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Bacterial Agents of Meningitis in Children and Detection of Their Antibiotic Resistance Patterns in Hamadan, Western Iran

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Abstract: Bacterial agents of meningitis in children and detection of their antibiotic resistance patterns in Hamadan, Western Iran. Bacterial meningitis is still one of the most dangerous infection diseases and causes serious complications in children. The aim of present study was to identify the most common of bacteria causing meningitis in children under 10 years of age and detection of their resistance to routine antibiotics in Hamadan. Overall 582 children suspected to meningitis were investigated for CSF cultures, elevation of CSF leukocyte count and clinical manifestations, from January 1998 to December 2002 in two hospitals. The required data of patients were gathered through a questionnaire and analyzed using Epi6 system. The species were identified by biochemical and latex-agglutination tests. Antibiogram tests were also performed by gel-diffusion method of Kirby-Bauer. Out of 582 children suspected to meningitis, 146 children (25.1%) had positive bacterial culture that %58.9 of isolates was Gram-positive cocci and %41.1 was also Gram-negative bacteria. The most common isolates were *Streptococcus pneumonia* (23.9%), *Staphylococcus aureus* (13.1%), *Escherichia coli* (10.9%), *Neisseria meningitides* (6.2%) and *Haemophilus influenzae* type b (4.1%). The most effective antibiotics against isolates were ceftizoxime, kanamycin and gentamicin while most of isolates showed high resistance to ampicillin, amoxicillin, sulfamthoxazole-trimethoprim and chloramphenicol. The present study showed that Gram-positive bacteria in particular, *S. pneumoniae* and *S. aureus* are predominant causes of bacterial meningitis in children involved in this region. Most species showed high resistance to routine antibiotics such as amoxicillin, ampicillin and chloramphenicol. The antimicrobial susceptibility pattern for bacteria causes meningitis may provide a guideline for the selection of appropriate drug treatment.

Key words: Bacteria, meningitis, children, antibiotic resistance

INTRODUCTION

Bacterial meningitis is one of the most potentially serious infections in infants and older children because it is associated with a high rate of acute complications (Feigin and Pearlman, 2004; Prober, 2004). Meningitis is considered as an endemic disease in our country. Bacterial meningitis usually is the first causes of meningitis in infants and children in this region (Borjian, 1999).

The incidence of bacterial meningitis in children aged <5 years and 5<or = <10 years in Hokkaido, Japan between 1999 and 2003 was 6.3 and 0.7 cases per 100,000 children/year (Sakata, 2005). Bacterial meningitis affected almost 6000 people every year in the United States and about half of all cases occurred in children 18 years old or younger (Schuchat *et al*., 1995). The incidence of pneumococcal meningitis in North Yorkshire, England, between 1997 and 2002, accounted for an incidence of 1.1 per 100,000 per year that mortality was 28% (Weightman and Sajith, 2005).

Etiologic agents of bacterial meningitis are variable and usually depend to time, geographical location and age of patients. There are three main organisms that account for over 90% of the world's cases of meningitis (Davey *et al*., 1982; Bedford *et al*., 2001). These are *Haemophilus* (*H*.) *influenzae* type b, *Neisseria* (*N*.) *meningitidis* and *Streptococcus* (*S*.) *pneumoniae*. However, other bacteria such as *Staphylococcus* (*S*.) *aureus, Streptococcus* (*S*.) *agalactiae, Escherichia* (*E*.) *coli, Pseudomonas* (*P*.) *aeruginosa* and *Klebsiella* (*K*.) *pneumonia* could be rarely caused of meningitis (Al-Mazrou *et al*., 2004; Foster and Rhoney, 2005). In a study from Egypt, the causes of bacterial meningitis in 310 children were *H. influenzae* 21%, *S. pneumoniae* 13.9% and *N. meningitidis* 14.2% (Farag *et al*., 2005). In

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other study from the United State revealed the most common isolated bacteria from newborns was *H. influenzae* type b, *S. pneumoniae* and *N. meningitides*, respectively (Wenger *et al*., 1990). Before the 1990, *H. influenzae* type b was the leading cause of bacterial meningitis, but new vaccines being given to children as part of their routine immunizations have reduced the occurrence of serious *H. influenzae* type b disease (Gessner, 2002; Prober, 2004). Today, *N. meningitidis* and *S. pneumoniae* are the leading causes of bacterial meningitis (King and Richmond, 2004; Faye *et al*., 2005).

