Respiratory Viruses and Mycoplasma as Cofactors for Epidemic Group A Meningococcal Meningitis

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To investigate the role of coincident respiratory viral and mycoplasmal agents in the pathogenesis of meningococcal meningitis, we performed a matched case-control study of 62 patients with group A meningococcal meningitis during an epidemic in Chad. Case patients were more likely than controls to have nasal colonization or infection with respiratory viruses and *Mycoplasma* species (matched odds ratio, 23; 95% confidence interval, 3.1 to 170). Respiratory pathogens were found more commonly in older patients with meningitis (odds ratios were 2.9 for children under age 5 years and 46.5 in those over age 15 years), consistent with the increasing risk of meningitis with age during epidemics. In controls, the presence of respiratory pathogens increased the risk of upper-respiratory-tract symptoms but did not significantly increase meningococcal carriage.

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EPIDEMIC meningococcal meningitis is a major cause of morbidity and mortality in developing countries. Although most industrialized nations have been free of epidemic group A meningococcal disease since the late 1940s,[1] cyclic group A meningococcal meningitis epidemics occur every 8 to 14 years in a broad region of sub-Saharan Africa known as the "meningitis belt."[2] During such epidemics, attack rates can exceed 1% of the general population,[3] and over 40 000 cases occurred during a recent epidemic in Ethiopia. These epidemics are highly seasonal, occurring primarily during the dry season and ending with the onset of rains.[4]

Coincident upper-respiratory-tract infections have been suggested as predisposing risk factors for the subsequent development of meningococcal disease.[5] Both sporadic cases and outbreaks of meningococcal disease have been associated with concurrent viral respiratory-tract illness.[5,6] However, these studies have not been widely accepted because they either lacked a proper control group or were limited in scope.[7,8] To investigate the relationship between meningococcal meningitis and respiratory pathogens, we conducted a case-control study of nasopharyngeal shedding of respiratory mycoplasma and viruses among patients with group A meningococcal meningitis during the 1988 epidemic at N'Djamena, Chad.

SUBJECTS AND METHODS

Background

In early spring 1988, physicians in N'Djamena noted a sudden increase in admissions due to invasive group A meningococcal disease (Fig 1). Daily case counts rose between late February and early April, reaching a peak of 141 hospital admissions per day on April 11. The serogroup A *Neisseria meningitidis* strain causing this epidemic has been previously shown to belong to the III-1 clonal group.[9] Overall, 4542 cases of meningococcal disease were reported from N'Djamena between February 22 and May 1, 1988, giving a citywide attack rate of 0.9%. This clonal group may have been imported into Chad by returning Islamic pilgrims after a major III-1 epidemic at the 1987 pilgrimage to Mecca, Saudi Arabia. Although these pilgrims were required to be vaccinated against group A meningococcus, vaccination does not prevent a person from becoming a carrier of meningococcus.[10]

Case-Control Study

Patients with signs and symptoms of meningococcal meningitis were enrolled into our study by an admitting physician in the emergency ward of Hôpital Central, N'Djamena. Cerebrospinal fluid was cultured and tested for group A meningococcal antigen using group A polysaccharide–specific latex agglutination kits (Directigen, Becton-Dickinson, Baltimore, Md). The serogroups of meningococci in positive cerebrospinal fluid cultures were determined using group A antisera. Our case definition for group A meningococcal meningitis was a patient who had compatible symptoms (fever, headache, and neck stiffness) and laboratory evidence of group A *N meningitidis* meningitis. A brief questionnaire was administered to patients, and nasopharyngeal washings were taken using cotton swabs soaked with phosphate-buffered saline. Oropharyngeal throat swabs were plated directly on selective agar to determine the meningococcal carrier status.[10]

Control patients were matched with patients suspected to have meningitis by age (±2 years for children under age 15 years and ±5 years for those over age 15 years), sex, and neighborhood. Controls were enrolled from the patient's neighborhood by systematically canvassing consecutive households until a matching volunteer was found. Controls were enrolled within 48 hours of admission of the case patient suspected to have meningitis, matching for the date of onset as well. One case-control pair was mismatched on sex (female case, male control) but met the remaining matching criteria. Questionnaire responses, nasopharyngeal washings, and throat cultures were obtained from neighborhood controls in the same manner as from suspected case patients.

