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Original Article

Invasive pediatric *Neisseria meningitidis* infections

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Background and purpose: *Neisseria meningitidis* usually causes severe infection in children, but occurs only sporadically in Taiwan. However, the number of infections increased in 2001 and 2002. This study was performed to ascertain the epidemiology and clinical manifestations of infections caused by meningococcus in a pediatric population.

Methods: The medical charts of patients with meningococcal diseases who were admitted to Chang Gung Children's Hospital, Taoyuan, Taiwan, from July 1998 to December 2005 were retrospectively reviewed. Data were analyzed for age distribution, serogroups, clinical diagnoses, treatment, acute complications, and outcomes.

Results: Sixteen children with meningococcal disease were identified. Their ages ranged from 1 month to 15 years (average, 3 years). Most patients (62.5%) were younger than 1 year and the second most frequent age group was 6 to 15 years (18.75%). There were 56.25% boys and 43.75% girls. The identified serogroups were B (43.75%), W135 (31.25%), A (6.25%), Y (6.25%), and undetermined (12.5%). The antibiotics used in this study were ampicillin, ceftriaxone, cefotaxime, and aqueous penicillin; the mean total treatment duration was 10 days. Purpura fulminans (37.5%), disseminated intravascular coagulopathy (31.25%), respiratory failure (25.0%), and shock (25.0%) were the commonest acute complications. Most (87.5%) of the patients survived. One patient had long-term sequelae of hearing impairment and speech delay. The mortality rate was 12.5%.

Conclusions: Serogroup B and W-135 were 2 predominant serogroups to cause pediatric meningococcus, and the majority of infections occurred in children younger than 1 year. Continuous surveillance and prevention of meningococcal infections are of great importance.

Key words: Meningitis, meningococcal; *Neisseria meningitidis*

Introduction

Neisseria meningitidis are Gram-negative aerobic diplococci, and humans are the only reservoir [1]. They can be classified into 13 different serogroups — A, B, C, D, X, Y, Z, 29E, W135, H, I, J, and L, according to their capsular polysaccharide antigen. They cause 2 major diseases, purulent meningitis and fulminant meningococcemia, as well as other sporadic forms of infection. Serogroups A, B, C, Y, and W135 are commonly isolated from patients with acute meningococcal infection. *N. meningitidis* serogroups B and C are predominant in industrialized nations [2], while serogroup A is an important cause of meningococcal infection in sub-Saharan Africa, especially in the meningitis belt [3].

Meningococcal infections occur only sporadically in Taiwan. The Centers for Disease Control (CDC) of Taiwan annual report shows an increased number of such infections in 2001 to 2002. The average confirmed number of infections in Taiwan is approximately 10 per year. In 1999, the number was 13, which increased to 15 in 2000, 43 in 2001, and 46 in 2002. This study was performed to clarify the clinical manifestations, serogroup distribution, and epidemiology of the pediatric population with meningococcal diseases in a 400-bed tertiary referral center.

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Methods

Patients

Patients admitted to Chang Gung Children's Hospital (CGCH), Taoyuan, Taiwan, with meningococcal disease from July 1998 to December 2005 were identified from the microbiology laboratory records. The medical records of patients younger than 18 years with meningococcal disease, who had positive cultures from sterile sites including cerebrospinal fluid (CSF), blood, or sputum, were retrospectively reviewed. The data collected from the medical records included patients' demographics, clinical diagnoses, laboratory findings, choice of antibiotics, treatment duration, acute complications, serogroups, and outcomes.

Microbiological methods

Blood specimens for culture of all patients included in this study were collected at admission, before the administration of antibiotics. The inoculated blood culture bottles were incubated in the BACTEC© 9240 blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). The bottles were inspected for macroscopic growth daily and subcultured blindly (despite clear broth) onto chocolate agar after 6 to 18 h and 72 h of incubation.

The CSF specimens were inoculated onto chocolate agar or sheep blood agar. The plates were incubated in 5% to 7% carbon dioxide at 35°C and inspected after 24, 48, and 72 h before a final report was issued.

Suspicious colonies were subcultured on blood and chocolate agars for further identification with a series of carbohydrate fermentations. Serogrouping of meningococci was obtained from the laboratory of the CDC. Serogroup was determined by using the slide agglutination method with antisera from Murex Biotech Ltd. (Dartford, UK) [4].

Results

During the study period, 16 patients with meningococcal disease were analyzed. There were 9 boys and 7 girls. The ages ranged from 1 month to 15 years (mean, 3 years). Patients younger than 1 year accounted for 62.5% and the second most common age group was 6 to 15 years, which accounted for 18.75% (Fig. 1).