Because of the major increasing of antibiotic resistance in bacteria causing bacterial meningitis in the last few years, attempts have been made to organize an appropriate antibiotic treatment regime with combination of synergistic antibiotics (Erdem and Pahsa, 2005; Saha *et al*., 2005; Prober, 2004). Therefore, the purpose of this study was to describe the frequency of etiologic agents of bacterial meningitis among children under 10 years of age in a sample of patients in the west of Iran, with emphasis on the frequency of bacterial meningitis of unusual etiology and detection of drug resistance of isolated bacteria from patients with bacterial meningitis.

MATERIALS AND METHODS

A cross-sectional and prospective descriptive study was conducted on children under 10 years of age who were suspected to bacterial meningitis and admitted in the pediatric department of two hospitals (Sina and Ekbatan) in Hamedan, the west of Iran between January 1998 and December 2002. Active surveillance for cases of bacterial meningitis among the study population, which comprised 582 children, was implemented. The required data of the patients including clinical manifestations, patient demographics (age, sex and season) and types of microorganisms isolated from Cerebrospinal Fluid (CSF), were recorded in a special questionnaire and then analyzed using EP1 INFO 6 software package.

After the establishing of indication, lumbar punction was performed. CSF was sent to cytological, biochemical and bacteriological analyses. Diagnosis of meningitis was established when at least three criteria of four were fulfilled: (1) isolation of bacterial pathogens by CSF culture and identification of bacteria; (2) elevation of CSF leukocyte count more than 20 with predominance of polymorphonuclear leukocytes; (3) hypoglucorrhachia (glycaemia less than 40% mg or less than 50% of glycaemia); (4) clinical manifestations including fever, consciousness, neck stiffness and sign of mental irritation. The sampling of CSF of each patient was done to culture at two times to make sure of growing any pathogenic microorganisms. The etiologic diagnosis was based on either stained-smears (Gram) of CSF sediment, culture and latex-agglutination test.

Cultivation and isolation of organisms were performed according to the methods outlined in the Bailey and Scott's Diagnostic Microbiology (Forbes *et al*., 2002). The sediment of spinal fluid was prepared for providing the smear and cultures. Specimens were then cultured on appropriated culture media including Thayer-Martine agar, Eeosin Methylen Blue (EMB) agar and Blood agar (Merck, Germany). The cultures were incubated in 37°C for 24-48 h and then the colonies were removed for further studying. Biochemical and antigenic properties of isolates were verified for identification purposes. In essential cases, specific antiserum against bacteria was used for precise identification of bacteria type (Koneman *et al*., 1997).

In order to detection of the susceptibility of isolates to routine antimicrobial drugs, the all isolates were tested by disc diffusion (Kirby-Bauer) method (Bauer *et al*., 1986). Eight antibiotics including amoxicillin (AMX), ampicillin (AM), chloramphenicol (CH), cephalexin (CF), ceftizoxime (CT), gentamicin (GM), kanamycin (KA) and sulfamthoxazole trimethoprim (SXT) were applied. Results were then collected and analyzed.

RESULTS

Out of 582 children less than 10 years suspected to meningitis, only 146 children (25.1%) had positive bacterial culture that 58.9% of isolates was Gram-positive cocci and 41.1% was also Gram-negative bacteria. The most common isolates of Gram-positive cocci were as follow: *S. pneumonia* (23.9%), *S. aureus* (13.1%), *S. agalactiae* and *Staphylococcus* (*S.*) *epidermidis* each 13 cases (8.9%). The most common isolates of Gram-negative bacteria were: *E. coli* (10.9%), *N. meningitidis* and *P. aeruginosa* each 9 cases (6.2%) and *H. influenzae* type b (4.1%). Frequencies of the all isolated bacteria from patients with bacterial meningitis are shown in Table 1.

