

The largest outbreak of Enteroviral Meningitis in Kosovo in the past 50 years

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Abstract

Aim: The purpose of the study was to analyze the largest outbreak of viral meningitis in Kosovo in the past 50 years.

Methods: This was a retrospective chart review of 1003 patients presenting with viral meningitis in Kosovo in 2006. An epidemic outbreak with a total of 1003 patients in a population of approximately two million (50 cases per 100.000 population) occurred between July and October 2006 with the peak incidence in August (44%).

Results: Duration of symptoms prior to admission was 1.68 ± 1.22 days and most of the patients presented a sudden onset of headache (93%), fever (92%) and vomiting (86.5%). Men (66%) dominated with a statistically significant difference compared to women ($P < 0.01$). Also, patients coming from rural areas (66%) dominated with a statistically significant difference compared to patients coming from urban settings ($P < 0.01$). The most affected population groups were children aged 5-9 years (42.5%). Meningeal signs were positive in 97% of the cases and increased pleocytosis in CSF was recorded in 99.6% of the cases. Conversely, mononuclears dominated in 98% of the cases. In CSF, proteins were increased in 39%, while glucose levels were normal in 99.7% of the cases. About 60% of the patients, mostly from rural areas, used unsafe water supply from wells, while 33% used swimming pools or other similar facilities during the hot weather.

Conclusions: Low socio-economic standards including unsafe water supply in rural areas and non-hygienic swimming facilities, or other recreational water sources facilitated the largest reported outbreak of viral meningitis in the past 50 years in Kosovo.

Keywords: children, Enteroviruses, Kosovo, Meningitis, outbreak, viral infections.

Introduction

Aseptic meningitis is a severe, potentially fatal infection of the central nervous system (CNS) and is characterized by meningeal inflammation that is not associated with any identifiable bacterial pathogen in the cerebrospinal fluid (CSF) (1). The most common cause of viral meningitis is enteroviruses, accounting for 80% to 92% of aseptic meningitis cases in which a causative agent has been identified (2). Enteroviruses are of fecal-oral origin and enteroviral meningitis is highly seasonal, usually occurring between the late summer and the fall (1). Children are more susceptible than adults to infections by these viruses (3). Enterovirus activity in populations may be either sporadic or epidemic (4). Outbreaks of infection with coxsackieviruses and echoviruses have occurred in various years in different countries (5). In Kosovo, the second largest outbreak of viral meningitis during the last 50 years has occurred in year 2000, first year after the war and is associated with low socio-economic standards. During the last decade, Kosovo experienced sporadic cases of enteroviral and mumps meningitis.

This study aimed to analyze the largest outbreak of enteroviral meningitis reported worldwide.

Methods

A total of 1066 patients who fulfilled the criteria for viral meningitis were admitted at the Infectious Diseases Clinic in Pristina during 2006. The diagnosis of viral meningitis was based on clinical symptoms (e.g., fever and meningeal signs), blood laboratory analyses and cyto-biochemical changes in cerebrospinal fluid (CSF). Confirmation of viral etiology by stool samples and detection of enteroviral RNA by reverse transcription-PCR, without specific genotyping for enteroviruses was

done only in few cases analyzed abroad as they are not available in our country.

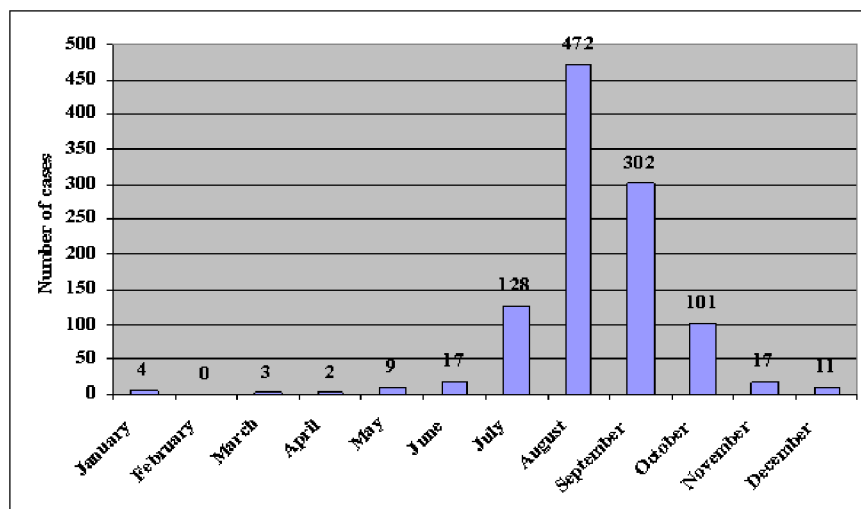
In the study, 959 patients with viral meningitis were analyzed, while 107 patients were excluded from the study, due to lack of data. The study analyzes the epidemiological, clinical, and laboratory characteristics of viral meningitis.

