International Journal of Medical Science and Dental Research

Comparison of Clinical and Laboratory Manifestations of Enteroviral Meningitis in Adults and Children

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Abstract: *The study included 42 patients with enteroviral meningitis. To confirm the enteroviral etiology of serous meningitis, the polymerase chain reaction method was used with identification of ribonucleic acid of enteroviruses in the feces and cerebrospinal fluid, followed by the determination of 71 types of enterovirus. The work was carried out within the framework of an open cohort study of the Joint EURO/STF Small Grants Program, aimed at implementing programs to combat infectious diseases. The aim of the study was to compare the clinical and laboratory parameters in adults and children with enterovirus meningitis, as well as to determine their possible connection with 71 types of enterovirus. The enterovirus etiology of serous meningitis is confirmed in all patients, however, 71 genotypes of enterovirus were not detected in any case. Enteroviral meningitis in children had more pronounced clinical symptoms due to the more frequent occurrence of nausea and vomiting (p <0.05), Kernig's positive symptom (p = 0.03), neutrophilic pleocytosis (p = 0.004) and low incidence of meningeal dissociation symptoms (p = 0.04) in combination with other manifestations of enterovirus infection, such as rash (7.4%) and enteritis (3.7%).*

I. INTRODUCTION

Enteroviral infection is an urgent problem of current health care since the infection is uncontrolled, polyethiologic, and the pathogens themselves are unpredictable [1]. It is known that the enterovirus of one serotype can cause quite different clinical syndromes of various degrees of severity, and also be the cause of either major epidemics or sporadic diseases. Instead, enteroviruses of different serotypes may cause the formation of the same clinical syndromes [1, 2]. The greatest attention of researchers is focused on the clinical forms of enteroviral infection, the development of which is associated with neurotropic character of enteroviruses. Enteroviruses cause more than 60% of serous meningitis, the occurrence of which is usually associated with representatives of ECHO30, ECHO6, ECHO9, ECHO11, ECHO13, Coxsackie A9 and B5 enteroviruses [3, 4, 5]. In the recent years there is a clear tendency of activation of the enteroviral infection, which is due to the beginning of the circulation of new serotypes of enteroviruses [6]. The most marked

neurotropism of the enterovirus type 71 has been reported, a range of epidemic outbreaks of the disease with the development of serous meningitis or meningoencephalitis, in particular, with the lethal outcomes of the disease have been described [7, 8, 9, 10]. The enterovirus type 71 is currently considered not only as a cause of the outbreaks of serous meningitis, but also of the viral exanthema of the oral cavity and extremities (Hand-foot-and-mouth disease) [7, 11]. However, the combination of enteroviral meningitis (EM) with other manifestations of enteroviral infection occurs when the patient is infected with different serotypes of enteroviruses [12]. The overwhelming number of researches relates to the defining clinical features of EM in children [8, 9, 11], herewith there is no works on comparing EM course in adults and children.

The aforementioned determined the purpose of our study to identify the clinical and laboratory characteristics of the course of EM in adults and children and their possible associations with the enterovirus type 71.

II.   PURPOSE OF THIS WORK

The purpose of this work is to compare clinical and laboratory readings in patients with enteroviral meningitis both adults and children and identify their possible association with the enterovirus type 71.

III.   MATERIALS AND METHODS

The study involved 42 patients with enteroviral meningitis who were treated in the department number 1 of the municipal institution of Zaporizhzhia Regional Infectious Clinical Hospital. All patients were included into the study according to the straight flow method, meaning that each patient with manifestations of meningitis with confirmed enteroviral etiology during 2016-2017 and under written consent of the patient or the pateint's parents is taken into account. Diagnosis of meningitis is confirmed by the results of cytological and biochemical studies of the cerebrospinal fluid. For confirmation of enteroviral etiology of meningitis a method of polymerase chain reaction with identification of ribonucleic acid of enteroviruses in feces and/or cerebrospinal fluid with further determination of enterovirus type 71 according to the methods proposed by the manufacturers of test-systems ("Ampli-sense", Russia) was used. The research was conducted at the laboratory for Molecular Genetic Researches of the Zaporizhzhia State Medical University in the framework of an open cohort study of the Small Grants Joint Programme WHO/HHWS focused on the implementation of programmes of the communicable disease control on the topic: "New approaches to the diagnosis of the main clinical forms of enteroviral infection in children and adults".

