Title:

Temporal analysis of the incidence of meningitis in the Tehran metropolitan area, 1999-2005.

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Abstract

Objectives: The aim of this study was to describe the temporal determinants of meningitis incidence in the population living in the Tehran metropolis.

Methods: All cases of meningitis reported to the health districts throughout the Tehran metropolis during 1999-2005 were abstracted from patient files. Referral cases (patients that did not reside in the Tehran metropolis) were excluded. For each year, sex and age specific incidence was estimated. Temporality and its determinants were analyzed using Poisson regression.

Results: The age-specific incidence is highest among males aged <5 years, at 10.2 cases per 100,000 population per year, and the lowest incidence was among females aged 30- 40 years, at 0.72 cases per 100,000 population per year, with an overall male to female incidence ratio of 2.1. The temporal analysis showed seasonality, with a higher risk of meningitis in spring, at a rate ratio of 1.31 with a 95% confidence interval (CI) of 1.20 to 1.41, as well as autumn (rate ratio = 1.16, 95% CI 1.06-1.27). For periodicity, we found a peak of occurrence around the years 2000 and 2003.

Conclusion: The epidemiology of meningitis in Iran follows similar patterns of age, sex, and seasonality distribution with other countries and populations.

Key words: Meningitis incidence, Temporal trend, Tehran, Iran

Introduction

Meningitis is an important cause of morbidity and mortality in developing countries with an estimated case fatality rate of about 4 to 27%[1]. Outbreaks of meningitis cause high degrees of anxiety in local populations, though a large portion of cases are sporadic. Although different infectious agents can cause meningitis, most of meningitis cases, especially in children under 15 years, are caused by meningococcal meningitis and *Haemophilus influenzae* type b (Hib). No information has been published regarding the incidence of meningitis in Iran and the estimated incidence for the country is based on mathematical modeling or report of limited cases[2]. The incidence of meningitis worldwide varies depending on the part of the world a community is located. High incidence (as high as 100 cases per 100,000 population) of meningococcal meningitis is reported in the sub-Saharan meningitis belt of Africa, which includes several countries of middle Africa from south of Mauritania to south of Sudan, whereas low incidences are reported in Europe (as low as 1.2 per 100,000 population). While the information regarding meningitis epidemics or annual incidence is not well documented in the countries of the Middle East and north Africa, the World Health Organization (WHO) reports that a meningitis epidemic is widespread in countries of Egypt, Morocco, Sudan (part of the African meningitis belt), as well as eastern Mediterranean countries, such as Saudi Arabia and Yemen[1]. In an outbreak of meningitis following the return of Haj pilgrims in August 1987, many countries in the region faced an unusual spread of meningococcal infection resulting in mandatory vaccination pilgrims going to Haj[3,4].

It is not clear how the bacteria spread through the population in time and space, or which determinants are most important in different areas and populations. Suggested environmental risk factors for meningitis include social deprivation, overcrowding[5], passive smoking[6], and weather conditions[7]. While the distribution of meningitis is known, the determinants for epidemic meningitis are not established all over the world. The broad worldwide picture, and the high risk area of the African meningitis belt, indicate seasonality as well as a periodic wave of changes in incidence every 5-12 years[8,9]. Epidemic meningitis has been associated with seasons of dry conditions and low temperatures[10]. It has been postulated that, in the sub-Saharan region of Africa, dry seasons have correlated with winds, spread of dust, as well as the congregation of people in small groups, increasing likelihood of person to person transmission.

The aim of this study was to determine the incidence of meningitis, as well as to describe the temporal determinants of meningitis in the greater Tehran metropolitan area from 1996 to 2005.

Materials and Methods

Subjects and case definitions:

All cases of meningitis reported to the District Health Centers (DHC) throughout Tehran metropolis were included in this study. In Iran, reporting of meningitis cases to the public health authorities are mandatory and all hospitals and private clinics must report any cases of meningitis to their corresponding DHC where a Standard Case Investigation Procedure (SCIP) is performed. The SCIP includes recording of patient's demography, diagnosis, clinical history as well as contact investigation. The information generated in the SCIP is kept in the District Health Center where further tabulated report is sent to the office of Disease Control headquarter at the Ministry of Health. Reported cases are mainly defined based on WHO definitions as *suspect, probable and confirmed*[11]. A detail description of adapted case definition is presented in exhibition number 1. Most of cases lack a definite microbiological diagnosis due to early and aggressive treatment or other practical shortcomings. For the purpose of this study, the file of each reported case was identified, reviewed and the following items of patient information were abstracted: identifier (name and detailed address), demographics (age, sex,), date of disease onset (date of hospitalization or reporting of cases to the health district), and survival status (alive or dead).