The following parameters were analyzed: structure index, mean, standard deviation and rank. The results were tested by using chi-square test for categorical data, t-test and one-way ANOVA for numerical data. Confidence intervals of 95% and 99% were calculated. A p-value ≤ 0.05 was considered as statistically significant and a p-value ≤ 0.01 was considered highly statistically significant. The statistical analysis of the data was conducted using Stata 9.0.

Results

A total of 1066 patients suspected for viral meningitis, were admitted at the Infectious Diseases Clinic in Prishtina during the year 2006. An epidemic outbreak with a total of 1003 patients (94%) (in a population of two million or 50 cases per 100,000 population) occurred in Kosovo between July and October with peak incidence in August, when there were 472 cases reported (44%) (Figure 1). The incidence of viral meningitis increased with a maximum of 50 admissions per day.

Male gender dominated with 632 cases (66%). The most affected population from the outbreak of viral meningitis were children aged 5-9 years, where there were 408 cases (42.5%), then 10-14 years with 300 cases (31%), and age-group 15-19 years with 112 cases (12%). For children 0-4 years, there were 61 cases (6.4%), while in adults 20 years and older, 78 cases (8%) (Table 1).

Figure 1. Distribution of patients with viral meningitis in 2006 by months**Table 1. Distribution of patients with viral meningitis according to age and gender**

Age groups (Years)	Gender				Total cases		
	Female		Male				
	N	%	N	%	N	%	
0-4	20	6.1	41	6.5	61	6.4	
9-May	143	43.7	265	41.9	408	42.5	
14-Oct	98	30	202	32	300	31.3	
15-19	34	10.4	78	12.3	112	11.7	
20-24	14	4.3	22	3.5	36	3.8	
25-29	9	2.8	11	1.7	20	2.1	
30+	9	2.8	13	2.1	22	2.3	
N	327	100	632	100	959	100	
Total	%	34.1	-	65.9	-	100	-

The youngest patient with viral meningitis was eight months old and the oldest patient was 36 years old. There were no statistical differences concerning gender according to age-groups.

The mean age of all viral meningitis cases was 11 years (standard deviation ± 6). There were no statistical differences concerning the mean age of the patients according to the gender (T-test 0.73, $P > 0.05$) (Table 2). Two thirds or 635 (66%) patients

came from rural areas (66%), while 324 patients (34%) came from urban settings (X^2 -test=100.9, $P < 0.01$).

The outbreak of viral meningitis was reported in 25 municipalities of Kosovo. There were 686 patients (72%) who belonged to five municipalities: Malisheva (198 patients or 22%), Mitrovica (134 or 14%), Drenas (132 or 14%), Vushtri (124 or 13%) and municipality of Pristina (98 patients or 10%).

Table 2. Distribution of patients according to the place of residence and gender

Gender	Place of residence				Total		X ² - test
	Rural		Urban		N	%	
	N	%	N	%			
Female	214	33.7	113	34.9	327	34.1	X ² = 0.085
Male	421	66.3	211	65.1	632	65.9	P > 0.05
Total	N	635	100.0	324	100.0	959	100.0
	%	66.2	-	33.8	-	100.0	-

The family anamnesis was positive in 93 cases (9.7%), and negative in 866 cases, without statistical differences between genders (X²-test=1.76, p>0.05). In 73 cases, the infection spread within a household with 1-9 members.

