

Meningitis and Meningoencephalitis among Israel Defense Force Soldiers: 20 Years Experience at the Hadassah Medical Centers

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ABSTRACT: **Background:** Meningitis and meningoencephalitis pose major risks of morbidity and mortality.

Objectives: To describe 20 years of experience treating infections of the central nervous system in Israel Defense Force (IDF) soldiers, including the common presentations, pathogens and sequelae, and to identify risk groups among soldiers.

Methods: All soldiers who were admitted to the Hadassah University Medical Center (both campuses: Ein Kerem and Mt. Scopus) due to meningitis and meningoencephalitis from January 1993 to January 2014 were included in this retrospective study. Clinical, laboratory and radiologic data were reviewed from their hospital and army medical corps files. Attention was given to patients' military job description, i.e., combat vs. non-combat soldier, soldiers in training, and medical personnel.

Results: We identified 97 cases of suspected meningitis or meningoencephalitis. Six were mistakenly filed and these patients were found to have other disorders. Four soldiers were diagnosed with epidural abscess and five with meningitis due to non-infectious inflammatory diseases. Eighty-two soldiers in active and reserve duty had infectious meningitis or meningoencephalitis. Of these, 46 (56.1%) were combat soldiers and 31 (37.8%) non-combat; 20 (29.2%) were soldiers in training, 10 (12.2%) were training staff and 8 (9.8%) were medical staff. The main pathogens were enteroviruses, Epstein-Barr virus and *Neisseria meningitidis*.

Conclusions: In our series, soldiers in training, combat soldiers and medical personnel had meningitis and meningoencephalitis more than other soldiers. Enteroviruses are highly infectious pathogens and can cause outbreaks. *N. meningitidis* among IDF soldiers is still a concern. Early and aggressive treatment with steroids should be considered especially in robust meningoencephalitis cases.

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KEY WORDS: meningitis, soldiers, Israel Defense Force (IDF), enterovirus, meningoencephalitis

Meningitis and meningoencephalitis pose major risks of morbidity and mortality. In the general population the risk of meningitis has been estimated at 2.5 per 100,000 patient-years [1] and the risk of meningoencephalitis at 3.5–7.4 per 100,000 patient-years [2]. Mortality rates are estimated at 3–20% for meningitis and up to 20–30% for encephalitis [1,2]. Morbidity and mortality rates vary markedly and depend on the age of the patient, cause of the disease, site of infection, and time from detection to treatment [1]. Meningoencephalitis is an extension of the inflammatory process from the meninges to the brain parenchyma.

Armed forces personnel represent a unique group that may exhibit different clinical and epidemiological features of meningitis and meningoencephalitis, and this may affect also the morbidity and mortality in patients with these infections. Several studies have shown an increased risk of meningitis and meningoencephalitis among soldiers in different parts of the world [3–5]. The overpopulated training bases can contribute to high transmission especially in soldiers experiencing new physiological adaptation process and mental distress. The motivation of recruits to military duty might affect the frequency and urgency of their seeking a physician. Over-motivated soldiers might postpone a visit to a physician until their condition rapidly declines, whereas under-motivated soldiers might seek a physician so frequently that complaints will be overlooked until they are overtly sick. Medical service in the armed forces also differs by the greater ratio of physicians relative to the population and the more comprehensive responsibility of the physicians for the soldiers' health.

Two major studies of infections of the central nervous system among Israel Defense Force (IDF) soldiers were conducted. The first, in 1995, presented findings of bacterial meningitis during 1975–1993 [6]. Grotto et al. [6] reported a major decrease in meningococcal meningitis cases after the introduction of the *Neisseria meningitidis* vaccine, and reviewed the major causes of infection. The second article, by Levine et al. in 2014 [7], reported the incidence rate of viral meningitis, seasonal variations and major viral pathogens. Therefore, in the present study

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we sought to analyze retrospectively the clinical and epidemiologic features of 82 soldiers admitted to our medical center with meningitis or meningoencephalitis due to any cause during the last 20 years. The unique features of this group highlight the many pitfalls (e.g., it may be falsely disregarded as simple headache, dehydration or enterocolitis) in the diagnosis and care of this seemingly healthy population, and allow us to shed light from the perspective of the hospital treating physician. Closer acquaintance with these pitfalls may improve the early identification and treatment of these urgent medical conditions.

