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Adult Community Acquired Bacterial Meningitis in a Singaporean Teaching Hospital. A Seven-Year Overview (1993-2000)

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ABSTRACT

Background: The objective of this study is to describe the bacteriological, clinical and laboratory features of community acquired bacterial meningitis in adults admitted to a Singapore tertiary-care hospital.

Methods: Two hundred sixty-nine cases of meningitis or meningoencephalitis admitted between 1993 and 2000 were identified by their discharge diagnosis codes. All case records except for 57 which could not be retrieved were retrospectively reviewed. Patients less than 14 years or with skull fractures, post-neurosurgery or with indwelling intracranial devices were excluded. Inclusion criteria was a clinical picture compatible with a diagnosis of bacterial meningitis with either (1) positive cerebral-spinal fluid (CSF) cultures or latex coagglutination or CSF neutrophilic pleocytosis accompanied by positive blood cultures or (2) in the absence of positive blood cultures, CSF cultures and latex agglutination, presence of CSF pleocytosis of at least 100 neutrophils per μL.

Results: Fifteen "culture-positive" and 11 "culture negative" cases were identified. Six (55%) of the "culture-negative" cases received antibiotics prior to admission. Cultures grew *Streptococcus pneumoniae* in four cases, three cases each of *Group B streptococci* and *Neisseria meningitides*. *Listeria monocytogenes* and *Klebsiella pneumoniae* were each seen twice and *Streptococcus suis* once. All cases of *Group B streptococci* occurred in the year 1998. Mortality was 19% (n=5), six developed infections in other sites, three epileptic seizures, three developed hydrocephalus, and two hearing loss.

Conclusions: Pathogens are similar to those reported in other studies but for an outbreak of *Group B Streptococcus* in 1998. There were a high number of "culture-negative" cases which may be due to preceding antibiotic intervention.

Keywords: Adult bacterial meningitis, Community acquired meningitis, South East Asia, Singapore, Coagglutination

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INTRODUCTION

There has been sparse information on the pattern of adult bacterial meningitis in Singapore. Previous studies have combined the data of paediatric and adult patients or have focused on paediatric patients only[1,2]. The etiological agents involved in paediatric and adult meningitis are different and the common etiological agents causing meningitis in Singaporean adult patients are not well known. Such knowledge is essential for rational empirical treatment of this potentially lethal condition. For example, *Listeria monocytogenes* (*L. monocytogenes*), which has become a fairly common cause of adult meningitis in the United States, is resistant to third generation Cephalosporins widely used for empirical treatment of bacterial meningitis[3-5]. Furthermore, cases of penicillin resistant *Streptococcus pneumonia* (*S. pneumonia*) meningitis have been increasingly reported in many countries[6-8].

The etiological agents for community acquired cases of meningitis are also different from hospital acquired cases; in particular those with skull fractures, cranial surgery or implants. The objective of our study was to characterise local adult community acquired bacterial meningitis by retrospectively studying cases admitted to one Singaporean tertiary referral hospital – the National University Hospital (NUH).

METHODS

Case notes of all patients above 14 years of age, admitted to NUH, Singapore, from 1993 till June 2000, with a diagnosis of meningitis or meningoencephalitis were retrospectively reviewed. Cases were identified by their assigned discharge diagnosis codes. This is a public government restructured teaching hospital with 900 in-patient beds. The Department of Medicine treats a yearly average of 8,000 inpatients per annum.

The criteria we used to include cases as bacterial meningitis were:

1. The presence of a clinical picture compatible with a diagnosis of bacterial meningitis with either criterion 2 or 3.
2. i. positive cerebral-spinal fluid (CSF) cultures or latex coagglutination or

ii. CSF neutrophilic pleocytosis accompanied by positive blood cultures.

3. In the absence of positive blood cultures, CSF cultures and latex agglutination, presence of CSF pleocytosis of at least 100 neutrophils per μL.

Patients that developed meningitis after a history of trauma or cranial surgery were also excluded.

Table I. Cases not fulfilling inclusion criteria

Encephalitis	38
Lymphocytic meningoencephalitis/ meningitis (>50% lymphocytes)	30
Post trauma or neurosurgical procedure meningitis	5
Serology positive herpes simplex encephalitis	6
Cryptococcal meningitis	3
Tuberculous meningitis	3
Neutrophilic meningitis (>50% neutrophils but less than 100 neutrophils/1)	2

RESULTS

Numbers reviewed and exclusions

There were 269 cases with diagnosis codes of meningitis or meningoencephalitis between 1993-2000. Fifty-seven of these case records were missing and could not be retrieved. Upon review of the retrieved case records, 87 cases were other forms of meningitis not fulfilling criteria for inclusion as bacterial meningitis. They were either caused by non-bacterial pathogens or in some cases mayhave possibly been partially treated bacterialmeningitis (Table I). Ninety-eight cases did nothave meningitis/meningoencephalitis but were inappropriately coded.

