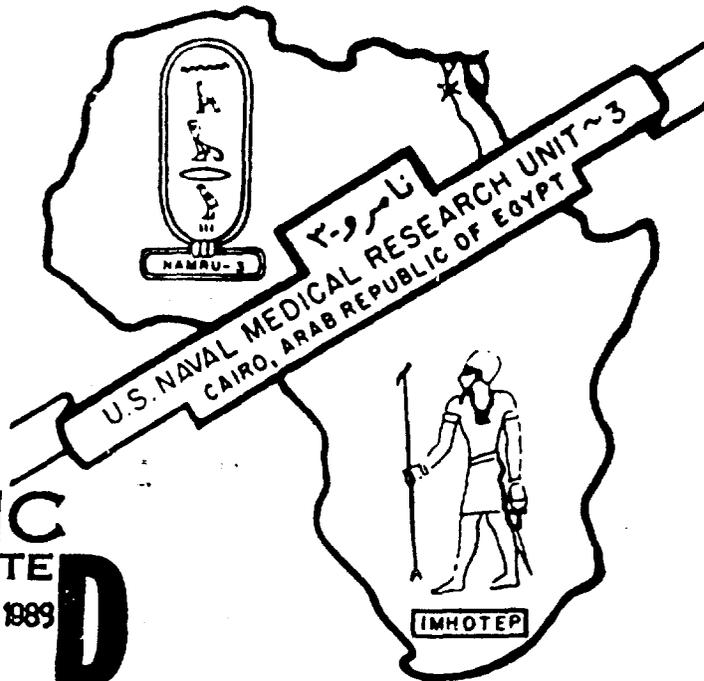


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EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE
IN NORTHEASTERN AFRICA

BY

John E. Sippel, and N.I. Girgis

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Chapter I

EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE IN NORTHEASTERN AFRICA

John E. Sippel and Nabil I. Girgis

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I. INTRODUCTION

As described in Volume I, Chapter 7, meningococcal meningitis occurs as major epidemics in the areas of Africa south of the Sahara designated by Lapeyssonnie¹ as the "meningitis belt". These outbreaks are generally sporadic and difficult or impossible to anticipate. Meningococcal disease is also a major public health problem in the Nile Valley from Alexandria, Egypt to the southern regions of the Sudan. Like the disease in the sub-Saharan region, meningococcal meningitis in the Nile Valley is seasonal and most frequently caused by *Neisseria meningitidis* serogroup A. However, meningitis in Egypt and the Sudan is unique in that it occurs in the large urban areas of Cairo and Khartoum with relatively minor variations in disease incidence between seasons; i.e., while epidemics tend to occur in these cities at approximately 5- to 10-year intervals, the incidence the year after a major outbreak is generally very high, and the number of cases seen at the infectious disease hospitals during any "meningitis season" is almost always considerable. This predictable availability of patients with meningococcal disease presented an unusual opportunity for investigating clinical, epidemiological, prophylactic, and therapeutic aspects of meningococcal infections. The Naval Medical Research Unit No. 3 in Cairo has accordingly conducted a research program on meningococcal meningitis since 1968. These investigations were performed primarily at the Abbassia Fever Hospital in Cairo, but "field studies" were also carried out in Alexandria and Khartoum.

II. MENINGOCOCCAL DISEASE

A. Meningococcal Meningitis at the Abbassia Fever Hospital, Cairo

There were over 5500 cases of cerebrospinal meningitis (CSM) admitted to the Abbassia Fever Hospital from January 1967 to December 1982. *Neisseria meningitidis* was cultured from the cerebrospinal fluid (CSF) of 1135 of these patients (Table 1). About 95% of the isolates belonged to serogroup A, with most of the others being serogroup B or C. Only 16.5% of the CSF culture-positive meningococcal meningitis patients also had the organism cultured from the blood. The mortality rate in this group (5.3%) was essentially the same as that in the culture-positive patients who did not have meningococci cultured from their blood (5.7%). During this entire period, there were only 18 CSM patients from which meningococci were cultured from the blood but not from the CSF; all but one of these were group A and there was only one death.