Considering the analysis of clinical and laboratory data, patients with EM were divided into the following groups: I group was 27 children (age from 3 to 13 years, the average age was 8 (6; 10) years); II Group was 15 adult patients of age from 18 to 55 years (average age was 18 (18; 25) years). All patients received a traditional background therapy that included the appointment of antibacterial drugs, as support therapy, if required, glucocorticosteroids, non-steroidal anti-inflammatory drugs, diuretics, nootropics, B vitamins, and agents that improve cerebral circulation, infusion therapy.

The data obtained were statistically processed on the PC using the created patients' database in the software application «STATISTICA® for Windows 6.0» (StatSoft Inc., No AXXR712D833214FAN5). For each sample, the median (Me) and percentiles (25; 75) were calculated. Non-parametric statistical methods Mann-Whitney U test (for quantitative attributes) and χ^2 test (for qualitative attributes) were used to assess the validity of the difference between two independent samples.

IV.   RESULTS

The results of the statistical analysis of age characteristics of patients with EM revealed a significant prevalence among ill children of primary school age (18-66.7%) and preschool age (7 - 25.9%), and among adults – patients of young age (14-93.3 %) The age structure of patients with EM is presented in Table 1.

Table 1

The age structure of patients (adults and children) with EM, abs.n. (%)

Children with EM (n=27)				Adults with EM (n=15)	
1-3 years old	4-7 years old	8-12 years old	13-17 years old	18-44 years old	45-59 years old
1 (3,7 %)	7 (25,9 %)	18 (66,7 %)	1 (3,7 %)	14 (93,3 %)	1 (6,7 %)

Regardless of the age of the patients, the EM had a predominantly moderate course: in 96.3% (26 out of 27) of children and 93.3% (14 out of 15) of adults. In rare cases, in children (1-3.7%) and adults (1 - 6.7%) EM had a severe course with the development of complications in the form of toxic encephalopathy. Duration of the disease at the time of hospitalization in adults and children did not differ (p>0.05) and was (3.6 ± 0.5) days and (3.5 ± 0.5) days of the disease respectively.

Analysis of clinical manifestations of EM showed that in all cases, the acute onset of the disease was associated with an increase in body temperature in most adults (10-66.7%) and children (17-62.9%) to subfebrile measures; each fourth adult (4-26.7%) and more than each third child (10-37.1%) had a temperature increase up to the febrile level, however, there was no statistically significant difference when comparing these parameters in adults and children (p> 0.05). The occurrence of fever in patients with EM was accompanied by a general weakness, and a certain number of patients had catarrhal manifestations, particularly in 53.3% (8 out of 15) adults and 74.1% (20 out of 27) children (p> 0.05). It is noteworthy that in the presence of cephalalgia, such clinical signs as nausea and vomiting were in 1.4 times significantly more common in children (22 - 81.5%) than in adults (8 - 53.3%) (p=0.009). The frequency of occurrence of such cerebral symptoms as photophobia and hyperacusis was not statistically different in the studied groups (p>0.05), that may be due to difficulties in the interpretation of clinical data of primary school children.

We noted that the peculiarity of the course of EM in children was the combination of EM with other manifestations of enteroviral infection in some patients, namely, exanthema (2 - 7.4%) and enteritis (1-3.7%). Unlike children with EM, EM of the adult patients was not combined with other clinical manifestations of this infection in any of the cases (Table 2).

Table 2

Comparison of clinical signs in patients (adults and children) with EM, abs.n. (%)

Clinical signs	Patients with EM (n=42)		Statistical validity
	adults (n=15)	children (n=27)	
Fever, incl.:	15 (100%)	27 (100%)	
Subfebrile	10 (66,7%)	17 (62,9%)	χ^2=0,06, p=0,81
Febrile	4 (26,7%)	10 (37,1%)	χ^2=0,47, p=0,49
Hyperthermia	1(6,6%)	0 (0%)	χ^2=1,84, p=0,17
Catarrhal syndrome	8 (53,3%)	20 (74,1%)	χ^2=1,87, p=0,17
Weakness	15 (100%)	27 (100%)	-
Cephalalgia	15 (100%)	26 (96,3%)	χ^2=0,57, p=0,45
Photophobia, hyperacusis	5 (33,3%)	3 (11,1%)	χ^2=3,09, p=0,07
Nausea,vomiting	8 (53,3%)	22 (81,5%)	χ^2=3,74, p=0,05
Other signs of the infection, incl.:	0 (0%)	3 (11,1%)	χ^2=1,79, p=0,17
Enteritis	0 (0%)	1(3,7%)	χ^2=0,57, p=0,45
Exanthema	0 (0%)	2 (7,4%)	χ^2=1,17, p=0,28

