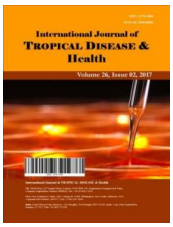

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Onychomadesis Following the Outbreak of Hand Foot Mouth Disease in Children: A Study from North India

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Authors' contributions

This work was carried out in collaboration between all authors. Author SJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AML and NJ managed the analyses of the study. All the authors managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hand, foot and mouth disease (HFMD) is a common viral disease that usually inflicts children. It usually resolves without major complications in about 1-3 weeks, however; there are various reports of onychomadesis occurring as a late complication of hand-foot-and-mouth disease (HFMD).
Aim: To study onychomadesis in children, following HFMD outbreak in Kashmir valley and review the available literature about same.
Methods: Children presenting with onychomadesis between June 2015 to August 2015 were studied in this prospective study. The parents were questioned regarding the history of any preceding acral skin and/or oral vesicular rash preceding the nail changes. Children were clinically

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examined, and their pediatric and dermatological records were studied to confirm precedent HFMD. Only those cases with the preceding history or documentation of onychomadesis were included in the study.

Results: Seventeen children with onychomadesis in 72 nails were included in the study. The mean number of affected nails was 4.23. Fingernails were more often involved (37/70). Preceding diagnosis of HFMD was clinically confirmed in all the cases. The mean time from HFMD diagnosis to onychomadesis development was 5.7 weeks (range: 3-10 weeks, SD: 1.89).

Conclusion: Our data indicate that onychomadesis outbreak in the Kashmir valley during summer 2015 was highly related to the epidemic of HFMD. Our study reinforces existing evidence for the association between onychomadesis and HFMD.

Keywords: Hand; foot and mouth disease (HFMD); onychomadesis; children.

1. INTRODUCTION

Hand, foot and mouth disease (HFMD) is caused by human enterovirus species. Coxsackie virus A16 (CA16) and enterovirus 71 (EV71) are two major causative agents [1]. HFMD is typically a febrile condition accompanied by a vesicular or macula-papular rash on the hands and feet as well as exanthema on oral mucosa.1 Onychomadesis or nail shedding is a rare complication of HFMD, which can be a major cause of parental anxiety if the etiology is not properly explained. In the last few decades, HFMD has been a very common pediatric infection reported from the Asia-Pacific region [2, 3]. The first epidemic of HFMD in India was reported from Kerala in 2003 [4]. This is the first outbreak of HFMD reported from Kashmir and the first such detailed study showing its association with onychomadesis from India, although there are many isolated case reports of onychomadesis following HFMD or other infections and drugs from India [5,6,7].

2. MATERIALS AND METHODS

This study included 17 children who reported to the outpatient departments of pediatrics and dermatology from a tertiary care center with the nail findings suggestive of onychomadesis following an episode of HFMD. Informed consent was obtained from the parents to include their children in the study. Ethical approval was sought from the hospital ethical committee. Patients having any history of major systemic disease, other febrile conditions, other blistering disorders, significant drug intake or nail trauma during the prior 2-3 months to the onset of the nail abnormalities were excluded from the study. As there was no evidence of HFMD in any child at the time of examination, a detailed history was obtained from the parents regarding any vesicular or maculopapular rash particularly involving acral parts and/or oral mucosa preceding the nail changes in the recent past. Retrospective medical records wherever available were looked into to document HMDF as diagnosed by clinician/pediatrician. Personal, family and demographic history of the children was obtained from the parents. Physical examination was performed, and documented. Detailed examination of nails was done and the change in the morphology of the nails whether in the form of transverse leuconychia, Beau's lines or onychomadesis was observed, but only onychomadesis was noted down. As there are numerous other reasons for transverse leuconychia and Beau's lines, these changes were not counted while documenting the nail changes. Direct microscopic examination of nail clipping using 20% KOH was done in all the cases to rule out any fungal etiology, which is very common and has diverse presentations in the children. However, the serologic testing for specific immunoglobulin antibodies or cultures to isolate the specific serotype of the virus were not available for any child.