A total of 95% of the meningococcal meningitis cases at the Abbassia Fever Hospital during the 16 years of this study occurred during the cool months of January through May (Table 1). Although the number of culture positive cases in any one year varied from 6 in 1977 and 1978 to 297 in 1971, the differences in the number of cases in successive years were less extreme and rarely more than doubled or halved.

The majority of group A strains isolated from both cases and asymptomatic nasopharyngeal carriers in the early 1970s were resistant to 1 mg% of sulfadiazine.² In a more recent evaluation of drug sensitivity, 32 group A strains isolated in 1980 and 1981 were resistant to this concentration of sulfadiazine with the average MIC being 8 mg%.³ A careful evaluation of the etiology of CSM seen at the Abbassia Fever Hospital from 1971 to 1975⁴ in which laboratory diagnosis by Gram stain and immunological detection of bacterial antigen (as well as diagnosis by culture) was included, showed that 56% of the acute bacterial cases were meningococcal, 12% were culture positive for *Haemophilus*, pneumococci, or other bacterial species, and 32% were culture negative. Epidemiologic data suggested that a major portion of the culture negative cases had meningococcal etiology. The male/female ratio of the confirmed meningococcal patients was 1:3; only 18% were less than 5 years of age while 50% were between 5 and 14 years.

In a previous report on laboratory findings made in this patient population between 1971 and 1974,⁵ it was noted that

Table 1
CULTURE-POSITIVE* MENINGOCOCCAL MENINGITIS PATIENTS, ABBASSIA FEVER HOSPITAL, CAIRO

Months	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	Total
January	5	7	9	8	65	47	33	5	8	1	1	1	2		8	13	212
February	4	9	8	13	98	81	21	17	4	4			1		15	7	282
March	4	6	16	23	82	57	22	9	3	2	2	1	1	1	26	18	273
April	8	5	5	31	40	25	12	5	3	1	1	1	1	3	12	16	169
May	2	3	6	4	6	11	16	4	1				1	4	11	18	86
June								2		2	1				8	3	26
July					5	2				1					5	4	12
August						2	2					3	2	1	2	2	12
September	1							1						1		3	6
October				3			1			1							5
November	1			2	1	2	1	2			1				1	3	14
December	5			8		12					1			3	5	4	38
Total	30	32	44	92	297	239	108	42	22	12	6	6	8	13	93	91	1135
Died	5	3	2	4	5	10	7	2	4	1	0	0	1	1	10	8	63 (5.5%)
Non-A ^b	0	3	2	1	3	8	12	2	6	8	4	2	5	5	0	0	61 (5.4%)
Blood culture positive ^c	1	3	6	27	60	18	19	5	2		1		4	3	19	20	188 (16.5%)

* CSF culture.
 b 26, B; 20, C; 1, D; 1, W-135; 1, X; 4, Y; 2, Z; 1, Poly 2; 2, unknown.
 c Number that were CSF and blood culture positive.

4 Evolution of Meningococcal Disease

In a previous report on laboratory findings made in this patient population between 1971 and 1974,⁵ it was noted that

1. Despite the hazy to purulent appearance of almost all of the CSF specimens that were culture positive, the number of viable organisms in these specimens varied from less than 1000/ml to more than 10⁶.
2. Over 83% of the culture-positive specimens contained sufficient group-specific polysaccharide (approximately 30 ng/ml) to be detected by counterimmunoelectrophoresis, and some of the specimens contained as much as 960 ng/ml of antigen.
3. Viable meningococci and polysaccharides were rarely detectable in CSF after 24 to 48 hr of ampicillin therapy.

