Etiology and occurrence of acute bacterial meningitis in children in Benghazi, Libyan Arab Jamahiriya

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سببيات التهاب السحايا الجرثومي الحاد وحدوثه بين الأطفال في بنغازي، الجماهيرية العربية الليبية

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خلاصة: على مدى أربعة عشر شهراً تم استقصاء حالات 77 من الأطفال ذوي التشخيص الظني لالتهاب السحايا الجرثومي الحاد. وتبين أن معدل وقوع هذا الالتهاب يبلغ 0.8%، بينما بلغ معدل إماتة الحالات 13.0%. وارتفعت معدلات الإصابة بين الأطفال البالغين من العمر سنة أو أقل (64.9%). وكانت النسبة بين الذكور وبين الإناث من المرضى 1:1.2. واكتشفت بالتلوين بطريقة غرام حالات (85.7%) أكثر مما كشف عنه زرع العينات (66.2%). وقد تم استعراف 48 من المستفردات المعزولة من المستنبتات، وحددت حساسيتها للمضادات الحيوية. وكانت أكثر الجراثيم التي تم التعرف عليها هي المستدميات النزلية (33.8%) ثم العقديات الرئوية (26.0%) ثم الكلبسيلات (6.5%) والنسيريات السحائية (2.6%). وكان كثير من المستفردات الجرثومية حساسة للجنتاميسين والسيفوتاكسيم، والسيفترياكسون، وأقل حساسية للتتراسيكلين والأمبيسيلين.

ABSTRACT Over a 14-month period, 77 children with a presumptive diagnosis of acute bacterial meningitis were investigated. The incidence of acute bacterial meningitis was 0.8%, with a case fatality rate of 13.0%. Children ≤ 1 year of age were more affected (64.9%). The total male to female ratio was 1.2:1. Gram stain detected more cases (85.7%) than culture (66.2%). A total of 48 isolates were identified by culture and their antibiotic sensitivity was determined. *Haemophilus influenzae* (33.8%) was the predominant organism identified, followed by *Streptococcus pneumoniae* (26.0%), *Klebsiella* spp. (6.5%) and *Neisseria meningitidis* (2.6%). Many of the bacterial isolates were sensitive to gentamicin, cefotaxime and ceftriaxone and least sensitive to tetracycline and ampicillin.

Etiologie de la méningite bactérienne aiguë et survenue de cas chez des enfants à Benghazi (Jamahiriya arabe libyenne)

RESUME On a procédé, sur une période de 14 mois, à l'examen de 77 enfants pour lesquels un diagnostic de présomption de méningite bactérienne aiguë a été posé. L'incidence de la méningite bactérienne aiguë était de 0,8% avec un taux de létalité de 13,0%. Les enfants âgés de moins d'un an ou d'un an étaient plus touchés (64,9%); le rapport global garçon/fille était de 1,2:1. Davantage de cas (85,7%) ont été détectés avec la coloration de Gram qu'à la culture (66,2%). Au total, 48 isolats ont été identifiés par la culture et leur sensibilité aux antibiotiques a été déterminée. *Haemophilus influenzae* (33,8%) était l'organisme principalement identifié, suivi par *Streptococcus pneumoniae* (26,0%), *Klebsiella* spp (6,5%) et *Neisseria meningitidis* (2,6%). De nombreux isolats bactériens étaient sensibles à la gentamicine, au céfotaxime et à la ceftriaxone et moins sensibles à la tétracycline et à l'ampicilline.

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Introduction

Bacterial meningitis is an important serious illness worldwide. Prior to the introduction of antibiotics in the 1940s, case fatality rates for epidemic and endemic bacterial meningitis exceeded 70%. Since then, antibiotic use has reduced case fatality rates for meningitis caused by most bacteria to 25% or less, but no further reduction has been documented in the past 20 years. Despite advances in vaccine development and chemoprophylaxis, bacterial meningitis remains a major cause of death and long-term neurological disabilities, such as mental retardation, convulsions and hydrocephalus. These are best prevented by early diagnosis and appropriate treatment of the disease.

Haemophilus influenzae, *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most common causes of bacterial meningitis in children [*1*]. The prevalence of these organisms varies from place to place, by age and by season [*1*], but *N. meningitidis* is more often the commonest cause of meningeal infection [*2*] with *S. pneumoniae* [*3*] and *H. influenzae* [*4*] being second and third respectively.