PATIENTS AND METHODS

We reviewed the clinical records of all soldiers who were admitted due to meningitis and meningoencephalitis to the Hadassah University Medical Center (both campuses: Ein Kerem and Mount Scopus) from January 1993 to January 2014. Both the hospital files and pre- and post-hospitalization medical files of the IDF Medical Corps were reviewed.

Data were extracted regarding presenting symptoms, time from first symptom to arrival to the hospital, and neurological examinations upon arrival to the hospital. Laboratory results including cerebrospinal fluid (CSF) and blood biochemistry were also recorded. Patients' medical records were reviewed until January 2014 in order to fully assess and ascertain delayed sequelae, as well as identify cases with non-infectious inflammatory diseases presenting as meningitis or meningoencephalitis.

Special attention was given to patients' army job description, i.e., combat soldiers vs. non-combat soldiers, soldiers in training, and medical personnel. Sequelae were recorded until the end of the study period.

Meningitis was diagnosed if there was a combination of meningeal irritation symptoms and signs and the presence of more than 5 white blood cells in CSF obtained by lumbar puncture (LP). Exclusion criteria included malignancies, various inflammatory conditions (e.g., acute disseminated encephalomyelitis, ADEM), sarcoidosis, and infections secondary to procedures. Meningoencephalitis was defined as any brain parenchymal involvement (e.g., seizures), behavioral change, confusion, dysphasia and other cortical deficits, with signs of meningeal irritation.

The microbiological protocol used in our cohort was changed from time to time by the Microbiology Unit at the two Hadassah hospitals. The following tests have always been performed on a routine basis: rapid gram stain, methylene blue stain, thioglycollate, tryptic soy broth, chocolate agar, blood agar and MacConkey agar medium cultures. In cases of low glucose in the CSF, the "indian ink" and acid-fast tests were performed on CSF samples in search of *Cryptococcus* or other fungal causes and tuberculous meningitis respectively. In the past 4 years, in cases of high clinical suspicion, RNA polymerase

chain reaction (PCR) test was conducted to look for bacterial RNA. In almost every case, herpes simplex virus (HSV) and enterovirus were tested by PCR in the CSF. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) and varicella zoster virus (VZV) were tested by PCR in the CSF upon request. In the past 6 years, in cases of suspected West Nile virus (WNV) or sand fly virus (SFV), blood and CSF samples were sent to the zoonotic laboratory of the Central Virology Laboratories at Sheba Medical Center, Tel Hashomer. The diagnosis of WNV and SFV is made according to the standardized criterion of the zoonotic laboratory by either specific serologic enzyme-linked immunosorbent assay (ELISA) results or a positive PCR from the CSF fluid.

Subgroups were compared using the chi-square test or Fisher's exact test. Statistical significance was defined as $P < 0.05$. The study was approved by the IDF Medical Corps Institutional Review Board.

RESULTS

We identified 97 cases of suspected meningitis and meningoencephalitis. Of them, six were mistakenly filed and these patients were found to have other diseases. Nine additional soldiers were excluded from the statistical analysis since alternative conditions caused the signs of meningitis/meningoencephalitis: three were diagnosed with spinal epidural abscess, two with cerebellitis, one with subdural empyema, one had meningitis secondary to a meningioma resection, one was diagnosed with ADEM and one was eventually diagnosed with sarcoidosis. Eighty-two soldiers on active and reserve duty were found to have meningitis or meningoencephalitis due to infectious causes.

