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Enterovirus infection: Hand-Foot-and-Mouth Disease (HFMD) in Ukraine

Энтеровирусная инфекция: Hand-Foot-and-Mouth Disease (HFMD) в Украине

Abstract

The relevance of the studied problem in Ukraine is determined by the increase in the incidence of patients with enterovirus infection with various clinical forms in recent years. Official statistical registration of this infection in Ukraine is not conducted. But the analysis of infectious diseases among children of Dnipro city and Dnepropetrovsk region over the past 5 years, gives grounds to state an increase in the incidence of enterovirus infection 3.6 times in the form of the following clinical forms: enterovirus meningitis confirmed by the detection of enterovirus RNA in CSF (68.6%), HFMD (17.9%), herpangina + diarrhea (13.3%).

The aim of the work is to study the clinical and epidemiological features of HFMD in children at the present stage, as well as to attract physicians' attention to the problem of HFMD and, in particular, to the features of heart disease in this disease.

Materials and methods. During the period from 2016 to 2017, 17 children with HFMD aged 3.5 to 17 years were under our supervision. The median age is 7.8 years.

Results. The incidence of HFMD in the last 5 years has not been seasonal and has been observed year-round in the form of sporadic cases in the age group of both younger and older age groups. Among the clinical manifestations of HFMD, the most frequent variant of the presentation was the combination of a rather long fever followed by the appearance of polymorphic exanthema (spots, papules and vesicles) on the palmar and interphalangeal surfaces of the hands and soles of the feet in combination with vesicular stomatitis. Repeated episodes of HFMD were registered in 17.64% (n=3) in 6–12 months after the initial episode of HFMD. Repeated cases of the disease were clinically little different from primary cases, not characterized by easier symptomatology. Heart lesions in two children with this phenomenon were observed in both the first episode and the repeated manifestation of HFMD. A feature of late manifestations of HFMD is desquamation of the nail plates on the hands and feet 2–4 weeks after the infection, as well as repeated cases of HFMD within the next year after the initial episode. A significant proportion of patients with HFMD have a risk of developing myocarditis, which most often has subclinical manifestations, in connection with which all children with enterovirus infection are recommended to conduct an ECG study and determine the serum CF fraction of creatinine phosphokinase.

Keywords: enterovirus infection, hand-foot-mouth syndrome, myocarditis, children.

Резюме

Актуальность проблемы в Украине определяется увеличением заболеваемости пациентов энтеровирусной инфекцией с различными клиническими формами в последние годы. Официальной статистической регистрации этой инфекции в Украине не ведется. Анализ инфекционной заболеваемости детей г. Днепра и Днепропетровской области за последние 5 лет позволяет констатировать рост заболеваемости энтеровирусной инфекцией в 3,6 раза в виде следующих клинических форм: энтеровирусный менингит, подтвержденный обнаружением РНК энтеровирусов в ликворе (68,6%), HFMD (17,9%), герпангина + диарея (13,3%).

Цель работы – изучить клинико-эпидемиологические особенности HFMD у детей на современном этапе, а также привлечь внимание врачей к проблеме HFMD, а главное – к особенностям поражения сердца при этой болезни.

Материалы и методы. В период с 2016 по 2017 г. 17 детей с HFMD в возрасте от 3,5 до 17 лет находились под наблюдением. Возрастная медиана – 7,8 лет.

Результаты. Заболеваемость HFMD за последние 5 лет не имела сезонности и отмечалась круглогодично в виде спорадичных случаев в возрастной группе как младшего, так и старшего возраста.

Среди клинических проявлений HFMD наиболее частым вариантом презентации было сочетание довольно длительной лихорадки с последующим появлением полиморфной экзантемы (пятна, папулы и везикулы) на ладонных и межфаланговых поверхностях рук и подошвах стоп в комбинации с везикулярным стоматитом.

Особенностью поздних проявлений HFMD является десквамация ногтевых пластинок на руках и ногах через 2–4 недели после перенесенной инфекции, а также повторные случаи заболевания HFMD в течение ближайшего года после первичного эпизода.