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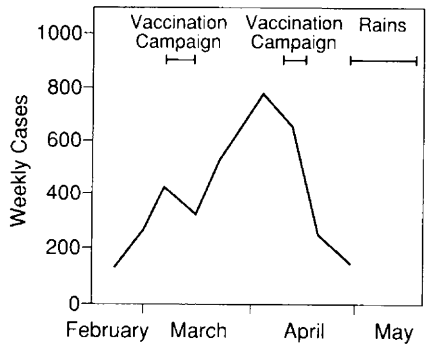

Fig 1.—Group A meningococcal meningitis, N'Djamena, Chad, 1988. Meningitis rates rapidly declined after two vaccination campaigns achieved an estimated 95% coverage of children and adults aged 2 through 25 years.

Microbiologic Procedures

Specimens from patients and controls were transported on ice to the laboratory, usually within 30 minutes of obtaining the sample. Nasopharyngeal washings were placed in liquid nitrogen on arrival at the laboratory and transported to the Centers for Disease Control, Atlanta, Ga, for further studies. At the Centers for Disease Control, nasopharyngeal washings were tested for respiratory viruses by both antigen assays and culture. Antigen testing was performed using time-resolved fluoroimmunoassays for adenovirus, respiratory syncytial virus, and parainfluenza viruses 1, 2, and 3.[11,12] Viral cultures were performed by inoculating undiluted specimens onto human embryonic lung diploid fibroblast, human heteroploid laryngeal epidermoid carcinoma, primary human embryonic kidney, and primary rhesus monkey kidney cell cultures after treatment with antibiotics (penicillin G, 100 U/mL, and streptomycin sulfate, 100 mg/L) and low-speed centrifugation.[13] Viruses detected by cytopathologic changes or by hemadsorption in these cells were identified by standard serum neutralization, hemagglutination-inhibition, enzyme immunoassay, and electron-microscopic techniques.[13] Nasopharyngeal washings from 10 of 108 suspected case patients and 13 of 103 controls were uninterpretable on time-resolved fluoroimmunoassays because of heavy bacterial and/or fungal contamination. These washings were considered negative for a respiratory infection if no growth was noted on either viral or mycoplasmal culture. Case specimens were processed before control specimens, but all remained at −70°C until they were analyzed.

Mycoplasma were suspected when nonspecific cytopathologic changes were observed in many of the initial cell cultures. Supernatants from cultures were inoculated onto *Mycoplasma* media and incubated under semianaerobic conditions to detect mycoplasma. Fifteen *Mycoplasma* cultures were isolated and identified based on distinctive colony morphologic characteristics on *Mycoplasma* media. Speciation by growth inhibition with specific antisera was possible in only six of these 15 isolates (all identified as *Mycoplasma hominis*) because of loss of the cultures.

Detection of respiratory viruses and Mycoplasma in nasopharyngeal samples may have represented a range of host-parasite responses, from harmless colonization to invasive disease. We have chosen the term *respiratory infection* to describe this relationship, denoting positive detection of a viral or mycoplasmal respiratory agent from either case patients or controls.

Statistical Analysis

Risk factors for group A meningococcal meningitis were examined using matched univariate analysis. For conditional logistic regression, case patients and controls were stratified into age and sex categories (0 to 4.9, 5 to 14.9, and >15 years). Living space was categorized into those who had 2.3 rooms or more per family in their dwelling vs those with less than 2.3 rooms per family. This cutoff point was based on the difference between the unmatched mean values of case and control households.

The association between symptoms, meningococcal carriage, and respiratory infection was analyzed in the neighborhood control group alone. Cases of meningococcal disease were excluded from this analysis since both symptoms and meningococcal carriage are associated with invasive meningococcal disease. By examining the control group alone, the potentially confounding effect of meningococcal disease on meningococcal carriage and respiratory symptoms was avoided.

