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Joint diagnosis of pediatric and dermatology clinics: Prospective observation of thirty-nine patients with hand, foot and mouth disease

Pediatri ve dermatoloji kliniklerinin ortak tanısı: El-ayak-ağız hastalığı olan otuz dokuz hastanın prospektif izlemi

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Abstract

Background and Design: Hand, foot and mouth disease (HFMD) is a childhood enteroviral eruptive disease presenting with fever and cutaneous and mucosal lesions. It is benign and generally resolves spontaneously, but may sometimes result in systemic involvement. The purpose of this study was to share our clinical experience concerning patients who were followed with the diagnosis of HFMD established by the pediatric and dermatology clinics.

Materials and Methods: We prospectively evaluated patients who attended our hospital with the complaints of fever and eruptions and received the diagnosis of HFMD based on the clinical findings between December 2014 and November 2015. Age, sex, month of presentation, presentation symptoms and duration of symptoms were investigated. Systemic and dermatological examination findings, laboratory results and tests such as echocardiography were reviewed.

Results: Thirty-nine patients were included; 19 (48.8%) were girl and 20 (51.2%) were boy. The mean age of the patients was 29.8±27.9 (6-155) months. Six (15.3%) patients were in the 0-12 month age group, while only 3 (7.8%) were older than 60 months. Presentations were most common in September, June and October. The most common presentation symptoms were eruptions on the hands and feet (100%), fever (82.1%) and oral aphthae (79.5%). The lesions were most commonly observed on the hands (94.9%, n=37) and feet (87.2%, n=34) and in the mouth (79.5%, n=31). Cardiac involvement was determined in 3 (7.7%) patients. Nail changes were observed during monitoring in 10 (25.6%) patients.

Conclusion: Our results show that the age of onset of HFMD in Turkey has decreased compared to that reported in the previous studies. Patients must be evaluated in detail in terms of clinical and laboratory findings showing severity of the disease. This study also shows that pediatricians/dermatologists collaboration is of great importance.

Keywords: Hand-foot-mouth disease, cardiac involvement, onychomadesis

Öz

Amaç: El-ayak-ağız hastalığı (EAAH); ateş, deri ve mukoza lezyonları ile seyreden, çocukluk çağının enteroviral döküntülü bir hastalığıdır. İyi seyirli ve kendiliğinden düzelme eğiliminde olmakla birlikte, nadiren sistemik tutuluma yol açabilir. Bu çalışmanın amacı, pediatri ve dermatoloji klinikleri tarafından EAAH tanısıyla takip edilen hastalara ait klinik deneyimlerimizi paylaşmaktır.

Gereç ve Yöntem: Hastanemize Aralık 2014-Kasım 2015 tarihleri arasında ateş ve döküntü şikayeti ile başvuran hastalardan, klinik bulgulara dayanılarak EAAH tanısı koyulan hastalar prospektif olarak değerlendirildi. Hastaların yaşı, cinsiyeti, başvuru ayı, başvuru şikayeti ve süresi sorgulandı. Sistemik ve dermatolojik muayene bulguları, laboratuvar sonuçları, ekokardiyografi gibi ek inceleme tetkikleri gözden geçirildi.

Bulgular: Çalışmaya toplam 39 hasta dahil edildi. Hastaların 19'u (%48,8) kız, 20'si (%51,2) erkek idi. Hastaların ortalama yaşı 29,8±27,9 (6-155) ay olarak hesaplandı. Yaş aralığına göre hastaların 6'sı (%15,3) 0-12 ay arasında iken, sadece 3'ü (%7,8) 60 aydan büyüktü. Başvurular en

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sık Eylül, Haziran ve Ekim aylarında görüldü. En sık başvuru şikayeti; el ve ayaklarda döküntü (%100), ateş (%82,1) ve oral aft (%79,5) idi. Lezyonlar, en sık el (%94,9, n=37), ayak (%87,2, n=34) ve ağız içinde (%79,5, n=31) görüldü. Üç hastada (%7,7) kardiyak tutulum saptandı. Takiplerde 10 hastada (%25,6) tırnak değişikliği gelişti.