Meningitis is a serious emergency in which the microbiological laboratory plays a critical role in the early identification of the causative bacterium and its antibiogram. However, it is usual practice to start antibiotic therapy before the complete laboratory result is available [*5*]. Such blind prescription requires knowledge of the most frequent etiological agents of meningitis in the local population. The antibiotic sensitivity patterns and the seasonal incidence of these isolates will help to influence the choice of initial therapy before a sensitivity result is available and in areas where laboratory facilities may not be available.

The present study was undertaken to establish the bacteriological profile and antibiogram of the isolates of bacterial meningitis in children in Benghazi in order to reduce morbidity and mortality among such cases.

Materials and methods

Seventy-seven (77) paediatric patients clinically suspected of having pyogenic meningitis were included in the study. They were admitted to Al-Fateh Children's Hospital, a teaching unit of the Faculty of Medicine, Al-Arab Medical University, Benghazi, during the period from April 1994 to May 1995. Information obtained at the time of admission included age, sex, race, period of illness, antibiotic intake before admission and clinical symptoms and signs at the time of admission and while the child was in hospital.

After admission, 2–3 ml of cerebrospinal fluid (CSF) were collected aseptically by lumbar puncture in two separate sterile test tubes. The last drops of CSF, before removing the lumbar puncture needle, were inoculated onto blood agar and chocolate agar at the bedside and incubated aerobically in a candle jar at 37 °C immediately. A drop of CSF was also placed on a dry, clean glass slide and fixed by flaming, ready for Gram staining. One of the two specimens from each patient was sent to the bacteriological laboratory for culture, Gram staining and latex agglutination tests. The second was used for cytology and for protein and sugar estimations. Blood cultures were done for each patient on admission and 2–3 ml of serum were also obtained at the time of admission and discharge (convalescence) of each patient for estimation of C-reactive protein.

Bacteriological studies on the CSF were performed in the Department of Microbiology and Parasitology, Al-Arab Medical

University, Benghazi. On receipt, each specimen was centrifuged at 1000 rpm for 5 minutes. The supernatant was removed aseptically into a separate tube and used for latex agglutination tests for the detection of bacteriological antigens, using Slidex meningite kit-5 (bioMérieux, France). The sediment was cultured using standard techniques and also used for Gram staining. All isolates were identified on the basis of their colony, morphology and culture characteristics, and their biochemical reactions according to standard procedures. Isolates were also tested for their antibiotic sensitivity by the disk diffusion technique of Kirby and Bauer using *Staphylococcus aureus* (ATCC no. 25923) and *Escherichia coli* (ATCC no. 25922) as control strains; 11 antibiotic disks were used.

Table 1 **Results of the various methods used to identify the etiological agents of 77 cases of bacterial meningitis**

Test	Positive		Negative	
	No.	%	No.	%
Gram staining	66	85.7	11	14.3
C-reactive protein (> 20 mg/l)	50	64.9	27	35.1
CSF culture	48	62.3	29	37.7
Blood culture	45	58.4	32	41.6
Latex agglutination (meningitis kit)	41	53.2	36	46.8
CSF sugar content (< 40 mg/dl)	77	100.0	0	–
CSF leukocyte count (> 1000 cells/ml)[a]	77	100.0	0	–

df = 4, $\chi^2 = 18.1962$, P < 0.005
[a] Not included in the analysis for χ^2

Results

The sex distribution and case fatality among the 77 bacterial meningitis cases in the children were studied; the male to female ratio was 1.2:1 and the case fatality rate (10 deaths) was 13.0%.

Gram-stained smears identified more etiological agents than culture (Table 1) in the clinically suspected cases of bacterial meningitis (statistically significant at $P < 0.001$). Clinically diagnosed pyogenic meningitis correlated biochemically and cytologically. There was an increase in the protein level and decrease in sugar levels in the CSF of all 77 cases with polymorphonuclear leukocytosis predominant in all cases.

Table 2 shows the etiological agents identified by combining Gram stain, latex agglutination tests and culture of CSF specimens. Among the identified etiological agents, *H. influenzae* was the predominant agent (33.8%) followed by *S. pneumoniae* (26.0%), and *Klebsiella* spp. (6.5%). A higher proportion of *H. influenzae* infection was observed in children <1 year of age (88.5%) than children >1 year compared with other organisms ($\chi^2 = 9.5423$, $P < 0.005$) (Table 3).

Culture of CSF was found to be positive in 62.3% of cases. Table 4 shows the antimicrobial sensitivity pattern of these isolates. The majority of isolates were highly sensitive to cefotaxime, ceftriaxone (the third-generation cephalosporins tested), gentamicin, amikacin and augmentin, and least sensitive to tetracycline and ampicillin.

