Meningococcal Disease in Taiwan 1996-2001: Epidemiology and Risk Factors for Death

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The incidence rate of meningococcal disease (MCD) was very low during last two decade in Taiwan, but the morbidity and fatality rate increased in 2000. We performed this study to review the epidemiology of MCD, and identify risk factors that may influence mortality. We performed a retrospective case-control study collecting the demographic characteristics, diagnoses and review of medical records of all the patients whom were reported through passive surveillance system from Jan. 1994 to Jun. 1998. A total of 115 patients were included. Average annual incidence was <0.02 per 100,000 population. Overall case fatality rate was 16.5%. On admission, the following clinical signs were significantly associated with fatality: fever, headache, neck stiffness, skin purpura (or petechia), and meningococcemia without meningitis. The laboratory parameters associated with death were a normal/low white blood cell count and a high serum GOT. The timing of antibiotics given also had influence on fatality. Parenteral antibiotics given before admission probably contributed to a reduction in the case fatality

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rate from MCD, and primary care physicians should be encouraged to give such treatment immediately on suspicion of the diagnosis before transferring the patient to hospital.

Keywords: meningococcal disease, epidemiology, risk factors for death

Preface

The Infectious Disease Law in Taiwan defines Meningococcal disease as a kind of "infectious meningitis". In Taiwan, this kind of infectious disease is sporadic. Up until 1996, there were fewer than ten reported cases of meningococcal disease per year, and very few mortalities were noted. However, in 2001, the number of reported cases began to increase. According to the statistics on legal infectious diseases of the CDC, during a six-month period, in 2001, seven of the reported cases proved fatal. In Taiwan, meningococcal disease is categorized in the sporadic transmissible disease group. Twenty to thirty cases of this larger group of diseases are reported per year and the mortality rate is 15%, even though the mortality rate in 1999 reached 38%. There have been few studies concerning the risk factors that cause death from meningococcal disease in Taiwan. Therefore, in addition to analyzing the epidemiology of meningococcal disease, a retrospective case-control study will be employed to explore the risk factors in fatal cases of meningococcal disease.

Materials and Methods

This study was designed as a retrospective case-control study. Subjects were defined by having clinical infectious syndromes, and *Neisseria meningitidis* was cultured through an aseptic site (blood or CSF fluid). We studied the cases of which the CDC has been informed from 1995/1/1 until 2000/6/30, and these cases must fulfill the definition aforementioned.

The author collected the data by going to each hospital that had reported cases and investigating the related medical records. For the remote areas that had reported only one case, a photocopy of the medical record was sent to the author. The data required for this study included demographic data, the clinical symptoms during admission, laboratory data, the diagnosis and medical arrangements by the physicians, the underlying disease and combination with other infections, treatment after admission, complications, sequelae or death, while the serotypes of cases were provided by the CDC.

For the collected cases, their data was keyed in, debugged and confirmed using Epi Info 2000 software. We divided the patients into a case group and a control group, depending on whether death occurred or not. The case group was defined as those patients who matched the case definition and had died because of the disease, while the control group was defined as patients who matched the case definition but had survived the disease. We use the Chi-square test for the categorical variables, while the t-test was used for the continuous variables. The groups were then compared in terms of variables such as their demographic data, situation during admission, whether antibiotics was used at an early stage or not, symptoms at the time of admission, whether they were suffering from other diseases at the same time, physical examination, laboratory data, treatment after admission, and serotypes of the bacteria strain. $P<0.05$ revealed a statistical difference.

Results

During the data collection period, of all of the reported cases, 117 were confirmed and two were ruled out as being incompatible with the case definition.

In total, there were 115 cases. Of these 115 cases, 67 were male and 48 female; 19 had died; and the mean mortality rate was 16.5%. Distributing the confirmed cases occurred by the month, it emerged that the number of cases increased in October, achieving a peak in April of the following year, and then declined rapidly. In previous years, only the B,W135 serogroup of *N. meningitidis* have been isolated from infected cases, and the B group accounted for the majority of cases, but, in 2001, the other serogroups (e.g. A, C, Y) of *N. meningitidis* have been identified. In 2000 and 2001, W135 accounted for the majority of cases.

Of the 115 confirmed cases, 8 were ruled out due to incomplete medical data. The cases were then divided into the case group (19) and the control (88) group, based on mortality, and these two groups were then analyzed.

Firstly, we compared the age distribution. If stratified by school age, most of these cases (38) are under a year old. The highest mortality occurred in the 19~25 year-old group (27.8%). As for gender, there are 9 males and 10 females in the case group, and 51 males and 37 females in the control group (P value = 0.556). Regarding the cases' occupations, 21 cases were ruled out, as the information was not recorded in their medical records. Among the remainder, most of the cases (52) were without a job (mainly children and elder males). Moreover, prostitutes, soldiers, and students have a higher mortality rate.