Sonuç: Çalışmamız sonucunda ülkemizde EAAH'nin görülme yaşının önceki yayınlara nazaran küçüldüğü tespit edildi. Hastaların hastalığın şiddetini gösteren klinik ve laboratuvar bulgular açısından ayrıntılı değerlendirilmesi gereklidir.

Anahtar Kelimeler: El-ayak-ağız hastalığı, kardiyak tutulum, onikomadezis

Introduction

Hand, foot and mouth disease (HFMD) is a contagious viral infection that can lead to varying levels of outbreak depending on geographical region and season. The condition was first described in New Zealand in 1957[1]. The agent has been reported to be Echovirus from the family *Picornaviridae, Coxsackievirus A5, A7, A9, A10, B2, B5* and *A16* and *Enterovirus 71* and *72*[2]. Typical clinical findings are erythematous papulovesicular lesions on the palms and the soles of the feet following a short prodromal stage[3]. The virus is transmitted via the air. Following a 5-7 day incubation period, it leads to lesions, first inside the mouth, and subsequently on the hands and feet[4]. Although the disease is called HFMD, lesions can also be seen in the gluteal region, knees, elbows and perioral areas[3,4]. All lesions resolve spontaneously in 1-2 weeks. Despite being a self-limiting and mild disease, complications, such as aseptic meningitis, encephalitis, myocarditis, pulmonary edema and/or hemorrhage, pleural effusion, acute flask paralysis, and dehydration may also be encountered[3].

Major outbreaks of HFMD were seen in Taiwan in 1998, in Singapore and Vietnam in 2008 and in China between 2008 and 2013[2,5,6]. The number of studies from Turkey, apart from those by Polat Ekinci et al.[4], Karadağ Öncel et al.[7], Uğraş et al.[8] and Topkarcı et al.[9], and a few case reports, is insufficient[10,11]. The purpose of this study was to share prospective monitoring and our experiences of patients presenting to our hospital with fever and eruptions and diagnosed with HFMD on the basis of clinical findings.

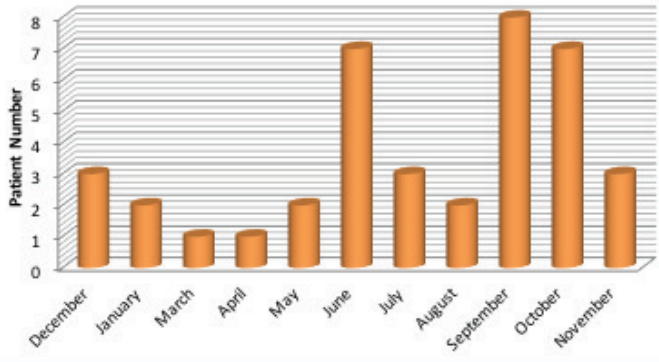
Materials and Methods

Patients, who presented to our pediatric and dermatology clinics with the complaints of fever and eruption and received the diagnosis of HFMD based on the clinical findings between December 2014 and November 2015, were evaluated prospectively. The diagnosis of HFMD was based on the presence of diffuse, erythematous aphthae-like lesions inside the mouth and erythematous papulovesicular lesions on the palms and soles and in the ventral and lateral regions of the fingers and toes. Age, sex, month of presentation, presentation symptoms and duration of symptoms were investigated. Patients aged 18 and over and with a known history of disease and/or medication use were excluded from the study. All patients' system examinations, physical and dermatological examination findings, and additional examination results in patients with systemic findings in complete blood count and biochemical tests were recorded. Serological and viral investigations aimed at agent identification could not be performed due to lack of technical means. The patients were monitored for 3 months for potential complication development. Families were informed about nail changes using specimen photographs. They were asked to provide feedback in the event of such changes.