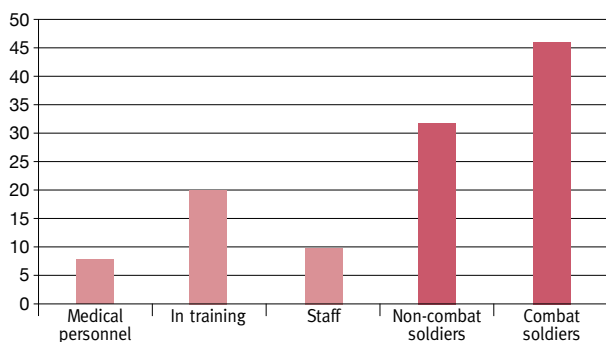
DEMOGRAPHICS AND ARMY SERVICE

Sixty-eight soldiers (82.9%) were men and 14 (17.1%) were women. The mean age was 22 years and the median age 20. Five (6.1%) were on reserve duty and 77 (93.9%) on active duty. The median time in service was 19 months and the mean time 41 months. Forty-six soldiers (56.1%) were combat soldiers and 31 (37.8%) non-combat; for 5 soldiers the type of service could not be established. Twenty (23.8%) were soldiers in training, 10 (12.2%) were staff in training camps or in basic training, and 8 (9.5%) were medical staff (doctors, nurses, paramedics, emergency medical technician). With regard to the IDF population, the data from our cohort suggest presumable overrepresentation of trainees (36% of the entire population) and their staff. Figure 1 shows the job descriptions of the soldiers.

PRESENTING SYMPTOMS, PATHOGENS AND SEASONALITY

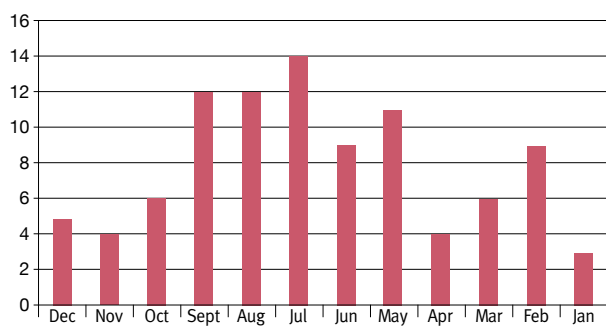
The mean time from the first symptom, which was usually headache, fever or vomiting, to evacuation to the hospital was 6.3 days, and the median time was 4 days. Seventy-eight patients (95%) had headaches and 73 (82%) fever. Forty-two

Figure 1. Job descriptions of soldiers diagnosed with meningitis and meningoencephalitis (soldiers may be included in more than one group, or not at all)



Staff = staff in training camps
 In training = soldiers in training or basic training
 Medical personnel = doctors, nurses, paramedics and medics

Figure 2. Seasonal variations in the incidence of meningitis and meningoencephalitis at Hadassah University Medical Centers (Ein Kerem and Mt. Scopus)



(51%) experienced vomiting and 35 (42%) had photophobia. The peak incidence rates of meningitis and meningoencephalitis were found for the period May to September, with another small peak in February [Figure 2].

A pathogen was identified in 36 patients (43.9%). Of these, 13 had an enterovirus infection. High transmissibility of enterovirus is evident by the fact that five cases occurred in soldiers in training or basic training, where poor sanitation and close contact of soldiers can amplify the transmissibility of the virus. Six EBV cases were identified. In three of these cases, LP was performed several months later and still showed white blood cells (WBC) in CSF, thus implying a long-term disease. Three were diagnosed with *N. meningitidis* and they all had a rapid course including high fever and headache, and critical illness, presenting to the Emergency Department (ED) within 1 day of symptom onset, with elevated intracranial pressure (ICP) in imaging studies. The cases of *N. meningitidis* were all detected after 1995, the year that *N. meningitidis* vaccination was implemented in the IDF. Eleven were diagnosed with other pathogens. One head trauma patient was infected with three

pathogens – *Cryptococcus*, *Acinetobacter* (sensitive to colistin and minocycline) and *Pseudomonas aeruginosa* (sensitive to ciprofloxacin and gentamicin), all isolated from CSF taken in LP or from a shunt. This is probably a representation of a postoperative nosocomial infection rather than a community acquired infection.

SEVERE MORBIDITY, MORTALITY AND SEQUELAE

Increased ICP was the major and imminent danger during the first days of hospitalization. Almost all patients had elevated CSF opening pressure especially in the bacterial cases. One patient developed rapid increase in ICP due to fulminant brain edema, which was localized mostly in the posterior fossa and led to tonsillar herniation and death. Another soldier complained of sudden headaches on the 6th day of his hospitalization and his examination revealed florid papilledema and bilateral abducens nerve palsy. This patient, as well as 14 other soldiers, was treated with intravenous dexamethasone to reduce clinical and radiologic evidence of brain edema. One patient was treated also with acetazolamide for that purpose. In two cases reduced consciousness and respiratory distress necessitated intubation and mechanical ventilation, one of which was complicated by ventilation-associated pneumonia.