3. RESULTS AND DISCUSSION

3.1 Results

During the period from 17 June 2015 to 5 august 2015, 17 cases of onychomadesis following an episode of HMDF, involving 72 nails were reported from a single center in a tertiary care hospital. Two children with nephrotic syndrome with onychomadesis were excluded from the study. Fig. 1 shows the relationship between the time-frame of HFMD cases reporting to this center and subsequent reports of onychomadesis from the same center. The interval from HFMD to the onset of nail changes ranged from 3 to 10 weeks (average 5.70 weeks, SD = 1.89).

The age of the children ranged from 12 months to 5 years with the median age of 26 months. Male: female ratio was 1.125:1. Table 1 shows the demographic and clinical details of all the patients.

The children presented with the nail changes in the form of transverse leuconychia, Beau's line or onychomadesis on the fingernails or toenails (Figs. 2, 3).

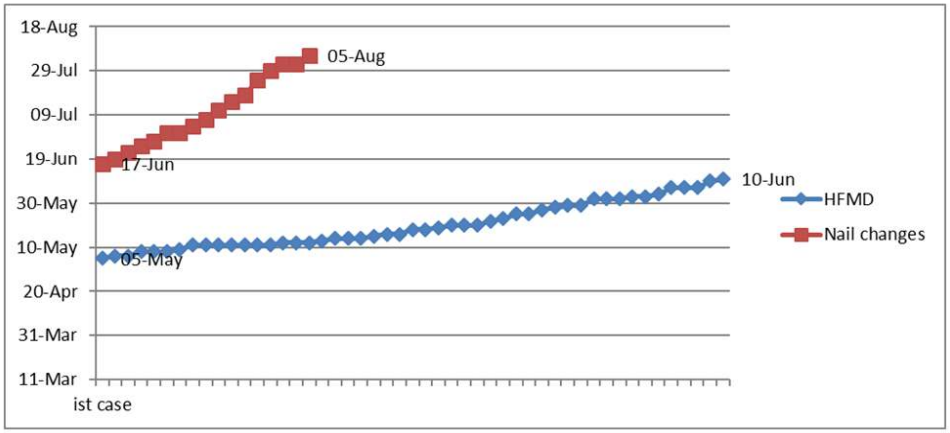

Fig. 1. Time frame between onset of HMDF to the subsequent development of onychomadesis

Table 1. Demographic and the clinical details of the children with HFMD associated onychomadesis

S.no	Age (months)	Sex*	Time interval in weeks b/w HFMD and onychomadesis	Distribution of lesions**				History of fever**	Family history of HFMD**	Onychomadesis	
				PALMS	SOLES	ORAL	OTHERS			FINGER NAILS***	TOE NAILS***
1	13	F	4	Y	Y	Y	-	Y	Y	L1,L2,L3,R1,R2	L1,R1
2	36	M	6	Y	Y	-	-	Y	-	L1,R1,	L1,R1
3	12	M	4	Y	Y	Y	Y	Y	Y	R1,L1	0
4	27	F	4	Y	Y	Y	-	-	-	L2,R1	L1,R1
5	32	M	6	Y	Y	Y	-	Y	-	L1,R1	L1,R1,R2
6	26	F	6	Y	Y	-	-	Y	Y	L1,R1,R2	L1,R1
7	60	M	5	Y	Y	-	Y	Y	-	L1,R1	L1,L2,L3,R1
8	28	F	3	Y	Y	Y	-	Y	Y	L1,L4,R1,R2	L1,R1
9	35	M	5	-	Y	Y	-	-	-	L1,L3	L1,R1
10	18	F	8	Y	-	Y	-	-	Y	0	L1,R1
11	30	M	8	Y	Y	Y	Y	Y	Y	0	L1,R1
12	22	M	4	-	Y	Y	-	Y	Y	L4,R1,R2	L1,R1
13	16	F	6	Y	Y	Y	-	-	-	L2,R2,R3	L1,R1
14	24	M	6	-	-	Y	-	Y	Y	L2,R2,R3	0
15	15	M	4	Y	Y	Y	-	-	-	L1,R1,R2	R1,R2,R3,L2
16	26	F	10	Y	Y	Y	Y	Y	-	R1	L1,R1
17	36	M	8	Y	-	-	-	Y	-	0	L1,R1