Approval for the study was granted by the Adıyaman University Biomedical Research Ethics Committee (permission no: 2014/10-13). Written informed consent was obtained from the families of all patients included in the study. The data obtained were analyzed using SPSS (IBM, version 21.0, Chicago, Illinois, USA) software. Categorical data were expressed as number and percentage, and constant data as mean±standard deviation. Statistical significance was set at $p<0.05$.

Results

Thirty-nine patients diagnosed with HFMD were enrolled, 19 (48.8%) were female and 20 (51.2%) were male. No significant difference was determined in terms of gender ($p>0.05$). The mean age of the patients was 29.8±27.9 (6-155) months. Presentations were most common in September (20.5%), June (17.9%) and October (17.9%). No presentation occurred in February. The most common presentation symptoms were eruptions on the hands and feet (100%), fever (82.1%) and oral aphthae (79.5%). Eruptions occurred after mild/moderate fever in all patients. Dermatological examination revealed lesions on the hands in 94.9% (n=37) of patients, on the feet in 87.2% (n=34), inside the mouth in 79.5% (n=31) and in the gluteal region, arms and/or legs in 61.5. Cutaneous lesions were localized in the hands, feet and/or neighboring arm and leg regions in 36 patients (92.3%) and diffuse lesions, involving the knees, elbows and gluteal and perioral areas in addition to these regions in 3 (7.7%). Cutaneous lesions were asymptomatic with the exception of itching in 3 patients and mild pain in 2. Oral aphthous lesions were most common in the inner lip mucosa, buccal areas and hard palate, respectively. Lesions were sufficiently painful and numerous to compromise nutrition in 7 (19%) of 31 patients with intraoral wounds. There was no history of recurrence of lesions. There were also no findings of dehydration in patients with oral involvement. Months of presentation are shown in Graphic 1 and demographic characteristics, symptoms and clinical findings in Table 1. Systemic inquiry revealed lack of appetite in 28 patients (71.8%), stomatitis in 24 (61.5%), vomiting in 11 (28.2%), myalgia in 8 (20.5%), sore throat in 7 (17.9%), diarrhea in 5 (12.8%), and abdominal pain in 3 patients (7.7%). No hyperglycemia, hyperchloremia, lymphocytosis or neutropenia was encountered in any patient on the basis of complete blood count and biochemical tests. Patients' laboratory results are



Graphic 1. Monthly presentation numbers from December 2014 to November 2015

summarized in Table 2. Echocardiography (ECHO) was performed in 3 patients (7.7%) with heart murmur detected at physical examination. Mitral incompetence was determined in 2 of these and apical hypertrophic cardiomyopathy in 1. These patients were followed up on an outpatient basis following a mean hospitalization of 3-7 days. ECHO was normal after one month in patients with mitral incompetence. No complications developed during monitoring of the patient diagnosed with apical hypertrophic cardiomyopathy and the cardiomyopathy gradually improved.

Since physical examination was normal in 19 patients with gastrointestinal symptoms, no additional imaging techniques were employed. A symptomatic therapeutic approach was employed in all cases. Nail changes such as onychomadesis and/or Beau's lines were determined in 10 patients (25.6%) during follow-up, but no palmoplantar desquamation was observed. The mean age of the patients with nail changes was 28.8±27.96 months, and time between onset of disease and development ranged between 3 and 6 weeks. Although more common in the fingernails, changes were observed in the fingernails and the toenails in 2 patients. More than 2 nails were affected in 60% (n=6) of patients. Patients' papulovesicular lesions and nail changes are shown in Figure 1.

