ISSN 1021-366X

Center for Disease Control
Department of Health
TAIWAN, R.O.C.

Vol. 16 No. 6/June 25, 2000

Epidemiology Bulletin

Fulminant Meningococcemia Complicated with Death

Introduction

Epidemic cerebrospinal meningitis and meningococcemia were initially reported by Vieusseaux in 1805 [1]. Nowadays meningococcal infection has become one of the major causes of morbidity and mortality in developing and developed countries [2]. According to the statistic data of Center for Disease Control, Department of Health, the mortality rate is 5 out of 13 confirmed cases in 1999 and 1 (the case in this report) out of 8 confirmed cases in 2000 (up to 18, April). The pathogen is *Neisseria meningitidis* and the major reservoir is human upper respiratory tract. Meningococcemia could cause fatal damage to the body. Furthermore, the meningococcal vaccine has limited effectiveness. Therefore, the physicians must be able to recognize and treat the infection as early as possible to minimize the mortality and morbidity [1, 3].

Case Report

Mr. X, 20 years old, is a systemic lupus erythematosus (SLE) patient with long-term corticosteroid usage for years. He was admitted to the hospital approximately at 3 a.m. with complaints of chillness, fever (39℃), headache, sore throat, and running nose for one hour. At the time he arrived in hospital, the consciousness was clear, body temperature was 39.6℃, blood pressure was 148/83 mm Hg, pulse rate was 142/min, respiratory rate was 24/min, and the

throat was injected. Blood culture, in addition to other tests, was performed. Then intravenous antibiotics with cephalosporin and gentamicin were used after examination. At 2:30 p.m. in the same day, widespread rash with petechiae and ecchymoses over conjunctivae and whole body skin of the patient, cold and cyanotic extremities, hypotension, breathing sound with wheezing, and consciousness change occurred. The clinical condition downed hill rapidly with death occurred about 11 hours after the admission.

Laboratory tests revealed that WBC : 10,000/μl (band : 2%; segment : 87%), ANA : 1 : 2560, Anti-nDNA : 1 : 640, C3 : 33.8mg/dl, C4 < 10.0mg/dl (normal value : C3 : 88-201 mg/dl, C4 : 6-47mg/dl), ESR : 3mm/h, CRP : 3.04 mg/dl, PT > 100 sec (control : 11.4 sec), APTT > 100 sec (control : 30.1 sec), FDP : 16-32μg/ml (normal value : 0-0.5 μg/ml). Gram stain of blood culture specimen revealed gram-negative diplococci 36 hours after admission. Menincococcemia was diagnosed immediately at that moment. Furthermore, it was showed that pathogen belonged to the serogroup W-135 of *Neisseria meningitidis* several days later. The causes of death were : (1) fulminant meningococcemia, (2) systemic lupus erythematosus.

Discussion

1.Epidemiology

N. meningitidis seems to be transmitted through inhalation of infected droplets of nasopharyngeal secretions or by direct and indirect oral contact. Through intimate contact, such as family members, classmates, and nursery school classmates are at 100-1,000 times higher risk of acquiring meningococcal infection. Previous respiratory infection, especially influenza, is related to the susceptibility of meningococcal infection. *N. meningitidis* could cause endemic and epidemic infections [2]. The occurrences of large-scale epidemics were related to overcrowding, poor sanitation, and malnutrition [4, 5].

Large-scale epidemics still occur in Africa, China, and South America. Most of these epidemics were caused by serogroup A meningococcus. Morbidity could be as high as 1/1000 of population. Furthermore, the morbidity in children under 2 years old could be as high as 1 in 100 [2,4]. The largest epidemics in history occurred in 1996 in England, the morbidity were 47 in 100,000. There were two peak epidemics in Taiwan, during 1920-1926 and 1934-1946. No more epidemics were found thereafter. The case number per year was around 5 during the period

from 1971 to 1991. From 1992 to 2000, there were 81 cases, including 8 deaths. Children younger than 2 years old is in the highest attack rate group. The next group was from 11 to 20 years old. Most of cases occurred in spring and winter. Therefore, meningococcal infection occurs sporadically in Taiwan [3].

2.Pathogen

N. meningitidis is a gram-negative diplococcus. The pathogen grows best at 37°C on enriched media such as Mueller-Hinton or chocolate agar in an atmosphere of 5-10% CO_2. The pathogen is differentiated from other microorganisms based on their ability to use sugar as source of energy. In contrast to other neisseriae, *N. meningitidis* is the only species with capsule. This species can be divided into 13 serogroups according to the antigenic differences among the capsular polysaccharides. More than 99% meningococcal infections are caused by serogroup A, B, C, 29E, W-135, and Y. Meningococci also could be divided into serotypes, subtypes, and immunotypes according to the outer membrane proteins and lipopolysaccharides. Moreover, the species can be subdivided into clonal types based on characteristic bacterial genome. *N. meningitidis* is sensitive to dryness and low temperature. Therefore the specimen should be cultured immediately [2, 4].