When the cases seek medical help, symptoms such as fever (>38℃), headaches, neck stiffness, and ecchymoses on the skin were the factors related to death. From their clinical manifestations, we found 36 cases presented with meningococcal bacteremia, of which 14 died (mortality rate: 38.9%) have a higher mortality rate than the cases with meningitis symptoms (mortality rate: 7.6%), with a statistical significance (P<0.001). Considering the laboratory results of these cases, white blood cell count and liver function were the risk factors related to death.

We analyzed the admission condition and treatment before and after admission. We found that “cases without prior medical help”, “no antibiotics used before seeking medical help” and “no antibiotics used after” were the risk factors related to death. Afterwards, we analyzed whether the cases had received antibiotic treatment before seeing a doctor. Among the 107 cases, 19 cases were ruled out due to unknown antibiotics used. Stratified by “days to antibiotics used from start of symptoms,” it is found that mortality rate is higher in “after 5 days” group (28.6%) than “Day 1” group (10.5%).

The antibiotics most frequently used in the case group and the control group was penicillin combined with third generation cephalosporin. The mean durations for major antibiotics use were 1 day (range 0-13 days) in the case group and 12 days in the control group(range 0-56 days) with a statistical significance if $P<0.001$. A total of 95 cases in the reported hospitals underwent an antibiotics sensibility test on the *N. meningitides* isolated from their specimen. Trivial differences in the antibiotics sensibility test were noted between the specimens isolated from the blood or CSF. Overall, the antibiotics sensibility results for penicillin were 50%. For third generation cephalosporins (cefotaxime, cefuroxime, ceftriaxone), the results were all above 90%.

Regarding the dexamethasone use, only 32 patients (7 in the case group and 25 in the control group) ever received such treatment. The statistical findings about the sequelae and dexamethasone use in surviving cases show that 11 cases have documented sequelae in their medical records. 5 of them had dexamethasone treatment while the remaining six cases had not. There is no significant difference between the two groups. These sequelae included 5 cases of focal neuropathy, 5 cases of loss of hearing and 1 case of hand amputation (the subject in this case was 4 months old, and he underwent left hand amputation to the palm and a skin graft due to skin gangrene).

Discussion

In the past 50 years, the known “Meningitis Belt” in Sub-Saharan Africa experiences one major meningitis epidemic every 8 to 12 years. No other regions reveal such cyclic outbreaks [1]. During Japanese occupation, two meningitis outbreaks occurred in Taiwan, with annual reported cases ranging from 300 to a maximum of 600 [7]; in the past 20 years, the number of reported infections was fewer than 10 [8]. However, since 1996 cases of meningitis started to rise, from 10 to 20. In 2001, the CDC’s statistics of legal infectious diseases confirmed more than 40 cases, proven by further investigation as individual infections. The Law of Infectious Disease Control and Prevention, published in Taiwan on June 2001, establishes clear regulations and penalties with regards to the notification of infectious diseases. CDC has also enhanced its promotion on the notification procedure by medical institutions and on the correct measure of sample delivery. These may have some effects on the increase of reported and confirmed cases of meningococcal disease.

Climatic change is crucial to the spread of meningococcal disease. This study shows that every year the increase of cases starts in October and after the peak season in April follows a rapid decline. It is important to notice that this seasonal pattern is very similar to other viral and bacterial respiratory infections, which should be differentiated during diagnosis [1]. In the “Meningitis Belt” of Sub-Saharan Africa, the outbreak initiates in the dry season when harmattan is frequent, and subsides with the arrival of the rainy season. The relatively low humidity level and dusty air would cause direct damage to the mucosal lining of the respiratory tract, inhibiting the immunological function of the mucosa, hence reducing human body's resistance to infections [1,9]. In endemic areas, winter and spring seasons have the highest infection level. In general, the number of cases starts to rise in December and peaks in March and April the following year, followed by a gradual decline after May. This study concludes a similar pattern.

In the past, from infected cases only *N. meningitidis* serogroup B and W135 have been isolated, and serogroup B accounted for most of the cases. In 2001 other *N. meningitidis* serogroups (ie. A, C, Y) were identified, and in 2000 and 2001, W135 serogroup became the predominant one. There are reports stating that in the year 2000 pilgrims returning from Mecca have caused an outbreak of serogroup W135 meningococcal infection in Europe, where serogroup A usually accounts for most cases. The increase of travelers abroad, thanks to the advance of international transportation, may have caused mutations of serogroup; however, the possibility of mutations inside Taiwan serogroups should also be considered. In the meantime, serologic investigation of infectious diseases provides information for future use of vaccines.