Table 1. Demographic characteristics, symptoms and clinical findings of patients

Demographic data		**n (%)**
Gender	Boy	20 (51.3)
	Girl	19 (48.7)
Age (month)	0-12	6 (15.3)
	13-24	16 (41.1)
	25-36	8 (20.4)
	37-48	4 (10.2)
	49-60	2 (5.2)
	≥61	3 (7.8)
Symptoms and clinical findings		n (%)
Skin findings	Hands	37 (94.9)
	Feet	34 (87.2)
	Others (Gluteal region, arms and legs e.g.)	24 (61.5)
Fever		32 (82.1)
Oral aphthae-ulcers		31 (79.5)
Lack of appetite		28 (71.8)
Stomatitis		24 (61.5)
Vomiting		11 (28.2)
Myalgia		8 (20.5)
Sore throat		7 (17.9)
Diarrhea		5 (12.8)
Abdominal pain		3 (7.7)
Heart murmur		3 (7.7)
Nail changes (Onychomadesis and/or Beau's lines)		10 (25.6)

Discussion

HFMD is a febrile disease complex characterized by exanthems and enanthems and capable of causing fatal outbreaks in Far Eastern countries such as Malaysia[12]. The most commonly involved pathogens are *Coxsackieivirus A16* followed by *Enterovirus 71*. However, *Enterovirus 71* has the highest disease and mortality rates[12,13]. Although it can be seen at almost any age, it particularly affects children under the age of 5 years[4]. In a study from China performed in 2008-2013, Huang et al.[6] reported that 90.89% of cases were under the age of 5 years, and that 6.78% of those were under 1 year of age. In their 2-year retrospective study, Liu et al.[14] reported that 92.9% of patients were aged under 5 years. Topkarcı et al.[9] reported a mean age of 5.38 years, with none under the age of 1 year. Karadağ Öncel et al.[7] reported that their youngest patients were aged 10 months, with a mean age of 3.9 years. Uğraş et al.[8] calculated a mean age of 3.32±2.58 years and Polat Ekinci et al.[4] reported a mean age of 2 years. The mean age in our study was 29.8±27.9 months (6 months-13 years). While 92.3% (n=36) of our patients were under the age of 5 years, in contrast, 6 (15.3%) were aged less than 1 year. This shows that, on the basis of data from Turkey, the age at diagnosis of HFMD has decreased and that cases less than 1 year of age may also be seen. Some studies from both Turkey and abroad have reported that the disease is more common in males[4,6-8,14], but no significant difference between the sexes was observed in our study, in agreement with that of Topkarcı et al.[9].

Studies from the Far East have reported that the disease exhibits seasonal variation depending on geographic regions[1,6]. The majority of cases occur during summer and in early fall[3]. Distribution by months in various studies of HFMD is shown in Table 3[4,7-9,15,16]. In our study, in agreement with the literature, the disease was seen to peak twice a year, in the fall and summer. Liu et al.[14] stated that the virus is inhibited

Table 2. Patients' laboratory results

	Mean±standard deviation (Minimum-maximum)	**Normal range**
WBC (/mm^3)	9825.5±3012.8 (5600-17400)	4000-10000
Hgb (g/dL)	11.2±1.2 (9-14)	11.5-15
Hct (%)	34.7±3.4 (29-42)	35-45
MCV (fL)	75±7.6 (56-95)	80-97
Thrombocyte (/mm^3)	350256±127554 (197000-722000)	150000-400000
CRP (mg/dL)	0.64±1.1 (0-4)	0-0.8
Glucose (mg/dL)	91.2±12.8	70-105
Urea (mg/dL)	22.3±6.5	18-55
Creatin (mg/dL)	0.4±0.03	0.7-1.3
Na (mmol/L)	137.5±2	136-145
K (mmol/L)	4.4±0.4	3.5-5.1
Cl (mmol/L)	105±2.7	98-107
Ca (mg/dL)	9.8±0.3	8.4-10.2
ALT (U/L)	20.4±10.6	0-40
AST (U/L)	37.8±18.1	0-40

WBC: White blood cell, Hgb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, CRP: C-reactive protein, Ca: Calcium, Cl: Chlorine, K: Potassium, Na: Sodium, ALT: Alanine amino transferase, AST: Aspartate amino transferase

in cold months, such as January and February; for which reason, HFMD is less common then. We also attribute the absence of any cases of HFMD in February to the weather being cold at that time. One study from China reported that mean monthly temperature had a significant positive effect on transmission of HFMD[17]. However, Wu et al.[18] reported that ultraviolet (UV) rays exhibited a protective effect against HFMD in their investigation of the role of environmental risk factors in the development of the disease. We assume that the data are open to interpretation. Since UV rays are more intense in the summer, when solar radiation has a greater impact, there should be fewer reported outbreaks. The data from the literature, however, conflict with the findings of the study by Wu et al.[18].

