VIRAL MENINGITES ADMITTED TO AN INFECTIOUS DISEASES HOSPITAL: A RETROSPECTIVE CASE SERIES

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VIRAL MENINGITES ADMITTED TO AN INFECTIOUS DISEASES HOSPITAL: A RETROSPECTIVE CASE SERIES (Abstract): Given its epidemic potential and development of severe forms of disease, viral meningitis (VM) is a serious public health problem. Aim: to characterize the main clinical, epidemiologic features, the etiology and treatment of VM cases admitted to the Iasi Infectious Diseases Hospital in 2012. Material and methods: We retrospectively analyzed the medical records of the patients admitted for viral meningitis at the Iasi “St. Parascheva” Infectious Diseases Hospital in the interval January 1- December 31, 2012 (98 cases). The etiologic diagnosis was made by determining the IgM/IgG antibodies against Coxsackie virus and/or West Nile virus in blood/CSF. Results: There was a four-fold increase in the number of cases as compared to the average for the years 2009-2011. Most cases (73.5%) were children aged 1 to 14 years. 61.8% of patients were males, 51.7% from urban areas. The most common symptom was headache (85.7%), followed by fever (77.6%), and vomiting (66.3%). Neck stiffness was absent in 28.6% cases. In 43.5% of the 39 patients serologically investigated a Coxsackie virus infection was confirmed and 1/20 was positive for West Nile virus in blood/CSF. Conclusions: The illness mainly affected children, fever and neck stiffness being sometimes absent. The etiology was known in 22.4% of cases; enter viruses being the most frequent causative agent. Most patients received antibiotic therapy. The course was favorable in all cases. Keywords: FEVER, HEADACHE, EPIDEMIC.

Viruses are an important cause of acute meningeal infections and sometimes may cause a dramatic clinical picture for which an etiologically focused therapy is not available (1).

Involvement of viruses easily transmitted between humans (digestive or respiratory route) gives them an epidemic potential, especially during the warmer months of the year.

The impact of immunization campaigns (mumps virus), spreading of some arboviroses (West Nile virus) to new areas, climatic and social factors have determined a change in the viral meningitis (VM) profile.

The aim of this study was to characterize the main clinical, epidemiologic fea-
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tures, the etiology and treatment of VM cases admitted to the Iasi Infectious Diseases Hospital, in Northeastern Romania, in 2012.

**MATERIAL AND METHODS**

We conducted a retrospective study based on the medical records of patients diagnosed with VM at "St. Parascheva" Infectious Diseases Hospital of Iași in the interval January 1 - December 31, 2012.

Patients of all ages, immunocompetent, with confirmed VM following lumbar puncture and cerebrospinal fluid (CSF) cytological and biochemical analysis were included in the study. Bacterial (culture and latex-agglutination), tuberculous (culture), and non-infectious causes were excluded.

The epidemiological, clinical, hematological and therapeutic variables were also studied. The etiologic diagnosis was made by determining serum IgM and IgG antibodies against Coxsackie virus (VirionSerion kit) and West Nile virus in blood and CSF in collaboration with the Iasi Regional Public Health Institute and Bucharest Cantacuzino Institute.

The collected data were analyzed using dedicated software (Microsoft Excel + Analyze-it) and various statistical tests (mean, Chi², 95% confidence intervals). A p <0.05 was considered significant.

**RESULTS**

A total of 98 cases met the inclusion criteria.

Compared with the interval 2009-2011, when the annual average of diagnosed cases was 24.3, in 2012 a four-fold increase was recorded (fig. 1).

Patients were aged 1 to 36 years, mean age 12.5 years (95% CI: 10.8 - 14.2 years).

73.5% of the cases were children under 14 years of age, with 52.8% of them belonging to the 7-14 years age group (fig. 2).

![Fig. 1. Yearly distribution of VM cases admitted to the Iasi Infectious Diseases Hospital (2009-2012)](image)

![Fig. 2. Age-group distribution of the study patients](image)

The male sex was prevalently affected - 61.8% of the cases, the percentage being slightly higher among patients over 14 years of age (66.7%), but lacking statistical significance (x²=0.04, p=0.84). Patients were from both urban (51.7%) and rural areas (48.3%).

The vast majority of VM cases - 74.1%, occurred during the warmer months of the year, between June 15 and September 15 (fig. 3). The highest number of cases was recorded in August - 36 (40.4%).
The most common symptom of VM was headache present in 85.7% of the patients since the onset. Increases in body temperature (above 37.5°C) were found in only 77.6% of the patients. Of these, in most cases (79.7%) it did not exceed 38.5°C. Fever lasted 1-4 days, average 2.45 days (95% CI: 1.93 - 2.96 days). Two thirds of the patients (66.3%) experienced central-type vomiting (most often before admission - 70.1%). The number of vomiting episodes ranged from 1 to 9 (mean 2.31 - 95% CI: 1.7 - 3.1). Other digestive manifestations were reported in 20.2% of cases: odynophagia - 6.7%, abdominal pain - 11.2% and diarrhea - 2.24%. Other common symptoms were photophobia - seen in approximately one third of cases (35.7%), nonspecific maculopapular exanthema - 19.4%, generalized myalgia - 15.3%, and impaired consciousness (dizziness or drowsiness) - 15.3% of the cases. Few cases presented generalized seizures - 4.1% or lower limb paresis - 1% (fig. 4).
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In nearly one third of the patients (28.6%) neck stiffness and other meningeal signs were mild or absent, possibly due to patients’ age.