This study finds out symptoms such as fever, headache, neck stiffness, ecchymoses are factors related to a case's mortality rate when he/she seeks medical help. As the first three are protective factors, the symptom of ecchymoses represents a risk factor. When examining cases' medical records, we find out that the first three symptoms on a patient often help doctors to suspect a meningococcal disease or other infections. Therefore, the immediate use of antibiotics prevents possible death. However, when a patient seeks treatment over signs of ecchymoses, his/her condition is usually more severe and prognosis less positive. Studies in other countries also suggested a higher mortality rate of cases presented with ecchymoses [11].

Cases presented with only symptoms of meningitis but no meningococcemia have shown a better prognosis. In this study, none of the 32 cases presented with only meningitis symptoms is fatal, echoing the results of Flægstad et al. [12]. When disseminated intravascular coagulation (DIC) occurs, the thrombi can adsorb white blood cells, causing them to reduce in number. The reduction of white blood cells often suggests the rise of mortality rate [14]. This study observes that the number of white blood cells below 10,000 cells/mm^3 is a risk factor related to death and has statistical significance. Similar results are found in Tüysüz et al. (1993) [11].

Analyzing the condition of seeking medical help and treatment, we find out that "cases didn't seek prior medical help", "no antibiotics were used before seeing a doctor" and "no antibiotics was used after seeing a doctor" are the risk factors related to death. The mortality rate is higher when cases have been treated with antibiotics more days after symptoms appeared. Many studies have proven that suspected or confirmed meningococcal infections should start antibiotics treatment as early as possible, therefore reducing their morality rates [9,11,15-18]. This study also shows that an untimely treatment of antibiotics due to acute symptoms or delayed diagnosis resulted in a high mortality rate. Clinical doctors, especially those working in emergency and pediatric sectors, should be given an enhanced training on the diagnosis of meningococcal disease. This would help them to diagnose such cases at first hand and start antibiotics in time to reduce mortality rate.

On the other hand, *N. meningitidis* isolated from our cases in this study demonstrates a 50% sensitivity rate to penicillin and more than 90% to the third generation of cephalosporins (efotaxime, cefuroxime, ceftriaxone). The combination of penicillin and the third generation cephalosporin is the most popular antibiotic choice among clinical doctors.

Host cells and macrophages infected with meningococcus would release cytokines, especially TNF-α and interleukin-1β, causing multiple organ failure. Adrenal corticosteroids can inhibit the release of cytokines and works best if used 20 to 30 minutes before antibiotic. According to some studies, the use of adrenal corticosteroids at the initial stage of infection (2-4 days) can reduce the risk of sequelae, though having no effect on the mortality rate [19,20]. This study shows that there is no relation between the use of adrenal corticosteroids and the mortality rate. In the control group, the use of adrenal corticosteroids demonstrates no link with the development of sequelae. In a further analysis, the reason that these cases presented with symptoms are not treated with adrenal corticosteroids is probably because their initial symptoms were not serious enough to convince doctors to choose such treatment.

There are doubts over whether restrictions set by the National Health Insurance on the use of antibiotics have something to do with the increase of meningococcal disease and its mortality rate. This study does not find such connections. Though an early treatment of antibiotics can effectively reduce the mortality rate of meningococcal disease, this disease remains very rare in Taiwan with less than 0.2 cases in a million every year [6]. We do not encourage the abuse of antibiotics, because it would create super bacteria with high resistance to medicines, resulting in far more severe disasters in public health protection.

Therefore, only in specific cases and circumstances (ex. in endemic areas, previous contacts with infected patients, cases developing fevers and ecchymoses) are antibiotics used as treatment [17]. The real way to reduce the mortality rate of meningococcal disease is via diagnosis. Continuing education arranged by medical associations (ex. Infectious Diseases Society of Taiwan, Society of Emergency and Critical Care Medicine, Taiwan Pediatric Association) for doctors can keep them alert to the disease and enable correct diagnosis to save precious time for treatment, hence reducing the mortality rate.

Conclusion

During the season of meningococcal infections, health authorities should promote the public's awareness of the disease's clinical features, which helps them seek medical help and treatment in time. More training should also be given to doctors who have most contact with meningococcal cases (such as in emergency or pediatric sectors), to enhance their diagnostic capability. Correct diagnosis and timely treatment of antibiotics can prevent possible deaths. These dual efforts, focusing the public and the doctors, should have a positive effect in reducing the mortality rate of meningococcal disease.

