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ARTICLE

Time trends of viral meningitis among young adults in Israel: 1978–2012

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Abstract Viral meningitis (VM) is a medical condition of public health concern, as it is a common sporadic and epidemic illness. However, there is limited data on the epidemiology of VM. The purpose of this study was to analyze long-term and seasonal trends of VM in a young adult military population. VM is a obligatory notifiable disease in the Israel Defense Forces. For the present study, the archives of the Army Health Branch were reviewed for all cases of VM from January 1, 1978 to December 31, 2012, and the annual, monthly, and seasonal rates were calculated. The annual incidence over the 35-year period showed a high peak every 3–5 years followed by a quiescent period of 2–3 years, reaching as high as 58.4 per 100,000 in 1980 and as low as 3.0 per 100,000 in 2005. This cyclic pattern has diminished over the last decade, reflected by a decline in mean incidence (10.46 per 100,000 in 2003–2012 compared to 19.79 per 100,000 in 1978–2002). Average monthly rates ranged from 1.0 cases per 100,000 soldiers in January/February to 2.2 per 100,000 in July/August. The difference in average rates between winter (1.2 cases per 100,000) and summer (1.9 cases per 100,000) was statistically significant ($p<0.001$). Analysis of the long-term epidemiology of VM shows an epidemic pattern, with predominance in the warmer months. Identifying viral causes of meningitis may spare patients unnecessary treatment while prompting the introduction of public health interventions and control measures, especially in crowded settings.

H. Levine and D. Mimouni made an equal contribution to this work.

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Introduction

Viral meningitis (VM) is a relatively common infection affecting the leptomeninges. Most cases are self-limited, with complete recovery within 10 days [1]. However, a rapid and correct diagnosis is very important. Careful evaluation of suspected cases is necessary to rule out other diseases. Appropriate and prompt treatment for other conditions in the differential diagnosis, such as antibiotics for bacterial meningitis and acyclovir for herpes encephalitis, may be life-saving or prevent permanent brain injury [2]. Occasionally the virus causing meningitis is more invasive and may lead to meningoencephalitis or meningomyelitis, which are associated with a more difficult course and possible complications. VM is a condition of public health concern as epidemics are common [3]. However, there is limited data on the epidemiology of VM and there are no clear guidelines regarding control measures, except for specific causative agents. In developed countries, the vast majority of VM cases are attributed to non-polio enteroviruses (>85 % of cases) and arthropod-borne viruses (arboviruses); in developing countries, the most frequent causative agent was the polio virus [4]. The causative agent has become particularly important with the continuous progression towards specific vaccines against entroviruses.

In the general population, VM is commonly not a notifiable disease. In some countries, notification is required for "aseptic meningitis", a broad term encompassing, besides VM, autoimmune, fungal, and chemical meningitis, among others [5].

As such, detailed information on the incidence of VM specifically is unknown [3].

The present study was performed in the Israel Defence Forces (IDF), where VM has been a notifiable disease for many years, and every case is investigated by a physician from the Epidemiology Section of the Army Health Branch. This has yielded a unique, large-population database on the condition. A recent cluster of four cases of VM in a single squad of an elite training unit of the IDF drew the attention of the Army Health Branch. Epidemiologic investigation revealed that all the cases were caused by echovirus 27. To control the outbreak, public health measures were introduced, including active surveillance, isolation of patients, and improved hygiene. This event prompted the present study, which sought to examine time trends, both annual epidemiology, reflecting long-term (secular) and seasonal epidemiology of VM in the young adult population in the military sector in order to inform policy making regarding surveillance and control of VM.

Patients and methods

VM is an obligatory notifiable disease in the Israel Defense Forces. The archives of the Epidemiology Section, Army Health Branch of the IDF were carefully reviewed for all documented cases of VM from January 1, 1978 (start of mandatory notification) to December 31, 2012 (latest available data).

Our analysis covered all compulsory and career IDF personnel. Since military service is mandatory in Israel for 18-year-old males and females, the study population was largely representative of the young adult population in Israel, excluding ultra-orthodox Jews and Israeli Arabs and individuals with severe chronic illnesses who are largely exempted from service.

