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Enteroviral meningitis in children in Turkey

Research Article

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Abstract: In the indexed medical literature, there have been a very limited number of studies to investigate the epidemiologic and clinical features of enteroviral meningitis in Turkey. The aim of the present retrospective study is to update the actual situation to recognize the spectrum and magnitude of this important clinical entity. Between June 1999 and December 2004, 612 cases of aseptic meningitis were followed up at our hospital. Enteroviral meningitis was defined by isolation of enteroviruses from cerebrospinal fluid (CSF) and/or stool samples. Mumps virus was detected in 310 cases (50.7%) and enteroviruses were the etiologic agents in 104 (17%) of the patients with aseptic meningitis. Most of the enteroviral meningitis cases (36 cases, 34.6%) were diagnosed in August and 70 (67.3%) of them were male. The mean age was 5.6 ± 3.4 years. The most common initial symptoms were fever (81.7%), vomiting (77.9%) and headache (57.7%). In the physical examination, 46.2% of the cases had neck stiffness and 38.5% had pharyngitis. Echovirus 30 was the most frequently (38 cases, 36.5%) isolated enterovirus with peaks in 1999, 2002 and 2004. The other frequently isolated enteroviruses were Coxsackie virus type B (17 cases, 16.3%), echovirus 6 (11 cases, 10.6%), echovirus 11 (6 cases, 5.8%), and echovirus 13 (4 cases, 3.8 %). Mean hospitalization time was 6.2 ± 2.4 days. All patients recovered without any sequelae. Enteroviruses have an important role in childhood aseptic meningitis cases in Turkey too, and the predominant serotypes vary according to years.

Keywords: *Meningitis • Viral etiology • Enteroviruses • Childhood*

1. Introduction

Enteroviruses belong to the family of Picornaviridae and are small, nonenveloped, single-stranded RNA viruses. At least 80 distinct enterovirus serotypes are known to cause disease in humans. Serotypes of human enteroviruses have traditionally been classified into echoviruses, Coxsackieviruses group A and B, and polioviruses based on the associated disease in humans and animal model systems. They have been recently reclassified based on nucleotide and amino acid sequences into 5 species, polioviruses and human enteroviruses A-D [1,2]. Most enteroviral infections cause a benign, self-limited disease; however they can also produce severe illness such as aseptic meningitis, encephalitis, paralysis, myocarditis and neonatal enteroviral sepsis. Enteroviruses are the most common cause of viral meningitis in mumps-immunized populations [1,3]. Some serotypes are epidemic and associate with outbreaks such as Coxsackievirus B5, and echovirus 6, 9 and 30 and some serotypes are endemic such as Coxsackievirus A9, B3 and B4 and enterovirus 71 [2]. The particular viral serotype associated with disease outbreaks varies with time and geographic location

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and is influenced by the background rate of community infection, socioeconomic condition, host immunity and possibly strain neurotropism [4]. Certain serotypes such as Coxsackie B5 virus, echovirus type 4, 6, 9, and 30 are associated with a greater frequency of meningitis than others [5-10]. Epidemiological surveillance plays a crucial role in understanding the changing patterns of enteroviral infection and disease association and may help in the control of infectious diseases [11].

In the summer season of 1999, we detected an echovirus 30 outbreak of aseptic meningitis in Turkey [12,13]. It was the first report about enteroviral meningitis from Turkey. There are still only limited studies about enteroviral meningitis in our country [14]. Since 1999, we aimed to investigate the role of enteroviruses in aseptic meningitis cases and the epidemiologic and the clinical picture of enteroviral meningitis in Turkish children.

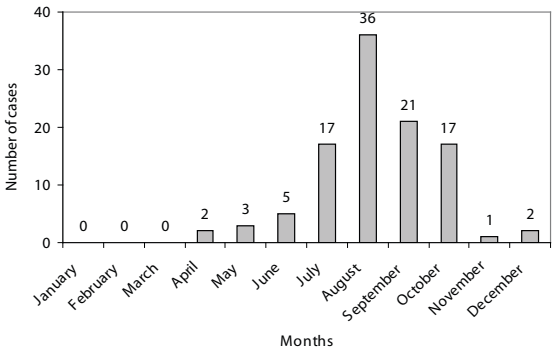
2. Material and Methods

The study was performed at Ankara Diskapı Children's Diseases Training and Investigation Hospital with 250 beds, a tertiary-care children's hospital including some diagnostic assistance of different referral centers. During the study period between June 1999 and December 2004, 612 cases of aseptic meningitis were followed up at the Children's Hospital. Aseptic meningitis was defined as an acute illness presenting with symptoms and signs of meningeal irritation, headache, nausea, vomiting and fever accompanied by a leukocyte count in the CSF of ≥ 5/mm^3 in the absence of bacterial growth in culture. Patients having parotitis and positive serum mumps IgM antibodies were diagnosed as mumps meningitis. Data including history, physical examination, peripheral blood and CSF laboratory findings and virological examination of specimens were collected from each patient. Stool and CSF samples of patients were examined in the Virology Department of Refik Saydam Central Institute of Hygiene (RSCIH) for virus isolation. All samples were collected in the acute phase of the disease. Enteroviral meningitis was defined as isolation of enterovirus from CSF and/or stool samples [4,15].

