REVIEW ARTICLE

NEUROLOGICAL COMPLICATIONS OF HAND, FOOT AND MOUTH DISEASE IN CHILDREN: A REVIEW

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Background: Hand-Foot-and-Mouth disease (HFMD) is a viral illness commonly seen in young children, characterized by fever, vomiting, ulcerative lesions in oral mucosa, and vesicles on hands and feet. The early symptoms resolve but sometimes, it leads to more harsh neurological complications and even death. Therefore, the objective of this review was set to provide an overview of the symptoms, pathogenic agents, and treatment of neurological complications associated with HFMD. **Methods:** We reviewed literature from PubMed and Science Direct covering at least one of our objectives from inception to 4th March 2018. **Result:** This review represents 6 countries including China, Vietnam, Cambodia, South Korea, Taiwan, and Australia. Fifteen studies with a total of 1043 patients were included. The majority of HFMD cases with neurological complications were reported in China, predominance in boys as compared to girls, with 97% cases under 15 years of age. Meningoencephalitis and brainstem encephalitis contributed 70% of all neurological complications related to HFMD. Human Enterovirus71 genotype C, especially C4a was a causative agent associated with severe complications. Among symptoms, fever, vomiting, myoclonic jerks or seizure, headache, convulsion, and rashes were reported in almost all neurological complications. The common and supportive treatments were the administration of intravenous immunoglobulin and glucocorticoid therapies. **Conclusion:** Early detection and appropriate treatment of severe neurological complications can minimize the risk of adverse health outcomes. Evidence based clinical practice guidelines for early detection and treatment would be significant in the management of these devastating neurological complications.

Keywords: Hand-foot-and-mouth-disease; Neurological complications; Central Nervous system disease, Aetiology; Clinical features

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INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a medical condition, principally observed in children less than 5 years of age and caused by two enteroviruses (EVs), family *Picornaviridae* that includes EVA71, and coxsackievirus A16. But recently, coxsackievirus A10 and coxsackievirus A6 have been widely correlated with both sporadic cases and outbreaks of HFMD in the world, especially in South East Asia and Europe with an increasing trend of neurological mortality.[1] It is estimated that 350–900 children die annually in China due to severe HFMD.[2] The first case of HFMD was reported in New Zealand in 1957, followed by several large outbreaks of EV71 infection with neurological disease in Southeast Asia.[3] Hence, HFMD poses a serious threat and put a huge disease burden on public health systems mainly in Western Pacific Regions.[4]

The basic clinical manifestations are fever, ulcers in the oral mucosa, and vesicular rashes on hands, feet, and buttocks.[5] The majority of clinical signs are mild and self-limited with a brief incubation period of 3–6 days.[1] Immature immunity in young children, lymphopenia, depletion of CD4 and CD8 T lymphocytes and decreased cellular immunity in the peripheral blood[6], systemic inflammatory response syndrome, and direct brainstem lesions were reported to play role in the pathogenesis of neurological complications in HFMD[7]. Generally, HFMD is fugacious but can also lead to a critical condition when accompanied by severe neurological complications, including brainstem encephalitis, aseptic meningitis, encephalomyelitis, cerebellar ataxia, APF, and polio-like paralytic syndrome.[8] Occasionally, pulmonary oedema/haemorrhaged, tachycardia, and immediate death due to cardiopulmonary failure are also reported.[1] EV71 is majorly involved in most severe neurological complications as compared to CVA16, especially in children under 4 years of age.[7]

Despite the huge impact of neurological complications associated with HFMD on the health care system, only a few therapeutic approaches and vaccines are applied in clinical practice for its control. Vaccines conferring protection against specific pathogenic agents have been developed.[9–17] Multiple causative viruses and changes in the molecular

epidemiology of the viruses make it difficult to prevent severe cases of HFMD. Therefore, vaccines with multiple components could be a possible solution.[18] This review is conducted to investigate the clinical characteristics, aetiology, and treatment options of neurological complications associated with HFMD to provide some practical guidelines for clinicians and follow up studies.

MATERIAL AND METHODS

A comprehensive literature search was performed in PubMed and Science Direct for articles addressing at least one of the three objectives of this review mentioned below, covering the period from inception to 4 March 2018. No time and language restriction was applied for the search of the literature. Preferred Reporting Items for Systematic Review and Meta analysis (PRISMA) 2009 flow diagram was used to show the study enrolment procedure. The following Medical subject heading, search queries, and keywords were typed using Boolean search operations, for online search: HFMD or Hand Foot and Mouth disease; Neurological complications or Neurological problems or Central Nervous system problems: Clinical features or symptoms; Etiological agent or pathogen; treatment or prevention.