Patients' demographics, clinical diagnoses, choice of antibiotics, treatment duration, acute complications, microbiology findings, and outcomes are summarized in Table 1. The clinical diagnoses included occult bacteremia

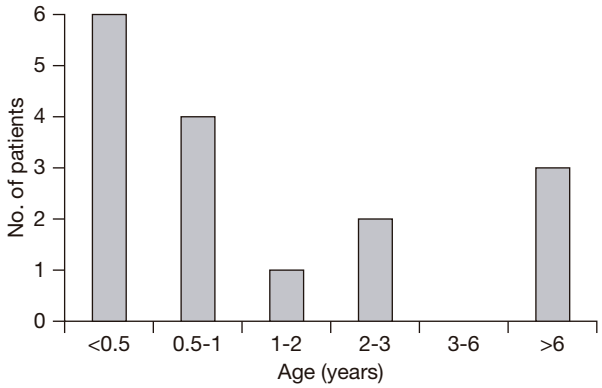

Fig. 1. Age distribution of patients with meningococcal disease (n = 16).

(n = 1; 6.25%), meningitis (n = 2; 12.50%), meningococcemia (n = 3; 18.75%), meningococcemia with meningitis (n = 9; 56.25%), and pneumonia (n = 1; 6.25%).

The identified serogroups were group B (43.75%), W135 (31.25%), A (6.25%), Y (6.25%), and undetermined (12.5%). Purpura fulminans (37.50%), disseminated intravascular coagulopathy (DIC; 31.25%), respiratory failure (25.00%), and shock (25.00%) were the 4 most common acute complications.

Among 4 patients with septic shock and DIC, 2 patients died. The overall mortality rate was 12.5%. The first patient who died was a girl aged 8 months, who presented with fever for 1 day, irritable crying, and consciousness disturbance. Her laboratory data showed leukopenia (white blood cells [WBCs], 2800/mm^3), pleocytosis of the CSF, (WBC, 4800/μL) and positive blood culture. Her final diagnoses were meningococcemia, meningitis, purpura fulminans, DIC, and multiple organ failure. The second patient who died was a girl aged 2 years and 4 months, who presented with fever for 1 day, cough, and rhinorrhea. Her laboratory data showed leukopenia (WBC, 4000/mm^3), positive blood culture, and negative CSF culture. Her final diagnoses were meningococcemia, meningitis, purpura fulminans, DIC, and multiple organ failure. Both patients died within a few hours of admission and received only 1 dose of antibiotic.

A 1-month-old patient was diagnosed with meningococcal pneumonia by radiographic study, which showed left upper lobe consolidation, sputum Gram stain showed a high neutrophil count and Gram-negative diplococci, and positive sputum culture with meningococcus. The blood culture, viral culture, respiratory syncytial viral, and chlamydial antigen tests were all negative. The clinical course of this patient improved rapidly after treatment with antibiotics.

Only 1 patient had sequelae of hearing impairment, and she received cochlea implantation at the age of 2 years. Antibiotic treatments for most of the patients was changed to aqueous penicillin or third-generation cephalosporins (ceftriaxone/cefotaxime) when invasive meningococcal disease was diagnosed from the positive cultures. The mean total treatment duration was 10 days (Table 1).

The results of 7 patients were available for antimicrobial susceptibility tests. Among them, 2 were

Table 1. Demographic data, clinical diagnoses, antibiotic treatment, outcomes, and microbiological findings of children with *Neisseria meningitidis* infection (n = 16).

Patient no.	Age (months)/ sex	Laboratory data		Diagnosis	Antibiotics			Acute complications	Outcome	Serogroup
		WBCs (/mm^3)	CRP (mg/L)		Empiric	Continued	Duration (days)			
1	1/F	6200	45	Pneumonia	AMP	Aq-PCN	14	-	Good	W135
2	1/M	6970	28	Meningococcemia Meningitis	AMP	Aq-PCN	12	-	Good	B
3	2/M	10,100	164	Meningococcemia Meningitis	AMP	CTX	14	DIC Seizure Purpura fulminans Respiratory failure	Good	B
4	2/F	8700	<2	Occult bacteremia	AMP	AMO	7	-	Good	W135
5	2/M	10,800	4	Meningitis	AMP	Aq-PCN	11	-	Good	B
6	5/M	19,400	11	Meningococcemia	AMP	CTX	13	-	Good	B
7[a]	8/F	2800[a]	48.5	Meningococcemia Meningitis	VAN CAZ		1 dose	Shock DIC Purpura fulminans Multiple organ failure	Died	B
8	10/F	14,700	290	Meningococcemia Meningitis	AMP	Aq-PCN	10	-	Hearing impairment	B
9	10/M	11,900	206	Meningococcemia Meningitis	CTX	CTX	13	Shock DIC Respiratory failure Purpura fulminans	Good	W135
10	12/M	23,500	201	Meningococcemia Meningitis	VAN CRO	CRO	10	-	Good	B
11	23/M	11,500	173	Meningococcemia Meningitis	CRO	CRO	10	-	Good	W135
12[a]	28/F	4000[a]	45	Meningococcemia	AMP		1 dose	Shock DIC Purpura fulminans Multiple organ failure	Died	Undertermined
13	36/F	26,000	225	Meningococcemia Meningitis	CRO	Aq-PCN	15	Purpura fulminans	Good	A
14	96/F	21,000	38	Meningococcemia	Aq-PCN CAZ	Aq-PCN	14	Shock DIC Purpura fulminans	Good	Undertermined
15	177/M	15,400	392	Meningococcemia Meningitis	CRO	Aq-PCN	11	-	Good	Y
16	180/M	20,700	287	Meningitis	CRO	CRO	9	-	Good	W135