Isolation of enteroviruses was performed according to standard procedures as described previously [16]. Briefly, sample aliquots (0.2 ml) of 10% suspensions were inoculated into tube monolayer cultures of HEp-2 and human rhabdomyosarcoma (RD) cells, CSF inoculated directly to the mediums. All cultures were incubated at 36°C and read daily for 14 days. Cultures showing a characteristic cytopathic effect for enteroviruses were identified by a micro-neutralization method using antiserum pools supplied by the RIVM Institute, Bilthoven, and the Netherlands. In order to exclude the involvement of polioviruses, L20B-cells (transgenic mouse cells with the human poliovirus receptor) were also used for virus cultivation.

SPSS version 11.0 was used for statistical analysis.

Figure 1. Incidence of enteroviral meningitis cases by month.



3. Results

Between June 1999 and December 2004, 612 cases of aseptic meningitis were included in the study. Three hundred and ten of the cases (50.7%) were diagnosed as mumps meningitis. From the rest of them, 299 stool and 76 CSF samples were submitted for viral cultures. In 198 of the cases (32.3%), the etiologic agent could not be identified. Enteroviral meningitis was diagnosed in 104 (17%) cases. Enteroviruses were isolated from 100 stool and 14 CSF samples. The highest number of cases (25 cases, 24%) was observed in 2002. Most of the cases (36 cases, 34.6%) were diagnosed in August (Figure 1). Seventy patients (67.3%) were male and 34 (32.7%) were female. The mean age of the patients diagnosed with enteroviral meningitis was 5.6 ± 3.4 (min: 0.1, max: 14) years. The most common initial symptoms were fever (81.7%), vomiting (77.9%) and headache (57.7%). In the physical examination, 46.2% of the cases had neck stiffness and 38.5% had pharyngitis (Table 1). The distribution of patients according to age and gender is shown in Figure 2.

In the laboratory investigation, mean serum leukocyte count was 14272 ± 4771.8/mm^3 (min: 4700/mm^3, max: 26700/mm^3), mean erythrocyte sedimentation rate was 29.4 ± 17.1 mm/h (min: 5 mm/h, max: 77 mm/h), and mean C-reactive protein value was 1.7 ± 1.9 mg/dL (min: 0.1, max: 8.9 mg/dL). On CSF analysis, mean white blood cell count was 318 ± 301.4/mm^3 (min: 20, max: 2000/mm^3). Differential CSF cell count revealed polymorph nuclear predominance in 36 (36.5%) of the patients. The mean protein concentration was 46.8

Table 1. Clinical features and laboratory findings in 104 patients with enteroviral meningitis.

Gender Female / Male n (%)	34 / 70 (32.7 / 67.3)
Age [mean±SD years (min.-max.)]	5.6±3.4 (0.1-14)
Most common symptoms	
Fever n (%)	85 (81.7)
Vomiting n (%)	81 (77.9)
Headache n (%)	60 (57.7)
Restlessness n (%)	9 (8.7)
Abdominal pain n (%)	6 (5.8)
Diarrhea n (%)	6 (5.8)
Most common findings in physical examination	
Neck stiffness n (%)	48 (46.2)
Pharyngitis n (%)	40 (38.5)
Fontanelle bulging n (%)	3 (2.9)
Conjunctivitis n (%)	3 (2.9)
Rash n (%)	2 (1.9)
Laboratory findings	
Hb* (mg/dL)	12.7 ± 1.4 (9.2-17)
WBC* (n/mm3)	14272 ± 4771.8 (4700-26700)
ESR* (mm/h)	29.4 ± 17.1 (5-77)
CRP* (mg/dL)	1.7 ± 1.9 (0.1-8.9)
CSF	
cell* (n/mm3)	318.0 ± 301.4 (20-2000)
protein* (mg/dL)	46.8 ± 15.8 (20-100)
glucose* (mg/dL)	52.4 ± 11 (32-89)
PMN predominance (%)	36.5

** mean ± SD (min.-max.)*

± 15.8 (min: 20, max: 100) mg/dL, and mean glucose concentration was 52.4 ± 11 (min: 32, max: 89) mg/dL.