All systemic meningococcal infections are preceded by colonization of the pathogen on nasopharyngeal mucosa. The pathogens iitially enter the mucosa, then transmigrate through these cells to submucosa and enter the capillaries. The endotoxin produced by the microorganisms can induce the release of cytokines and other free radicals by macrophage, leading to shock and disseminated intravascular coagulation (DIC) [2]

Clinical Syndromes

1.The carrier state.

During endemic periods, the nasopharyngeal carriers could be 5% of the population but may be as high as 60-80% in crowding locations, such as military recruit camps and schools. The carrier state could persist for a long period of time. The patients could have nasopharyngeal symptoms. The specific serologic titers to the pathogen increase. The carrier state seldom enters the disease state [2,4].

2.Meningitis and meningococcemia.

Meningococci could cause acute infectious illness. Usually upper respiratory infection occurs initially, followed by acute systemic infection with

meningococcemia and meningitis and death [2, 4].

Upper respiratory infection. Meningococci invade nasopharynx first. Most patients are asymptomatic, or only have fever in this period. Some patients with invasive infection had prodromal symptoms of sore throat, cough, rhinorrhea, headache, and conjunctivitis for one week before the hospital admission. These symptoms often are misdiagnosed as streptococcal infection or viral infection. Usually the clinical manifestations of meningococcal infection are more serious than streptococcal infection or viral infection [2, 4].

Acute systemic infection. Acute systemic infection could be presented by three syndromes : meningitis, meningococcemia with meningitis, and meningococcemia without obvious signs of meningitis. The typical manifestations are following : sudden onset of fever, nausea, vomiting, headache, difficulty in concentration, myalgia, skin rash, and arthralgias. High fever (between 39 and 41°C) occurs often. The most characteristic manifestation is skin rash with petechiae and ecchymoses. The rash occurs on the trunk and extremities. Patients with meningococcemia could have no manifestations of meningitis. But 50-80% of these patients will have petechiae. The blood pressures are low and pulse rates are elevated. Very often the patient felt that this is the most serious illness they ever met. Many patients have the sense of impending death [2, 4].

About 10-20% of meningococcal infections progress rapidly to fulminant meningococcemia with purpura, cold extremities, cyanosis, and hypotension [2]. Prognosis is related to the severity of the clinical condition at presentation, the skill of the physician, and the facilities. Patients with meningococcemia only have a higher mortality rate. Early treatment could lower the mortality rate significantly [2].

Laboratory Diagnosis

The laboratory diagnosis is based on the isolation of *N. meningitidis* from blood or CSF cultures, or the detection of the antigens of the pathogen. Cultures of blood samples taken before the use of antibiotic give positive results in 60-80% of cases. That of CSF is 50-70%. There are several methods of rapid diagnosis, such as gram stain, immunoassays and PCR (polymerase chain reaction). The gram stains of CSF from patients with meningococcal meningitis give positive results in 50% of cases. Those of punch biopsy from hemorrhagic skin lesions or needle aspiration is 70%. Immunoassays could be clinical valuable for sample

taken after the use of antibiotics. Combination use of cultures, gram stain, and immunoassays detection methods could increase the diagnosis rate up to 90%. Recently, the specificity and sensitivity of PCR are higher than 90% [2,4].

Treatment of systemic meningococcal infection

The mortality rate of meningococcal infection is high, therefore early diagnosis and treatment are crucial. All cases with fever and petechiae should be considered to have meningococcal infection. Blood culture should be performed and patient should be treated immediately. Early use of appropriate antibiotics is very important. Intravenous penicillin G (60,000-100,000 units/kg) should be administered immediately [2,4,6].

Penicillin remains the main therapeutic regimen presently. The dosage is intravenous 300,000 units/kg/day (up to 24,000,000 units/day) in divided doses until fever has subsided for at least 5 days. Patients allergic to penicillin can be treated with chloramphenicol (75-100mg/kg/day IV, up to 4g/day, in divided doses). The third-generation cephalosporins, such as cefotaxime or ceftriaxone could be used for penicillin-resistant meningococci [2,4,6].

Several bacterial infections could have similar clinical manifestations to those of meningococcus. The third-generation cephalosporins such as cefotaxime (150-200 mg/kg/day IV, up to 12g/day, in divided doses) or ceftriaxone (75-100 mg/kg/day IV, up to 5g/day, in divided doses) could be used empirically [4].