Discussion

Over the same period of the present study (April 1994 to May 1995), 10 081 patients were admitted to Al-Fateh Children's Hospital, out of which 77 were diagnosed as

Table 2 **Etiological organisms identified from 77 cases of meningitis**

Organisms identified	Culture, Gram stain or latex agglutination		Culture only	
	No.	%	No.	%
Gram-positive (36.7%)				
Streptococcus pneumoniae	20	26.0	17	22.1
S. pyogenes	1	1.3	1	1.3
Diphtheroids	1	1.3	1	1.3
Gram-negative (63.3%)				
Haemophilus influenzae	26	33.8	18	23.4
Klebsiella spp.	5	6.5	5	6.5
Neisseria meningitidis	2	2.6	1	1.3
Non-typohoid salmonellae	2	2.6	2	2.6
Escherichia coli	1	1.3	1	1.3
Proteus spp.	1	1.3	1	1.3
Acinetobacter spp.	1	1.3	1	1.3
Unidentified	17	22.1		

Table 3 **Distribution by age and causative organism of 77 cases of meningitis**

Age (years)	Total (n = 77) No.	%	*H. influenzae*	*S. pneumoniae*	*N. meningitidis*	Others	Unidentified
<1	50	64.9	23	10	1	9	7
1–2	11	14.3	2	4	0	2	2
>2–5	6	7.8	1	3	0	0	2
>5	10	13.0	0	3	1	1	6
Total	77	100.0	26	20	2	12	17

df = 4, $\chi^2 = 13.3238$, $P < 0.01$

bacterial meningitis. This constitutes a prevalence rate of 0.8% of the total admissions and around 2.6 cases per 100 000 of the Benghazi population. These figures may be reasonably accurate for the city since there is only one central hospital which deals with paediatric patients, and all child cases requiring special attention, such as suspected meningitis, are referred to this hospital. This figure is within the annual pathogen-specific rates reported around the world which range from 0.1 to 10 cases per 100 000 population [*6*].

The majority of our cases were found in children of ≤ 1 year (64.9%) (statistically significant as $P < 0.01$), which concurs with the findings of other authors [*1,7*]. In this age group, there were more male children affected than females (male to female ratio of 1.8:1). Other authors have made similar observations [*1,6,7*].

The case fatality rate among the 77 cases was 13.0% despite treatment. Although

Table 4 **Antibiotic sensitivity of isolates from cases of meningitis**

Antibiotic	Gram-positive organism		Gram-negative organism			
	S. pneumoniae (n = 17)		*H. influenzae* (n = 18)		*Klebsiella* spp. (n =5)	
	No.	%	No.	%	No.	%
Amikacin (30 mg)	16	94	17	94	5	100
Ampicillin (2 mg)	15	88	14	77	1	20
Augmentin (30 mg)	16	94	17	94	4	80
Cefotaxime (5 mg)	17	100	18	100	4	80
Ceftriaxone (30 mg)	17	100	18	100	4	80
Chloramphenicol (30 mg)	17	100	16	89	2	40
Ciprofloxacin (5 mg)	16	94	16	89	4	80
Gentamicin (5 mg)	17	100	18	100	4	80
Kanamycin (5 mg)	17	100	15	83	3	60
Penicillin (10 mg)	14	82	NT	–	NT	–
Tetracycline (30 mg)	15	88	9	50	2	40

NT = not tested

lower mortality rates have been reported in industrialized countries such as the United States of America (2.6%) [*8*], higher rates have been reported in some developing countries and countries in the Middle East, such as Turkey (38%) [*9*], Saudi Arabia (14.7%) [*10*], Sudan (28.6%) [*11*] and India (21.8%) [*12*]. Of the developing countries, the case fatality rate of 13.0% in the Libyan Arab Jamahiriya is not the highest among the world reports.

The predominance of Gram-negative organisms reported as etiological agents of bacterial meningitis [*13*] was also seen in our study, where Gram-negative bacteria were isolated from 63.3%, while Gram-positive bacteria were found only in 36.7% of the cases.

The incidence of specific pathogens causing bacterial meningitis varies around the world [*1,14–20*] as shown in Table 5. In our study the predominant organism isolated was *H. influenzae* (33.8%), followed by *S. pneumoniae* (26.0%). *N. meningitidis* caused only 2.6% of the total number of pyogenic meningitis cases. Similar findings have been reported from Benghazi in a previous study [*19*] and from other parts of the world, although in many other reports *N. meningitidis* was more common (Table 5). This is probably due to the endemicity of the organism and to the larger number of cases that may be involved in epidemic situations.