Echovirus type 30 was the most frequently isolated (38 cases, 36.5%) enterovirus type during these six years with peaks in 1999, 2002 and 2004 (Figure 3). The other frequently isolated enteroviruses were Coxsackie virus type B (17 cases, 16.3%), echovirus 6 (11 cases, 10.6%), echovirus 11 (6 cases, 5.8%), and echovirus 13 (4 cases, 3.8 %). Seventeen cases (16.3%) were reported as non-polio enteroviruses. These isolates were not fully typed. Echovirus 25 was isolated in three patients, echovirus 18 in two, and echovirus 4, 14, 5, 9, and Coxsackie A in one each. In one case Coxsackie B and echovirus 14 were isolated together. The mean ages for Coxsackie virus B, echovirus 6, and echovirus 30 were 2.8, 5.9, and 6.8 years respectively. The mean age of the patients with Coxsackie virus type B was significantly smaller than that of the patients with other enteroviral serotypes. Mean hospitalization time was 6.2 ± 2.4 (min: 3, max: 14) days. Sixty-one of the 104 patients with acute enteroviral meningitis were initially treated with antibiotics at the beginning, because of the severe clinical picture and polymorph nuclear leukocyte predominance in the CSF samples. After the final diagnosis established enough evidence for viral origin, the broad spectrum anti-microbial treatments were withdrawn. All patients recovered without any sequelae.

Figure 2. Distribution of enteroviral meningitis patients according to age and gender.

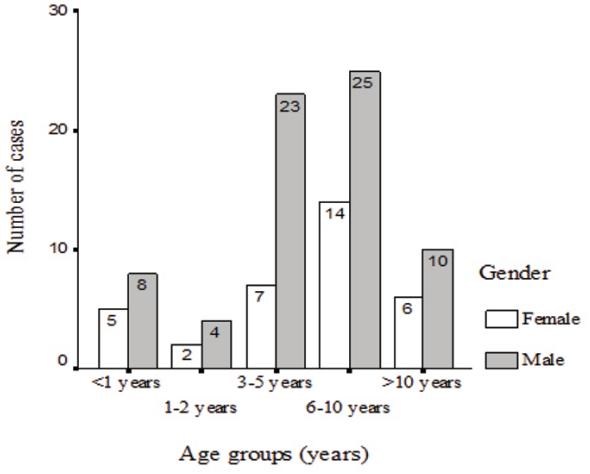
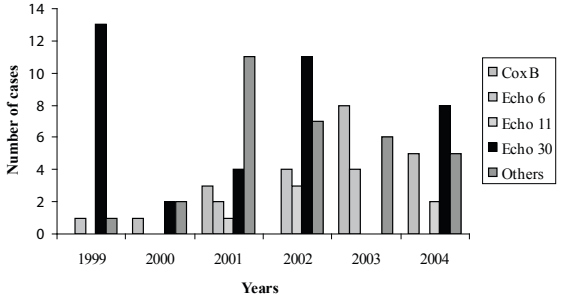


Figure 3. Yearly distribution of patients with enteroviral meningitis due to enterovirus serotypes.



4. Discussion

Enteroviruses account for approximately 85 percent of all cases of aseptic meningitis [3]. They are also the major etiologic agents of aseptic meningitis cases for which an etiologic agent was identified [17-19]. Since the introduction of the mumps vaccine, mumps meningitis has become far less common in those countries in which it is widely used. In this study, mumps virus was the most frequent agent identified. In the study period mumps vaccine was not routinely used in Turkey and our patients also had not had the vaccine against mumps. Enteroviruses were the second most identified agents in this study. We could not investigate the other possible

viruses and could not detect the non-viral etiologic agent in approximately in one-third of cases. Similarly, Lee et all [20] detected enteroviruses as the predominant pathogen in Canadian children with aseptic meningitis but no pathogen in the majority of cases, although they investigated the respiratory viruses in the samples from non-CSF sites. The failure of some enteroviruses to grow in cell cultures such as most of the group A Coxsackie viruses might be a reason for not identifying an etiologic agent in some of the cases.