"Culture-positive" and "culture-negative" cases

Twenty-six cases fulfilled our criteria for inclusion as cases of bacterial meningitis. We subdivided them into "culture-positive" and "culture-negative" cases. "Culture-positive" bacterial meningitis was recorded in the presence of a clinical picture compatible with a diagnosis of bacterial meningitis with either positive CSF cultures or CSF neutrophilic pleocytosis accompanied by positive CSF bacterial antigen coagglutination or positive blood cultures. "Culture-negative" bacterial meningitis was scored in the presence of a clinical picture compatible with bacterial meningitis accompanied by CSF pleocytosis of at least 100 neutrophils per μL, negative blood cultures, CSF cultures and latex agglutination. Fifteen cases were "culture-positive" while 11 were "culture-negative".

Bacteriological findings

Among the 15 culture-positive cases, *S. pneumoniae* was the most common isolate (4/15 = 27%), followed by equal numbers of *Group B streptococci* and *Neisseria meningitides* (*N. meningitides*) (each with 3/15 cases = 20%). *L. monocytogenes* and *Klebsiella pneumoniae* (*K. pneumoniae)* each contributed 2/15 (13%) and *Streptococcus suis* (*S. suis*) 1/15 (7%).

Blood cultures were positive in 13 cases while CSF cultures yielded an organism in 6 patients. CSF latex agglutination tests (for *Group B streptococcus*, *N. meningitides, S. pneumoniae and Haemophilus influenzae* (*H. influenzae*)) were performed in 20 cases and were positive in six patients.

One of the *S. pneumoniae* strains was Penicillin-resistant. The minimum inhibitory concentrations (MICs) to Penicillin, Ceftriaxone and Cefotaxime in this case were 1.5 μg/ml, 0.75 μg/ml, 1.5 μg/ml respectively. The patient was successfully treated with two weeks of intravenous vancomycin and oral rifampicin.

No *H. influenzae* meningitis was identified. All three cases of *Group B streptococci* occurred in the year 1998. Both patients with *K. pneumoniae* meningitishad concomitant liver abscesses. Two patients had recurrent episodes of meningitis. Both have negative cultures.

Prior antibiotics in culture-negative cases

Six (55%) of the culture-negative cases were documented to have received antibiotics from primary physicians prior to admission. In addition, all 26 patients underwent neuro-imaging prior to lumbar puncture and had initiation of antibiotics prior to the procedure. Delay in the performance of lumbar punctures of between six hours to two days occurred in four patients. Reasons that contributed to this delay included the wait for neuro-imaging, reluctance of patients and relatives to give consent for the procedure or patients were initially thought to have alternative diagnosis.

Patient characteristics

The age of the 26 patients with bacterial meningitis ranged from 14 to 72, with a median age of 50 years. There were seven females and 19 males. Eighteen patients were ethnic Chinese, three Indians, four Malays and one Vietnamese.

The age range of the four cases with *S. pneumoniae* meningitis was 14 to 67 (ages 14, 46, 60, 62), the three patients with *Group B streptococci* meningitis were between age 35 and 40 (ages 35, 36, 40) while *N. meningitides* cases were between 20 to 64 years of age (ages 20, 50, 64).

Clinical features, morbidity and mortality

On presentation, 18 (69%) patients were febrile, 20 (77%) patients had neck stiffness and 17 (65%)

Table II. NUH meningitis cases.