**= M- Male, F- Female, **= Y- Yes, ***R- Right, L-Left*

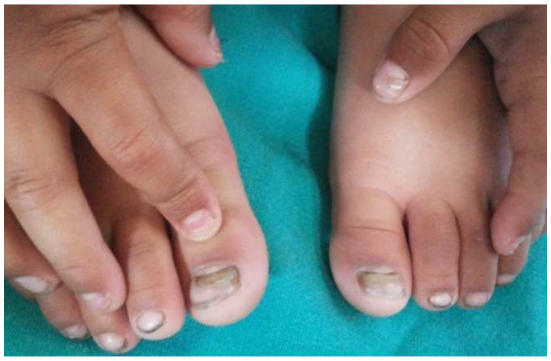

Fig. 2. Three year boy with onychomadesis of right and left thumb nails and right and big toe nails. There are also Beau's lines on all other finger nails with transverse leuconychia on left thumb nail

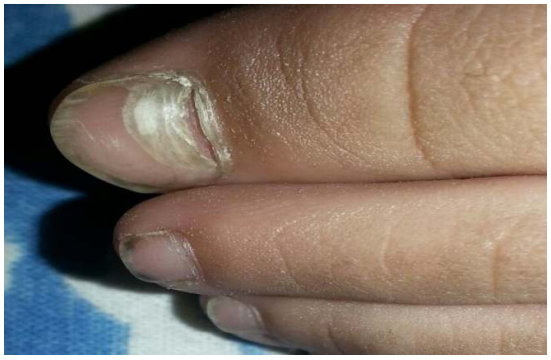

Fig. 3. Onychomadesis involving right toe nail of 18 month old girl. (Close-up view)

The average number of involved nails with onychomadesis was 4.23 with a range of 2 to 7 nails. Fingernails (37/72) were slightly more commonly involved than toenails (35/72); however the most common nails involved were those of great toe (15/17, 88.23%) (Table 1). On eliciting the history from parents, the palms and soles were most frequently involved sites of muco-cutaneous lesions in the cases of HFMD (14/17, 82.35%), and the oral cavity was the second most common site involved (13/17, 76.47%). 12/17 (70.59%) patients reported a history of a fever associated with HFMD, while 5 patients had no history of fever. In 8 out of 17 (47.06%) children there was definite family history of HFMD in other siblings. All parents of children denied any history of major systemic disease or nail trauma, during the 2-3 months prior to the onset of the nail abnormalities. None of the children had taken any medications leading to HFMD. Serological testing or cultures to detect the virus at the time of HFMD were however not performed in any of the children due to the non-availability of the same. Direct microscopic examination of the nails was negative for the whole sample size to rule out the fungal infection of nails. All the nail changes were transient with spontaneous regrowth after about three months.

3.2 Discussion

Onychomadesis is a reversible, painless, non-inflammatory condition in which there is proximal shedding of the nail plate from the nail matrix caused by the temporary arrest of the function of the nail matrix [8]. It can occur in both fingernails and toenails. Trauma is the leading cause of onychomadesis involving a single nail [9,10] while onychomadesis affecting the multiple nails is usually caused by a systemic disease (eg, blistering illnesses) [11]. Other causes include high fevers, periungual dermatitis, acute paronychia, and drug reactions [9]. In addition to these causes, many cases are idiopathic [12, 13]. Since the first case reports in 2000 by Clementz et al. [14] there have been several reports of associations between HFMD and outbreaks of onychomadesis [15-21]. In a study from turkey on 39 patients with HFMD nail changes were seen in 10 (25.6%) patients only [22]. Nail matrix damage in HFMD may also present as transverse leukonychia or Beau's lines which reflect milder interruptions in nail growth [20].