Some enteroviruses tend to occur continuously at rather low levels, while other serotypes tend to occur in outbreaks. The particular enteroviral serotype associated with disease outbreaks varies with time and geographic location. Certain serotypes such as Coxsackie B5 virus, echovirus type 4, 6, 9, and 30 are associated with a greater frequency of meningitis than others [5]. Enterovirus 30 is known to be one of the most frequent enteroviruses causing outbreaks of sporadic cases of aseptic meningitis worldwide. An outbreak of echovirus 30 meningitis has occurred in Switzerland in the summer of 1996 [21]. Reintjes *et al.* [15] reported the echovirus 30 meningitis outbreak in Germany in 1997. In Turkey, we detected an echovirus 30 aseptic meningitis outbreak during the summer of 1999 [12,13]. Also in Belgium, Spain and France echovirus 30 was the most frequently isolated aseptic meningitis agent in year 2000 [7,8,22]. It was also reported in Cyprus as the main cause of aseptic meningitis outbreaks in 2000-2002 [23]. Outbreaks may occur not only in several countries within one continent but also in different continents indicating an active worldwide circulation of these serotypes. Wang *et al.* [24] reported a large outbreak of echovirus 30-associated aseptic meningitis in 2001 in Taiwan. Also in China, echovirus 30 was the probable cause of the aseptic meningitis outbreak from January to July in 2003; it was also the most prevalent etiological agent of viral meningitis in Brazil in 1998-2003 and in Argentina in the 2002-2003 outbreaks [25-27]. In Druyts-Voegts' [7] survey different patterns in the presence of virus types became evident: echo 30, echo 11, echo 6, Coxsackie B3, Coxsackie B5 had outbreaks every three years; Coxsackie B2, B4, A9 were endemic and did not cause outbreaks; and echo 33 and echo 20 occurred only in outbreaks. Similarly, in our study, echovirus 30 was the most frequent enteroviral agent with peaks in 1999, 2002 and 2004. The other frequently identified enteroviral agents were Coxsackie B and echovirus 6 in accordance to the literature [5,8]. Coxsackie virus B was the predominant serotype in 2003, and the second most frequent serotype in 2004. Echovirus 11 was predominant in Greek aseptic meningitis cases in 2004-2005 [28]. We detected it in 6 patients, 3 of them in 2003, 2 cases in 2004 and 1 case in 2001. Although echovirus 13 had been reported only rarely until the spring of 2000, it has been reported as one of the main causes of several outbreaks of aseptic meningitis in recent years [29-33]. We detected echovirus 13 in one case in 2001, and in three cases in 2002.

Enteroviral infections predominate in summer and fall, but sporadic cases occur throughout the year. Winter outbreaks of enteroviral meningitis are rare [34]. The majority of our cases occurred between July and October and mostly in August, and we have seen one case in November and two cases in December. Chambon et al [35] reported the continuation of enterovirus circulation and meningitis cases over the winter of 1999-2000.

Most patients presented with fever, vomiting and headache in accordance to the literature [29]. There was male predominance in enteroviral and other aseptic meningitis cases in this study. A significant male predominance was observed in similar studies [2,7,30,32,36]. It has been postulated that a relative immunodeficiency might account for the male predominance [37].

Enteroviral meningitis is usually seen in young children and rarely in adults [7,25,31,32]. In this study the mean age of patients was 5.6 years in accordance with other studies [30,36]. One noticeable value in our study was that the mean age of enteroviral meningitis cases caused by Coxsackie virus B was statistically younger than that of the other types. Khetsuriani *et al.* [2] and Mistchenko *et al.* [27] also found Coxsackie virus B5 mostly in small infants.

We detected polymorph nuclear leukocyte predominance in CSF samples in 36.5% of cases with enteroviral meningitis. Böttner [29], Somekh [32] and Meqdam [38] have reported similar predominance in more than 50% (up to 90%) of their patients. This is the main problem in the clinical settings for discrimination of aseptic meningitis from bacterial meningitis for treatment choices. So far, 58% of our cases were initially treated with broad-spectrum antibiotics; similarly three-quarters of patients with aseptic meningitis received antibiotics in the study of Lee *et al.* [20]. Knowing the epidemiological patterns and early detection of etiological exact agents causing meningitis, by using rapid molecular techniques such as polymerase chain reaction, may aid to avoid the irrational usage of antibiotics and may have a positive impact for the patient care by the hospitalization period. In conclusion, enteroviruses have an important role in childhood aseptic meningitis cases in our country as well and the predominant serotypes have been changing periodically. This retrospective study characterizes the up to date contribution of enteroviruses in the syndrome of aseptic meningitis in Turkey. Among patients meeting

the criteria for aseptic meningitis, those also presenting with parotitis and positive mumps IgM serology were considered to be suffering from mumps virus aseptic meningitis. The remainder had CSF and stool samples cultured for enteroviruses. It should be noted that our findings, in terms of the enterovirus types encountered, of the clinical presentation, and of the seasonal pattern, are neither novel nor surprising.

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