Blood constants have contributed to the initial etiological orientation (tab. I). Baseline fibrinogen was determined in only 43.8% of the patients, being above 4 g/l in 41% of them.

Thirty-nine patients (39.8%) were investigated serologically for the detection of Coxsackie virus infection. The infection was confirmed in 43.5% of them: 33.3% had IgM and IgG antibodies, and the remaining 10.2% only IgM antibodies. Twenty patients (20.4%) were investigated for West Nile virus infection. The infection was confirmed in one case. Three patients were diagnosed clinically with varicella-zoster virus meningo-encephalitis (2 immune compromised patients with a recent history of herpes zoster and one with chickenpox). One case of mumps meningitis was diagnosed clinically.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Baseline laboratory findings</th>
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<tbody>
<tr>
<td><strong>Peripheral blood</strong></td>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td>WBC (/mm$^3$)</td>
<td>10,911.9</td>
</tr>
<tr>
<td>PMN (%)</td>
<td>73.2</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>27.6</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
</tr>
<tr>
<td>No. leukocytes (/mm$^3$)</td>
<td>212.5</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>75.2</td>
</tr>
<tr>
<td>CSF albumin(g/l)</td>
<td>0.69</td>
</tr>
<tr>
<td>Glycorrhachia (g/l)</td>
<td>0.65</td>
</tr>
<tr>
<td>Glycorrhachia/glycemia</td>
<td>0.63</td>
</tr>
<tr>
<td>Chlorurorrhachia</td>
<td>7.35</td>
</tr>
</tbody>
</table>

Most patients (68.3%) received first-line antibiotic treatment for a period of 48 hours to 10 days, average 4.5 days (95% CI: 3.49 - 5.46). Dexamethasone was administered in 57.3% of the patients for 2 to 10 days (average 6.9 days, 95% CI: 5.43 - 8.43).

The disease had a favorable course in all cases. No death was recorded. The average length of hospital stay was 7.9 days (95% CI: 6.1 - 10.6).

DISCUSSION

Viruses are considered to be the most frequent cause of meningeal infections. The incidence of VM in the US or UK varies between 5 and 20 cases per 100,000 inhabitants per year (2, 3). However, given the difficulties in making an etiological diagnosis and the different reporting methods it is likely that the true incidence is underestimated.

In 2012, at the Iasi Infectious Diseases Hospital, the number of VM cases (98) exceeded that of bacterial (42c), tuberculous (12c) or fungal meningitis (3) and was four times higher than the average for the interval 2009-2011. Other counties (Botoșani, Suceava) from Northeastern Moldova reported outbreaks of viral meningitis that started in June 2012 and affected mainly kindergarten children. The highest number of cases was reported in Suceava County, where the incidence of
VM was more than two standard deviations above the regional average (41.78 cases/100,000 inhabitants for the interval May 28-August 12, 2012). Although in the Iasi County the number of cases reported in 2012 has seriously increased as compared to the previous period, the incidence of VM was below the regional average (8.54‰).

Both enteroviral and mumps meningitis are more common in children (1), most likely due to the absence of previously acquired immunity (primary infection). A similar situation was found in our study patients, 73.5% of the cases being under 14 years of age.

Sex ratio in VM varies with the involved virus and is in favor of women for herpes viruses (4) and of men for enteroviruses (5) and mumps virus (3); the slight predominance of male patients in our study group may suggest the more frequent involvement of the latter.

Both enteroviruses and West Nile virus commonly cause disease during the warm season. Our group of patients is no exception, 74.1% of the cases being recorded in the interval June 15 – September 15. Compared with 2009-2011, the number of cases began to rise in June, with a peak in August (40.4%) and a significant number of cases reported in September and October (fig. 3).

The association of fever, headache, vomiting, photophobia, and neck stiffness is common in the infectious inflammation of the meninges. However, some authors have shown that sometimes one or more of these symptoms may be absent, making the diagnosis more difficult. In our study, fever was present during the disease course in only 77.6% of the patients, percentage similar to that reported by Gulnar (5) for enteroviral meningitis and Nowak (6) in a series of 43 cases of clear-fluid meningitis (85%). Headache was the most common clinical manifestation in our group of patients, being present in 85.7% of the cases compared with 60-100% in the literature (5, 7). Jet vomiting was described in only 66.3% of our patients, compared to 80% in Turkey (5). Occurrence of transient rash or other digestive phenomena (odynophagia, diarrhea) is common in enteroviral infection, these symptoms often preceding the onset of meningitis (3). These were present in 19.4% of our patients, more often than in other studies (5), and could suggest the involvement of echovirus 9 (3). Neck stiffness was present in 70.8% of the study patients, more frequently than in other similar studies (3, 5, 6).