Case number	Sex	Age	Temp (°C)	Neck stiffness	CSF pressure (CM)	CSF white cells per µl	CSF white cells differentials (%)	CSF Protein (mg/dl)	CSF glucose (Blood glucose) (mmol/l)	CSF Culture	CSF Latex Agglutination	Blood Culture
1	F	14	39.6	yes		4030	P79	1.28	2.8(6.1)	n	n	S. pneumoniae
2	M	23	38.6	yes	29	540	P61L26	0.78	3.4(4.6)	n	n	n
3	F	65	36.7	no		2340	P40L56	2.47	2.8(7.4)	n	n	n
4	F	36	36.8	no	high	3150	P94L4	1.18	3.0(5.1)	Group B strep	Group B strep	Group B strep
5	M	61	37.5	no		380	P93	1.02	5(9.7)	n		n
6	M	50	35.2	yes		2088	P86	6	1.2(9.3)	n	N. meningitidis	n
7	F	46	39.8	yes		300	P60	7.39	0.8(9.8)	n	S. pneumoniae	S. pneumoniae
8	F	45	36.5	no	38	810	P81	1.08	1.2(5.4)	n	n	n
9	M	35	38.5	yes		891	P13L85	1.19	3.2(5.2)	n		Group B strep
10	F	44	40	no	34	433	P38L53	2.63	2.5(7.3)	n	n	n
11	M	64	38	no	26	873	P40	1.91	3.5(7)	n		n
12	M	27	39	yes	26	370	mostly P	2.86	4.5(7)	n	n	n
13	F	64	39.5	yes	42	300	P38L44	3.87	5.3(16.8)	n	n	L. monocytogenes
14	M	42	40.8	yes		136	P24L69	1.92	<0.6(6.4)	L. monocytogenes	n	L. monocytogenes
15	M	60	39.3	yes		13000	P98	6	0.5(6.2)	n	n	S. pneumoniae
16	M	20	febrile	yes	33	1400	P84	1.97	1.1(5.7)	S. pneumoniae	H. influenzae	n
17	M	32	38.7	yes	31	4050	P85L12	3.99	4.5(7.1)	n	n	n
18	M	70	36.7	yes	13.8	1035	P84L16	13.65	10(17.6)	n	n	K. pneumoniae
19	M	62	37.7	yes	18	954	mixed P/L	5.02	0(9.4)	N. meningitidis	S. pneumoniae	S. pneumoniae
20	M	55	38.9	yes	23	25	P94L5	1.94	0.1(5.4)	n		S. suis
21	M	71	37.6	yes	23	216	mostly P	20	4.8(12.8)	n		n
22	M	40	36	yes	22	28	P88L14	>12	<0.6(11.2)	Group B strep	Group B strep	Group B strep
23	M	47	39.6	yes		244	P50L46	15.7	0.8(15)	n	n	n
24	M	59	37.8	yes	19	133	P84L2	14	6.5(13.3)	n	n	K. pneumoniae
25	M	72	35	yes	low	3645	P82L19	0	5.3(14)	n		n
26	M	64	38.6	yes		1210	P90L8	8.4	2.1(7.7)	n	n	N. meningitidis

P: polymorphs, L: lymphocytes, L: Listeria S: Streptococcus, strep: streptococci, N: Neisseria, H: Haemophilus, K:Klebsiella

patients had both. At least one epileptic seizure (not further classified) occurred in three patients (12%) during the course of their illnesses. One patient with *Group B streptococci* and another with *S. pneumoniae* developed significant permanent hearing loss. Two *L. monocytogenes* and three "culture-negative" meningitis died (age range: 42-72). In six patients, coexisting other sites of infection were identified: four with pneumonia, and two with liver abscesses. One patient with meningococcal meningitis developed arthritis.

Computed Tomography (CT) brain scanning

All 26 patients had CT brain prior to lumbar puncture. three patients were noted to have hydrocephalus in the initial CT scans. These were a case of *L. monocytogenes* (case no.14), a case of *S. pneumoniae* (case no. 19) and a "culture negative" case (case no. 23). All three cases had impaired consciousness and were non-communicative at the time of the imaging. The patient with *L. monocytogenes* had documented localising neurological signs and was the only patient that required surgical shunting. The *L. monocytogenes* and the "culture negative" patients eventually died.

One CT showed an incidental pituitary adenoma. No fresh cerebral infarctions, abscesses or mastoiditis were found.

CSF findings

CSF opening pressure was measured in 18 of the 26 cases. Pressure was elevated above 20 cm H_2O in 13 (72%). In two patients, pressure was between 15-20 cm H_2O while in three, pressure was below 15 cm H_2O.

Nineteen of 26 patients had CSF glucose level less than 50% of concomitant blood glucose level and CSF protein levels were raised (>0.4 mg/dl) in 25 of 26 samples.

Eighty percent of culture-positive cases had more than 50% CSF neutrophilia. Five patients, however have predominant CSF lymphophilia. They were a case of *Group B streptococcus,* both cases of *L. monocytogenes* and twoculture-negative cases.

CSF Latex agglutination tests

CSF latex agglutination tests (for *Group B streptococcus*, *N. meningitides, S. pneumoniae* and *H. influenzae)* were performed in 20 cases and were positive

in six patients. CSF latex agglutination tests were positive in two of the four *S. pneumoniae* cases, both of the *Group B streptococcus* cases and were negative in both the *N. meningitides* cases with positive cultures. In one case, CSF culture grew *N. meningitides* but cross reactivity resulted in a false positive latex agglutination test for *H. influenzae*. In another, latex agglutination test identified *N. meningitides* when both CSF and blood cultures were negative.