The diagnosis of VM in the IDF is based on the anamnesis (including antibiotic use), clinical presentation and follow-up, relevant epidemiologic data, cerebral spinal fluid and other lab results such as viral culture or serological tests as well as negative work-up for bacteria and other etiologies. In each suspected case other possible causes of meningitis, such as bacterial, chemical, fungal and autoimmune, were ruled out by clinical and epidemiological investigation, with active follow-up until diagnosis. This alertness is justified by implications of the correct diagnosis of the etiology on risk assessment of possible transmission to other soldiers in the unit and decision making regarding control measures as well as assessment of soldier's health and functional status prognosis including legal and other implications. For the present study, cases of VM were identified by the diagnosis reported by the treating physician with verification by a trained physician from the Epidemiology Section. Such verification might include, as needed, re-evaluation of diagnosis based on clinical and epidemiological investigation, referral to further evaluation and/or request for further specific diagnostic tests, including transfer of samples to ministry of health central viral laboratory. Cases recorded by other codes of notifiable diseases in the IDF are not included in the analysis, such as bacterial meningitis, partially treated bacterial meningitis, polio, fungal meningitis, encephalitis including herpes encephalitis, mumps, measles, varicella, infectious mononucleosis, human immunodeficiency virus infection, and west Nile fever.

Statistical analysis The annual rate of VM was calculated by dividing the number of cases each year by the mean military population in the same year. The average monthly rate of VM was calculated by dividing the number of cases each month by the mean annual population and calculating the average. Average rates of VM for summer (April to September) and winter (October to March) were calculated in the same manner. The two-tailed binomial test was used to compare incidence rates between summer and winter and between the last decade and previous period. All statistical tests were performed with WINPEPI (Abramson, J.H. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. Epidemiologic Perspectives & Innovations 2011, 8:1).

Results

The age and sex distribution of the study population for the whole period was as follows: male conscripts (aged 18–21 years), 53 %; female conscripts (aged 18–20 years), 25 %; male career personnel (aged 22–45 years, mainly 22–30 years), 19 %; and female career personnel (aged 21–45 years), 3 %.

Annual epidemiology

Analysis of the annual incidence rates of VM over the whole study period revealed a high peak every 3–5 years followed by a quiescent period of 2–3 years. The rates in 1980, 1986, and 1997 (58.4, 44.7, and 36.7 cases per 100,000 soldiers) were more than ten times the (lowest) rate in 2005 (3.0 per 100,000). This cyclic pattern was diminished over the last decade, with disappearance of high peaks, reflected also by the decline in mean incidence compared to previous period (10.46 per 100,000 in 2003–2012 compared to 19.79 per 100,000 in 1978–2002) (Fig. 1). On careful evaluation of the dynamics over time, we found that incidence rates tended to rise in certain months (outbreak period) and to decline to the level of sporadic cases in the other months. For example, during the epidemic of 1997, in which echovirus 4 was the causative pathogen, more than 90 % of the cases in the IDF occurred in the second half of the year.

Seasonal epidemiology

The seasonal incidence of VM in the military population is presented in Fig. 2. The average monthly rate varied from 1.0 cases per 100,000 soldiers in January and February to over double that rate of 2.2 per 100,000 in July and August. The average rate for the summer months (1.9 cases per 100,000) was significantly higher than the average rate for the winter months (1.2 cases per 100,000; $p<0.001$).

Discussion

This unique long-term epidemiological study demonstrates a yearly epidemic pattern of VM manifested by high peaks in specific years, with a clear summer predominance in a large population of young adults in the IDF. These are important findings in light of relatively scarce reliable data on the epidemiology of VM, a common cause of sporadic and epidemic illness. The source used is highly reliable given the mandatory reportage of all cases of meningitis (bacterial or viral) to the Epidemiology Section of the Army Health Branch and the army's policy of conducting a thorough clinical and epidemiologic investigation of each and every case of suspected meningitis (bacterial or viral) by a well-trained public health physician. Understanding of the epidemiology and burden of VM is important both directly for control of VM, as well as by comparison to other illnesses of differential diagnosis such as bacterial meningitis and meningitis caused by specific viral agents such as polio.

The impact and sequelae of bacterial meningitis at the patient level are far more severe than those of VM. However, the presentation may be similar and in many cases of VM, bacterial meningitis was initially suspected. A good surveillance system of VM, such as those in the IDF, identifies periods of high and low incidence as well as epidemiological link to other cases and gives an additional supportive tool to assess the risk for bacterial meningitis. Both conditions often necessitate prolonged hospital admission, a full medical work-up including lumbar puncture, and antibiotic treatment pending the laboratory results. However, the incidence of bacterial meningitis is much lower. According to the Army Health Branch notifications data, since 1983, incidence rates of VM have exceeded those of bacterial meningitis by tenfold. Approximately half of all cases were caused by meningicocci and half by various bacteria [6]. Thus, the burden of VM is much higher than that of bacterial meningitis. This is especially true in Israel, where enteroviruses are endemic and outbreaks are common [7, 8]. Military settings are at particular risk because of their crowded conditions and compromised hygiene.