Fever (88.3%), Leukocytosis (74.6%), nausea and vomiting (67.1%), sleepness (66.4%) and headache (46.6%) were most common clinical manifestations of meningitis in children under 10 years of age with bacterial meningitis. Frequencies of clinical manifestations of patients are shown in Table 2.

Of 146 patients with bacterial meningitis, 79 cases (54.2%) were males and 67 cases (45.8%) were females. The frequencies of age groups of patients with bacterial meningitis are shown in Table 3, the most frequent patients were belonged to the 0-2 years old (28.3%) and the least frequent patients were belonged to the 8-10

Table 1: Frequencies of microorganisms isolated from patients with bacterial meningitis

Isolate	Frequency of isolates	Percentage
Streptococcus pneumonia	35	23.9
Staphylococcus aureus	19	13.7
Escherichia coli	16	10.9
Streptococcus agalactiae	13	8.9
Staphylococcus epidermidis	13	8.9
Neisseria meningitides	9	6.2
Pseudomonas aeruginosa	9	6.2
Citrobacter freundii	7	4.8
Klebsiella pneumonia	7	4.8
Haemophilus influenzae	6	4.1
Enterococci spp.	3	2.1
Proteus spp.	3	2.1
Unknown	6	4.1
Total	146	100

Table 2: The frequencies of clinical manifestations of the patients with bacterial meningitis

Symptoms	Frequency	Percentage
Fever	129	88.3
Leukocytosis	109	74.6
Nausea and vomiting	98	67.1
Sleepiness	97	66.4
Headache	68	46.6
Hydrocephalus	59	40.4
Neck stiffness	55	37.6
Irritability	52	35.7
Anorexia	51	34.9
Confusion	48	32.9
Feeding poorly	46	31.8
Sensitivity to light	34	23.3
Dyspnea	11	16.4
Seizures	10	6.8

Table 3: The frequencies of the age groups of patients with bacterial meningitis

Age groups	Frequency	Percentage
0-2 years old	41	28.3
2-4 years old	35	23.9
4-6 years old	22	15.2
6-8 years old	29	19.6
8-10 years old	19	13.1
Total	146	100

Table 4: Antibiotics resistance patterns of isolated bacteria from patients with bacterial meningitis

	Frequencies of resistance to antibiotics (%)							
Isolate	SXT*	KA	GM	CT	CF	CH	AM	AMX
Streptococcus pneumonia	27	9	0	0	18	36	63	54
Staphylococcus aureus	68	48	16	33	48	84	100	84
Escherichia coli	44	25	13	0	38	38	57	19
Streptococcus agalactiae	47	0	23	23	0	70	23	0
Staphylococcus epidermidis	70	23	31	39	54	77	100	85
Neisseria meningitides	0	0	0	0	33	33	55	33
Pseudomonas aeruginosa	100	33	33	66	100	66	100	100
Citrobacter freundii	72	58	43	58	43	72	85	100
Klebsiella pneumonia	43	29	29	15	29	85	100	58
Haemophilus influenzae	50	0	0	0	0	0	50	50

*: SXT = Sulfamthoxazole-trimethoprim, KA = Kanamycin, GM = Gentamicin, CT = Ceftizoxime, CF = Cephalexin, CH = Chloramphenicol, AM =Ampicillin, AMX = Amoxicillin

years old (13.1%). Present results showed that the most frequent bacterial meningitis (43.7%) was occurred during fall and then winter with frequency of 27.6% and summer 14.8%. The lowest frequency (13.9%) was belonged to winter.

As it is observed (Table 4), the most effective antibiotics against both Gram-negative bacteria and gram-positive cocci were ceftizoxime, kanamycin and gentamicin while most of isolates showed high resistance against ampicillin, sulfamthoxazole-trimethoprim, chloramphenicol and amoxicillin. *P. aeruginosa*, *S. aureus*, *S. epidermidis* and *K. pneumonia* showed the highest resistance to many of antibiotics applied in this study. *P. aeruginosa* showed hundred percent resistances to four antibiotics including ampicillin, sulfamthoxazole-trimethoprim, cephalexin and amoxicillin. *S. aureus*, *S. epidermidis* and *K. pneumoniae* were also resistant (100%) to ampicillin. However, *S. pneumonia*, *S. agalactiae*, *N. meningitidis* and *H. influenzae* type b, showed low or moderate resistance to antibiotics used in this study. *S. pneumonia*, *N. meningitidis* and *H. influenzae* type b showed no resistance (0%) to ceftizoxime and gentamicin, they were sensitive to antibiotics of aminoglycosides groups including kanamycin and gentamicin and group of cephalosporines including cephalexin and ceftizoxime.