У значительной части пациентов с HFMD имеется риск развития миокардита, который чаще всего имеет субклинические проявления, в связи с чем всем детям с энтеровирусной инфекцией рекомендуется проведение ЭКГ-исследования и определение уровня сывороточной МВ – фракции креатининфосфокиназы как фактора воспаления и некроза кардиомиоцитов. В проведенном исследовании отмечено увеличение значений этого маркера, которые в 1,5–2,3 раза превышали норму у 11 детей (78,57%).

Отмечен факт повторных эпизодов регистрации HFMD у 17,64% (n=3) пациентов через 6–12 месяцев после первичного эпизода HFMD, которые мало отличались от первичных, не характеризовались более легкой симптоматикой. Поражения сердца у 2 детей с указанным феноменом наблюдались как при первом эпизоде, так и при повторном проявлении HFMD.

Ключевые слова: энтеровирусная инфекция, синдром рука-нога-рот, миокардит, дети.

■ INTRODUCTION

Hand-Foot-and-Mouth Disease (HFMD) is a symptom complex consisting of vesiculose of the oral mucosa – enanthema, as well as exanthema on the limbs, palms, and soles. This syndrome is one of the variants of enterovirus infection, namely, Boston exanthema. A synonym for this disease is vesicular stomatitis with exanthema.

The main pathogens of the hand-foot-mouth syndrome are representatives of the enterovirus family: coxsackievirus A16, A6 and enterovirus 71. However, sporadic cases can be caused by coxsackieviruses A4-A7, A9, A10, B1-B3, and B5. These are RNA-containing viruses that are

sufficiently stable in the external environment, capable of remaining at room temperature for up to 2 weeks in a viable state. Sporadic cases of the disease are usually noted, but epidemic outbreaks are observed with a certain regularity [1]. A significant outbreak of HFMD caused by echovirus 19 was noted in China in 2003. Similar forms of infection with a broader presentation included a petechial-purple rash, herpetiform eczema (Gianotti-Crosti-like syndrome), severe systemic complications, and in the late period – onychomadesis – dystrophic damage to the nail plate (onychomadesis), characteristic of coxsackievirus A6 [2]. HFMD outbreaks are recorded periodically in different countries. The most significant were noted in Spain in 2011 when the total number of cases reached 4,540 children under the age of 14 [3].

According to the authors' observation, children <5 years are the most susceptible to the development of HFMD, although older age groups may also be involved in the epidemic process with equal distribution among boys and girls. Observations based on a clinical analysis of 931 children with HFMD during an outbreak in China showed that symptoms such as prolonged fever, increased C-reactive protein and hyperglycemia are risk factors that determine the more severe course of the disease [4].

The relevance of the studied problem in Ukraine is determined by the increase in the incidence of patients with enterovirus infection with various clinical forms in recent years. Official statistical registration of this infection in Ukraine is not conducted. But the analysis of infectious diseases among children of Dnipro city and Dnepropetrovsk region over the past 5 years, gives grounds to state an increase in the incidence of enterovirus infection 3.6 times in the form of the following clinical forms: enterovirus meningitis confirmed by the detection of enterovirus RNA in CSF (68.6%), HFMD (17.9%), herpangina + diarrhea (13.3%). The epidemiological situation with enterovirus infection is characterized, on the one hand, by the increase in the incidence of this pathology among the child population, and on the other – by the improvement of the quality of laboratory diagnostics.

The presence of a typical triad of symptoms (spot-vesicular rash on the hands, feet and on the oral mucosa) suggests that HFMD is the calling card of enterovirus infection. The incubation period with HFMD lasts, on average, 4–7 days. The patient becomes infectious with the first symptoms of the disease and this is the whole heat of the disease. The first symptom is an increase in temperature to 37.5–38 °C, symptoms of intoxication – weakness, headache, sore throat, muscle pain. Duration of fever is up to 3–5 days. That is, the onset of the disease is very similar to ARVI. However, unlike ARVI in 1–2 days on the palms (sometimes on the back of the hand) and feet (more often soles), less often on the back of the thighs and buttocks, there is a rash in the form of small vesicles up to 3 mm in diameter, surrounded by a whisk of redness. In the dynamics of the reverse development of the rash: the elements are not opened, their contents disappear, they are compared with the surface of the normal skin, reddening disappears. The rash is held by the patient for 5–7 days, and then disappears completely. Simultaneously with the appearance of exanthema, the vesicular enanthem appears in the oral cavity. In a day – two vesicles are transformed into sores (or aphthae), accompanied by soreness, sensitivity to hot and spicy food. The phenomena of aphthous stomatitis can be found on the inner surface of cheeks, tongue,

gums, hard and soft palate. When stomatitis appears, appetite decreases, irritability, capriciousness, sore throat, difficulty in eating, excessive salivation. By external signs, enterovirus stomatitis with HFMD resembles herpetic stomatitis.