B. Meningococcal Meningitis in Alexandria

Although the incidence of CSM in Alexandria generally reflects that in Cairo,⁶ there is little data on its etiology. The available information suggests that the group A meningococcus is a major cause of the disease. In one report of 145 meningococcal case strains isolated in 1970 and 1971, 134 were group A.² During a group A vaccine trial conducted in Alexandria at this same time, the incidence of group A disease in school children was determined: in 1971, there were 16 group A cases among 210,659 students for an incidence per 100,000 of 7.6; the following year there were 10 cases among 260,473 students for an incidence of 3.8.⁷

C. Meningococcal Meningitis in the Sudan

CSM has been a major public health problem in the Sudan throughout this century. With a population approximately one third that of Egypt, the number of cases occurring annually in the Sudan between 1955 and 1968 were generally five to ten times greater than the number in Egypt.⁸ Immediately prior to the mass vaccination program with meningococcal group A polysaccharide vaccine, Sudan was experiencing 4000 to 5000 cases of CSM a year, or an incidence of approximately 3/10,000.⁹ A population included in a vaccination trial near Khartoum in 1973 had an incidence of 9 cases per 10,000. The incidence of disease dropped sharply when vaccine was employed; however, significant numbers of cases persisted.

The meningitis attack rates that can be obtained in the Sudan were demonstrated during an epidemic in Bahr el Ghazal Province in the southern part of the country during the first 3 months of 1981.¹⁰ There was a total of 411 documented cases with 20 (4.8%) deaths. Rumbek Civil Hospital serves a population of approximately 50,000 and admitted 161 meningitis patients. Timik and Karic, villages with populations of less than 10,000 had more than 50 cases. Although it was not established that this was a meningococcal outbreak, this etiology is consistent with the epidemiologic parameters observed, and the only two cases with a confirmed laboratory diagnosis had group A infections.

As in Egypt, group A is the most frequently occurring meningococcal serogroup. The most overwhelming evidence for this is the marked decreased incidence in meningococcal disease when group A vaccine was tested in controlled field trials¹¹ or when it was administered extensively throughout the country.⁹ In a report on CSM in Khartoum,¹² group A meningococcal etiology was established in 46 of 114 meningitis patients; there were also 2 group C and 1 group Y meningococcal cases, 1 *Haemophilus*, 1 pneumococcus, and 63 cases for which the etiology could not be determined. All of the group A strains were sensitive to sulfadiazine, but the two group C case isolates were resistant to this drug. The "meningitis season" in Khartoum (and most of sub-Saharan Africa) begins with the extremely hot and dry weather in February or March and ends with the onset of spring rains in May or June.

Table 2
ASYMPTOMATIC MENINGOCOCCAL PHARYNGEAL CARRIAGE IN
NORTHEAST AFRICA

City	Population	Number tested	Percent carriers	Percent group A carriers
Cairo	Culture-positive group A meningococcal meningitis patients	380	61	55
	Culture-negative meningococcal meningitis patients	46	35	30
	Culture-positive nonmeningococcal meningitis patients	58	2	2
	Family contacts of meningococcal meningitis patients	318	34	16
Alexandria	School contacts of meningococcal meningitis patients	378	NA	13
Cairo	Outpatients and accompanying family members	2740	26	1
	Public school children	900	27	1
	Private school children	765	8	0
	Closed population experiencing group A meningitis outbreak	4800	73	63
Khartoum	Military, prisons, markets	1300	7	3

Note: NA, data not available.

III. ASYMPTOMATIC *NEISSERIA MENINGITIDIS* NASOPHARYNGEAL INFECTION

Asymptomatic meningococcal carriage was monitored in meningitis patients, outpatients, and members of their immediate families, at the Abbassia Fever Hospital, and in Egyptian and foreign school children in Cairo in studies conducted from 1971 to 1974 (Table 2).⁵

Of 380 patients who presented CSF specimens which were culture positive for *N. meningitidis* group A, 231 (61%) were throat culture positive; 90% of the isolates were group A with the rest being nongroupable (agglutinate in more than one grouping serum). A total of 16 (35%) of 46 patients who were CSF culture negative but diagnosed as having meningococcal meningitis by Gram stain or counterimmunoelectrophoresis assay for meningococcal antigen were also carriers and 14 of their isolates were group A. Only 1 of 58 patients who were CSF culture positive for bacterial species other than *Neisseria* was a carrier.