Of the total patients, only 385 (40%) cases had hygienic water supply, while the rest of the patients used drinking water from wells, especially in the rural areas; 314 (33%) patients indicated that they had used pools or similar spaces: 184 patients (58.6%) used public pools, 58 patients (18.5%) used rubber pools, 74 patients (23.6%) went to the seaside, and 24 patients (7.6%) swam in rivers.

Duration of symptoms prior to admission was on average 1.68 days (standard deviation ± 1.22). Most patients or 898 cases (94%) had duration of illness from 1-3 days, the majority of which occurred on day one (640 cases, or 67%) (range: 1-10 days).

Meningeal symptoms dominated in most of the patients: headache in 894 patients (93%), fever in 884 patients (92%) and vomiting in 830 patients (86.5%). Sore throat was reported in 215 patients (22.4%) without statistical differences between the genders

(X²-test=5.09, P>0.05). Five children developed febrile seizures (0.5%). There were no statistical differences concerning symptoms between genders (X²-test=0.83, P>0.05). Other symptoms were: stiff neck in 75 patients (7.8%), diarrhea in 70 cases (7.3%), somnolence in 5 cases (0.5%), febrile seizures in 3 cases (0.3%), maculo-papular exanthemas in 3 cases (0.3%) and herpangina in 1 case (0.1%).

Upon admission, 703 patients (73%) were febrile. Meningeal signs were positive in 926 patients (97%). Erythrocytopenia was recorded in 889 patients (98.8%) and decreased hemoglobin was recorded in 892 patients (99%) without statistical differences between genders (X²-test=1.72, P>0.05; X²-test=4.69, P>0.05). Leucocytosis was recorded in 588 patients (61%) without statistical differences according to gender (X²-test=0.213; P>0.05).

Increased pleocytosis (>16 cells/mm³) was recorded in 955 patients (99.6%). The majority of the patients, 831 (86.6%), had pleocytosis from 16-499, 93 patients (9.7%) had pleocytosis from 500-1000 and 31 (3.2%) had pleocytosis >1000 cells/mm³ (Table 3).

Table 3. Pleocytosis in CSF in patients with viral meningitis

Pleocytosis in CSF (cells/mm ³)	Total					
	Female		Male		Total	
	N	Percent	N	Percent	N	Percent
< 16	3	0.9	1	0.2	4	0.4
16 - 499	277	85.2	546	87.2	823	86.5
500 - 1000	37	11.4	56	8.9	93	9.8
1000+	8	2.5	23	3.7	31	3.3
Total	325	100.0	626	100.0	951	100.0

Mononuclears dominated in 941 patients (98%) and polynuclears dominated in only 18 patients (1.9%). Normal proteins levels in CSF were recorded in 587 patients (61%) and increased proteins in 372 patients (39%). Normal levels of glucose in CSF were recorded in 956 patients (99.7%) and decreased level of glucose only in three patients (0.3%).

Patients with viral meningitis were treated with symptomatic treatment and none of them were treated with antibiotics. Chest X-ray was done in 4.9% of the patients, X-ray of paranasal sinuses in 2.3% of the patients and the head computed tomography in 1.4% of the patients. The mean duration of hospital stay for patients treated for viral meningitis was 6.5 days (SD: ± 3.5 days). Of the 25 stool samples sent abroad for virological verification, 16 samples were cultured echoviruses: echovirus 4 was isolated and identified in 13 samples, whereas Echovirus 2 was isolated and identified in three samples. Detection of enteroviral RNA by reverse transcription-PCR, without specific genotyping for enteroviruses, was done only in four samples of cerebrospinal fluid (CSF) sent abroad since in our country this is not available.

Discussion

In the post-war period since 1999, Kosovo faces every year cases of viral meningitis especially in the young age-groups where the number of cases ranges between tens and hundreds. An epidemic outbreak with a total of 1003 patients (94%) (50 cases per 100,000 population) occurred in Kosovo between July and October 2006 with a peak incidence in August, when 472 cases (44%) were diagnosed. The incidence of viral meningitis was particularly high one day of August where 50 lumbar punctions resulted positive for suspected viral meningitis. This is the largest outbreak of viral meningitis reported in Kosovo in the past five decades.