DISCUSSION

Low yield of cultures

The most striking feature of this study is the high rate (42%) of cases with no identifiable pathogen. Two of the largest studies on acute adult bacterial meningitis show far lower rates of culture negativity at 11 - 15%[5,9]. The cause of this is not immediately clear. A recent Iranian study reported an even lower rate of pathogen detection (28%) probably explained by the administration of antibiotics prior to hospitalisation[10]. In this study, nearly 50% of culture-negative cases had been given pre-hospitalisation antibiotics[10]. In our series, 55% of the culture-negative cases had antibiotics prior to admission. In addition, all patients hadantibiotics initiated prior to neuro-imaging and lumbar puncture. Thus, prior administration of antibiotics is likely to be a factor in our low rate of pathogen detection.

Pathogens

Our study identified *S. pneumoniae*, *N. meningitides* and G*roup B streptococcus* as the three most common pathogens in local adult community acquired meningitis. Other studies on community acquired adult bacterial meningitis also found *S. pneumoniae* and *N. meningitides* as the most commonly encountered pathogens[5,9]. G*roup B streptococcus* meningitis, however, is an unusual cause of adult community acquired bacterial meningitis. It was noted that all three cases were isolated in the year 1998. An increase in the number of this unusual disease in adults was also noted in another local hospital and a hospital in Hong Kong that year but not in the following two years, suggesting the presence of an outbreak of undetermined cause[11].

One case of *S. suis* meningitis was encountered. This is a porcine organism that causes disease mainly among people with occupational exposure to pigs or pork[12-14]. A history of skin injury is also common. There is a strong likelihood of acquiring permanent hearing loss as a result of this disease [12]. The majority of reported cases have come from Northern Europe and from Southeast Asia. Our patient had no exposure to pigs, history of skin injury or travel to other countries. He was also fortunate in not having hearing loss.

The finding of a case of Penicillin-resistant *S. pneumonia* (PRSP) meningitis confirms the relentless global increase in resistance observed in this organism[3, 6, 15, 16]. The prevalence of PRSP needs to be studied and monitored as high prevalence would influence the choice of antibiotics for initial empiric treatment.

The rates of meningitis due to *L. monocytogenes* and Gram-negative organisms in our study are similar to those in the literature[5,9]. Both cases of *L. monocytogenes* were noted in the year 2000. The pathogen should be considered in the elderly and the immmunocompromised. Due to the increasing frequency of *L. monocytogenes* in adult community acquired bacterial meningitis[17-19], empirical treatment should include Ampicillin, as the organism is resistant to the commonly used Cephalosporins[18].

Clinical features, laboratory tests, morbidity and mortality

The clinical features and CSF findings of our patients were typical of bacterial meningitis. The majority had fever, neck stiffness, elevated CSF opening pressure, low CSF glucose levels, raised CSF protein levels and CSF neutrophilia (see Table I). The fact that some cases of bacterial meningitis can have CSF lymphophilia is also illustrated by five cases (cases 3, 9, 10, 13, 14).

The mortality rate of 19% appears slightly lower than some other studies (20-25%)[5, 9]. However, it should be noted that we have excluded patients with a history of trauma or cranial surgery who are more likely to have complications. The five patients who died were two cases of *L. monocytogenes* and three "culture-negative" meningitis. Delay in use of appropriate antibiotics may have contributed to the poor outcome in the two cases of *L. monocytogenes* who received the appropriate antibiotics only three to four days after hospitalisation.

Several studies have found CSF coagglutination tests to be sensitive and specific when compared with cultures[20, 21]. Based on our results, coagglutination tests appear to identify G*roup B streptococcus* reliably (positive in both cases) but is less so in identifying *S. pneumonia* cases (positive in two of four cases). The tests were negative in both the culture positive *N. meningitides* cases. The test's main advantage is allowing earlier identification of pathogens then cultures and may also supply additional etiological information when cultures are negative (e.g. case 6).

CT brain scanning was mainly used to exclude raised intracranial pressure. This reflects a growing lack of confidence and experience in clinical methods of detecting raised intracranial pressure. Apart from

this, CT brain scanning served the function of searching for a portal of entry (none found in our series) and excluding other possible diseases and complications.

In summary, our study of community acquired meningitis in adults show nearly half the cases to be culture-negative, probably due to preceding antibiotics intervention. The spectrum of isolated pathogens as well as the associated morbidity and mortality was similar to that of previous studies.

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