In clinical terms, HFMD begins with fever which generally persists for 3-4 days. Approximately 2 days later, large numbers of small vesicles resembling aphthae appear inside the mouth. These vesicles are fragile and may make eating difficult. Such difficulty was present in 7 (19%) of the 31 patients with oral lesions in our study. These findings may be accompanied by lethargy, lack of appetite, sore throat, diarrhea, vomiting or adenopathy[13]. Erythematous maculae 3-7 mm in diameter subsequently form on the hands and feet. These quickly turn into small, open, white, oval vesicles with a thin wall and erythematous ring. Cutaneous lesions typically run parallel to the skin lines of the long axes[19]. Lesions may also be seen on the knee, elbow, gluteal region and perioral areas[3]. The most common findings in this study were typical papulovesicular lesions on the hands and feet (100%), fever (82.1%) and aphthae-like lesions inside the mouth (79.5%). The lesions were observed on the hands in 94.9% of patients, on the feet in 87.2% and on the arms, legs and/or gluteal region in 61.5%. These findings were compatible with those of previous studies from Turkey and abroad[4,6-9,14-18].

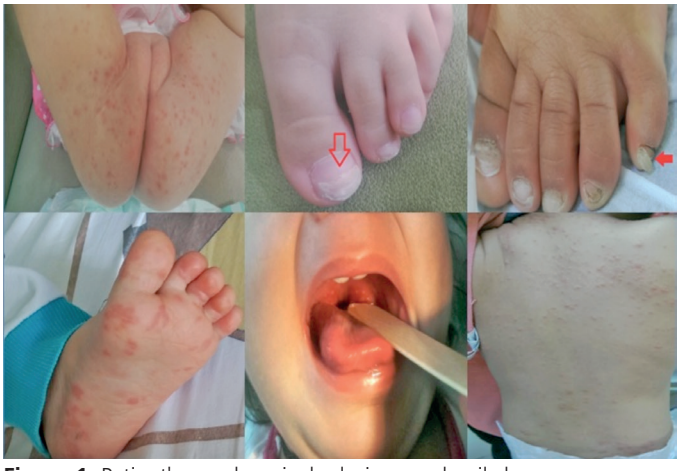


Figure 1. Patient's papulovesicular lesions and nail changes

Table 3. Distribution by months in various studies of hand, foot and mouth disease

Ni et al.[15]	April
Zou et al.[16]	April-May/October-November
Polat Ekinci et al.[4]	June
Karadağ Öncel et al.[7]	July-August
Uğraş et al.[8]	June-July-August
Topkarcı et al.[9]	August-October

Clinical findings are generally sufficient for diagnosis of HFMD, while diagnosis can be confirmed by detection of the virus in uncertain cases[4]. Oral lesions of HFMD can easily be confused with aphthous ulcers, herpes stomatitis, varicella or herpangina[3,19]. Herpes lesions tend to be painful and to merge together[19]. Aphthous lesions, which are more painful and more numerous, tend to recur and have no prodromal symptoms. Oral lesions are rare in varicella, and cutaneous lesions are predominantly on the trunk[3]. Oral lesions in herpangina are commonly located on the tonsils, pharyngeal mucosa, soft palate and the posterior parts of the buccal mucosa[3,19]. Aphthae-like oral lesions were seen in the mucosa of the cheeks, lip and hard palate, and there was no history of recurrence of lesions in our patient.

The literature contains disease severity scorings that can alert physicians. The criteria showing the severity of HMFD are presented in Table 4[14,20,21]. Although the majority of our patients were children aged under 5, no clinical or laboratory indications that the disease might follow a severe course were encountered in any cases. We also think that every patient diagnosed with HFMD should be assessed in the light of these criteria indicating disease severity.