The comparative analysis of meningeal syndrome in patients with EM showed that meningeal symptomology in children was clearer than in adults. Meningeal signs were positive in the vast majority of both adults (14-93.4%) and children (26 - 96.3%), but it is noteworthy that a dissociation of meningeal symptoms in adults was 1.8 times more often than in children (73.3% vs. 40.7%, p = 0.04). If the stiffness of neck muscles was detected in more than half of adults (10-66.7%) and children (18-66.7%), then the positive Kernig's sign was 1.6 times more common in children than in adult patients (74.1% vs. 40.0%, p = 0.03). The Kernig's sign in every third adult patient was negative, that was 4.5 times more frequent than in children (33.3% vs. 7.4%, p = 0.03), besides, this sign was doubtful (4-26.7%) in every fourth adult patient with EM. Much less frequently, the positive Brudzinski's sign (upper or lower) was recorded in adults (2 - 13.3%) and in children (6 - 22.2%) in with EM. (Table 3).

Table 3

Comparative analysis of meningeal syndrome in patients (adults and children) with EM, abs. n. (%)

Clinical signs	Patients with EM (n=42)		Statistical validity
	adults (n=15)	children (n=27)	
Meningeal signs: negative positive dissociation	1(6,6 %) 4 (26,7 %) 11 (73,3 %)	1(3,7 %) 16 (59,3 %) 11 (40,7 %)	χ^2=0,19, p=0,66 χ^2=0,18, p=0,67 χ^2=4,11, p=0,04
Stiffness of neck muscles: positive doubtful negative	10 (66,7%) 2 (13,3%) 3(20,0%)	18(66,7%) 2 (7,4%) 7(25,9%)	χ^2=0,00, p=1 χ^2=0,39, p=0,53 χ^2=0,19, p=0,66
Kernig's sign: positive doubtful negative	6 (40,0%) 4 (26,7%) 5 (33,3%)	20(74,1%) 5 (18,5%) 2(7,4%)	χ^2=4,75, p=0,03 χ^2=0,38, p=0,53 χ^2=4,67, p=0,03
Brudzinski's sign: positive doubtful negative	2 (13,3%) 0 (0%) 13 (86,7%)	6 (22,2%) 3 (11,1%) 18 (66,7%)	χ^2=0,49, p=0,48 χ^2=1,79, p=0,18 χ^2=2,00, p=0,15

Particular attention deserves the results of comparing the indicators of cerebrospinal fluid in patients with EM (adults and children). In the vast majority of patients, regardless of age, pleocytosis was within the range of 500 cells/µl, namely in 80% (12 out of 15) of adults and 81.5% (22 of 27) of children, however the pleocytosis structure in children were statistically different from adult patients. First of all, regardless of the viral etiology of meningitis, 40.7% (11 out of 27) children had a neutrophilic character of pleocytosis, against the absence of such changes in adult patients with EM (p = 0.004). The prevalence of neutrophils in the pleocytosis structure in these children required the administration of appropriate antibiotic therapy (Table 4). Neutrophilic pleocytosis was registered more often in primary-school-age patients - in 90.9% (10 out of 11) and in one pre-school-age child.

Table 4
Comparative analysis of cerebrospinal fluid in patients (adults and children) with EM

Indicators	Patients with EM (n=42)		Statistical validity
	adults (n=15)	children (n=27)	
Lymphocytic pleocytosis, abs. n. (%)	15 (100 %)	16 (59,3 %)	χ^2=8,28, p=0,004
Lymphocytes, %	94 (67; 99)	55 (42; 96)	p=0,01
Neutrophilic pleocytosis, abs. n. (%)	0 (0 %)	11 (40,7 %)	χ^2=8,28, p=0,004
Neutrophils, %	6 (1; 23)	45 (4; 58)	p=0,01
Protein, g/L	0,165 (0,099; 0,198)	0,132 (0,066; 0,165)	p=0,51
Glucose, mmol/L	3,3 (2,2; 3,6)	2,5 (2,2; 3,0)	p=0,41
Chlorides, mmol/L	118,8 (115,0; 116,0)	115,0 (115,0; 116,0)	p=0,08

Analysis of the parameters of the leukocyte hemogram of patients with EM revealed the presence of more marked changes in children. In adults (5 - 33.3%), the absence of changes was recorded 3 times more often than in children (3 - 11.1%). Statistically significant was the more frequent development of neutrophilosis in the range of 75-94% in the absence of leukocytosis in children, unlike adults: 13 (48.2%) vs. 1 (6.6%) patients (χ2 = 7.47, p = 0.006). In 2 (13.3%) adult patients with EM lymphomonocytosis was found in the range of 89-93%, in contrast to the absence of this feature in children (χ^2=3,78, p=0,049).

