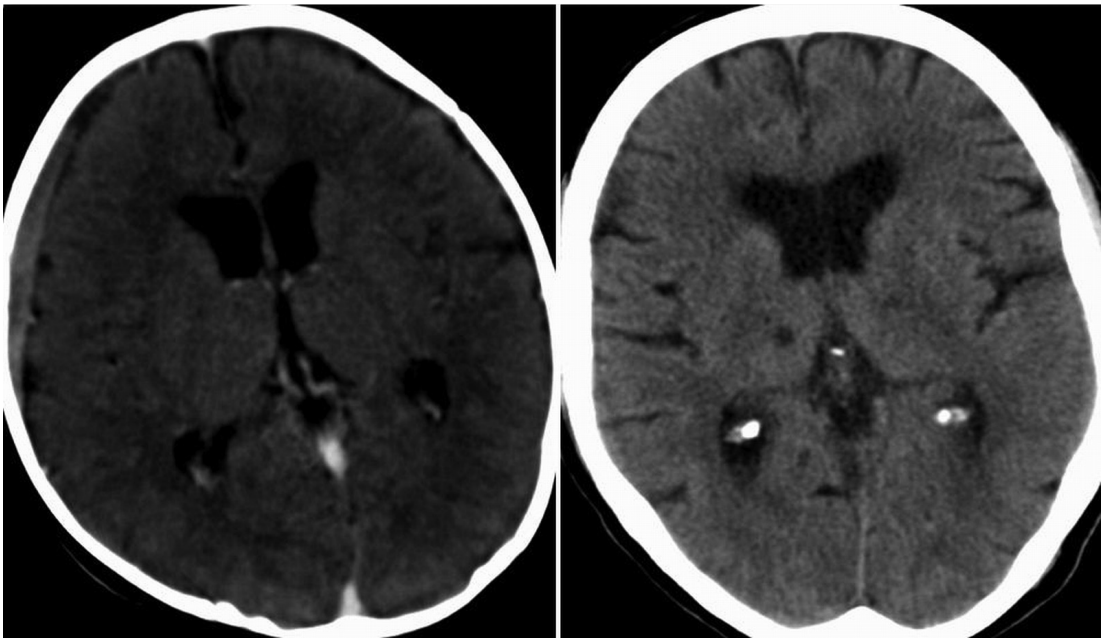

Figure 1: Subdural empyema (A) and infarct in L. thalamus (B) in bacterial meningitis with acute symptomatic seizure

Abnormal cranial imaging was noted in 51% of the patients and it was significantly associated with the occurrence of seizure. Other features that had significant association with seizures in this study were disturbed consciousness at admission, age, and low CSF glucose level.[15] In a meta analysis by Baraff *et al* (1993), this probability was the highest for *S pneumoniae* meningitis (14.8%) in comparison to meningitis due to *H influenzae* (6.1%) and *N meningitides* (1.4%).[23] In a recent study, multivariate analysis of prognostic factors in Pneumococcal meningitis, which is the leading cause of mortality in bacterial meningitis, did not show an association of seizure with an adverse outcome.[24] In the present study, presence of tachycardia, an abnormal cranial imaging, and pathogenic bacteriae like *S pneumoniae* meningitis and *H influenzae* had a significant association with the occurrence of seizures. Acute symptomatic seizures in acute bacterial meningitis are a relatively common presentation and are significantly associated with a poor outcome.

Seizures can occur in children with CNS infection mainly due to vasculitis, thrombosis, ischemia, cerebral abscess formation and subdural collections.[5] In severe cases of central infection, where an association between vasculitis and cerebral edema occur, brain perfusion is intensively committed resulting in an increased risk of ischemic brain injury and seizures. In elderly population, according to a study published recently, seizures had occurred in 7% of patients with acute bacterial meningitis.[26] The study also reported that the presence of seizure following antibiotic therapy is an independent indicator of death and argued for prophylactic treatment with antiepileptic drugs in the elderly population.

Most of the patients in this study were referred back to their primary health care center after establishing the diagnosis of bacterial meningitis with an advised treatment regimen. The role of prophylactic administration of anti-epileptic drugs has not been recommended until now. Nevertheless, another study observed that anti-seizure prophylaxis might be useful in patients, particularly elderly with bacterial meningitis, after they reported a strong association of mortality in patients in this age group with seizures after therapy.[26]

A few studies show that acute symptomatic seizures in CNS infection are mediated by pro-inflammatory cytokines.[27-29] The main mechanism for acute symptomatic seizures in bacterial meningitis has been classically attributed as cortical inflammation though seizures in such a setting could be due to fever itself or complications like subdural empyema or focal infarctions.[3,30]

The strengths of this study are that only patients with etiologically proven acute bacterial meningitis were included. Though this provides the opportunity to evaluate the relation between the etio-pathological agent and acute symptomatic seizures, this also becomes one of the limitations as about 30% cases with culture negative bacterial meningitis cases were excluded. The other limitations are retrospective study, poor documentation of the alteration in sensorium, outcome measurement and no follow-up in this cohort.

This study showed that new-onset acute symptomatic seizures were observed in almost one-fourth of patients with acute bacterial meningitis and the risk factors were young age(<0.05), abnormal brain imaging (p<0.005), and pneumococcal meningitis and *H. influenzae* type b meningitis (P<0.001). Status epilepticus was noted in 17% of patients with seizures.

DISCLOSURE

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