DISCUSSION

Knowing whether a virus causes meningitis or bacterium is important because the severity of illness and the treatment differ. Most researchers have demonstrated that *H. influenzae* type b; *S. pneumonia* and *N. meningitidis* are as main agents of bacterial meningitis especially in children (Ignjatovic, 2001; Bedford *et al*., 2001). In this study, *S. pneumoniae*, *S. aureus* and *E. coli* have been the most important causes of bacterial meningitis in involved children (Table 1). Nonetheless a considerable percentage was attributed to other unusual bacteria, which may be *K. pneumoniae*, *P. aeruginosa* and *Citrobacter* (*C.*) *freundii* and others as shown by Gebremariam in Addis Ababa (Gebremariam, 1998). However, in India, a low incidence of infection with *N. meningitidis* has been reported (Grimwood *et al*., 2000). These findings are also slightly similar to results obtained by Laxer and Marks (1977) in third world countries.

Present findings in some cases were differed from other reports (Farag *et al*., 2005; Bedford *et al*., 2001). In a study, bacterial agents of meningitis in 70% of children between 1 to 5 years of age were *H. influenzae* type b, *N. meningitidis* and *S. pneumoniae*, respectively (Gold, 1993). In other study from Central Iran, the most common causes of meningitis in children were *H. influenzae* type b, *S. pneumonia*, *N. meningitidis* and *Salmonlla*

paratiphy A, respectively (Borjian, 1999). As observed, in most studies, *H. influenzae* type b and *N. meningitidis* are known as main causes of meningitis in infants and children, whereas in present study only 4.4% of patients had *H. influenzae* type b and 6.5% had *N. meningitides*. This event may be because of widespread of vaccination against these strains. With the decline in *H. influenzae* type b disease, cases of bacterial meningitis have decreased since 1986 (Feigin and Pearlman, 2004; Prober, 2004). Present study also revealed a decrease in the proportion of *H. influenzae* type b and *N. meningitides* in children. Meningococcal meningitis is a continuing threat in day-care centers and schools. Healthy children and young adults are susceptible and death can occur within a few hours of onset. In this study, *N. meningitidis* was not a common isolate.

In this study, Gram-negative bacilli including *E. coli*, *P. aeruginosa*, *C. freundii* and *K. pneumonia* had important contribution in creating bacterial meningitis (Table 1). *S. aureus* was also the second predominant cause of bacterial meningitis in patients involved. *P. aeruginosa* and *S. aureus* are versatile human pathogen that continues to be an important cause of nosocomial infections especially in pediatric units (Lin *et al*., 2004; Mihalache *et al*., 1999). *P. aeruginosa* and *S. aureus* meningitis in children and neonates were presented to withdraw attention to this clinical entity.

Clinical manifestation of bacterial meningitis in children in this study was not significantly different from that of other developing and developed countries, however it will help us in speedy diagnosis of our pediatrics patients. The diagnosis of bacterial meningitis is rarely a difficult diagnostic dilemma when a patient presents with fever, headache, neck stiffness and altered mental status. Although the clinical scenario may suggest meningitis, it is the cerebrospinal fluid white blood cell count that establishes the definitive diagnosis (Faria and Farhat, 1999). In our experience, fever, Leukocytosis, nausea and vomiting were the predominant of clinical findings of children with bacterial meningitis (Table 2). These findings are is agreement with some other studies (Al-Mazrou *et al*., 2004; Chang *et al*., 2004).