Laboratory investigations of CSF specimens in suspected acute meningitis are extremely important for prompt recognition of the nature of the infecting organism as management and therapy of the patient depend on this information. Another test of value is the raised levels of C-reactive protein in CSF of patients with bacterial meningitis as opposed to viral meningitis. In our study, 50 cases of bacterial meningitis (confirmed microscopically and/or by culture) had C-reactive protein levels > 20 mg/l. The simple Gram-stain smear of CSF is reported to be the most useful single

Table 5 **Percentage of occurrence of major pathogens in childhood bacterial meningitis from various studies**

Country	Year	Reference	*H. influenzae*	*S. pneumoniae*	*N. meningitidis*	Others and unidentified
Chad	1968–71	14	2	5	81	12
United Kingdom	1969–73	15	33	11	45	11
Dakar, Senegal	1970–79	14	27	39	15	19
Zaria, Nigeria	1970–79	16	9	11	57	23
Blantyre, Malawi	1972–73	17	36	30	19	15
Cairo, Egypt	1977–78	18	15	49	21	15
Benghazi, Libyan Arab Jamahiriya	1978–80	19	39	24	12	25
United States of America	1978–81	1	48	13	19	20
India	1989–90	12	51	27	2	20
Saudi Arabia	1990–91	20	36	26	3	35
Sudan	1994–95	20	38	23	38	1
Present study (Benghazi)	1994–95		33.8	26	2.6	37.6

test for identifying bacterial meningitis [*7,12,21*]. In this study, Gram staining revealed the probable etiological organisms in 85.7% of cases, while only 72.7% were positive by either CSF and/or blood culture. This confirms the value of the Gram stain as a presumptive diagnostic aid. Bacterial antigens of the primary causative agents of childhood meningitis, namely those of *N. meningitidis*, *S. pneumoniae* and *H. influenzae* type b, can be detected in the CSF using commerically available kits. In our study, simple latex agglutination tests for these pathogens in the CSF detected 41 cases of 48 cases that were positive by CSF culture (85.4%).

Culture of CSF and blood by the bedside was positive in 62.3% and 58.4% of cases respectively. Thus the simple Gram stain combined with the latex agglutination test will help give a rapid diagnosis of bacterial meningitis, and may indicate the most probable causative organisms in more than 85% (66/77) of cases before culture results are available. This is extremely important in the rapid management of such cases [*7,12,21*]. However, culture remains important in assessing the antibiotic susceptibility pattern of the causative organisms.

It is worth noting that 22% of bacterial meningitis cases (17 out of 77 cases) had an unidentified etiology (Table 2), which has also been observed by other workers. This is not likely to be the result of prior antibiotic therapy as many think, since it was reported even before the antibiotic era [*22*]. Some of these cases may be caused by *N. meningitidis*, which is known in some cases to show a lack of organisms in smears, CSF and blood cultures, and even in antigen detection tests [*22*]. The devel-

opment of new and very sensitive tests may throw light on this group.

The antimicrobial sensitivity pattern of our isolates showed that all Gram-positive, and many of the Gram-negative organisms were 100% sensitive to gentamicin and the third generation cephalosporins (cefotaxime and ceftriaxone). Ampicillin and tetracycline were the least effective. These findings are in accordance with the findings of other investigators [*7,19,23*]. There is increasing resistance among the major pathogens which cause meningitis to most of the traditional antimicrobial agents used as initial therapy prior to the availability of bacteriological results. A high percentage of ampicillin-resistant (23%) and chloramphenicol-resistant (11%) *H. influenzae* were isolated in the present study. Similar findings have been observed by other workers [*19,24*]. This resistance was mainly due to the production of β-lactamase against ampicillin and transferases against chloramphenicol. Tests for the production of β-lactamase and transferases were not done in our study as the materials were not available. The standard antibiotic therapy, using ampicillin and chloramphenicol before the bacteriological report reaches the paediatrician, may need to be modified. In our study, we found that the majority of isolates were highly sensitive to cefotaxime and ceftriaxone. Recently, ceftriaxone was used as the drug of choice in many centres in treating bacterial meningitis, especially with *H. influenzae* type b infection [*23,25, 26*]. As well as having a broad spectrum of activity, ceftriaxone has excellent penetration into the CSF with a ratio of achievable CSF concentration to minimum inhibitory concentration levels in the range of 100:1 [*27*]. A ratio greater than 10:1 has been suggested as the most critical determining factor for the success of therapy [*28*].

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