RESULTS

Respiratory Viruses and Mycoplasma Species

During the study period, 108 patients suspected to have meningitis and 103 matched neighborhood controls were enrolled. Seventy-three (68%) of these 108 suspected patients had laboratory-confirmed group A meningococcal meningitis. Of the 73 confirmed case patients, four case patients had no matching controls, and another four case patients and three controls had uninterpretable nasopharyngeal washings due to insufficient quantity or severe fungal contamination. The remaining 62 case-control sets were available for matched analysis. The average age of these case patients was 10.2 years compared with 10.6 years for the controls. Forty-two (68%) of the 62 patients with meningococcal meningitis and 16 (26%) of the 62 controls carried group A meningococcus.

Nasopharyngeal washings from case patients and controls were positive for a variety of respiratory viruses, including adenoviruses, parainfluenza virus, rhinovirus, and respiratory syncytial virus (Table 1). Herpes simplex virus, type 1, was isolated from one patient, but this case was considered negative for a respiratory isolate since herpes simplex virus, type 1, is commonly reactivated during febrile illness. Cultures of 15 nasopharyngeal washings were positive for mycoplasma, and six of these 15 isolates were identified as *M hominis* by growth inhibition with specific antisera. There were no nasopharyngeal samples positive for both a viral and a mycoplasmal pathogen.

Overall, results of nasopharyngeal washings were positive for either a viral or mycoplasmal respiratory agent for 29 (47%) of 62 patients with group A meningococcal meningitis compared with seven (11%) of 62 neighborhood controls. In the matched analysis (Fig 2), there were 23 discordant case-control pairs in which results of nasopharyngeal washings from cases were positive for respiratory pathogens while results from corresponding controls were negative. In comparison, there was only one discordant pair in which nasopharyngeal results were negative for the case and positive for the corresponding control, resulting in a matched odds ratio of 23 and a 95% confidence interval (CI) of 3.1 to 170.

To separately determine the risk associated with either a viral or a mycoplasmal infection, these two groups of respiratory pathogens were analyzed individually. Respiratory viruses were found significantly more often in case patients than controls (matched odds ratio, 5.5; 95% CI, 1.2 to 24.8). Respiratory mycoplasma were also strongly associated with meningococcal meningitis, but the odds ratio could not be calculated since there were no discordant pairs in which nasopharyngeal results were positive for mycoplasma for the case and negative for the corresponding control (lower 95% confidence limit, 3.9).

Older patients with meningitis were significantly more likely to have cultures positive for a coincident respiratory agent than younger patients. Patients with meningococcal meningitis

Table 1.—Upper-Respiratory-Tract Pathogens Identified From Patients With Group A Meningococcal Meningitis and Controls, Chad, 1988

Pathogen*	No. (%) With Pathogen	
	Patients With Group A Meningococcal Meningitis (n = 62)	Neighborhood Controls (n = 62)
Adenoviruses (types 2 and 7)	4	2
Parainfluenza (types 1 and 3)	6	4
Respiratory syncytial virus	2	0
Rhinoviruses	3	0
Mycoplasma species	14	1
No pathogen	33	55
Total with pathogens	29/62 (47)	7/62 (11)

*Six of the viral pathogens were detected by time-resolved fluoroimmunoassays alone and 15 were detected by culture alone or by culture and time-resolved fluoroimmunoassay. Six of the 15 *Mycoplasma* isolates were speciated as *Mycoplasma hominis* by growth inhibition.

Table 2.—Effect of Age on the Risk of Group A Meningococcal Meningitis and Coincident Respiratory Infection

Age, y	No. of Case-Control Pairs	Odds Ratio (95% Confidence Interval)*
0-4.9	31	2.9 (0.9-9.1)
5-14.9	16	11.6 (3.0-44.7)
≥15	15	46.5 (3.3-661)

*Odds ratios are determined from maximum likelihood estimates by conditional logistic regression. Likelihood ratio test for trend in age, $\chi 2 = 4.17$, $P < .05$.

under 5 years of age had the lowest odds ratio for being carriers of respiratory viruses and mycoplasma, patients 5 to 15 years old had an intermediate risk, and patients over 15 years of age had the highest risk (Table 2).

