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Is the diagnosis and treatment of childhood acute bacterial meningitis in Turkey evidence-based?

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Background/aim: Evidence-based guidance is likely to significantly improve patient care. We aimed to characterize the adequacy of standard diagnostic methods and treatment in children with acute bacterial meningitis (ABM) in Turkey.

Materials and methods: We conducted a retrospective study among children 1 month to 5 years old hospitalized with ABM in İstanbul. The World Health Organization case definition and laboratory criteria were used for diagnosis.

Results: Of the 283 cases, 250 were probable and 33 (11.2%) were confirmed as bacterial meningitis. The majority of patients (92%) were treated at 9 governmental hospitals and the remaining 21 at 2 university hospitals. Blood culture, cerebrospinal fluid (CSF) culture, and CSF Gram smear examinations were performed in 68%, 87%, and 13% of the cases, respectively. A third-generation cephalosporin, alone or in combination with other antibiotics, was the drug of choice in 90% of cases. Dexamethasone was given as adjunctive therapy in 43%. Initial antibiotics were modified during the course of treatment for 43 patients, with culture-confirmed indications for only 5 of them.

Conclusion: Recommended laboratory tests including blood culture and CSF Gram smears were insufficiently performed. Appropriate antibiotics were used in the majority of cases. Better identification of the causative pathogens will improve stewardship of antimicrobial therapy.

Key words: Children, bacterial meningitis, diagnosis, treatment

1. Introduction

Acute bacterial meningitis (ABM) is a medical emergency requiring immediate diagnostic steps and appropriate therapy (1,2). Epidemiology of ABM in children has changed, especially following the introduction of *Haemophilus influenzae* type B (Hib) and pneumococcal conjugate vaccines in the routine childhood immunization schedule. Recognition of changing epidemiology and bacterial resistance patterns is important for decisions on empirical therapy.

Evidence-based medicine has been defined as the integration of the best research evidence with clinical expertise and patient values (3). International guidelines providing clinicians with recommendations are presented for several diseases including bacterial meningitis (2,4). Several studies determining the etiology and prognostic factors in children with bacterial meningitis have been performed in Turkey (5,6). Nevertheless, practice patterns for management of childhood ABM have not been evaluated previously. Health care facilities have different resources for doing microbiological diagnosis in Turkey with almost no estimates of appliance of standard early diagnostic methods and treatment modalities. In this study, we aimed to identify how accurate the utility of diagnostic methods and treatment in children with ABM was in comparison to recommendations presented by international guidelines.

2. Materials and methods

We reviewed the records of children of 1 month to 5 years of age who were admitted to 11 tertiary hospitals in İstanbul with a diagnosis of ABM during 2005. The study centers included 2 university hospitals (Marmara University Hospital, Cerrahpaşa Medical Faculty Hospital) and 9 governmental hospitals (Bezmialem Vakıf Gureba Training and Research Hospital, Zeynep Kamil Training and Research Hospital, Bakırköy Maternity and Children Training and Research Hospital, Haseki Training