The appropriate treatment of bacterial meningitis has been controversial and has become more complex with the emergence of resistance to commonly used antibiotics. The pathogens that cause bacterial meningitis were found to be becoming increasingly resistant to the some common antimicrobial agents used in this study. Out of 8 tested antibiotics in this study, gentamicin, kanamycin and ceftizoxime were the most effective antibiotics in both Gram-positive cocci and Gram-negative bacilli. Regarding some reports (Saha *et al*., 2005; Karen *et al*., 2001; Foster and Rhoney, 2005), antibiotics of beta-lactam (ampicillin and amoxicllin), cephalosporin and also chloramphenicol have been recommended as effective drugs for those affected by bacterial meningitis, whereas most of the isolated bacteria in this study, showed high drugs resistance (between 20 to 100%) to many of these mentioned antibiotics (Table 4). *S. pneumoniae*, a common pathogen in pediatric infections, has become resistant to penicillin and makes these infections difficult to treat (Erdem and Pahsa, 2005; Hernandez *et al*., 2003). The National Reference Center in France for Pneumococci determined the susceptibility to antibiotics of 2,837 *S. pneumoniae* isolated in 1997 (Geslin, 1997). The incidence of *S. pneumoniae* with reduced susceptibility to penicillin G increased from 3.8% in 1987 to 48% in 1996 (Geslin, 1997). In this study, *S. pneumoniae* was the most common causes of meningitis and showed high resistance to amoxicllin, ampicillin and chloramphenicol. Rifampin and chloramphenicol have been recommended as alternative therapies, since they are less costly and more accessible to communities with limited resources (Hernandez *et al*., 2003). However, the differing levels of resistance found in target populations may restrict their use. In our communities, the increasing cost of treating resistant infections supports economic arguments for prevention through conjugate *S. pneumoniae* immunization.

The percentage of beta-lactamase-producing *H. influenzae* increased progressively in last few years (Dabernat *et al*., 2004). In Papua New Guinea more than 20% of *H. influenzae* type b meningitis are now resistant to chloramphenicol and resistant *H. influenzae* meningitis treated with chloramphenicol results in certain death or severe brain injury (Duke, 2002). Third-generation cephalosporins are a therapeutic option but are very expensive. In this study, *H. influenzae* type b, showed good susceptibility to kanamycin, gentamicin, chloramphenicol and cephalosporin.

Meningococcal resistance to antibiotics is emerging in some part of world. The incidence of *N. meningitidis* with reduced susceptibility to penicillin G increased from less than 1% in 1991 to 18% in 1996 in France. (Guibourdenche, 1997; Struillou *et al*., 1998). The strains belonged to various serogroups; most belonged to serogroup b, none produced a beta-lactamase and all were susceptible to cefotaxime and ceftriaxone. In our study, *N. meningitidis* showed a moderate resistance to cephalexin, amoxicllin, ampicillin and chloramphenicol.

In present study, *S. aureus and* Gram-negative bacilli such as *E. coli*, *P. aeruginosa* and *K. pneumonia* showed high resistance to many of tested antibiotics (Table 4). The emergence and spread multidrug-resistance among

species of *P. aeruginosa* and *S. aureus* has become a major concern worldwide and is seriously challenging current treatment strategies (Karen *et al*., 2001; Foster and Rhoney, 2005). The emergence of third-generation cephalosporin non-susceptible *E. coli* strains in infant bacterial meningitis, as shown in this study, has caused a therapeutic challenge in choosing initial empirical antibiotics for treating infant patients with post-neurosurgical meningitis. Present results emphasize that the timely use of appropriate antibiotics is essential for the management of this potentially fatal central nervous system infection. However, it should be noted that the number of cases examined in this study is too small to reach a therapeutic conclusion regarding infant bacterial meningitis, and further large-scale studies will be needed for this purpose.

We may come to this conclusion that Gram-positive cocci are major agents in causing bacterial meningitis in children investigated in this region that showed quite high resistance to routine antibiotics like amoxicillin, ampicillin, sulfamethoxazole-trimethoprim and chloramphenical. Through this experience, it became apparent that for the initial treatment of bacterial meningitis in infants, it is necessary to apply a combination of two antibiotics, instead of a single agent and new antibiotics should be considered for such combinations rather than persisting on conventional of cephalosporin and beta-lactam antibiotics.

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