Other countries and regions have also reported outbreaks of infection with enteroviruses, such as Latvia in 2010, Greece in 2003-2005, Germany in

2001, Japan in 2008, China in 2005, Italy in 1997, Korea in 2008, England in 2001, Japan in 2007, Mexico in 2004, Spain in 2005, China in 2003 and 2005 (6-18).

Most of the cases occur during summer and autumn, although sporadic cases can occur throughout the year (19-21). In the outbreak of viral meningitis in Kosovo, the majority of infections are seen during August and September (81%).

There were 25 municipalities of Kosovo involved in the outbreak of viral meningitis, with the peak incidence in five of the municipalities with 686 patients (72%). As in other studies, children were more susceptible than adults to infections by these viruses (3). Infants and young children, due to their developing immune system, are more susceptible to enteroviral infections (1,3). Enteroviral infections in older children are less common and are often associated with recreational water activities (22).

In this outbreak of enteroviral meningitis, the most affected population consisted of children aged 5-9 years (42.5%) and those aged 10-14 years (31%). In children 0-4 years and adults >20 years of age, viral meningitis was less common (6.4% and 8.0%, respectively). There were no cases involving adults >36 years of age. From the first report of enteroviral meningitis in Kosovo in 2000, the most affected population also consisted of children aged 6-10 years (47%) (23).

The dominant clinical symptoms were fever (92%) accompanied by complaints of headache (93%), vomiting (86.5%) and sore throat (22%). Meningeal signs were positive in 97% of the patients and increased pleocytosis in CSF was recorded in 99.6% of samples. The majority of the patients (87%) had pleocytosis <500 cells/mm³ and only 3.2% had pleocytosis >1000 cells/mm³. Male gender (66%) and rural residence (66%) dominated significantly. When present in the family, the infection spread in a family of 1-9 members in 10% of cases, mainly in rural areas.

The epidemic spread was mostly caused by the lack of safe water supply systems and the use of wells

as the source for drinking water, which is especially the case in the rural areas. The opening of private swimming pools without the correct disinfection infrastructure and overcrowding of pools with children also contributed to the outbreak of viral meningitis in Kosovo in 2006. About 60% of the patients, mainly from rural areas used unsafe water supply from the wells, while 33% used recreational places consisting mainly of different pools.

A limitation of the study is that we could not identify the enteroviral etiology except in few cases sent abroad, since viral cultures and PCR of CSF samples are not available in Kosovo.

Of the 25 stool samples, 16 samples showed cultured echoviruses: E 4 in 13 samples and E 2 in 3 samples. Detection of enteroviral RNA by reverse transcription-PCR, without specific genotyping for enteroviruses, was done only in four samples of CSF sent abroad since, again, this test is not available in Kosovo. From the previous report for Kosovo, out of the total 306 cases of suspected enteroviral meningitis in 2000, 40 samples of CSF were sent abroad (Vienna); enteroviral RNA by RT-PCR was detected in 33 samples, while virus culture of the CSF samples was positive in 26 cases: E 30 was detected in 25

patients, while E 13 in one patient (23).

Most studies have shown that predominant strains of enteroviruses change over time at a given location and the majority of infections are seen during summer to fall season (1,22,24,25). Echoviruses, particularly E6, E9 and E30 have also been most commonly found in both, sporadic and outbreak of aseptic meningitis cases in USA, Canada and other countries (22,26-28).

This is the first report of the largest outbreak of viral meningitis in Kosovo without being able to characterize different enterovirus genotypes associated with enteroviral meningitis in Kosovo. Identifying the causative agent of meningitis can have a positive impact on patients' treatment and outcomes, but can also reduce health care costs. In conclusion, poor socio-economic standards including unsafe water supply in rural areas and unsafe recreational water sources in Kosovo facilitated one of the largest outbreaks of viral meningitis reported to date.

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