The carriage rate (40%) in 186 family members of group A meningococcal meningitis patients who were carriers was almost twice the rate (23%) found in 132 family members of meningococcal patients who were not carriers. Of the 107 carriage strains isolated from the family members, 50 were group A and 46 were nongroupable. Thus, the overall carriage rate for family members of group A meningitis patients was 33.6% and the group A carriage rate for this population was 15.7%.

A total of 82% of the group A meningococci isolated from the CSF of the meningitis patients were resistant to 1 mg% sulfadiazine, as were 80% of the group A strains isolated from the throats of these patients and 70% of the group A strains isolated from the family members. A total of 92% of patient nasopharyngeal isolates had the same sulfadiazine sensitivity pattern as the CSF isolate from the same patient, as did 86% of the strains isolated from contacts of the index case.

The outpatients tested for meningococcal carriage were divided into three groups: 670 subjects were 5 years of age or under, 382 subjects were between 6 and 16 years, and 469 subjects were over 16 years. The meningococcal nasopharyngeal carriage rates in these

groups were 25, 25, and 27%, respectively. A total of 25% of 1219 family members of the outpatients were also carriers. Only 177 of the 762 carriage strains isolated from the outpatients and their family members were groupable, and only 28 of these belonged to group A. Thus, only 3.7% of the strains isolated from this population were group A.

Children between the ages of 6 and 10 years attending a large public school in downtown Cairo and two private schools in an affluent suburb were tested for meningococcal carriage. A total of 27% of 900 public school students were carriers; 34 (13.8%) of the 245 isolates were group A and 162 (66%) were nongroupable. A total of 10% of 375 students attending an Egyptian private school, and 6% of 390 students at a foreign private school, were carriers; none of the meningococci isolated from these populations was group A. In a carrier study conducted in Alexandria during a group A meningococcal vaccine trial in school children,⁷ 48 (12.7%) of 378 nonvaccinated school contacts of group A meningococcal meningitis patients were group A carriers.

Meningococcal carrier studies were conducted in a closed population of 4800 men, 18 to 21 years of age, in Cairo in 1971.¹³ A total of 24 group A meningococcal meningitis cases occurred in this population during the 3 months of this study. Throat cultures were obtained from 725 subjects; 529 (73%) were positive for *Neisseria meningitidis*. A total of 86% of these isolates were group A. A total of 21 (88%) of the 24 case isolates and 396 (94%) of 423 group A throat isolates were resistant to 1 mg% sulfadiazine.

Carrier studies were conducted in Khartoum in March and April of 1981;¹⁰ approximately half of the 1300 subjects tested were from closed populations (military or prison personnel) and half were individuals at various markets in and around the city. There were 97 (7.4%) positive throat cultures, of which 32 were group A. The total group A carriage was therefore only 2.5%.

IV. DISCUSSION

Although the incidence of meningococcal meningitis in Egypt is less than that in the Sudan, and the climatic conditions during the Egyptian "meningitis season" are considerably different from those to the south, most of the epidemiologic characteristics of meningococcal meningitis in the entire Nile Valley suggest that this region is an extension of the "meningitis belt" of Africa: meningococcal meningitis occurs during winter and early spring with major outbreaks or epidemics at approximately 10-year intervals; almost all case isolates belong to serogroup A, and most of the meningococcal cases are in children above the age of 5 years. The male-to-female case ratio is slightly higher than 1; and especially when one considers that most patients are admitted to the hospital after 2 or 3 days of clinical symptoms and present CSF specimens that are highly purulent, the mortality rate is surprisingly low. While the climatic conditions during the "meningitis season" in Egypt and Sudan differ, in both regions, it is the period of the most extreme weather during which people spend more time in their homes. The increased incidence during these months appears to result from crowding rather than the weather itself.