Interaction of Risk Factors

Meningococcal carrier status, vaccination, the number of rooms per family, and the number of rooms in the dwelling were also either significant risk factors or protective factors for meningococcal disease (Table 3). Several other measures of crowding, such as the number of persons sleeping with the case or control, were not significantly associated with disease risk. The polysaccharide vaccine was highly effective during the Chad epidemic; the unadjusted vaccine efficacy was 95% (95% CI, 64% to 99%). It is likely that this is actually an underestimate of the true vaccine efficacy, since adjustment was not made for the lag time necessary for the development of protective antibodies.

To evaluate potential interactions between respiratory infections and other risk factors, conditional logistic regression was performed using risk factors found to be significant in the univariate analysis. Since there was only one discordant set in which nasopharyngeal results were positive for respiratory pathogens for a case and negative for the corresponding control, it was necessary to group cases and controls into larger sex- and age-matched categories to perform the logistic regression. Although the estimated odds ratio for respiratory infection declined because of this group matching, the association remained significant after adjusting for potential confounding by meningococcal carriage, crowding, and vaccination (Table 4). The significance of crowding as a risk factor decreased after adjusting for both meningococcal carriage and respiratory infection, suggesting that crowding may increase the risk of meningococcal disease by increasing the rate of meningococcal carriage or respiratory infections.

Respiratory Symptoms and Meningococcal Carriage

If respiratory infections increase person-to-person transmission of meningococci, respiratory infections should significantly increase the incidence of meningococcal carriage as well as invasive meningococcal disease. Since group A meningococcal meningitis is highly correlated with both respiratory infection and meningococcal carriage, we studied this association in the control group alone.

Nasopharyngeal washings and meningococcal throat swabs were available from 98 of the 103 controls. Of these, 27 were carriers of group A meningococcus. Respiratory viruses and mycoplasma were found in four (15%) of these 27 carriers compared with five (7%) of the 71 noncarriers (relative risk, 2.1; 95% CI, 0.6 to 7.2). This risk, although marginally elevated, suggests that coincident respiratory agents did not significantly increase meningococcal carriage.

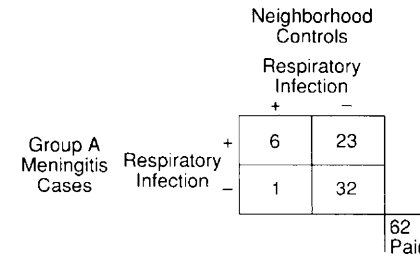

Fig 2.—Association between group A meningococcal meningitis and coincident upper-respiratory-tract infection in 62 case-control pairs (odds ratio, 23; 95% confidence interval, 3.1 to 170).

In the control group, cough was associated with coincident respiratory virus and *Mycoplasma* infections (relative risk, 5.0; 95% CI, 1.5 to 16.5). Other respiratory and systemic symptoms, such as sore throat, fever, and diarrhea, were increased in patients with respiratory virus and *Mycoplasma* infections, but these relative risks were not significantly greater than 1. Carriers of group A meningococcus were more likely to report recent fever than noncarriers (relative risk, 2.2; 95% CI, 1.0 to 4.7). Sore throat, cough, and diarrhea were not found to be associated with meningococcal carrier status.

COMMENT

Coincident viral infections are an important cause of secondary bacterial disease in humans.[7] For example, the role of the influenza virus in promoting secondary bacterial pneumonitis is well established,[14] and viral respiratory infections have been implicated as a cause of acute bacterial otitis media.[15] Our study demonstrates that coincident viral and mycoplasmal respiratory agents are risk factors for epidemic group A meningococcal meningitis as well.

