Outbreak of Meningococcal Disease after an Influenza B Epidemic at a Hellenic Air Force Recruit Training Center

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In January 1996, during an outbreak of meningococcal disease at a Hellenic Air Force recruit center in southern Greece, we collected paired serum specimens from 55 randomly selected recruits and tested for antibodies against influenza virus types A and B. Of 55 specimens, 15 (27%) were found to be positive for recent influenza B infection, confirming previous reports that respiratory tract infection due to influenza is probably a predisposing factor for meningococcal disease.

Meningococcal disease is a major public health problem in both developed and developing countries. Neisseria meningitidis can cause outbreaks of meningitis among individuals in schools and military camps. There are pieces of evidence supporting the hypothesis that respiratory tract infections caused by virus or mycoplasma may play a role in the pathogenesis of meningococcal disease [1–5]. In January 1996, an outbreak of meningococcal disease occurred at a Hellenic Air Force recruit center and training base in southern Greece. During the 15-day period when this outbreak occurred, a large number of recruits presented to the training base infirmary and complained of influenza-like symptoms. The fact that these events coincided provided us with the opportunity to study the proposed association between the 2 types of infection.

Case report. From 8 January through 10 January, a total of 1304 men were recruited at the training base. One week later, a significant number of recruits (593 [45.4%] of 1304) presented to the infirmary complaining of fever and influenza-like symptoms. The clinical syndrome of upper respiratory tract symptoms, which included high fever, headache, and myalgia, and the sudden expansion of the epidemic were compatible with a possible outbreak of influenza. On 19 January, while taking a short leave of absence, a squadron trainer was admitted to the Hellenic Air Force General Hospital in Athens because of meningitis. Two days later, 2 recruits from the same squadron developed high fever, headache, vomiting, and confusion. They were both transferred to the local hospital, where meningococcal meningitis was diagnosed. On the same day (21 January), the epidemic of influenza-like illness among the recruits reached its peak (figure 1). A team of physicians was sent to the base to deploy a clinic for the recruits affected by the epidemic. During the following 3 days, 7 more cases of meningococcal meningitis occurred among the personnel of the same squadron.

All patients were transferred to the local hospital and began receiving treatment with either ceftriaxone or penicillin G within 1 h of arrival. Because of a lack of facilities and personnel, not all patients underwent lumbar puncture. A total of 10 cases of infection due to invasive group C N. meningitidis (3 clinically confirmed cases and 7 laboratory-confirmed cases) were diagnosed among the 432 men of the squadron (attack rate, 2.31%). The clinical presentation of meningococcal disease included meningococcal sepsis without meningitis (1 case), meningitis (6 cases), meningitis and arthritis (2 cases), and

Figure 1. Influenza B epidemic and outbreak of meningococcal disease at a Hellenic Air Force training base in southern Greece in 1996. The red line denotes the curve of the epidemic of influenza cases, and each box that is part of a bar denotes a case of meningitis.
meningitis and myocarditis (1 case). Three of the patients developed the typical hemorrhagic rash. All patients survived without major complications (1 had hearing impairment and 1 had peroneal nerve paralysis).

**Materials and methods.** Cases were regarded as presumed invasive meningococcal disease (i.e., they were only clinically confirmed) on the basis of the presence of fever (temperature 38.5°C), headache or confusion, and either cervical stiffness or typical hemorrhagic rash. Cases of invasive meningococcal disease were regarded as laboratory confirmed on the basis of either (1) a positive blood culture result or (2) a positive CSF Gram stain result, a positive CSF culture result, or the presence of CSF characteristics that suggested microbial infection. A case of influenza was defined according to the following criteria: fever (temperature >37.8°C) and the presence of ≥1 symptom of influenza (e.g., myalgia, headache, cough, sore throat, and nasal congestion). The criteria for serologic diagnosis included either a 4-fold increase in the antibody titers of 2 serum samples obtained during the acute and convalescent phases of the disease or a permanent high antibody titer of ≥1:64 in both serum samples.

On 28 January and 26 February, paired blood samples were obtained from 55 randomly selected squadron recruits and from 9 of the patients with meningococcal disease. The conventional CF assay (Hoechst Laboratory) was used for the detection of antibodies against influenza A and B antigens [6]. Complement and hemolysin (bioMérieux) were used in their optimal dilution, as determined by chessboard titration. The serum samples were examined in serial dilutions that ranged from 1:8 to 1:512. Paired serum samples were examined in parallel. A positive result was considered to show 50% hemolysis.

**Results and discussion.** Antibodies against influenza B that were compatible with recent infection were found in 11 of 25 recruits with the clinical syndrome of influenza and in 4 of 30 recruits without symptoms. This finding suggested a positive association between influenza B infection and the clinical syndrome (Mantel-Haenszel χ² test value, 6.35; P = .01; maximum likelihood estimate of the OR, 4.95; 95% CI, 1.19 < OR < 25.42). In addition, 5 of the 9 patients were also found to have antibodies against influenza B.

In the present study, we showed that an epidemic of infection due to influenza B preceded the outbreak of meningococcal disease. Several reports have proposed an association between influenza infection and meningococcal meningitis [1–3, 5, 7, 8]. Possible mechanisms by which a viral infection may increase the risk of invasive meningococcal disease are (1) increased transmission of meningococci through cough and respiratory excretions and (2) increased invasiveness of meningococci due to local inflammation of the upper respiratory tract and/or interference of viral infections with humoral immunity against *N. meningitidis.*

Adenovirus, respiratory syncytial virus, and parainfluenza viruses are other possible causes of the clinical syndrome that preceded the outbreak of meningococcal disease. These alternative diagnoses were empirically excluded because both the constellation of clinical symptoms and signs and the pattern of epidemic spread were highly suggestive of influenza.

Of interest, we observed that the beginning of the influenza epidemic coincided with a substantial decrease in the local temperature to levels below the average minimum temperature recorded for this month. The role of exposure to cold weather with regard to the emergence of respiratory diseases is unclear. The cold weather–related increase in the incidence of and morbidity associated with respiratory diseases is generally attributed to cross-infection resulting from indoor crowding, the effects of low temperature on the immune system, and, possibly, the cold weather–facilitated survival of bacteria in droplets [9].

To prevent secondary cases, chemoprophylaxis is recommended for all individuals who have had close contact with persons who have meningococcal meningitis. Several reports of outbreaks of meningococcal disease among individuals at schools and among military personnel have shown that early implementation of chemoprophylaxis controls the progress of the epidemic [10]. In our study, a program of rifampin prophylaxis was initiated on day 2 of the epidemic. Compliance exceeded 98%, and it is of interest that 2 of the consecutive cases occurred among the 2% of recruits who did not follow the program.

Since 1990, only a small cluster of group C invasive meningococcal disease (2 cases) have occurred in the Hellenic Air Force (D.H., author’s unpublished data). At the time of occurrence of the 2 epidemics, the meningococcal vaccine was not included in the immunization program of the recruit center mentioned in the present study. In military settings, vaccination with the tetravalent vaccine (A, C, Y, and W135) is the most effective strategy for prevention of epidemic meningococcal disease. A disadvantage of this strategy is the lack of protection against group B meningococci, which cause almost 40% of the total number of cases of meningococcal disease in Greece. On the other hand, an program for immunization against influenza and other respiratory viruses may indirectly prevent outbreaks of meningococcal disease, including those caused by group B meningococci.

**References**