Some children after HFMD can experience dystrophic lesion of the nail plates with their exfoliation (onychomadesis), the cause of which has not been fully established. Interest in the modern presentation of HFMD served as a motive for this study. It is difficult to eat, abundant salivation. By external signs, enterovirus stomatitis with HFMD resembles herpetic stomatitis.

■ THE AIM OF THE WORK

Is to study the clinical and epidemiological features of HFMD in children at the present stage, as well as to attract physicians' attention to the problem of HFMD and, in particular, to the features of heart disease in this disease.

■ MATERIALS AND METHODS

During the period from 2016 to 2017, 17 children with HFMD aged 3.5 to 17 years were under our supervision. The median age is 7.8 years.

In the routine screening of children, we included the addition of an ECG and a study of serum creatine kinase-MB (CFK-MB). Thus, 14 children from 17 were examined. The validity of the inclusion of the cardiologic examination was dictated by the presence of cardiac tropisms in enteroviruses and the assumption of possible heart damage in the children under examination due to viremia.

Since HFMD is a pathognomonic syndrome for enterovirus infection, there was no task of laboratory confirmation of the etiology of the disease, the diagnosis was established clinically. Treatment of the disease was pathogenetic (hydration for the purpose of detoxication – 100 ml/kg per day) and symptomatic (acetaminophen or ibuprofen with an increase in body temperature, desloratadine – with itching on the background of exanthema, local antiseptic, and analgesic therapy of stomatitis).

■ RESULTS AND DISCUSSION

All children had a sporadic incidence; none of them came from a hotbed of infection. There was no significant dependence of the incidence of HFMD on the season of the year. The registration of this disease was equally distributed throughout the year, in contrast to enterovirus serous meningitis and the clinical form herpangina + diarrhea, which are characterized by summer-autumn seasonality. There were no lethal outcomes. The mild form of the disease was noted in the majority of children – 85.4% (n=14), in the rest – registered with a moderate form, but still closer to mild. Criteria for severity were two clinical symptoms: the severity and duration of fever and the nature of the rash.

The disease in all children was characterized by moderate intoxication and an increase in body temperature to subfebrile digits (38–38.5 °C). The fever stopped within 3–5–7 days. A day after the onset of the disease, 76.47% of children (n=13) had a rash on their fingers and feet, spots, papules and vesicles 1–5 mm in diameter, surrounded by a corolla of hyperemia; in some children, it was slightly itchy. At the part of children with the easiest course of

Fig. 1. Rash elements located in the interphalangeal folds, both on the palmar and on the back of the hands

Fig. 2. Rash elements located on the feet

the disease, parents noticed a rash only for 2–3 days of the disease. Elements were located in the interphalangeal folds, both on the palmar and on the back of the hands (Fig. 1). On the feet, the arrangement of the elements was similar (Fig. 2). Simultaneously with the appearance of exanthema, the appearance of vesicular stomatitis was noted in varying degrees of severity. Vesicular papular eruptions were located on the lips, the skin of the

nasolabial triangle, on the mucous membrane of the oral cavity (more often on the mucous membrane of the cheeks and palatine arches, less often in the tongue). In some children (17.64%, n=3), the transformation of vesicles into aphthae was recorded. More often drying took place with the formation of crusts or vesicles turned into small erosions also with subsequent drying. Almost half of the children (47.05%, n=8) had vesicular rashes located on the skin of the gluteus and axillary regions (Fig. 3).

In our observation, we recorded in 17.64% of children (n=3) the proximal separation of the nail plate from the nail bed, followed by desquamation of the nail plate (Fig. 4). This symptom was observed equally on the nails of the hands and feet. This phenomenon was observed 3–4 weeks after the acute infection.