Several studies have reported that enteroviruses lead to cardiac involvement[22-24]. Jan et al.[25] emphasized that a low ejection fraction on ECHO and a shorter duration of ejection fraction, together with mitral insufficiency, were significant indicators in terms of cardiac involvement. In our study, cardiac involvement was determined in 3 patients (7.7%). Previously undetected heart murmurs appearing together with HFMD were present on physical examination of these patients. Mitral incompetence was detected in 2 of these patients on ECHO and apical hypertrophic cardiomyopathy in 1, while ejection fraction was normal in all. These findings all improved gradually at check-ups performed at 2-week intervals. Presence of previously undetected heart murmur in patients with HFMD should be considered as a significant indication for referral to pediatric cardiology department. With the exception of the patients with cardiac involvement, no systemic involvement was observed in the other patients. These findings were significant in terms of no systemic involvement or complication having been observed in any patients in studies from Turkey[4,7-9].

Delayed cutaneous markers of HFMD include onychomadesis, Beau's lines and palmoplantar desquamation[26]. Beau's lines may be described as grooves running from side to side on the nail, and onychomadesis as

Table 4. Criteria showing the severity of hand, foot and mouth disease

Li et al.[21]	Liu et al.[14]	Ooi et al.[20]
Respiratory Rate 26/min	Constipation	Age <2 year
Age <4 year	Lethargy	Male gender
Glucose >150 mg/dL	Vomiting	Tachypnea, tachycardia
Clor <98 mmol/L	Bullous skin lesions	Hypo/hypertension
Lymphocytosis		Gastrointestinal bleeding and the presence of neurological deficits
		The absence of oral lesions
		Leukocytosis

complete shedding of the nail from the proximal matrix. The majority of cases are idiopathic, although they may also develop secondary to various systemic diseases, fever, trauma, drugs, periungual dermatitis and infections such as HFMD. Inflammation developing during the course of the disease, viral replication and fever are thought to lead to nail changes in HFMD[27]. These generally develop 4-8 weeks after diagnosis[3]. No nail involvement has been encountered in some studies from Turkey, while Uğraş et al.[8] reported onychomadesis in only 1 out of 127 patients[7,9]. Nail involvement at levels between 37.6% and 46.6% has been reported in studies from abroad[13,28]. Onychomadesis and/or Beau's line were seen in 10 (25.6%) of our patients. This finding is compatible with the international data but considerably higher than the data from Turkey. Time from onset of the disease to occurrence of nail changes was 3-6 weeks, in agreement with the literature. Since the families in our study were informed beforehand through photographs concerning nail changes, we think that this notification was important in the finding obtained. We recommend such notification to all physicians, in terms of both reducing families' concerns and of permitting to obtain more reliable data.

Study Limitations

The limitation of this study is that it was not intended to identify an agent. Comparisons with the literature will be more reliable in terms of agent identification.

Conclusion

As a result, the age at which HFMD is seen is decreasing in comparison with previous studies from Turkey, and it may now increasingly be seen below the age of 1 year. Patients diagnosed with HFMD must be evaluated in the light of clinical and laboratory markers showing disease severity. Pediatric cardiology consultation must be considered in case of cardiac murmurs appearing subsequently. Informing families about late cutaneous changes will permit more reliable findings to be obtained. Therefore, pediatric and dermatology specialists must collaborate even more closely in the diagnosing and monitoring of this disease.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Adıyaman University Biomedical Research Ethics Committee (permission no: 2014/10-13).
Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.H.B., B.T., Concept: İ.H.B., H.A., A.K., M.T., Design: İ.H.B., B.T., M.T., Data Collection or Processing: İ.H.B., H.A., A.K., Analysis or Interpretation: İ.H.B., H.A., A.K., Literature Search: İ.H.B., H.A., B.T., Writing: İ.H.B., B.T.
Conflict of Interest: No conflict of interest was declared by the authors.
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