The enteroviral etiology of meningitis was confirmed in all patients by DNA detection of enterovirus using PCR method, but genotypes 71 of the enterovirus was not detected in any case.

V.   DISCUSSION

Much attention in the contemporary literature is paid to the study of the features of enteroviral infection, but given that in the structure of this infection the share of meningitis is 3.0% [13], studies on the study of the features of this form of the disease are much smaller and, as a rule, they relate to the study of EM in children [8, 9, 11]. In addition, there are significant controversies regarding the frequency of registration of combined lesions in the development of EM. Researchers [3] believe that the feature of EM is the detection of combined forms of infection with the involvement of other organs and systems in the process in more than half of patients. In contrast to these data, the authors [14] showed that EM in the vast majority of children (82.8%) was not accompanied by other clinical manifestations of enteroviral infection, and only a small number of patients suffered from exanthema (10.8%), gerpangina (2,1%), and in rare cases from myalgia. According to our study, any adult patient with EM had no other manifestations of enteroviral infection, and only every tenth child with EM was detected to have a combination of manifestations of the disease, namely, exanthema (7.4%) or enteritis (3.7%). There are some difficulties in clinical diagnosis of EM, according to our data, since meningeal signs in a significant group of patients (mostly adults) are absent (in adults 1.8 times more often than in children (73.3% vs. 40.7%, p = 0.04)). In addition, dissociation of meningeal symptoms often was noted. Dissociation of meningeal signs was also noted by other authors, and even in a higher percentage of patients. Thus, researchers [15] observed the dissociation of meningeal signs in 78.8% of patients, and the study [13] showed that EM has a few feverish waves with significant mid-day fluctuations in temperature, which is accompanied by instability and dissociation of meningeal signs, causing the difficulty in clinical diagnostics.

The references [13] indicate a frequent predominance of neutrophil pleocytosis in the first two days of EM that is changed further into lymphocytic one. However, according to the results of our study, it has been proved that the rate of development of these changes in the cerebrospinal fluid depends on the age of the patient, meaning that neutrophilic pleocytosis with EM does not develop in adult patients, and the risk of development of these changes in children is present in patients of primary school age (90.9%)

Our study has showed the prevalence of the moderate course of EM in both adults and children that coincides with the references [16]. Despite a significant number of current studies on a specific neurotropism of enteroviruses type 71 [9, 17, 18], according to our research, this type of agent was not identified in any patient with EM.

VI.　　　Conclusions:

1. EM has a predominantly moderate course in both adults (93.3%) and children (96.3%) with acute onset of disease, subfebrile or febrile fever, more than half of patients with catarrhal manifestations in the beginning of the disease, and cephalalgia. Clinical symptomatology of EM in children is more pronounced than in adults due to the more frequent occurrence of nausea and vomiting (1.4 times, $p < 0.05$), as well as combination of EM with other manifestations of enteroviral infection, such as, exanthema (7.4 %) and enteritis (3.7%).

2. Meningeal symptomatology is more marked in children with EM than in adults due to the lower frequency of dissociation of meningeal symptoms (1.8 times, $p = 0.04$) and more often then positive Kernig's sign (1.6 times, $p = 0,03$). Most patients, regardless of age, had pleocytosis within the range of 500 cells / μl, but regardless of viral etiology of meningitis neutrophilic pleocytosis was noted in 40.7% of children against the absence of such changes in adult patients with EM ($p = 0.004$).

The enteroviral etiology of meningitis was confirmed in all patients by detection of the DNA of the enterovirus, however, the enterovirus type 71 was not detected in any case in Zaporizhzhia region.

REFERENCES

[1]. Доан С.И., Малыш Н.Г., Проблемные вопросы эпидемиологического надзора за энтеровирусными неполиомиелитными инфекциями в Украине, *Журнал Гродненского государственного медицинского университета*, *16(1), 2018*, 18-22.

[2]. Канаева О. И., Энтеровирусная инфекция: многообразие возбудителей и клинических форм, *Инфекция и иммунитет*, *4, 2014*, 27-36.