The role of coincident respiratory agents in epidemic group A meningococcal meningitis may help to explain the unusual epidemiologic characteristics of this disease. For example, invasive meningococcal disease occurs almost exclusively during the dry season in Africa, but person-to-person transmission of carriage occurs year-round.[4,16] Additional risk factors, such as seasonal respiratory infections, may be required for expression of an epidemic once a pathogenic meningococcus strain becomes established in a susceptible population.[16]

Coincident viral and mycoplasmal respiratory agents may also contribute

Table 3.—Potential Risk Factors for Group A Meningococcal Meningitis

Risk Factor	No. of Sets*	Matched Odds Ratio (95% Confidence Interval)			
		Categorical Variables			
Respiratory infection	62	23.0 (3.1-170.3)			
Group A meningococcal carrier	62	6.2 (1.38-10.1)			
Vaccination	62	0.05 (0.01-0.36)			
<2.3 Rooms per family	46	2.4 (1.1-5.1)			
	No. of Sets*	Cases†	Controls†	Mean Difference Between Pairs	P‡
		Continuous Variables			
No. of families in dwelling	52	2.7 ± 0.2	3.1 ± 0.3	−0.4	.25
No. of rooms in dwelling	50	5.0 ± 0.5	7.7 ± 0.6	−2.7	.001
No. of persons sleeping in same room	58	5.2 ± 0.3	4.6 ± 0.3	+0.6	.30
No. of rooms per family in dwelling	46	2.1 ± 0.2	3.1 ± 0.3	−1.0	.003

*Number of case-control sets with information on the risk factor.
†Values are mean ± SEM.
‡Difference between pairs of cases and controls by the two-sided Wilcoxon Rank-Sum Test.

Table 4.—Conditional Logistic Regression Analysis of Potential Risk Factors for Group A Meningococcal Meningitis

Model No.	Outcome Variable	Odds Ratio (95% Confidence Interval)	Exposure Variables
1	Meningitis	7.8 (3.1-19.3)	Respiratory infection alone
2	Meningitis	5.6 (1.9-16.5)	Respiratory infection
		5.0 (2.0-12.4)	Meningococcal carrier
		2.0 (0.8-5.1)	<2.3 rooms per family
3	Meningitis	5.3 (1.7-16.1)	Respiratory infection
		4.6 (1.8-11.6)	Meningococcal carrier
		1.8 (0.7-4.7)	<2.3 rooms per family
		0.26 (0.08-0.81)	Vaccination

to an upward shift in age-specific attack rates during meningococcal meningitis epidemics. While the highest age-specific rates for sporadic meningococcal meningitis are in children under 1 year old,[17] older age groups are disproportionately affected during epidemics.[3,18] In our study, respiratory infections were associated with a significantly higher risk of meningococcal disease in patients over 15 years old. One possible explanation for this finding is that respiratory infections are necessary to overcome protection afforded by preexistent antibodies. Protective antibodies against pathogenic *N meningitidis* form while a person is an oropharyngeal carrier of nonpathogenic *Neisseria* species.[19] Infants and younger children generally have lower protective meningococcal antibody titers than adults[20] and may be more susceptible to disease on first encounter with a pathogenic *N meningitidis* strain. However, in adults with preexistent antibodies, the additional insult of a respiratory infection may be needed to initiate invasive meningococcal disease. Respiratory infections could recruit previously resistant, older patients into the susceptible population during a group A meningococcal meningitis epidemic, resulting in rapid enlargement of the population at risk.

The mechanism by which viral and mycoplasmal respiratory agents increase the risk of meningococcal disease is not known. Respiratory infections could increase the efficiency of meningococcus transmission, through increased coughing for example. This would result in increased rates of both meningococcal carriage and disease. Alternatively, respiratory viruses and mycoplasma could increase the invasiveness of meningococci once a person becomes a carrier. In this case, respiratory infections would be significantly associated with invasive meningococcal disease but not with meningococcal carrier status. We addressed this question by examining the relationship between respiratory agents and meningococcal carrier status in the control group. Consistent with earlier studies,[21] coincident respiratory infections were only weakly associated with meningococcal carrier status. This suggests that respiratory virus and *Mycoplasma* infections may increase meningococcus invasiveness in persons who become carriers. Mechanisms by which respiratory infections could facilitate meningococcus invasiveness include disruption of the pharyngeal mucosal barrier,[22] enhanced endocytosis of meningococci,[23] and inhibition of the phagocytic response to meningococci.[24] Since meningococcal carriage was marginally elevated among persons who had respiratory infections, we cannot eliminate the possibility that respiratory infections also enhance meningococcal transmission to some extent, accounting for the high rates of meningococcal carriage that occur during epidemics.