The inclusion criteria were followed based on: (1) papers that placed focus on clinical features or symptoms of neurological complications in HFMD patients; (2) articles that studied etiological agents of neurological complications associated with HFMD; (3) research based on treatment and management of neurological complications in HFMD patients. Only original research articles were included. The latest research articles were selected when more than one study has the same information. Duplicates articles, reviews, case reports, conference reports, and comments, etc. were excluded. The extracted data included the author's name, year, study design, age, gender, geographical locations, and the number of deaths reported among cases, types, and symptoms of neurological complications, pathogens, treatment, or management strategies available. A checklist recommended by the Joanna Briggs Institute (JBI) was used to assess the reporting quality of the included case series. Methodological quality was assessed, based on the checklist criteria by two independent reviewers following JBI guidelines. A consensus was made out if there were contradictions about the methodological quality of a paper between the two reviewers. We applied a practical approach to choose the most pertinent literature where two or more publications reported data from the same study.

RESULTS

A flowchart of the article's selection method is described in figure-1. Total of 2646 papers were retrieved in the initial stage through different electronic databases. Two thousand and twenty-three were duplicated studies and removed, the remaining 623 papers were screened through title and abstract. Five hundred and twenty-one records were excluded, including 519 irrelevant studies and 2 duplications. One hundred and two papers were assessed for eligibility and 87 studies were removed based on insufficient data (n=83) and duplicate records (n=4). Conclusively, 15 studies published from 1999 to 2018 were selected for qualitative analysis. All the selected studies were case series including two Chinese language and 13 English language papers.[19]

There were 10 questions on the critical appraisal checklist and answers to at least 8 questions were present in the selected papers. Only two papers answered 10 questions and 4 of them answered 8 questions while the remaining answered 9 questions. The last question on the checklist which is about statistical analysis were not applicable for 7 studies as all of them were case series which mainly reported the medical description of patients without applying any statistical analysis. One study did not mention clearly the complete inclusion of cases. Another study could not report the demographics of patients clearly and one study did not report clearly about the presenting sites/ clinic(s) demographics sites. Overall, as all of the studies answered at least 8 questions out of 10, this indicates that all the included papers have a highly satisfactory methodological quality (Table-1).

The entire review included 1043 patients with different types of neurological complications associated with HFMD. The patients represent a variety of geographical regions with 6 different countries. The countries with the number of patients include Vietnam (n=69, 6.61%), Cambodia (n=150, 14.38%), China (n=628, 60.21%), Australia (n=57, 5.46%), South Korea (n=21, 2.01%) and Taiwan (118, 11.31%). A large proportion of participants was from China followed by Taiwan and Vietnam. The proportion of boys (629/1043, 60.30%) was high as compared to girls (414/1043, 39.69%). Only 27 (2.58%) patients were above 15 years of age while the remaining participants were under 15 years of age in general; most of them were under 5 years of age. Only 29 (2.78%) deaths were reported among the patients with a variety of medical reasons, most of the deaths were among the patients from Vietnam (51.72%) followed by China (31.03%), Australia (13.79%), and South Korea (3.44%). (Table-2)

Figure-2 shows the total number of neurological complications related to HFMD with the

number of studies reported. The most common neurological complications associated with HFMD were brainstem encephalitis and meningoencephalitis by 7 studies each, followed by aseptic meningitis, acute flaccid paralysis, and encephalomyelitis, which were observed in 6, 5, and 4 articles respectively. Neurogenic pulmonary oedema was reported by 2 articles while the other neurological complications such as autonomic dysregulation with pulmonary oedema and panencephalitis were reported by only one study each. The summary of reported symptoms, pathogens, and treatment strategies is presented in Table-3.