[3]. Logan S. A. E., E. Mac Mahon, Viral meningitis, *BMJ, Vol. 336, № 7634, 2008*, 36-40.

[4]. Pickering L. K., Enterovirus (nonpoliovirus) and parechovirus infections (group A and B coxsackieviruses, echoviruses, numbered enteroviruses, and human parechoviruses in Red book (American Academy of Pediatrics, Elk Grove Village, IL: 2012, 315)

[5] Ешмолов С. Н., Сытников И. Г., Мельникова И. М., Клинико-лабораторные особенности энтеровирусных менингитов в современных условиях, *Эпидемиология и инфекционные заболевания, №3, 2012*, 38-42.

[6]. Oberste S. K. Maher, W. Nix [et al.], Molecular identification of 13 new 1 enterovirus types, EV79–88, EV97, and EV100–101, members of the species Human Enterovirus, *Virus Research, Vol. 128, 2007*, 34-42.

[7]. Duong V., C. Mey, M. Eloit [et al.], Molecular epidemiology of human enterovirus 71 at the origin of an epidemic of fatal hand, foot and mouth disease cases in Cambodia, *Emerging Microbes & Infections., № 5(9), 2016*, 104.

[8]. T.H. Khanh, S. Sabanathan, T.T. Thanh, P.K. Thoa, T.C. Thuong, V.T. Hang, J. Farrar, T.T. Hien, N. Chau, H.R. van Doorn, Enterovirus 71-associated Hand, Foot, and Mouth Disease, Southern Vietnam, 2011, *Emerg. Infect. Dis, Vol. 18 (12), 2012*, 2002–2005.

[9]. M. Zeng, N.F. El Khatib, S. Tu, P. Ren, S. Xu, Q. Zhu, X. Mo, D. Pu, X. Wang, R. Altmeyer, Seroepidemiology of Enterovirus 71 infection prior to the 2011 season in children in Shanghai, *J. Clin. Virol., Vol. 53 (4), 2012*, 285–289.

[10]. Huaman J. L., Carrion G., Ampuero J. S., Enterovirus-71 genotype C isolated in Peru between 2006 and 2009, *Journal of clinical virology, № 85, 2016*, 40 – 43.

[11]. Li W., Gao H. H., Zhanq Q. [et al.], Large outbreak of herpangina in children caused by enterovirus in summer of 2015 in Hangzhou, China, *Journal of Scientific Reports, № 6, 2016*, 353 – 388.

[12]. Иванова О. Е. Еремеева Т. П., Лукашев А. Н. [и др.], Наблюдение за циркуляцией неполиомиелитных энтеровирусов в Российской Федерации в 1999-2007 гг., *Труды Института полиомиелита и вирусных энцефалитов имени М. П. Чумакова, Т. XXV, 2008*, 11-23.

[13]. Бортникова В.А. Проявления эпидемического процесса энтеровирусных инфекций в г. Минске, *Материалы 69-ой научно-практической конференция студентов и молодых ученых с международным участием «Актуальные проблемы современной медицины и фармации-2015», Минск, 2015*, 930-935.

[14]. Мартынова Г.П., Страшникова Н.С., Кутищева И.А., Белкина А.Б., Карасев А.В. Энтеровирусные менингиты у детей: современные подходы к диагностике и лечению, *Детские инфекции, Т.17(3), 2018*, 11-16.

[15] Будаєва І.В., Ревенко Г.О., Якімова С.В., Олійник В.В., Дорошенко В.Ф., Найпоширеніші клінічні форми ентеровірусної інфекції у Дніпропетровському регіоні, *Актуальна інфектологія, Т.5, № 5, 2017*, 213-216.

[16]. Dos Santos G.P., Skraba I., Oliveira D., Enterovirus meningitis in Brazil, 1998–2003, *J. Med. Virol., № 78, 2006,* 98-104.

[17]. T. Solomon, P. Lewthwaite, D. Perera, M. J. Cardosa, P. McMinn, M. H. Ooi, Virology, epidemiology, pathogenesis, and control of enterovirus 71, *Lancet Infect. Dis., Vol. 10, № 11, 2010,* 778–790.

[18]. Zeng M. N.F. El Khatib, S. Tu, P. Ren, S. Xu, Q. Zhu, X. Mo, D. Pu, X. Wang, R. Altmeyer, Seroepidemiology of Enterovirus 71 infection prior to the 2011 season in children in Shanghai, *J. Clin. Virol, Vol. 53 (4), 2012,* 285–289.