INVASIVE MENINGOCOCCAL DISEASE, CEREBROSPINAL FLUID PLEOCYTOSIS AND ACUTE ADVERSE OUTCOME OF CHILDREN IN TEHRAN, IRAN BETWEEN 1991-2000

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Abstract - The absence of cerebrospinal fluid (CSF) pleocytosis in invasive meningococcal disease (IMD) has been associated with an increased risk of death. It is unknown whether patients who lack a cellular response to central nervous system (CNS) infection are at the same risk of adverse outcome as patiens without CNS infection. To determine the frequency of presentation and outcome of three groups of children with IMD, Group 1, children with CSF pleocytosis (cells ≥ 10 mm^3) and negative or positive cultures, Group2, children without CSF pleocytosis and with negative CSF cultures (bacteremia alone), and Group 3, children without CSF pleocytosis but with positive CSF cultures (CNS infection without CSF pleocytosis), we reviewed the medical records of children with IMD. Clinical and laboratory indices and severe adverse outcomes (definded as death or limb loss due to gangrene) were compared in three groups. Multivariable logistic regression analysis was performed. Of the 108 available patients, 75 (69%) had CSF pleocytosis, 24 (23%) had bacteremia alone and 18 (16/7%) had CNS infection without CNS pleocytosis. Patients with CNS infection without CSF pleocytosis had significantly lower white blood cell and platelet counts and more coagulopathy than patients with bacteremia (P < 0.05) or patients with CSF bleocytosis (P < 0.01). The frequency of adverse outcome was 61% for patients with CNS infection without CSF pleocytosis compared with 41.6% for patients with bacteremia alone (P < 0.001) and (26.4%) for patients with CSF pleocytosis (P < 0.001). CNS infection without CSF pleocytosis was independently associated with adverse outcome by multivariable logistic regression analysis (P < 0.03). Approximately 38.5% of all children with IMD presented without CSF pleocytosis. Of these patients those with CNS infection without CSF pleocytosis were at higher risk of adverse outcomes than either patients with CSF pleocytosis or patients with bacteremia alone.

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Key Words: Invasive meningococcal disease, CSF pleocytosis, acute adverse outcome, children

INTRODUCTION

Meningococcal disease has a rapid onset, fulminant course and mortality and a dreadful outcome unlike other infections with clearly. Despite recent advances in the pathogenesis and immunobiology of the meningococcus and the development of effective vaccines against certain serotypes of this pathogen, serious infection remains a major worldwide health problem. Clinical manifestations of meningococcal disease can be quite variable. These can range from transient fever and bacteremia to fulminant disease with death ensuing within hours of the onset of clinical symptoms.

Invasive meningococcal disease (IMD) is usually categorized clinically as either meningitis, meningococcemia or both. This distinction is widely regarded as having important prognostic significance. Numerous studies of IMD have shown that patients with cerebrospinal fluid (CSF) pleocytosis have a more favorable outcome than patients with meningococcemia without CSF pleocytsis (1,6).

Various CSF white blood cell cutoffs have been used to define CSF pleocytosis in these studies with similar results (2,4,6).

Previous studies investigating the outcome of IMD have failed to consider the status of CSF cultures in these patients, therefore it is unknown as to what proportion of patients without CSF pleocytosis actually had central nervous system (CNS) infections. Two subgroups of IMD patients without CSF pleocytosis can be distinguished: those with bacteremia alone (defined as absence of both CNS infection and CSF pleocytosis) and those with CNS infection in the absence of CSF pleocytosis.

Wolfe and Birbara have described four clinical forms:

1- Bacteremia without sepsis (occult bacteremia) or with sepsis;

2- Meningococcemia without meningitis (poor prognosis);

3- Meningitis with or without meningococcemia (CNS pleocytosis);

4- The meningoencephalitic presentation (profoundly obtunded).

We hypothesized that patients with CNS infection without CNS pleocytosis are at a greater risk of adverse outcome than either patients with bacteremia alone or those with CSF pleocytosis. Here we report 108 patients with different clinical situations.

MATERIALS AND METHODS

Population: Cases were identified by a review of the discharge diagnosis and bacteriologic laboratory records. After obtaining approval from the investigational review board, we studied the medical records of all patients younger than 16 year old with a diagnosis of IMD.