Respiratory agents were associated with upper-respiratory-tract infection symptoms in the control group. Furthermore, meningococcal carrier status was also associated with a recent history of fever, as has been found in other studies.[10,25] In patients with meningococcal meningitis, the respiratory symptoms due to coincident respiratory agents could be masked by the more severe, subsequent symptoms of meningitis. This may be why a link between respiratory infections and epidemic meningococcal disease has not been previously noted.

In addition to respiratory virus and *Mycoplasma* infections, household crowding also increased the risk of meningococcal disease. Since socioeconomic indicators were not measured in our study, it is possible that crowding actually reflects the influence of other factors, such as nutritional status or housing construction. However, after adjusting for respiratory agents and meningococcal carrier status in the logistic regression analysis, we found that crowding was no longer a significant risk factor. This suggests that crowding may increase the risk of meningococcal disease by promoting the transmission of either respiratory or meningococcal pathogens within the household.

Several studies of patients with sporadic meningococcal meningitis suggest that meningococcal disease is associated with new onset of mycoplasmal[26] and viral[6] respiratory infections. One intriguing study by Kleemola and Käyhty[26] has shown that patients with endemic meningococcal meningitis are more likely than controls to have a fourfold rise in complement fixation titers

against *Mycoplasma pneumoniae*.[26] These authors attributed their results to nonspecific cross-reaction with tissue antigens released during tissue injury, since immunoblotting failed to show a parallel rise in antibodies to other *M pneumoniae* protein antigens.[27] Another possible explanation for these results is that these authors actually measured complement-fixing antibodies to other *Mycoplasma* species, such as *M hominis*. Experimental *M hominis* infection has been associated with pharyngitis,[28] and this organism can be isolated from respiratory secretions, but it is not a frequent cause of respiratory illness.[29] Since we were able to identify only six of the 15 mycoplasmal isolates obtained in our study, the conclusion that *M hominis* infection is associated with epidemic meningococcal disease must await further confirmation.

Although our study was not initially designed to detect respiratory *Mycoplasma* infection, it is unlikely that our findings are due to specimen handling or laboratory error. There was no evidence that differential detection between cases and controls could account for our findings, and a systematic error is unlikely to result in the increasing risk with age that was found in our study. Indeed, our estimate of the relationship between respiratory *Mycoplasma* infection and meningococcal meningitis is likely to be conservative—due to misclassification bias—if our *Mycoplasma* detection method was relatively insensitive. Furthermore, viral respiratory pathogens also increased the risk of meningococcal meningitis. These viruses were independently detected by both culture and immunofluorescent techniques.

The results of our study taken together with clonal studies of group A meningococcus strains[9] suggest that epidemics result from a complex interaction of the host, the organism, and the environment. After the 1987 epidemic in Mecca, the group A *N meningitidis* clone III-1 was widely distributed throughout the world.[9,10] Secondary clone III-1 epidemics occurred in the African meningitis belt, indicating that strain virulence (an organism factor) is an important cause of epidemics.[9] Nonetheless, subsequent epidemics were limited to only a few countries despite widespread dispersion of the clone.[30] Presumably, two additional requirements for the initiation of an epidemic are low herd immunity in the population (a host factor) and concurrent upper-respiratory-tract infections (an environmental factor). Once a virulent clone becomes established in a susceptible community, coincident respiratory infections may increase the likelihood of invasive disease and, perhaps, transmission of the strain within the community. Other environmental factors are also required for the initiation and maintenance of a meningococcal meningitis epidemic. For example, the reason for the relative resistance of industrialized nations to epidemic disease is unknown. Determining which additional factors play a role in epidemic meningococcal disease may help to predict outbreaks in both developing and industrialized nations.

This study was conducted during an epidemic in a developing country, but its findings also appear to be relevant to industrialized nations. Surveillance records from France show a clear seasonal correlation between meningococcal disease and upper-respiratory-tract infections.[31] In the United States, meningococcal disease rates peak during the midwinter months, when respiratory infections are common.[15,17] Given the relationship between epidemic meningococcal disease and respiratory infections found in our study, well-controlled studies are needed to examine the relationship between coincident respiratory infections and bacterial meningitis in industrialized countries as well.

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