A case of meningitis was considered as an *incidence case* if it was reported to one of the 15 district health centers throughout Tehran from 1999 through 2005, with proof of residency (having a residency address in the greater Tehran metropolitan area).

The population and study area description:

The study population consisted of the residents of the Tehran metropolitan area. The population of Tehran was 6758840, 7659804, 7506608, 7356475, 7209346, 6993066, and 6783274 for the years 1995 to 2005 (respectively), with more than 20% of the population under 15 years of age. To estimate the incidences, population figures were obtained from the bureau of vital statistics. The bureau provides population estimates for each year based on ten-year census data and the rate of mortality, birth and immigration. The population includes a diverse population of various ethnicities who have migrated to Tehran from different geographic parts of the country, localizing in different districts and sub-districts within the city.

Geographically, Tehran is located at foothills of the Alborz Mountain Rang and distances 1500 kilometers from the Persian Gulf at the geographic coordinates of 48° (latitude) and 34° (longitude), with an area of 150 square kilometers. The average annual precipitation is about 0.5 cm, occurring mainly in the winter and spring with semi-desert climate for summer and fall[12].

Analysis:

Incidence of meningitis was calculated as seven-year average for five-year age groups and presented as age and sex specific curves. In addition, age was categorized as less than 15 and more than 15 years and yearly incidences were calculated for male and female in each age category.

The temporal analysis of meningitis incidence was performed using Poisson regression with the following variables: age (categorized as <15, 15-50, more than 50 years), sex (male or female), seasonality (spring, summer, fall and winter), and year of occurrence. The computer software STATA (version 8) was used to perform Poisson regression and MS Excel was used to calculate frequency and incidence.

Results:

A total of 4,633 meningitis cases were recorded for the 7-year study period (1996-2005 inclusive). Out of the 4,633 cases, mortality information was available for 2,906 cases. Of these, only 131 patients died of meningitis, resulting in a case-fatality rate of 4.5% for Iran.

Out of these 4,633 cases, 1,687 had verified Tehran residences and the onset of disease was between 1999-2005 therefore eligible to be incidence cases. The remaining cases were referral cases from other cities or the disease onset was not in the time period of the study therefore excluded from the study.

Among the under 15 years age group, the year 2000 with total of 219 cases (corresponding to yearly incidence of 20.1 and 9.9 cases per 100,000 population for male and female, respectively) and year 2004 with total cases of 91 (corresponding to yearly incidence of 9.2 and 4.5 per 100,000 populations for male and female, respectively) were the highest and lowest year in terms of disease frequency (table 1). The age-specific incidence averaged over the study period (1999-2005 inclusive) showed the highest incidence among male population less than five years of age, with average yearly incidence of 10.2 cases per 100,000 populations, and the lowest incidence among women aged 30-40 years, with average yearly incidence of 0.72 cases per 100,000 populations. In average, the frequency of male cases was more than that of females, with an overall male to female incidence ratio of 2.1. Comparing the age-specific incidence curve between males and females, the age group 15-30 years showed the largest differences between the two sexes (Figure 1).

Temporal analysis:

The frequency of meningitis for each year and the year of occurrence were determined and customized for Poisson regression. Several models were evaluated using different combinations of variables and their interaction terms. The final model included all the variables without any interaction terms. Based on the final model: males had 2.26 times more risk for meningitis compared to females (95% CI 2.12 and 2.41), younger age was associated with higher risk compared to older age with a rate ratio of 8.48 (95% CI 7.53-9.54) for <15 years and a rate ratio of 4.50 (95% CI of 3.97 to 5.09) for 15-50 years.

As shown in Table 2, from this temporal analysis we found that the seasonal variations in the occurrence of meningitis showed a higher risk for spring, with a rate ratio of 1.31 (95% CI 1.20-1.41) as well as fall, with a rate ratio of 1.16 (95% CI 1.06-1.27).