Definitions: We defined IMD as bacteremia or meningitis or both caused by Neisseria meningitidis as evidenced by blood or CSF cultures. All patients without CSF pleocytosis had two LP (lumbar puncture) with 24 hour interval; those with CSF pleocytosis for second time were classified in Group 1. In this study we found only two patients with change to CSF pleocytosis (1.8%). There was no relation between Latex and CSF culture (all Latex positive were culture negative). CSF pleocytosis means CSF white blood cell count (WBC) $\geq$ 10 cell/mm^3 . In the absence of CSF pleocytosis a patient was classified as having CNS infection if CSF cultures, Latex agglutination or both studies were positive for N. meningitidis.

Adverse outcome was defined as death during hospitalization, limb amputation or loss of all five digits on an extremity due to gangrene. Other sequelae, such as hearing loss or seizure disorder, were not considered adverse outcomes for the purposes of this study. Low systolic blood pressure was defined according to the following : up to 1 month of age $\leq$ 70mm Hg; between 1 month and 5 year old $\leq$ 80 mmHg and 5 year old or older $\leq$ 90 mmHg. These cutoff points represent systolic blood pressures at least 1 SD below age - adjusted norms (7).

We categorized patients as having poor perfusion if they had not any evidence of mottling cyanosis or delayed capillary refill (>2s) in association with low systolic blood pressure.

Data collection: We got demographic and clinical data from the medical records using a standardized data collection sheet. We recorded informations for the following variables: address, age, gender, signs and symptoms, assessment of perfusion, the presence of a petechial or purpuric rash, CSF WBC, Prothrombin time (PT), partial thromboplastin time (PTT), results of cultures of blood or CSF and the occurrance of an adverse outcome or death (Table 1, 2 and 3).

Statistics: We analyzed differences in continuous variables using student's t-test.

Comparison of continuous variables between three groups was performed using one - way analysis of variance (ANOVA). We used the Sheff's mulitple comparison test after ANOVA to analyze differences between specific pairs of groups. For comparative variables Chi- square test was used. If fewer than 5 data points were expected in any cell, the fisher exact test was used. The Bonferroni correction was used for multiple comparisons. All calculations were based on two - tailed altervatives ($P < 0.05$ was considered significant).

We performed forward stepwise multiple logistic regression analysis to evaluate whether CNS infection without CSF pleocytosis was independently associated with adverse outcome in patients with IMD after adjusting for other important and confounding variables. Variables significantly associated with adverse outcome in univariate analysis ($P < 0.05$) were included in the logistic regression equation, provided that they were available in the majority (> 50%) of patients. Because a patient could be classified into one of the three possible categories (CSF pleocytosis, bacteremia alone or CNS infection without CSF pleocytosis), two indicator variables were created: bacteremia alone and CNS infection without CSF pleocytosis. Patients with CSF pleocytosis constituted reference group because most patients fell into this category and had the lowest incidence of adverse outcome among patients with IMD. In addition, we created a dichotomous variable for CSF Pleocytosis (i.e CSF WBC $\leq$ 10 or $\geq$ 10 cells/mm^3), independent of the status of CSF cultures. We compared the independent effect of this variable with that of indicator variables to assess the importance of absence of CSF pleocytosis vs. the presence of CSF pleocytosis in the setting of CNS infection.

All statistical analyses were performed with the statistical package for the social sciences for windows (SPSS), and STATA statistical software.

RESULTS

Study population: 108 patients with IMD were indentified; of these patients 47 (43.5%) had an adverse outcome, including 27 (25%) deaths and 20 (18.5%) patients who required limb amputation or had lost 5 digits on an extremity due to gangrene. CSF pleocytosis was present in 66 (61%) patients; 42 (38.5%) patients

did not have CSF pleocytosis, 24 (22%) with bacteremia alone and 18 (17%) with CNS infection without CSF pleocytosis.