The most frequent clinical feature of meningoencephalitis was fever reported by 5 studies, followed by vomiting evident by 4 studies, then headache and seizure mentioned by 3 articles each. The major pathogen responsible was EV71 including sub genotypes such as C4, C4a concluded by one and two studies respectively and a serotype (EVA71) mentioned by 2 studies. Intravenous immunoglobulin, acyclovir, supportive and symptomatic treatment were reported by 1 study each as helpful for patients with meningoencephalitis. Symptoms reported by studies with brain encephalitis were fever (9), myoclonus (7), vomiting (6), tremor (5), ataxia (5), lethargy (4), and oculomotor dysfunction (4). The main virus involved in its pathogenesis was EV71 reported by 6 articles including sub genotype C4a. Similarly, a frequently used therapeutic approach for brainstem encephalitis patients was glucocorticoids therapy as concluded by 4 studies. Fever, myoclonic jerks, or seizure and vomiting were associated with encephalomyelitis, documented by 4 studies each. Besides lethargy, tachycardia, limb weakness, and ataxia were also reported with encephalomyelitis by 2 papers. Four studies reported EV71 as a sole pathogen responsible for encephalomyelitis. Patients with encephalomyelitis were treated with glucocorticoid therapy as evidence by 2 articles. Six studies reported fever as symptoms of aseptic meningitis while, symptoms such as vomiting, ataxia were concluded by 4 studies each, and myoclonus jerks, headache, low consciousness, lethargy, and tremor were mentioned by 3 articles each. Six studies reported EV71 as a sole pathogen responsible for aseptic meningitis. Symptomatic treatment and supportive therapy were applied as a treatment approach toward aseptic meningitis mentioned by 2 studies. Symptoms such as fever, hypotension, tachypnoea, tachycardia, vomiting, and lethargy were reported by 2 study each as the clinical features of neurogenic pulmonary oedema. The main virus involved was EV71. Patients of neurogenic pulmonary oedema were administered with intravenous immunoglobulin, Mannitol, Milrinone, methylprednisolone in addition to positive mechanical ventilation, fluid balance, and supportive therapy as reported by 3 studies.

Symptoms of acute flaccid paralysis evidence by studies include fever (7), myoclonic jerks (6), vomiting (5), ataxia (4), and cranial nerve dysfunction (4), Tremor (3), low consciousness (3), and headache (3). EV71 was identified as a cause for acute flaccid paralysis by 5 studies including two studies that reported sub genotype C4a and one study which reported EVA71. IVIG was commonly used for the treatment of acute flaccid paralysis patients as reported by 4 studies.

Ataxia, vomiting, headache, myoclonic seizure, fever were reported as the main symptoms of panencephalitis. The pathogen detected was EV71 as reported by 1 study. Supportive therapy and mechanical ventilation were provided to panencephalitis patients as evident by 1 article.

Tachycardia, hypertension, shock, respiratory distress, and cranial nerve dysfunction were reported as symptoms of Autonomic dysregulation with pulmonary oedema by one study each. The pathogen responsible was EV71 as reported by 1 study. One study concluded 2-IVIG-2-methylprednisolone and supportive therapy as treatment options for autonomic dysregulation with pulmonary oedema patients.

Table-1: Critical appraisal results for included studies using the JBI Critical Appraisal checklist for case series

Study (Authors)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
B' Krong *et al*	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
Chen *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Duong *et al*	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Hu *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lee *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Ma *et al*	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Teoh *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Tsai *et al*	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Wang *et al*	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Zhang *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Liao *et al*	Y	Y	Y	Y	Y	Y	Y	Y	U	NA
He *et al*	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Huang *et al*	Y	Y	Y	Y	Y	U	Y	Y	Y	NA
S.M.wang *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
X.J Liu	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA

Y=Yes, N= No, U= Unclear, NA= Not applicable

Table-2: General characteristic of the studies included in the systematic review

Author	Year of publication	Country	No of cases	Gender		Age groups (year)		Death
				Male	Female	< 15	>15	
B' Krong *et al*	2018	Vietnam	69	53	16	42	27	15
Chen *et al*	2014	China	12	7	5	12	0	0
Duong *et al*	2016	Cambodia	150	76	74	150	0	0
Hu *et al*	2015	China	134	82	52	134	0	0
Lee *et al*	2014	South Korea	21	13	8	21	0	1
Ma *et al*	2015	China	244	149	95	244	0	0
Teoh *et al*	2016	Australia	57	36	21	57	0	4
Tsai *et al*	2014	Taiwan	42	26	16	42	0	0
Wang *et al*	2018	China	90	53	37	90	0	2
Zhang *et al*	2010	China	36	23	13	36	0	7
Liao *et al*	2001	Taiwan	12	12	0	12	0	0
He *et al*	2009	China	80	47	33	80	0	0
Huang *et al*	1999	Taiwan	30	15	15	30	0	0
S.M.Wang *et al*	1999	Taiwan	34	20	14	34	0	0
X.J Liu *et al*	2009	China	32	17	15	32	0	0

Table-3: Summary of reported symptoms, pathogens and treatment strategies of neurological complications associated with HFMD