[a]Two patients with leukopenia died.

Abbreviations: F = female; M = male; WBCs = white blood cells; CRP = C-reactive protein; AMP = ampicillin; VAN = vancomycin; CAZ = ceftazidime; CTX = cefotaxime; CRO = ceftriaxone; Aq-PCN = aqueous penicillin; AMO = amoxicillin; DIC = disseminated intravascular coagulopathy.

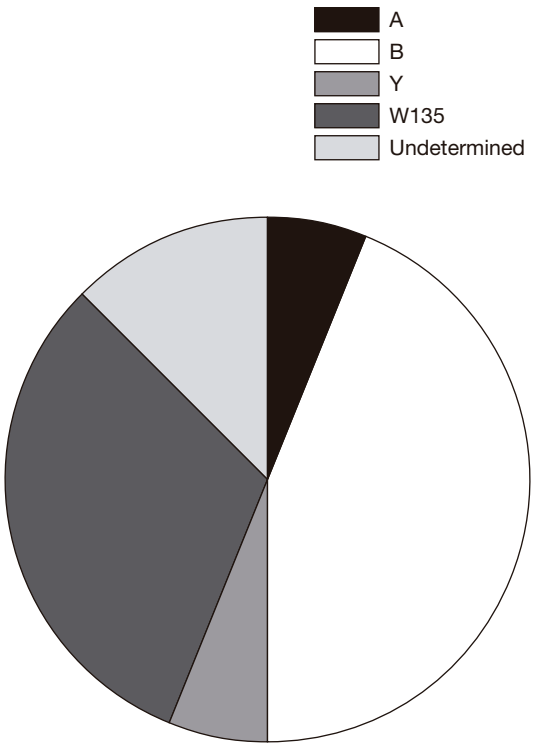

Fig. 2. Serogroups of meningococcal isolates (n = 16).

susceptible to penicillin, 4 were intermediate, and 1 was resistant. Only 1 isolate was resistant to rifampicin. All 7 isolates were susceptible to ceftriaxone.

Serogroups B and W135 were the 2 most common serogroups, accounting for 43.75% and 31.25% of infections, respectively (Fig. 2).

At least 1 patient with meningococcal disease was identified at the CGCH each year during the study period. An increase in infections to 6 was found in 2001 and W135 was the main serogroup (Fig. 3).

Discussion

In this study, more than half of the patients with meningococcal infection were younger than 1 year. This may be due to the decrease in maternal bactericidal antibody after birth, which reaches its nadir between 6 and 24 months of age. Pastor et al suggested that the peak incidence of meningococcal disease occurs in the first year of life, with 35% to 40% of cases occurring in children younger than 5 years [5].

In this study, the 2 most common clinical diagnoses were meningococcemia and meningitis. Among 5 patients with fulminant meningococcal sepsis, 3 survived and 2 died. Both of the patients who died had presentations of shock, DIC, and purpura fulminans, and died within a few hours of admission. Densen et al [6], Fijen et al [7], and Mathew and Overturf [8] have shown that properdin deficiency and complement deficiency will increase susceptibility to meningococcal disease, and results in a high mortality rate. However, no patients in this study underwent immunity testing, which was one of the limitations of this retrospective study.

The mortality rate in this study was 12.5%. Sharip et al found a mortality rate of 8% to 13% in the United States [9].

The nasopharyngeal swabs of 3 healthy relatives of a patient with pneumonia had positive isolates for meningococci of the same serogroup, W135, and the same molecular type of interspersed repetitive sequence–polymerase chain reaction type II and pulsed field gel electrophoresis type C, suggesting clonal dissemination. The carrier rates of disease-associated meningococcal strains in the general public are <5% [10].