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and Research Hospital, Haydarpaşa Numune Training and Research Hospital, Şişli Etfal Training and Research Hospital, Kartal Lütfi Training and Research Hospital, Göztepe Training and Research Hospital, Okmeydanı Training and Research Hospital). These 11 centers are among the major tertiary referral centers for treatment of pediatric patients in İstanbul. Clinical and laboratory criteria of the World Health Organization (WHO) were used for diagnosis of bacterial meningitis (7). Clinical description included acute onset of fever, headache, and one of the following signs: neck stiffness, altered consciousness, or other meningeal signs. Laboratory criteria included: 1) culture [isolation of a bacterial pathogen from a normally sterile clinical specimen such as cerebrospinal fluid (CSF) or blood]; 2) antigen detection (isolation of a bacterial antigen from normally sterile fluid, i.e. CSF or blood); 3) Gram stain results. A probable case was defined as presence of clinical findings with CSF examination showing at least one of the following: 1) turbid appearance; 2) leukocytosis (>100 cells/mm^3); 3) leukocytosis (10–100 cells/mm^3) AND either an elevated protein level (100 mg/dL) or decreased glucose (<40 mg/dL). A confirmed case was defined as laboratory-confirmed by growing (i.e. culturing) or identifying (i.e. by Gram stain or antigen detection methods) a bacterial pathogen (Hib, pneumococcus, or meningococcus) in the CSF or from the blood in a child with a clinical syndrome consistent with bacterial meningitis. Both probable and confirmed bacterial meningitis cases were included in the study. Patients with recurrent meningitis, posttraumatic meningitis, shunt-related meningitis, and underlying illnesses were excluded. Data including diagnostic tests, etiological organisms, neuroimaging procedures, corticosteroid use, antibiotics used initially, and reasons for modification of antibiotics were collected from patient abstracts and tabulated according to centers.

3. Results

Of the 283 patients with ABM, the majority (92%) were treated at 9 governmental hospitals and the remaining 21 patients were treated at 2 university hospitals. The number of patients treated at each center is given in Table 1. Male-to-female ratio was 2.17 and median age was 12 months. Prior to admission, 105 (38%) patients had received antibiotics (70% parenteral). A total of 194 (92%) patients had a complete blood count examination with differential and platelet count. C-reactive protein was measured in 82% of cases. Gram smears of CSF samples were examined in 38 (13%) of cases, while 248 (87.6%) patients had a CSF culture taken and blood cultures were available for 194 (68.5%) patients. Only patients treated at a single center had CSF latex agglutination test (LAT) results. The LAT was not performed at the remaining centers.

An etiological organism could be identified in 33 (11.2%) patients. One-third of these patients had received antibiotics before admission. The most common organisms were Hib (36.3%), *Streptococcus pneumonia* (30.3%), and *Neisseria meningitidis* (21%) (Table 2). Among 19 patients with positive CSF cultures, 8 (42%) had also bacteria detected in their blood cultures. Seven out of 10 patients

Table 1. Diagnostic methods and drugs used for treatment of meningitis in 11 centers.

	Center no. (number of patients)										
	1 (9)	2 (41)	3 (23)	4 (19)	5 (55)	6 (30)	7 (25)	8 (40)	9 (5)	10 (16)	11 (20)
Diagnostic method											
%CSF culture	77	100	91	94	70	100	84	100	100	93	55
%Blood culture	77	87	86	84	43	96	72	75	100	43	10
%CSF Gram smear	0	9.7	21	5.2	1.8	0	3	5	100	81	5
Cranial imaging											
%CT	0	12	34.7	15	49	16	28	25	0	37	15
%MRI	7.8	4.8	4.3	5.2	18	6.6	12	2.5	0	12	0
Antibiotics used											
%CFT/CTX	55.6	19.5	73.9	84.2	0	60	52	85	100	6.7	60
%SAM+CFT/CTX	44.4	56.1	26.1	5.3	81.8	3.3	16	7.5	0	26.7	20
%VA+CFT/CTX %	0	0	0	0	7.3	16.7	24	0	0	13.3	20
P+CHL	0	9.8	0	10.5	5.5	3.3	0	0	0	53.3	0
%Dexamethasone	100	44.4	52.4	73.7	33.3	66.7	70.8	57.9	100	35.7	80

CFT: Ceftriaxone, CTX: cefotaxime, SAM: ampicillin-sulbactam, VA: vancomycin, P: penicillin, CHL: chloramphenicol.

Table 2. Bacterial etiology in children with acute bacterial meningitis.