Baseline WBC count was not very useful in the diagnosis of VM, the average being at the upper normal limit, as reported by other authors (3, 5, 8). Our study showed an increased proportion of polymorphonuclear leukocytes in 72.4% of the patients upon admission. An average ESR of 27.6 mm/h is comparable with the data in the literature (5). The mean levels of CSF parameters were characteristic of viral meningitis and significantly contributed to the diagnosis in most cases.

VM etiological diagnosis rate is relatively low due to its cost and required technical equipment. Recent prospective studies reported the identification of the causative virus in 14.3 - 57.1% of the cases (9, 10). Simion and colleagues found the etiology in only 16.5% of a series of 103 VM cases (11) admitted to the "Dr. Victor Babes” Hospital of Infectious and Tropical Diseases at Bucharest. Under these circumstances, we believe that the identification of the causative agent in 22.4% of VMs in our study (17 cases with Coxsackie virus, 3
Viral meningitis cases with varicella-zoster virus, 1 case with mumps virus and 1 case with West Nile virus) is satisfactory, especially if we take into account that not all patients underwent the necessary viro-immunological investigations.

Non-polio enteroviruses, and especially echoviruses and Coxsackie B viruses, are the most common cause of VM (70-85% of the cases) (3, 4, 10). The confirmation of Coxsackie virus B2 as the causative agent in 31 VM cases in Suceava County made us focus the serological investigation in our patients on this viral subtype. Besides the presence of acute phase antibodies against Coxsackie virus in 17 of our cases, the affected age group, the relatively frequent occurrence of skin rash and involvement of the digestive system (odynophagia, diarrhea) as well as seasonality, all plead for a greater involvement of this type of virus in the etiology of VM cases at the Iasi Infectious Diseases Hospital in 2012.

The incidence of mumps meningitis has decreased significantly (4) in areas where routine vaccination of children is practiced, Romania included. In 2012, in our clinic only one case (1.02% of all cases) of mumps meningitis was diagnosed clinically; since some authors estimate that only 50-60% of mumps meningitis is preceded by parotid swelling (1), and immunological tests have not been performed in all our cases, the actual number could be higher.

Arboviruses are an important cause of viral meningoencephalitis especially in certain geographical areas. An extensive outbreak of neuromeningeal West Nile virus infection occurred in 1996 (12) prevalently affecting adults living in South Romania (morbidity 12.4/100,000 inhabitants in Bucharest). In 2012, only one such case was confirmed in the Iasi County.

Herpes simplex viruses 1 and 2 and varicella-zoster virus can sometimes cause meningitis, especially in women after primary infection or if immunosuppressed (5, 9). In our series one case of varicella encephalitis in an immunocompetent child and 2 cases of zoster meningitis in immune compromised adults (chemotherapy and therapy with antibody to TNF-alpha) were found.

Differentiation between viral and bacterial infection upon admission based solely on clinical and CSF characteristics is sometimes very difficult. Persistence of uncertainty about the true cause of the disease is leading to the administration (sometimes unnecessary) of antibiotic treatment, which contributes to higher costs, risk for undesirable side effects, development of bacterial resistance, and disruption of endogenous ecosystem (13). This was also highlighted by our research, in which more than half of the patients were treated with antibiotics for at least a few days. Antibiotics were discontinued as soon as a bacterial etiology was excluded by additional laboratory investigations (hematology, microbiology, immunology and virology).

Based on clinical findings and controlled studies, the administration of dexamethasone as adjunctive therapy is recommended in bacterial meningitis, especially in severe forms with altered consciousness (14). In our series, more than half of patients (57.3%) received dexamethasone for an average of 6.9 days.

It is estimated that 98% of VM patients fully recover within 3 months from the disease onset. Rarely, mild cognitive impairment or unusual fatigue may persist over longer periods of time (1). Although no psycho-cognitive tests were performed, our patients were clinically assessed at the
end of the acute phase and one month after discharge, no persistent abnormalities being recorded.

CONCLUSIONS
During the year 2012 there was a significant increase in the number of viral meningitis cases as compared to the average for the previous years, but still below the regional average.

Children were mainly affected. The peak incidence was recorded in August. Fever and neck stiffness were sometimes absent.

Etiological confirmation was possible in 22.4% of cases. The most frequent causative agents were Coxsackie viruses; West Nile, mumps and varicella-zoster viruses were also involved.

Differentiation from other types of meningitis was often difficult at onset prompting the administration of first-line antibiotics in a significant proportion of the cases.

REFERENCES