Discussion:

This study, for the first time, determined detailed age- and sex-specific incidences of meningitis in the population of Tehran metropolis. The peculiar pattern of age- and sex-specific incidence (presented as the age specific curves), shows a sharp differences in incidence ratios between the sexes according to age. The 3- to 4-fold increase in male cases aged 15 to 35 years presents a challenging issue in the epidemiology of meningitis in Iran. It is particularly important to note that a large portion of the male population is drafted into military service at approximately 20 years of age, at which point these men receive a compulsory meningitis vaccine (the compulsory vaccination of serotypes A and C was started before the 1999). On the other hand, the female population has no military service and no required exposure to vaccination. The effective decline in the incidence of meningitis due to vaccination has been documented in populations where vaccination has been applied[13]. There is an overall male predominance for meningitis and other infectious diseases reported from various countries. Nevertheless, with more than 70% of the men in the Iranian population are vaccinated after age 18, one would expect to see a different sex- and age-specific pattern of meningitis incidences after this age. Exploring the underlying cause of this discrepancy can help better understand the epidemiology of meningitis in our population.

We report a low case-fatality rate for the studied population compared to that of other parts of the world[1]. Most of the countries of Africa and Southeast Asia have case-fatality rates of higher than 8% according to the WHO[1]. In our study, since the survival status of a large number of cases was not available, this loss of data may, in fact, have an effect on our estimated case fatality rate.

The temporal variations of meningitis have been associated with seasonal variations as well as periodicity. The seasonal variations in incidence seen in the sub-Saharan region of the meningitis belt include a higher incidence in dry seasons associated with wind and dust in the dry season. This pattern of seasonality has also been observed in other areas of the world, such as the US[10]. Our data showed a higher risk of disease in the spring and fall compared to summer and winter. While there is not much difference in terms of humidity during the four seasons, Tehran has dry weather, with precipitation barely exceeding 0.5 cm per year[12]. Furthermore, one of the main sources of air pollution in Tehran is a high concentration of particulate matter consisting mainly of dust[14] that could contribute to higher risk of meningitis in this population. To what extent the climatic factors affect the risk of meningitis in our population requires further study, however, there are reports of higher frequency of meningitis in the city of Qom, which is 250 km south of Tehran and very close to desert with almost zero rain and very dry whether[15].

While the seasonality of meningitis is almost established, studies of temporal changes in incidence over the years have shown elements of periodicity in broad and longer time periods[16]. The periodicity of epidemic meningitis in countries located in the sub-Sahara and meningitis belt has been demonstrated, occurring an average of every 10 to 12 years[8]. The reasoning behind a periodicity is related to the dynamic interaction of the disease with a population's indicators of susceptibility, herd immunity, and the antigenic changes in the causative agent. The establishment of a temporal trend by looking for an increase or decrease in incidence may not be a suitable trend analysis for infectious diseases compared to that of chronic non-infectious diseases, such as cancer, where herd immunity has no place in the dynamics of temporal changes of incidence. However, our data, for a relatively short period of time of seven years, showed that there are some fluctuations in the incidences with two peaks of high incidences in years of 2000-2001 and 2003-2004. The high level of completeness in meningitis reporting combined with our ability to exclude referral cases results in a good degree of case ascertainment. Therefore, this fluctuation may be part of the broader dynamics of epidemic meningitis in the studied population. Further and longer periods of studies are needed to demonstrate how epidemic meningitis behaves in terms of temporality.

The results of our study must be interpreted in the light of: 1) completeness of case ascertainment, 2) quality of data available, and 3) the overall nature of epidemic meningitis.

The completeness of reporting of meningitis cases has been the subject of several studies in various countries with some countries reporting 95% completeness. In Iran, it is mandatory to report all meningitis cases to the district health centers where a standard case investigation procedure (SCIP) is performed for each case. As a standard procedure, the SCIP information is actively collected by a trained epidemiologist and includes patient's history, microbiology, and clinical as well as contact information. The information generated in the SCIP is kept in the district health center where further tabulated reports are sent to the office of disease control at the Ministry of Health. No data is available about the completeness of meningitis reporting in Iran; however, the incidence estimates obtained in our study conform with another study using a different methodology[2]. The fact that our study was able to differentiate eligible cases from referral cases adds to quality of data available resulting in a higher validity of the incidence estimates and descriptive measures.