Pathogen	Prior antibiotics use	
	Yes	No
Haemophilus influenzae type B	2	10
Streptococcus pneumonia	5	5
Neisseria meningitidis	1	6
Other	2	2
Total	10	23

Other: 1 Group D streptococci, 2 *Staphylococcus aureus*, 1 *Escherichia coli*.

with positive blood cultures (70%) also had positive CSF cultures. Bacteria were detected by Gram smears in 17 patients, and in 7 of these (40%), CSF and blood cultures remained sterile. Hib was identified by LAT in 3 patients.

A total of 111 (40%) patients were evaluated with neuroimaging procedures, including ultrasonography in 41 (14%), computerized tomography (CT) in 74 (26%), and magnetic resonance imaging (MRI) in 23 (8%) of the cases. The majority of cranial imaging procedures were performed during hospital stay due to complaints such as ongoing fever or convulsions with suspicion of emergence of a complication. Few patients had cranial imaging at the beginning of the treatment before lumbar puncture (LP) due to pathological findings in fundoscopy or physical examination. A second LP was performed in 115 (40.6%) patients and 107 (37.8%) patients had LP 3 or more times, while 60% of patients had LP examination at the end of treatment.

Fifteen different antibiotic regimens were used in treatment. Ninety percent of patients received ceftriaxone/cefotaxime alone or in combination with other antibiotics. A penicillin and chloramphenicol combination was used in 18 (6%) cases. Dexamethasone was given as adjunctive therapy in 117 (43%) cases (Table 1). During treatment, antibiotics were modified in 43 (15.1%) cases. The most common reasons for antibiotic modification were persistent or breakthrough fevers (37%); only 5 patients had culture-confirmed indications for antibiotic modification. Primary antibiotics were changed due to insufficient response in CSF findings, subdural effusion, and convulsions in 32%, 20%, and 17% of the patients, respectively.

Thirty-eight patients (13.4%) developed neurologic complications and 2 patients died. Sequelae were detected in 26% of patients. Prognostic factors of patients with ABM were presented in a previous report (8).

4. Discussion

An accurate laboratory confirmation of the etiology in bacterial meningitis is essential. CSF culture should be obtained in all patients with suspicion of ABM despite the absence of pleocytosis (9). In a study of 128 children with ABM, CSF cultures were positive in 97% of patients without previous antibiotic therapy, 67% of patients who received oral antibiotics, and 56% of patients who received parenteral antibiotics (10). Isolation of bacteria from blood culture in a patient with CSF pleocytosis also confirms the diagnosis (9,11). In the study by Nigrovic et al., of the 85 patients who received antibiotics before LP, 46 (54%) had blood culture specimens obtained before administration of antibiotics revealing the bacterial pathogen in 35% of them (12). In the present study, almost 90% of the patients had CSF culture examinations; however, blood culture was taken in 68% of cases. Bacteria can be detected by Gram smears in 60%–90% of patients with ABM (13). The presence of an organism upon CSF Gram stain may suggest bacterial etiology 1 day or more before culture results are available (14). Only 38 (13%) patients had CSF Gram smear examinations; nevertheless, 7 patients who had negative CSF and blood cultures were confirmed by CSF Gram smear examinations, proving the importance of CSF Gram smear. In a previous analysis of 218 episodes of ABM, CSF and blood cultures were negative but Gram stains were positive in 54 (24.8%) cases (15). In a study evaluating the sensitivity of the bacterial meningitis score in 889 children with bacterial meningitis, CSF Gram stain was positive in 89.1% of cases (16). CSF polymerase chain reaction (PCR) analysis is also very useful for defining bacterial etiology. Among 408 children with bacterial meningitis, PCR analysis of CSF was the most sensitive method, confirming 59.6% of the cases (5). None of the patients in our study had CSF PCR results. CSF antigen detection tests are not recommended routinely in the diagnosis of bacterial meningitis, but can be helpful in

patients pretreated with antibiotics (17). Additional use of LAT identified 3 patients with Hib meningitis who were culture-negative.