Table 1. Patients's Age and Gender Variations

Age	Gender	Male	Female	Total No.
0-12 months		9 (13.5%)	15 (12%)	14 (13%)
1-5 yr		17 (31%)	14 (31%)	31 (27.5%)
5-10 yr*		21 (29%)	13 (29%)	34 (28%)
10-16 yr		20 (25%)	9 (19%)	29 (23%)
Total		67 (62%)	41 (38%)	108

* Between 5-6 yr = 14 (12%)

Table 2. Clinical and physical findings in IMD patients

Signs & symptoms	No.	Percent
Fever	101	93.5
Rash (petechia)	100	92.5
Low blood pressure	40	37
Tachycardia	71	65.7
Meningeal signs	79	73.1
Headache	79	73.1
Vomiting	99	91.7
Bulged fontanelle	14	13
Low consciousness level	80	74.1
Anorrhexia	55	50.9

Table 3. Laboratory Data in IMD patients

Tests	T. number	Percent
Blood culture	42	38
Blood smear	17	15.7
CSF culture	42	38
CSF smear	62	57.4
Rash culture	18	16.6
Rash smear	17	15.7
Latex (LPA)	7	6.4
Reduced Complement	10	9.2
Reduced Plt.	21	19.4
Increased PT	65	60.1
Increased PTT	82	75.9

Characteristics of IMD patients with CSF pleocytosis, bacteremia alone and CNS infection without CSF pleocytosis

The mean age of patients with CSF pleocytosis (83.4 months) was higher than that of patients with bacteremia alone (61.9 months) and CNS infection without CSF pleocytosis (75.3 months) ($P < 0.05$ by ANOVA). Patients with CNS infection without CSF pleocytosis were more likely to have poor perfusion, lower peripheral WBC and lower absolute neutrophil counts (ANC) and more evidence of coagulopathy (elevated PT, PTT) than patients with CSF pleocytosis ($P \geq 0.05$). In addition patients with CNS infection without CSF pleocytosis had significantly lower platelet counts and higher PT and PTT than patients with bacteremia alone ($P < 0.05$).

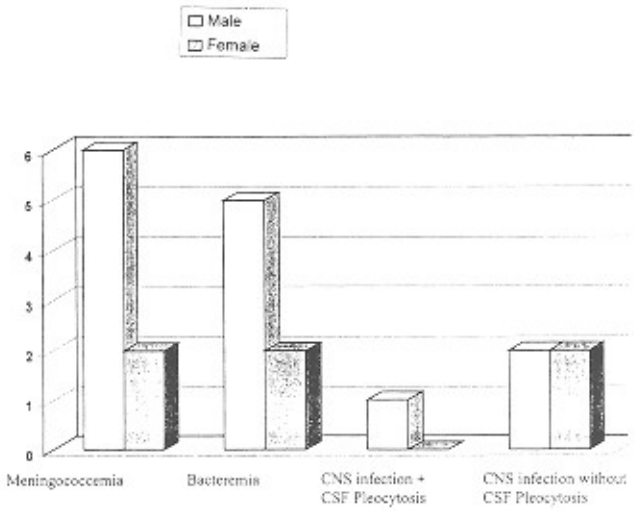

Fig. 1. Comparisons of limb amputation between patients with bacteremia only, CNS Infection without CSF pleocytosis and CSF pleocytosis and meningococcemia

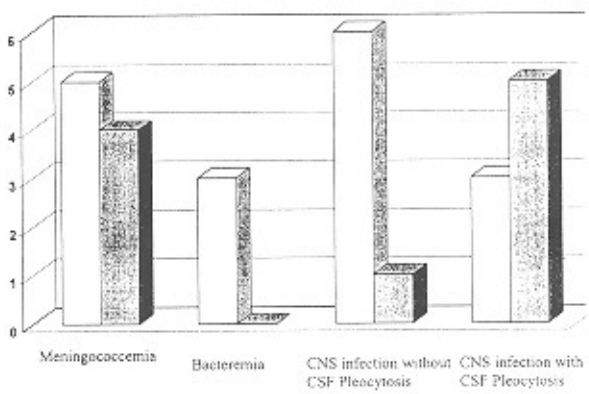

Fig. 2. Comparisons of death between patients with bactermia only, CNS Infection without CSF Pleocytosis and CSF pleocytosis and meningococcemia

Frequency of adverse outcomes

Patients with CNS infection without CSF pleocytosis had more frequent adverse outcomes (11 of 18, 61%) than either patients with bacteremia alone [10 of 24, 41.6% ; 95% confidence interval (0.21, 0.61); P < 0.001] or patients with CSF pleocytosis [9 of 34, 26.4%; 95% confidence interval (0.3, 0.7); P<0.001]. Fig. 1 and 2.