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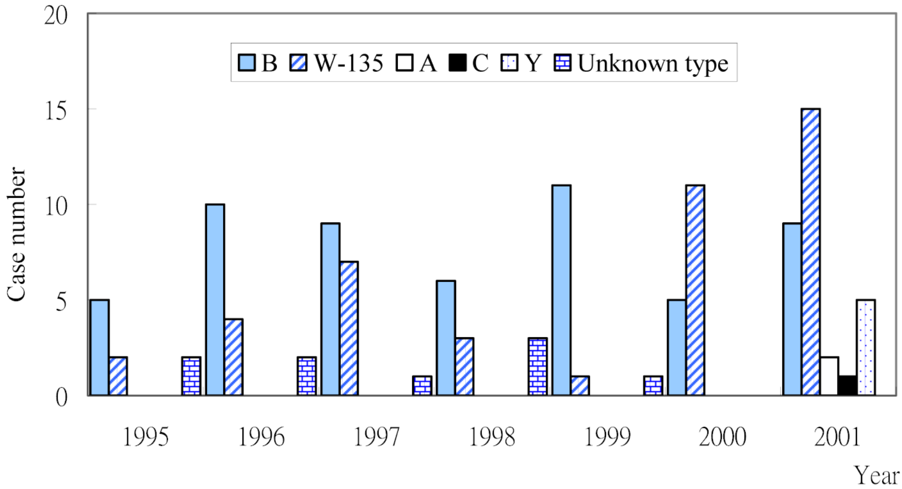

Figure 1: serotype (ps: case number between Jan-Jun 2001)

Table 1: An analysis on the clinical symptoms/laboratory data related to fatal cases of meningococcal meningitis

Clinical symptoms／items	Case number N=19	control number N=88	OR	95%CI	P value
Infection sign					
Fever*	14	82	0.20	0.06 - 0.76	0.034
Chills	4	13	0.78	0.21 - 2.93	0.972
URI symptoms within 2weeks	14	61	1.24	0.41 - 3.79	0.920
Neurological sign					
Headache*	2	38	0.15	0.03 - 0.71	0.016
Neck stiffness*	1	45	0.05	0.01 - 0.42	0.001
Seizure	5	13	2.06	0.63 - 6.70	0.378
Coma	2	1	10.23	0.88 - 119.34	0.138
Drowsy	5	26	0.85	0.28 - 2.61	0.998
Dermatological symptoms					
Rash	2	11	0.82	0.17 - 4.06	0.882
Petechia/Purpura*	13	18	8.43	2.50 30.29	0.000
GI symptoms					
Nausea/Vomiting	7	49	0.46	0.17 - 1.29	0.216
Abd. pain	2	11	0.82	0.17 - 4.06	0.882
Diarrhea	1	8	0.56	0.07 - 4.73	0.929
WBC count (cells/mm^3)*					
<10000	10	24	3.75	1.12 - 12.89	0.026
>10000	7	63			
Platelet count (thrombocytes /mm^3)					
<130,000	8	19	2.95	0.85 - 9.89	0.069
>130,000	9	63			
GOT (IU/L)*					
>50	8	10	4.90	1.24 - 18.9	0.017
<50	8	49			
Na (meq/L)					
<135 or >145	7	18	2.42	0.66 - 8.47	0.132
135-145	9	56			
K (meq/L)					
<3.5 or >5.3	4	16	1.21	0.25 - 4.73	0.748
3.5-5.3	12	58			
PT,PTT prolong					
Yes	10	12	2.50	0.57 - 11.81	0.289
No	5	15			

*The results have a statistically significant difference if P<0.05

Table 2: Antibiotics susceptibility to *N. meningitidis* isolated from the cases' specimens

Blood cultur	P	AM	CTX	CXM	C	SXT	RIF	CRO
R No.(%)	10(23)	2(7)	0	1(3)	0	26(79)	2(17)	1(3)
I No.(%)	12(27)	0	0	0	0	1(3)	0	1(3)
S No.(%)	22(50)	26(93)	22(100)	30(97)	14(100)	6(18)	10(83)	29(94)

CSFfluid culture	P	AM	CTX	CXM	C	SXT	RIF	CRO
R No.(%)	7(20)	0	0	0	0	16(76)	2(25)	0
I No.(%)	11(31)	0	2(10)	0	0	0	0	1(4)
S No.(%)	17(49)	20(100)	19(90)	26(100)	11(100)	5(24)	6(75)	24(96)

P: penicillin, AM: ampicillin, CTX: cefotaxime, CXM: cefuroxime, C: chloramphenicol,
SXT: Co-trimoxazole, RIF: rifampin, CRO: ceftriaxone, R: resistance, I: intermediate resistance, S: sensitivity.
No.: number of cases that received a specific antibiotics sensibility test