A fluctuating annual pattern is a very frequent observation in the epidemiology of VM. The secular annual trends probably reflect the trends in the circulation of the most prevalent causative agents, the enteroviruses [9], namely, echoviruses, coxsackieviruses A and B, polioviruses, and the numbered enteroviruses. Over the last decade we observed disappearance of the high peaks (large outbreaks) and declining incidence. We can only hypothesize that the decline is related to improvements in infrastructure and enhanced attention to surveillance, education, and infection control leading to reduced transmission. This hypothesis is supported by similar decline previously observed for infectious diarrheal outbreaks in our population [10]. Further support stems from different secular and seasonal trends of VM in our population in comparison to our previous studies of the epidemiology of diseases with different mode of transmission such as infectious mononucleosis (Epstein-Barr virus) and chickenpox (varicella-zoster virus) [11, 12].

Nonpolio enteroviruses are common pathogens [13]. Enteroviruses usually enter the human host via the oral-fecal route, although they can also spread through the respiratory route. Rates of infection are usually higher in younger age groups. The pattern and magnitude of the annual rates observed in our study in the young adult Israeli military population correlate very well with trends reported in the whole Israeli civilian population [14]. However, they were higher than that for the same-age group (18–45 years) in the civilian sector, perhaps because of the higher reportage in the military or the higher risk in the crowded military setting.

The summer seasonality of enterovirus infections in temperate climates has been well established [15–17]. The tendency of enteroviruses to cause infection in the warmer months is the most important reason for the higher incidence of VM during that season. A long-term (1977–2001) study of VM hospitalizations in childhood in Denmark found trends similar to the present study [18], that is, declining incidence over time, outbreaks occurring every 3 to 5 years and summer and early fall peaks. The authors suggested improved hygiene contributed to declining incidence, which may be true in our population as well.

A surveillance system of VM, as well as surveillance of enteroviruses, could be an aiding tool for polio surveillance, as was previously done in France [19]. During 2013, wild polio virus type 1 was detected from environmental samples in Israel as well as from stool samples of healthy children, without any case of paralytic polio [20]. In addition to routine acute flaccid paralysis, public health authorities have expanded the surveillance to all age groups and have increased enterovirus surveillance as well as added screening aseptic meningitis cases for polio. These events strengthen the possible contribution to polio preparedness of the ongoing surveillance system of VM, such as the one presented in this study.

The findings of this study have led to a change in the infection-control policy of the Army Health Branch of the IDF. In cases of meningitis, after a bacterial cause is ruled out,