Patients with bacteremia alone also had more frequent adverse outcomes than patients with CSF pleocytosis but this difference was statistically nonsignificant.

When CSF pleocytosis was considered irrespective of the status of CSF cultures, patients without CSF pleocytosis had more frequent adverse outcomes than patients with CSF pleocytosis (11 of 18 Vs 9 of 34).

The following variables were found to be significantly associated ($P \leq 0.05$) with adverse outcome by univariate analysis: temperature, poor perfusion, WBC, ANC, platelet count, PT and PTT. Multiple logistic regression analysis revealed that in addition to poor perfusion and low WBC, the variable CNS infection without CSF pleocytosis, retained statistical significance [95% confidence interval (0.3; 0.8); $P = 0.033$] and thus was independently associated with adverse outcome.

Finally when the variable "absence of CSF pleocytosis" was entered into the stepwise multiple logistic regression analysis instead of the variable CNS infection without CSF pleocytosis, it was not selected as a variable independently, associated with adverse outcome ($P > 0.05$).

DISCUSSION

Carpenter and Sullivan in 53 cases of meningococcal infection reported that 70% had meningitis with positive CSF smear or culture and pleocytosis while 12% were with bacteremia alone; 3 deaths (8.5%) occurred in patients with meningitis as compared with 1 death (16%) in meningococcemia. These investigators have demonstrated a close correlation between plasma lipo - oligosaccharide levels and actue prognosis (3,4,9).

This observation correlated with post mortem findings by Thomas and Dodge who showed that focal neurologic findings were less common in IMD than Pneumococcal or Haemophilus meningitis in children and perhaps the cause of death was related to toxins produced by the agent or by cerebral edema and to secondary effects without pleocytosis on the vital centers in the midbrain region (6,7,8,17).

In this study, 38.5% of patients with invasive meningococcal disease who had lumbar punctures at the time of clinical presentation didn't have CSF pleocytosis. Of these patients, 22% had bacteremia alone and 18 (17%) had CSF infection without pleocytosis. Patients with CNS infection, and without pleocytosis had significantly more adverse outcomes than bacteremia alone or patients with CSF pleocytosis. Using multivariable logistic regression analysis, we found that CSF infection without CSF pleocytosis was independently associated with adverse outcome in IMD.

Previous studies of predictors about IMD have shown CSF pleocytosis to be 65.1%, which in our study is 61%; bacteremia alone 20%, but ours is 22%; meningitis without pleocytosis 13%, but ours is 17%; that is almost the same.

In previous studies as Adler's and co-workers patients without CSF pleocytosis have been repeatedly found to have a less favorable outcome than those with CSF pleocytosis (1,2,4,6). In our study this finding was confirmed but an important distinction was that meningococcal bactereinia alone was similar to that of all the patients with IMD (13,15).

The results of the current study suggest that absence of CSF pleocytosis has prognostic utility only when the CSF cultures or Latex agglutination studies is known.

Because bacteriologic results are almost certainly unavailable at the time of acute presentation, the absence of CSF pleocytosis is of uncertain prognostic value unless Latex agglutination test (LAT) is done in 3 minutes.

Therefore we would favor the use of predictive models of IMD that do not rely only on lumbar punctures for the prediction of outcome. Several such methods, which are highly sensitive and specific for outcome in IMD, have been reported and validated (e.g., PCR, Baetec...) (10,11).

Because of the retrospective nature of this study, certain limitations exist.

False negative CSF cultures and few latex agglutination studies in patients with meningococcal meningitis are not uncommon (12,13). So the frequency of CSF infection without pleocytosis may be higher than that reported in this study, because patients without pleocytosis and with false negative CSF cultures would have been incorrectly categorized as patients with bacteremia alone (14).

In conclusion approximately one - third of children with IMD present without CSF pleocytosis, either with bacteremia alone or CNS infection without CSF pleocytosis. All patients without CSF pleocytosis are not at a uniform risk of adverse outcome; however, patients with CNS infection without CSF pleocytosis are at significantly higher risk of death or limb loss due to gangrene than patients with meningococcal bacteremia alone. We conclude that the presence of CNS infection without CSF pleocytosis, but not the absence of pleocytosis alone, is independently associated with

adverse outcome in IMD.

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