Although, the majority of cases of HFMD do not present with onychomadesis still the nail changes after HFMD are underestimated because onychomadesis spontaneously regresses, and the time interval between HFMD and onychomadesis is about a month. In all our cases, the onset of onychomadesis was about 5.7 weeks later than the peak prevalence of HFMD (May-June 2015). This average latency period between HFMD and onychomadesis correlates very well with results from other studies [23,24]. The temporal association between the HFMD and the onset of nail changes clearly points to a direct or indirect virally induced cytopathic damage caused to the nail matrix. However, the exact mechanism of onychomadesis after HFMD is not fully elucidated. Inflammation around the nail matrix secondary to the direct viral infection or indirectly as a result of distal embolisation induced by virus–specific immunoglobulins has been postulated by Bettoli et al. [8] to be the cause for this matrix arrest. However most of the patients from the present study did not recall the changes specifically around the nail fold. Cabrerizo et al.

[24]; however suggested that virus replication causes a direct damage to the nail matrix, based on the presence of coxsackievirus 6 in shed nails. Osterback et al. [17] used reverse transcription-polymerase chain reaction (rt-pcr) to detect coxsackievirus 6 in the shed nail fragments. These studies have found that coxsackievirus 6 infections attacked a broader spectrum of skin sites and caused more profound tissue damage, [24]; however as no sero-studies were done, this question remains unsolved in our study. Whether nail matrix arrest is specific to this serotype still remains to be shown. Another reason for the nail matrix arrest may also be the fever occurring during HFMD. However, fevers associated with HFMD are typically low grade, and remain for only a short duration, also in our cases, only 12 patients reported a fever during the duration of the HFMD, thus fever seems unlikely as the sole underlying cause. Finally, although many drugs may result in nail matrix arrest, in all our cases only symptomatic treatment was given for the acute viral episode and no other drugs were taken during the preceding one or two months. However, not all the children with HFMD develop the nail changes. In a family of four children, all developed HFMD but only one child developed onychomadesis, which points not only to the virally induced cytopathic changes but also to certain still undefined host factors that may also contribute to the development of nail disease.

Although there are only isolated case reports of onychomadesis following HFMD from India, many may have been missed out due to unawareness among treating clinicians. The specific serotype of the causative virus behind this complication of HFMD and the other predisposing host factors for developing this complication also need to be studied in India.

There are still certain unanswered questions that are posing a query in the minds of physicians as to whether this condition occurs as a mere co-incidence following viral infection or there is a definite mechanism which is yet to be fully understood. In our study, there was a clear temporal association of nail changes with HFMD and there was also a definite geographical clustering of the cases seen.

4. LIMITATIONS OF THE STUDY

Diagnosis of HFMD was purely clinical, as the serological testing was not available in our setting. In future outbreaks of the HFMD associated nail disease, molecular characterization of enterovirus from appropriate clinical samples should be studied.

5. CONCLUSION

Treating clinicians should be aware of this late outcome of HFMD, that causes unnecessary parental worry even though the condition is self-resolving. As the nail disease presents a month after the HFMD outbreak, there would not be any evidence of HFMD at the time the child presents with onychomadesis. Hence, we highlight the significance of recognizing the association between the acute viral episode and nail shedding, to reassure the parents and to avoid the unnecessary treatment for this otherwise benign complication of HFMD. Further studies are needed from India, to clearly elucidate the virus-associated mechanism of nail matrix arrest following HFMD, and also to find out which specific serotype is responsible for this complication of HFMD.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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