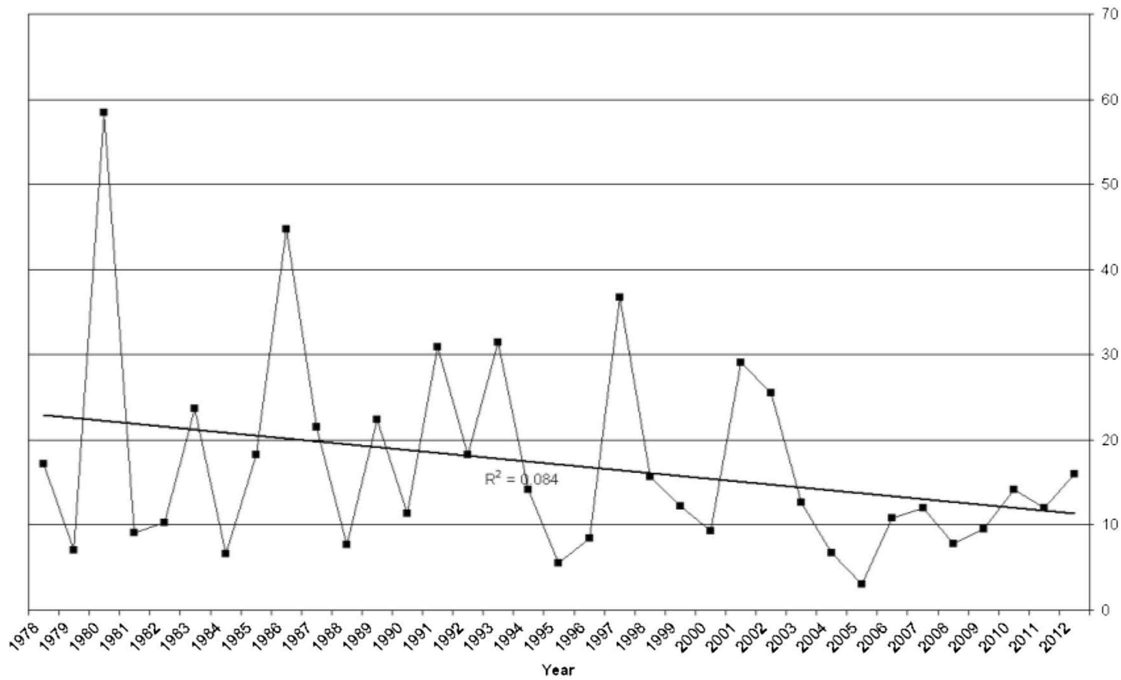
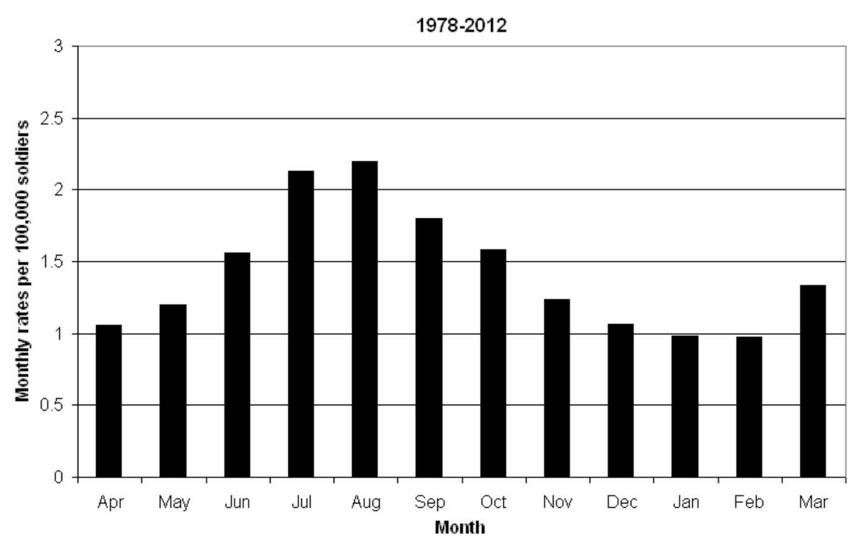


Fig. 1 Viral meningitis in the Israeli Defense Forces, 1978–2012. Annual rates per 100,000 soldiers

a viral cause is sought. When VM is suspected on the basis of clinical, laboratory, and epidemiological data, several interventional steps are taken, as appropriate to the individual case, especially in field or training units. These include isolation of the patient, active surveillance for the identification of additional cases, and improvements in hygiene practices in the unit (sanitation, hand washing, discouraging individuals from sharing personal items), much like for other relevant communicable diseases. The present study could serve as a baseline to evaluate the impact of the change in control policy, as there is no strong scientific evidence that these measures are effective. However, we take a VM event as an opportunity to improve hygiene practices in field conditions, which could be beneficial in any case, for VM and other communicable diseases.

This study has several limitations. The database of the Epidemiology Section does not contain full data regarding the distribution of cases by age or sex, which reduces the possibility of focusing on target populations. In addition, the causative agent of VM is usually not known. The lack of data on the distribution of the different pathogens makes it difficult to determine the exact proportion of enteroviruses. There may also be some under-reportage of VM compared to bacterial

Fig. 2 Seasonal trends of viral meningitis in the Israeli Defense Forces, 1978–2012. Monthly rates per 100,000 soldiers



meningitis, especially of less severe cases, although the obligation to report suspected cases immediately, when final diagnosis in unknown, argues against significant underreportage. We cannot completely rule out some methodological changes in the surveillance system over the years, although we and our predecessors are unaware of such significant changes. Improvements in laboratory diagnosis methods over the years might affect, to some extent, the diagnosis of meningitis, although it is unlikely to explain seasonal trends or disappearance of high peaks over the last decade.

Our findings suggest that particular attention should be addressed to the epidemic nature of VM and its increased rates during the warmer months of the year. Identifying viral causes of meningitis may spare patients unnecessary treatment while prompting the introduction of public health interventions and control measures, especially in crowded settings. The current study will inform policy making regarding the surveillance and control of VM.

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Conflict of interest None.

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