Fourteen patients had sequelae as a result of their illness. Four developed ataxia, two of them after EBV infection, further highlighting the long recovery from this pathogen. Three patients were deemed epileptic and two were diagnosed with residual migraines. One patient developed schizophrenia after SFV meningoencephalitis. This observation correlates with the hypothesis that encephalitis generates a risk for the development of schizophrenia [8]. It was suggested that in a subgroup of affective and schizophrenic disorders the underlying cause and main mechanism of the disease is a low level neuroinflammation. One patient had fixed visual spatial impairment. Five patients developed a cognitive impairment, and three of them were diagnosed with *N. meningitidis*. The cognitive deficits in all patients with *N. meningitidis* infection were short-term memory loss, reduced attention span and defective executive function. Despite neurocognitive rehabilitation, the soldiers did not return to their pre-morbid state during follow-up. The full list of pathogens and their major sequelae are presented in Table 1.

DISCUSSION

The armed forces population is a generally healthy population that is screened for previous illness but has unique features. There are disproportionately more males. Soldiers are faced with an accelerated adaptation process to military life in the first months of service. This adaptation is characterized by a marked increase in physical activity and stress. Living

Table 1. Identified pathogens and notable sequelae

Sequelae	No. of patients with sequelae	No. of infections	Pathogen
Migraines	3	13	Enterovirus
Ataxia	2	6	EBV
None	0	2	VZV
None	0	1	HSV
Psychosis	1	1	Sand fly virus
Asymmetric flaccid paralysis	1	1	West Nile virus
Cognitive impairment	3	3	<i>N. meningitidis</i>
Cognitive impairment and motor disorder	1	2	<i>M. pneumonia</i>
Epilepsy	1	1	<i>S. milleri</i>
None	0	1	<i>D. pneumosites</i>
None	0	1	<i>S. pneumoniae</i>
Spasticity and cognitive impairment	1	1	Co-infection
Epilepsy, migraines, visual spatial disturbance	4	49	No pathogen identified

EBV = Epstein-Barr virus, VZV = varicella zoster virus, HSV = herpes simplex virus, WNV = West Nile virus

conditions, including sanitation and crowding, differ from civilian life. A number of studies have established a higher prevalence of meningitis in armed force personnel [4,5]. The prevalence of viral meningitis in the U.S. Armed Forces was found to be 18.1 per 100,000 patient-years [3].

Several conditions might present with a meningitis/meningoencephalitis-like disease. In this series we encountered cases of epidural and brain abscess, sarcoidosis and ADEM. Proper clinical evaluation, quick and relevant imaging studies, and laboratory workup can help distinguish life-threatening conditions and guide the correct therapy.

ETIOLOGY

Similar to studies in the U.S. military, we found viral infections of meningitis and meningoencephalitis to be more common than bacterial infections. Other U.S. data showed incidence rates for viral and bacterial meningitis at 11 and 1.4 for 100,000 person years, respectively [1,9,10].

Enteroviruses, EBV and local arboviruses (WNV and SFV) are the most important viral causes of meningitis and meningoencephalitis. Enteroviruses are highly infectious and are known to cause outbreaks of meningitis and meningoencephalitis [11]. Armed forces are susceptible for outbreaks due to improper sanitation conditions and close contact of a crowded population, and some of the cases in our cohort were infected during such outbreaks. Of 13 patients who were diagnosed with enterovirus infection in the current cohort, 3 arrived at the hospital after one week of symptoms and 2 arrived after 3 weeks. The tendency of enteroviral meningitis to appear after recovery

from the systemic illness may cause a delay in diagnosis. Better acquaintance with this phenomenon is necessary to achieve the correct diagnosis.

The peak incidence of infection was found in the period May to September, with another small peak in February. This reflects the predominance of viral infections, similar to that reported by Levine et al. [7] and contrasts with findings of an earlier study conducted in Israel which showed a peak incidence from December to March and an additional peak in the summer [6]. According to that study most infections occurred during the first 6 months of army conscription.

WNV can cause severe motor sequelae, including delayed asymmetric flaccid paralysis that may not resolve. Soldiers are exposed to WNV during long outdoor training periods [12].

In our series three cases of bacterial meningitis were due to *N. meningitidis*, despite the vaccination for *N. meningitidis* administered since 1995. The strains isolated were not included in the vaccine routinely administered. Although vaccination of IDF soldiers [13] was proven effective in reducing rates of *N. meningitidis*, this pathogen remains a significant risk, especially due to its neurocognitive sequelae.