On the other hand, the quality of our data had two limitations: the inherent problem of retrospective data, and symptomatic diagnosis rather than specific causative-agent confirmed diagnosis. Epidemiologic investigations of meningitis addressing case definition have reported different rates of case confirmation in compulsory meningitis reporting programs. One large study examining hospitalized cases for 32 years revealed that only 54% of the cases were considered confirmed as meningitis and the remainder of the cases were considered probable[17]. Studies investigating specific causative-agent meningitis have shown different patterns of agent-specific meningitis in various countries. In one study in Niger[18], 57.7% of the cases were caused by *Neisseria meningitidis*. In another study in Mexico, more than 50% of cases were confirmed as Hib[13]. An in-depth description of epidemic meningitis should have detailed information on the causative agents, as different serotypes of meningococcal meningitis or other bacterial or viral agents are associated with different epidemic characteristics. Our study suffers from the fact that no information about the specific causative–agent meningitis was available to the study. More in-depth studies are needed to explore more detailed and causative agent specific characteristics of meningitis in our population.

Conclusion: We described a broad picture of meningitis epidemic in Tehran, Iran. The age and sex distribution of cases mainly follow the same pattern as seen in other countries and populations. We found a pattern of seasonality as well as small periodic incidence peaks.

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Conflict of Interest statement:

No conflict of interest

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Table 1. Number of cases and incidences of meningitis based on age and sex over the study period (1999-2005), Tehran metropolis

Variable Name	Male				Female			
	0-15		>50		0-15		>50	
	No. (%)	Incidence*	No (%)	Incidence*	No. (%)	Incidence*	No. (%)	Incidence*
1999	39 (12.5)	10.3	16 (8.0)	1.7	78 (12.3)	5.4	56 (10.4)	0.5
2000	70 (22.4)	20.1	37 (18.6)	3.5	149 (23.4)	9.9	110 (20.4)	1.2
2001	49 (15.7)	18.6	31(15.6)	3.3	135 (21.2)	7.1	104 (19.3)	1.0
2002	39 (12.5)	8.3	40 (21.1)	2.6	59 (9.3)	5.8	78 (14.4)	1.4
2003	36 (11.5)	9.5	27 (13.6)	2.4	66 (10.4)	5.4	72 (13.3)	0.9
2004	29 (9.3)	9.2	22 (11.1)	2.1	62 (9.7)	4.5	61 (11.3)	0.8
2005	50 (16.0)	13.3	26 (13.1)	2.1	87 (13.7)	8.0	59 (10.9)	1.0
All years combined	312 (100)	12.8**	199 (100)	2.5**	636 (100)	6.6**	540 (100)	1.0**

* Incidences are reported as per 100,000 populations

** Averaged over 7 years of the study period

Table 2. The rate ratios and their 95% confidence intervals for factors associated with temporal variations of meningitis.

Variables	Rate Ratios	95% CI	
		Lower	Upper
Seasonality			
Spring	1.31	1.20	1.42
Fall	1.16	1.06	1.27
Summer	1.05	0.96	1.15
Winter	1.00		
Age group			
< 15	8.48	7.53	9.54
16-50	4.50	3.97	5.09
>50	1.00		
Gender			
Male	2.26	2.12	2.41
Female	1.00		
Year of incidence			
1999	0.99	0.85	1.15
2000	1.78	1.56	2.04
2001	1.87	1.64	2.13
2002	0.96	0.82	1.12
2003	1.98	1.74	2.26
2004	1.96	1.72	2.23
2005	1.00		