Interesting is the fact of repeated episodes of HFMD registration in patients. In our observation, this phenomenon was registered in 17.64% (n=3) 6–12 months after the initial episode of HFMD. Repeated cases of the disease were clinically little different from primary cases, not characterized by easier symptomatology. Heart lesions in 2 children with this phenomenon were observed in both the first episode and the repeated manifestation of HFMD.

Analysis of the results of the cardiac examination in 14 children showed signs of heart involvement in 64.28% (n=9). Clinical manifestations were minimal and manifested in all children with nonspecific symptoms, such as weakness, increased fatigue, reduced exercise tolerance. The presence of tachycardia in the midst of the underlying disease, not associated with fever, was observed in only 3 children. Nevertheless, the ECG examination revealed a number of signs that support heart damage, namely: changes in the end part of the ventricular complex (ST segment depression and the formation of a smoothed or negative symmetrical or asymmetric T wave in

a **b**

Fig. 3. Vesicular rashes located on the skin of the gluteus (a) and axillary (b) regions

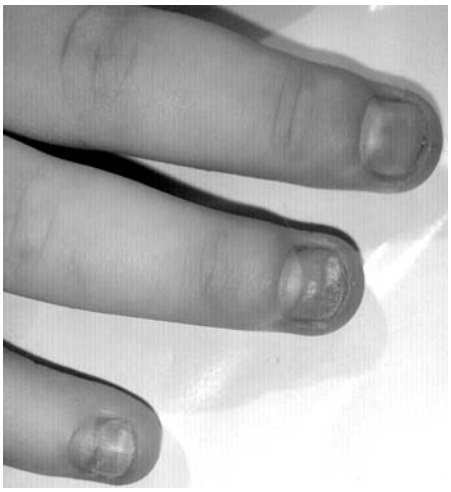

Fig. 4. Desquamation of the nail plate

several ECG leads in 28,57% (n=4), detection of cardiac arrhythmias and conduction in the form of extrasystole, atrioventricular and intraventricular blockades – 21,42% (n=3), decrease in the voltage of the ECG teeth – 14,28% (n=2).

Determination of the level of serum CFK-MB as a factor of inflammation and necrosis of cardiomyocytes revealed an increase in the values of this marker, which in 1.5–2.3 times exceeded the norm in 11 children (78,57%). The overwhelming majority of children (64,28%, n=9) had a combination of signs of myocardial cytolysis and ECG changes, which gave grounds for diagnosing acute myocarditis, while only two children showed an increase in the CFK-MB without symptoms of ECG disorders. The child showed changes in the ECG without an increase in the level of CFK-MB fraction.

It should be noted that heart disease in children with HFMD did not always correlate with the severity of manifestations of the disease itself and was observed in both severe and mild forms. In 2 of 3 children with repeated episodes of HFMD, heart failure was noted with ECG changes and an increase in the MB fraction of CFK, as in the primary disease.

Thus, the conducted epidemiological observations indicate an increase in the incidence of various forms of enterovirus infection, and in particular in the form of Hand-Foot-and-Mouth Disease in children. Analysis of the current picture of the clinical presentation of Hand-Foot-and-Mouth Disease in Ukraine made it possible to identify certain features of clinical manifestations and possible complications from the central nervous system, myocardium, skin and nail plates, the forecasting of which is of great practical importance.

■ CONCLUSIONS

1. The incidence of HFMD in the last 5 years has not been seasonal and has been observed year-round in the form of sporadic cases in the age group of both younger and older age groups.

2. Among the clinical manifestations of HFMD, the most frequent variant of the presentation was the combination of a rather long fever followed by the appearance of polymorphic exanthema (spots, papules and vesicles) on the palmar and interphalangeal surfaces of the hands and soles of the feet in combination with vesicular stomatitis.
3. A feature of late manifestations of HFMD is desquamation of the nail plates on the hands and feet 2–4 weeks after the infection, as well as repeated cases of HFMD within the next year after the initial episode.
4. A significant proportion of patients with HFMD have a risk of developing myocarditis, which most often has subclinical manifestations, in connection with which all children with enterovirus infection are recommended to conduct an ECG study and determine the serum MB fraction of creatinine phosphokinase.

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