RISK FACTORS

In our series, patients were more likely to be combat soldiers than non-combat soldiers. This parallels the greater incidence among soldiers than in the civilian population. Also, 29.2% of the affected soldiers were in training. Although we do not have the exact numbers of soldiers in training, this figure is probably more than their proportion among IDF soldiers.

There are several explanations for the observation that soldiers in training and combat soldiers were frequently represented in our cohort. First, exposure to potential pathogens at army bases is expectedly higher than for non-combat soldiers who frequently stay at their home overnight during their service. Second, sanitation is usually not as good at training bases as in other military facilities. Third, these groups of soldiers are exposed to more stress than are other soldiers. Their sleeping is deprived and rapid physical adaptation to military life is demanding. Decreased sleeping hours is known to compromise the immune system and has been shown as a risk factor for breast cancer [14] and an immunosuppression-like state [15]. Staff in training camps are also at high risk for infections due to their contact with soldiers in training.

The presumably high representation of infected training staff (12.1% in our sample) and medical staff (9.8%) in our cohort suggests that this population also warrants special attention. The elevated frequency may be explained by their exposure to similar environmental hazards as well as to the sick population.

Head trauma is an important risk factor for meningitis and meningoencephalitis in combat soldiers. One soldier in our sample exemplified this danger. The soldier had a traumatic brain injury and was co-contaminated with *Cryptococcus*,

Acinetobacter and *Pseudomonas aeruginosa*. Studies in the U.S. showed that 9.1–24.8% of combat soldiers who were diagnosed with infectious meningitis had experienced head trauma [16,17]. The main pathogen in head trauma-associated meningitis was multidrug-resistant *Acinetobacter*.

SEQUELAE

Studies suggest that more than 40% of patients who had acute viral meningitis episodes did not completely recover [18]. Our study shows much lower rates of sequelae. This can be explained by the fact that our patients were previously healthy and generally young and were treated in a tertiary center, usually within a week of the first presenting symptoms. Clinically important viruses, due to their severity and sequelae, are herpes simplex virus (HSV) 1 and 2, other herpes viruses and WNV [19,20].

The leading sequel of meningitis and meningoencephalitis described in the literature is attention deficit, followed by behavioral disturbance, speech impairment and memory loss [2,21]. In our study, 14 patients (16.86%) had sequelae. Similarly, the leading deficit was cognitive, followed by ataxia, epilepsy and migraines.

Only 1 of the 82 soldiers died as a result of bacterial infection. Since most of our cohort was diagnosed with viral or aseptic meningitis, this low mortality rate is consistent with the lower mortality rates from viral infections [1,9,10].

Young adults are highly susceptible to elevated ICP and posterior fossa edema. Subtle/early signs of increased ICP should be actively sought. For cases where early steroid administration is not effective in decreasing ICP, urgent posterior decompression surgery should be considered.

The low mortality rate reported here may be explained by several factors. First, treatment in hospitals has become more aggressive, in accordance with updated guidelines [22]. Second, routine vaccination on the first day of service has caused a rapid decline in infections.

STUDY LIMITATIONS

Due to case coding in the computerized system and the retrospective nature of this study, there may have been over-diagnosis or under-diagnosis of meningitis and meningoencephalitis. In cases of death for which no postmortem information was given, we cannot know if one of these infections may have been the cause. LP is sometimes underused [23], and if so, meningitis and meningoencephalitis might have been under-diagnosed. Furthermore, due to the nature of a tertiary center cohort, it is possible that our cohort does not represent the IDF soldier population, yet it represents the population attending or referred to the two Hadassah hospitals only.

CONCLUSIONS

Meningitis and meningoencephalitis continue to pose a threat to the health and wellbeing of IDF soldiers, especially combat

soldiers, soldiers in training and medical staff. Less crowding and improved accessibility to health services may lead to a decline in morbidity. It is important to be aware of the local pathogens and sensitivity patterns [24]. *N. meningitidis* is still a threat to IDF soldiers. Caregivers should not rule out the diagnosis of *N. meningitidis* even if a vaccine was previously administered. Special attention should be given to a soldier during the first year of service who had experienced a few days of unexplained fever or a new complaint of fever and headaches a few days after an abdominal pain or other systemic illness.

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