The low mortality rate and incidence of meningococemia with group A meningococcal disease in Egypt cannot be attributed to the etiologic agent: during an epidemic caused by sulfadiazine-resistant group A meningococci in Helsinki, Finland in 1973, over 20% of the cases were diagnosed as meningococemia, more than half of the meningitis patients had positive meningococcal blood cultures, and despite the excellent health care in Finland, the mortality rate was almost 10%.¹⁴ Conversely, during an outbreak in 1975 in Nigeria (a country in which group A epidemics are common) caused by group A and C meningococci there were no meningococemia among 42 group A cases, but there were 14 meningococemia cases among the 71 patients with group C disease, and although the mortality rates among patients with group A and group C meningitis were the same (12%), 9 of the 14

group C meningococemia cases died.¹⁵ Thus, it appears that populations that have had previous experience with a particular meningococcal serogroup are less susceptible to the more severe forms of the disease.

Mortality due to meningococcal meningitis at the Abbassia Fever Hospital varied from 17% in 1967 when there were only 30 cases to less than 2% during the 1971 epidemic. An inverse relationship between mortality and numbers of cases has been reported earlier for meningococcal meningitis in Africa.¹ The extremely low mortality in this population during the height of the epidemic in the early 1970s is difficult to address as rates of 10% or greater are generally experienced in group A epidemics in Africa.^{15,16} The inverse correlation of mortality and disease incidence may be a reflection of the greater awareness of the disease during periods of high incidence resulting in more effective diagnosis and aggressive treatment. However, the relatively constant number of deaths each year (Table 1) may also suggest a subpopulation that is extremely susceptible to these infections.

A striking feature of the meningococcal disease seen at the Abbassia Fever Hospital was the negative culture data. There were usually as many CSF culture-negative purulent meningitis cases as their were culture-proven meningococcal cases (and many of these were undoubtedly meningococcal),⁴ most CSF culture-positive meningococcal cases were blood culture negative, and almost 40% of the CSF culture-positive cases had negative throat cultures, many of the negative cultures were undoubtedly due to the frequent use of pre-hospital antibiotic therapy.¹⁷ However, the negative blood and throat cultures also suggest that the organism rapidly localizes in the meninges and that many of the negative blood and throat cultures resulted from the delay between onset of symptoms and hospital admission.

Some of the meningococci isolated from the throats of culture-positive group A meningococcal meningitis patients were nongroupable. This is presumably a nonpathogenic form of the meningococcus as it was never isolated from the CSF of a patient. It is possible that these were second infections obtained either with or after an initial group A challenge as nongroupable meningococci were the most frequently isolated from the throats of asymptomatic carriers. However, it may also be possible that these are degenerative forms of group A organisms that initially infected these patients. If this is so, many of the nongroupable meningococci isolated from asymptomatic carriers may have originally been group A.

The rate of asymptomatic meningococcal carriage in the general population (i.e., individuals not associated with patients with meningococcal disease) of Cairo was usually around 25% in all age groups. Although this is a higher carriage rate than has been reported in Western countries,¹⁸ few of the isolates belonged to group A and the large majority were nongroupable. As expected, students from high socioeconomic neighborhoods had lower carriage rates and no group A carriage. Another population that had few meningococcal carriers was culture-positive nonmeningococcal meningitis patients; this suggests that their infecting organisms interfere with the establishment of meningococcal infections¹⁹ or that the patients produce some antimicrobial substance.

The extremely low carriage rates observed in the study conducted in Khartoum during the period that would normally be the beginning of the "meningitis season" were unexpected as it is generally assumed that the highest rates of carriage occur immediately before or during periods of highest case incidence. However, neither the usual hot, dry weather nor the onset of elevated case incidence had begun suggesting that that the year this investigation was performed was atypical.

The populations that had carrier rates higher than the "background" rate and significant rates of group A meningococcal carriage were associated with group A cases (Table 2). Family contacts of group A meningococcal meningitis patients at the Abbassia Fever Hospital had a carrier rate of 34% with half of the isolates belonging to group A, and the rate in the closed population experiencing an outbreak of group A disease was 73%, with the majority of the isolates being group A. In addition, the group A carriage rate in school contacts of

group A patients in Alexandria was similar to the group A rate in family contacts of patients at the Abbassia Fever Hospital. The close association between the isolate from the asymptomatic carriers and the index cases was further established by the sulfadiazine sensitivity patterns of the isolates.

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