Several hours after admission, Mr. X had sudden onset of typical manifestations of fulminant meningococcemia with widespread petechiae, ecchymoses, cyanotic and cold extremities, hypotension, and consciousness change were found. Fulminant meningococcemia, previously called Waterhouse-Friderichsen syndrome, is characterized by rapid development of shock, DIC, and multi-organ failure. Hemorrhages could occur in muscles, adrenal and pituitary glands. The mortality rate is high, about 50-60%. Major causes of death are cardiac and respiratory failures. Coagulopathy could be used as a good predictor of poor prognosis. It is defined as a partial thromboplastin time of > 50 sec or a fibrinogen concentration of > 150 μg/dl [2, 4]。

As described previously, Mr. X suffered from SLE, an autoimmune disorder. According to the record, the complement levels, including those in the past [mean of C3：62 mg/dl (normal：88-201 mg/dl)；mean of C4：14 mg/dl (normal：16-47 mg/dl)] and during this admission (C3：33.8 mg/dl，C4：<10.0

mg/dl) were low. Complement plays an important role in immunity. It has been shown that patients with complement deficiency are susceptible to meningococcal infection with the uncommon serogroup of Y and W-135[4,7]. It is not known whether Mr. X patient suffered from complement deficiency. What we know for sure are: (1) the complement levels did be low; (2) the pathogen did belong to the uncommon serogroup W-135; (3) DIC did occur (PT>100 sec, APTT >100 sec; controls were 11.4 and 30.1 sec, respectively; FDP: 16-32 μg/ml; normal: 0-0.5 μg/ml) (4) patient suffered from SLE with long-term corticosteroid usage, and, generally, SLE patients are more susceptible to environmental pathogens. Finally, typical manifestations of fulminant meningococcemia occurred and clinical conditions progressed rapidly. Patient died about 11 hours after admission. Therefore such kinds of patients should be managed cautiously and treatment should be instituted early.

Prevention

The concept of chemoprophylaxis came from the observation that short-term use of antibiotic therapy can eradicate meningococci from the nasopharynx for a long period of time. Effective medications for chemoprophylaxis are: rifampin, ceftriaxone, and quinoline[2,4].

Patient should be isolated and treated for at least 24 hours. Any one, who has had contact with the patients at home, nursery, or hospital, should receive chemoprophylaxis[2]. Current recommended regimen for chemoprophylaxis is rifampin at a dosage of 10mg/kg /12 h (up to 600mg) for 2 days for adults and children over one year of age and 5 mg/kg/12h for 2 days for children younger than one year of age. The alternative for rifampin is ciprofloxacin (single oral dose of 500mg) or ofloxacin (single oral dose of 400 mg). These medications are for adults only, not recommended for children or pregnant women. Pregnant women can use single intramuscular injection of 250 mg of ceftriaxone; children younger than age 12 can use 120mg of ceftriaxone[2,4].

Capsule of some serogroups can induce protective immune responses. Tetravalent vaccine containing capsular polysaccharides of serogroup A, C, Y, and W-135 is presently available. It is effective for prevention of meningococcal infection in adults and children over two years of age. The vaccine should be used for all intimate contacts of index cases at the initial use of chemoprophylaxis[2]. Other indications include travelers to epidemic regions, people with dysfunction

of spleen, or deficiencies in properdin or complement. The major drawback of the vaccine is the lack of immunogenicity in children less than 2 years old and the lack of an antigen that can induce protective response against serogroup B infection, leading to limited widespread use of the vaccine [2, 4].

Prepared by : Jaw-Ming Cherng[1] and Wang Lih-Shinn[2]

1. Department of Allergy, Immunology, and Rheumatology, Tzu-Chi General Hospital
2. Vice-Superintendent and Chief, Department of Infectious Disease, Tzu-Chi General Hospital

References

1. Stephens DS. Uncloaking the meningococcus: dynamics of carriage and disease. Lancet 1999;353:941-2.
2. Apicella MA. Meningococcal infection. In: Bennett JC et al, eds. Cecil textbook of medicine. Philadelphia: Saunders, 1996:1618-1622.
3. Statistics of Meningococcal Infection in Taiwan, Center For Disease Control, Department Of Health, Executive Yuan, Taiwan, ROC
4. Solberg CO. Meningococcal infections. In: Fauci AS et al., eds. Harrison's Principles of internal medicine, New York: McGraw-Hill, 1998:910-915.
5. van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. Clin Microbiol Rev 2000;13:144-166.
6. Mundy LM and L'Ecuyer PB. Treatment of infectious diseases. In: Carey CF, Lee HH, Woeltje, eds. The Washington manual of medical therapeutics. Philadelphia: Lippincott Williams & Wilkins, 1996:260-287.
7. Feliciano R, Swedler W, Varga J. Infection with uncommon subgroup Y Neisseria meningitidis in patients with systemic lupus erythematosus. Clin Exp Rheum 1999;17:737-740.