In patients suspected of having ABM with contraindications for LP, CT (or MRI) scanning of the brain should be the first step of management (4). Neuroimaging may be indicated in the presence of focal neurological signs, persistently positive CSF cultures despite appropriate antibiotic therapy, persistent elevation of CSF neutrophils (>30%–40%) after more than 10 days of therapy, and recurrent meningitis (18). About one-fourth of the patients in this study had undergone cranial CT imaging, revealing subdural effusion as the most common pathology. The majority of cranial imaging procedures were performed during hospital stay because of complaints such as ongoing fever or convulsions with a suspicion of development of a complication. In a previous study, Uysal et al. reported that 42 out of 125 patients had cranial CT examination, revealing pathology in 20% of them (6).

A third-generation cephalosporin is recommended as the first-line agent in children older than 1 month of age with community-acquired bacterial meningitis (4). The use of ceftriaxone or cefotaxime in 90% of the patients is in accordance with literature. If penicillin- or cephalosporin-resistant pneumococcus is suspected, in geographic regions or in patients with a recent travel history to countries with high rates of penicillin and ceftriaxone resistance (e.g., the United States), the use of ceftriaxone or cefotaxime plus vancomycin is recommended (4,19,20). Resistance to cefotaxime was reported as 4% in isolates from children with invasive pneumococcal disease in Turkey (21). Ampicillin plus chloramphenicol can be used when third-generation cephalosporins are not available and the locally isolated bacteria do not show significant resistance (4). In our study, combination regimens were used in 54% of the cases; however, surveys in Canada and the United States showed that over 90% of physicians preferred monotherapy with ceftriaxone or cefotaxime for treatment of meningitis in children after the neonatal period (22).

Nearly half of the patients that we reviewed had received dexamethasone. Except for hearing loss after Hib meningitis, no clear evidence establishes that dexamethasone alters long-term sequelae of meningitis (2). Decisions regarding the administration of dexamethasone should be individualized depending on careful analysis of risks and benefits. In a multicenter study including 27 tertiary care children's hospitals located in 18 US states and the District of Columbia, adjuvant corticosteroid therapy was not associated with time to death or time to hospital discharge (23). Despite opposite results in several metaanalyses, dexamethasone is advised in the European guideline (4). Dexamethasone administered before the first parenteral antibiotic dose was shown to decrease nitric oxide production in CSF during bacterial meningitis (24). Çetin et al. demonstrated that CSF nitrite level could have a prognostic effect in meningitis (25).

The most common reasons for antibiotic modification in this study were fever and abnormalities in repeat CSF examinations. A repeat CSF examination is recommended for patients who have a poor clinical response despite 24–36 h of appropriate antimicrobial therapy, for children with gram-negative bacillary meningitis**,** and for those with cephalosporin resistant pneumococci or pneumococcal meningitis treated with dexamethasone (2). In addition to glucose and protein abnormalities, CSF pleocytosis may be evident even after appropriate antibacterial therapy (26). If at the conclusion of the standard duration of treatment CSF examination shows >30% neutrophils or CSF glucose of <20 mg/dL, extension of the duration of treatment is indicated (1). The duration of fever in meningitis is usually 4–6 days after the initiation of appropriate therapy. Fever may be due to development of a suppurative complication or of discontinuation of dexamethasone, but in many cases a specific cause of prolonged fever cannot be determined (27).

We detected that the rate of microbiological confirmation was only 11.2%. The WHO criteria for confirmation of bacterial meningitis, including blood culture, CSF Gram smears, and antigen detection tests, were insufficiently applied. Prior use of antibiotics before LP, problems in direct plating of CSF at bed site, and storage and laboratory support of CSF samples could have negatively affected culture positivity. Availability of highly sensitive methods such as PCR will increase detection of bacterial pathogens. More than half of patients had LP examination at the end of treatment, which is not routinely recommended. Antibiotic modifications depended on factors other than microbiological results. Identification of the causative pathogen may provide definitive therapy with a narrow spectrum of agents with decreased toxicity, decreased selective pressure, and decreased cost.

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