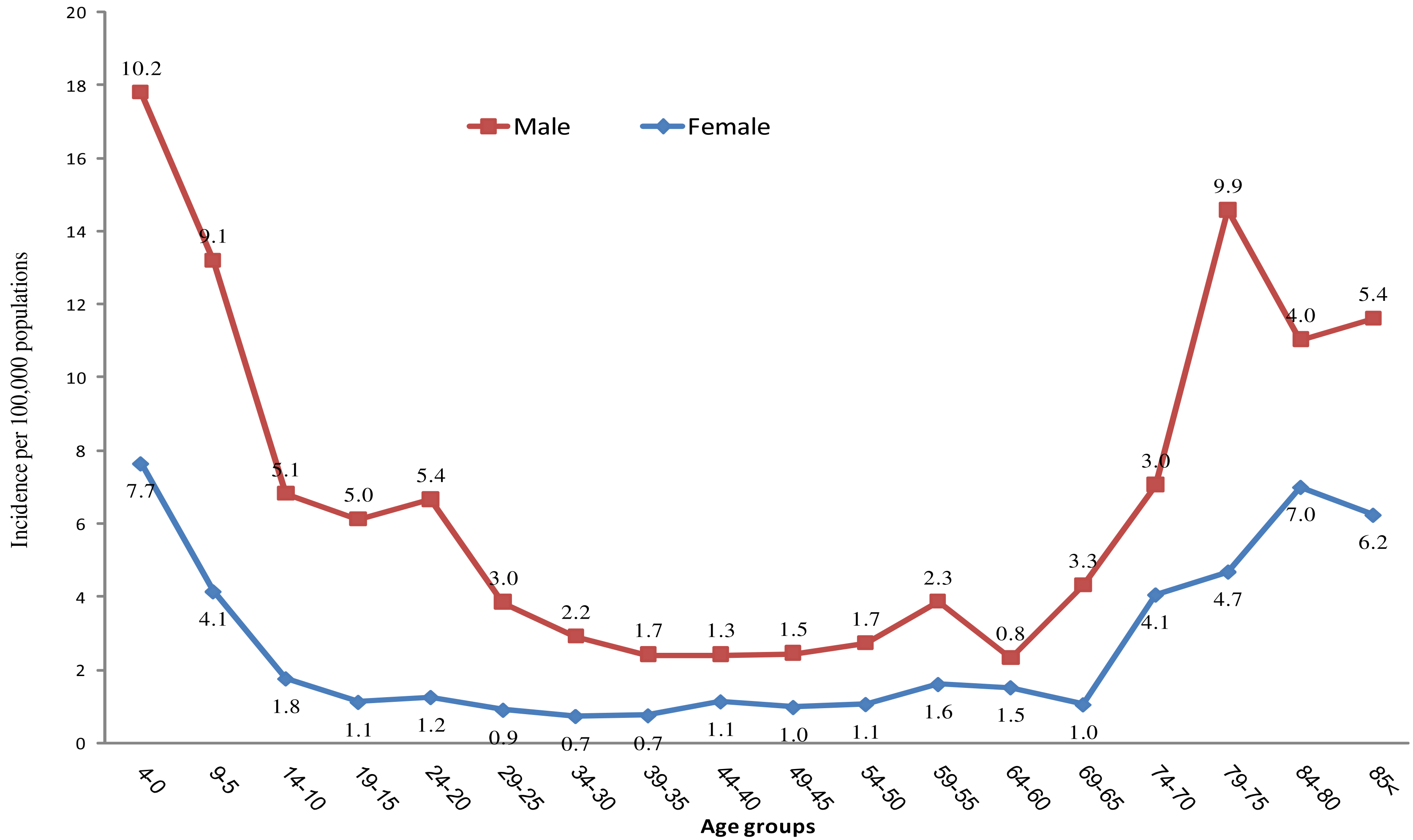

Figure 1. The age specific incidence of meningitis based on gender (incidences averaged over 7 years). The value in the lines present the actual incidence values

Exhibition 1. Standard case definition of meningococcal meningitis based on WHO recommendations** and adapted by the ministry of health

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Suspected case of acute meningitis:

1) sudden onset of fever (>38.5 °C rectal or 38.0 °C axillary)
WITH
2) stiff neck

In patients under one year of age, a suspected case of meningitis occurs
when fever is accompanied by a bulging fontanelle

Probable case of bacterial meningitis

1) suspected case of acute meningitis as defined above
WITH
2) turbid CSF

Probable case of meningococcal meningitis

1) suspected case of either acute or bacterial meningitis as defined above
WITH
2)Gram stain showing Gram-negative diplococcus
OR
3) ongoing epidemic
OR
4) petechial or purpural rash

Confirmed case:

1)suspected or probable case as defined above
WITH EITHER
2) positive CSF antigen detection for *N. meningitidis*
OR
3) positive culture of CSF or blood with identification of *N. meningitidis*

** Adapted from the Control of epidemic meningococcal disease, WHO practical guidelines. 2nd edition, World Health Organization, Document number: WHO/EMC/BAC/98.3