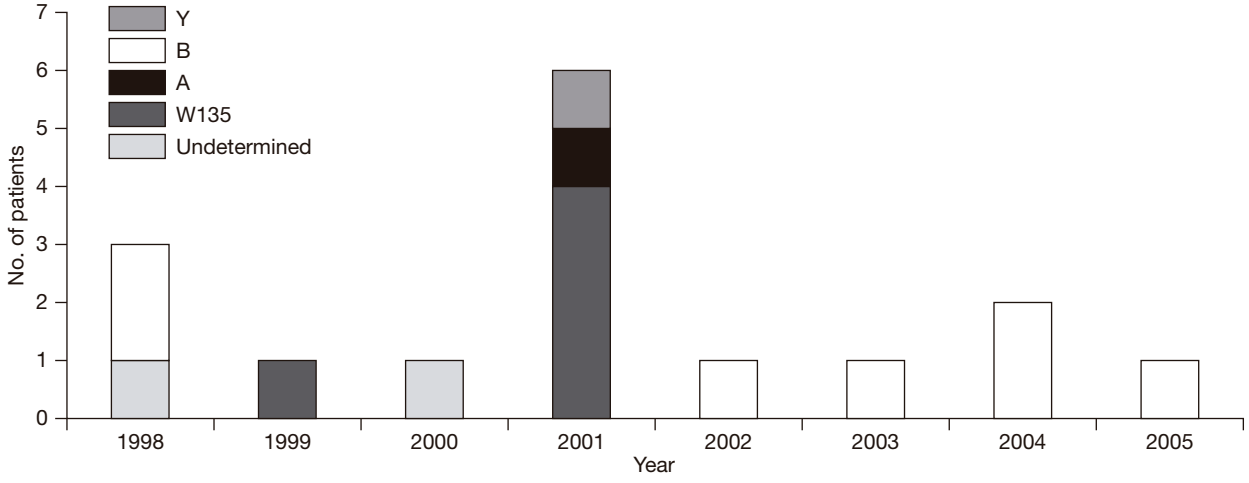

Fig. 3. Annual distribution of serogroups causing meningococcal disease (n = 16).

The family had the opportunity to transmit the pathogen to the infant via direct contact or airway droplets [2,11]. Although establishing the diagnosis of meningococcal pneumonia by sputum culture alone is uncertain due to the possibility of colonization from the sputum Gram stain with Gram-negative diplococci, along with the neutrophil count, radiographic study, and negative results of other possible pathogens, the pneumonia of this patient was considered to be related to meningococci infection.

Only 1 of the patients with meningococcemia and meningitis had neurological sequelae in the form of a hearing impairment. The rate of neurological sequelae caused by meningococcus is lower than for other types of bacterial meningitis [2].

Serogroup B and W135 were the 2 most predominant serogroups to cause meningococcal diseases in this study. According to the CDC data, these 2 serogroups are primarily responsible for culture-confirmed cases of meningococcal disease in Taiwan [12]. An increase in number of infections caused by serogroup W135 isolates was found in 2001. Previous reports have shown that there were increased serogroup W135 isolates in many African countries in 2001 [3]. However, molecular epidemiological data showed that the isolates in Taiwan have a distinct genetic pattern. This study also showed that serogroup A and Y isolates emerged in 2001, and this finding is consistent with the CDC study [12]. These emergent meninogococci also caused a small outbreak of disease in Taiwan from 2001 to 2002.

Immunization with meningococcal vaccine is important in pediatric populations, but no routine immunization use is recommended in Taiwan. Among the currently available meningococcal vaccines, conjugated quadrivalent vaccine (serogroups A, C, Y, and W135) have better immunogenicity for younger patients than capsular polysaccharide quadrivalent vaccine, as the conjugated vaccine elicits a T cell–dependent memory response resulting in increased effectiveness of the vaccine [13,14]. Although serogroup B is a major cause of endemic meningococcal disease, there is no effective vaccine available currently. As the group B polysaccharide has a structural and immunologic similarity to the neural cell adhesion molecule, a membrane glycoprotein on human brain cells [15], the development of a polysaccharide vaccine against this group is difficult and remains a challenge.

There are 2 limitations to this study. First, it described the experience of a single tertiary care pediatric center and the number of patients was small. Second, it was a retrospective study, with incomplete data for some patients.

In conclusion, the majority of meningococcal infections occurred in children younger than 1 year. The 2 predominant serogroups were identified as serogroup B and W135. Most of the patients survived, and the mortality rate was 12.5%. Continuous surveillance and prevention of meningococcal infections are of great importance.

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