Author(year)	Type of Complication	No of cases	Symptoms	Pathogens	Treatment strategy
B' krong *et al* (2018) Duong *et al* (2016) Lee *et al* (2013) Ma *et al* (2015) Teoh *et al* (2016) Wang *et al* (2018) Liao *et al* (2001)	Meningoencephalitis	567	Fever, Convulsion, Focal neurology, Limb weakness, Meningeal sign, seizure, aggressive behaviour, headache, impaired consciousness, neck stiffness, irritability, vomiting, autonomic dysregulation, cranial nerve dysfunction, urinary retention, truncal weakness, myoclonic jerks, mouth ulcer, hand and foot ulcer, diarrhoea, abdominal pain, sore throat	(Species A) serotype EVA71, EVB80, EVD68, CV-A16(CV-A1,2,4,6,8,9,10 and B5), CVB2, CVB3, CVB4, CVA20, CVA24, EVB83, Echovirus E-1, E- 2, E-3, E-6, E-31, EVC116, EVC96 and PV-3	Supportive therapy, IVIG, symptomatic, acyclovir
Chen *et al* (2014) Hu *et al* (2015) Lee *et al* (2013) Teoh *et al* (2016) Huang *et al* (1999) S.M. Wang *et al* (1999) X.J Liu *et al* (2009)	Brain stem Encephalitis	156	Fever, cyanosis, Lethargy, Skin rash, Ataxia, Positive Kerning's signs, Positive Babinski signs, Tendon hyperreflexia, Loss of swallowing reflex or dysphasia, Facial paralysis, Myoclonus, tremor, Limb weakness, Bulbar Palsy, Oculomotor dysfunction, Low consciousness, Headache, Tachycardia, Cool extremities, Aggressive behaviour, Vomiting	EV71, sub genotype C4a	Intravenous dexamethasone, Intravenous Milrinone Methylprednisolone, Fluid resuscitation, Positive mechanical ventilation, Intravenous immunoglobulin, 1-IVIG-2-methylprednisolone, Supportive therapy, symptomatic treatment
Hu *et al* (2015) Teoh *et al* (2016) Tsai *et al* (2013) Liao *et al* (2001)	Encephalomyelitis	72	Cranial nerve dysfunction, Urinary retention, Truncal weakness, Limb weakness, Ataxia Vomiting, Myoclonus jerks or seizure, Fever, oculomotor palsy, bulbar palsy, Tachycardia, Lethargy, Disturbance of consciousness, Rashes, Headache	EV71	Glucocorticoid therapy (10 IVIG with methylprednisolone, 5 IVIG, 4 methyl prednisolones) Mechanical ventilation, IVIG, Glycerol, Ionotropic agents, supportive therapy, Antibodies
Teoh *et al* (2016)	Autonomic dysregulation with pulmonary oedema	4	Tachycardia, hypertension, shock, respiratory distress, Cranial nerve dysfunction	EV71	2-IVIG-2-methylprednisolone, supportive therapy
Chen *et al* (2014) Hu *et al* (2015) Lee *et al* (2013) Liao *et al* (2001) Huang *et al* (1999) S.M. wang *et al*	Aseptic Meningitis	86	Disturbance of consciousness, Vomiting, Headache, seizure, Convulsion, Rashes, Fever, Neck stiffness, Lethargy, Irritability, Tachycardia, positive kernig's sign	EV71, Sub genotype C4a	supportive, symptomatic treatment
Zhang *et al* (2010) He *et al* (2009)	Neurogenic pulmonary oedema,	116	Fever, severe malaise, vomiting, tachypnea, tachycardia, cool extremities, hypotension, pink or bloody bubble sputum, limb trembling	EV71	Mannitol, mechanical ventilation, IVIG, acyclovir, supportive, Milrinone, fluid balance, methylprednisolone.
Chen *et al* (2014) Hu *et al* (2015) Teo *et al* (2016) Huang *et al* (1999) Wang *et al* (2018)	Acute Flaccid Paralysis	30	Truncal weaknesses, Limb weakness, Ataxia, Vomiting, Myoclonus jerk, Fever, Paralysis Rashes, Reduced muscle tone, Tendon hyper reflexes, Loss of swallowing reflex, Irritability	EV71, Sub genotype C4a, CVA16, CVA2,4,6,9,10, CV B5, E-9	Intravenous immunoglobulin, 1-IVIG-2-methylprednisolone, Supportive therapy
Hu *et al* (2015)	Parencephalitis	12	Ataxia, Vomiting, Headache, Myoclonic seizure, Fever	EV71	mechanical ventilation, supportive therapy

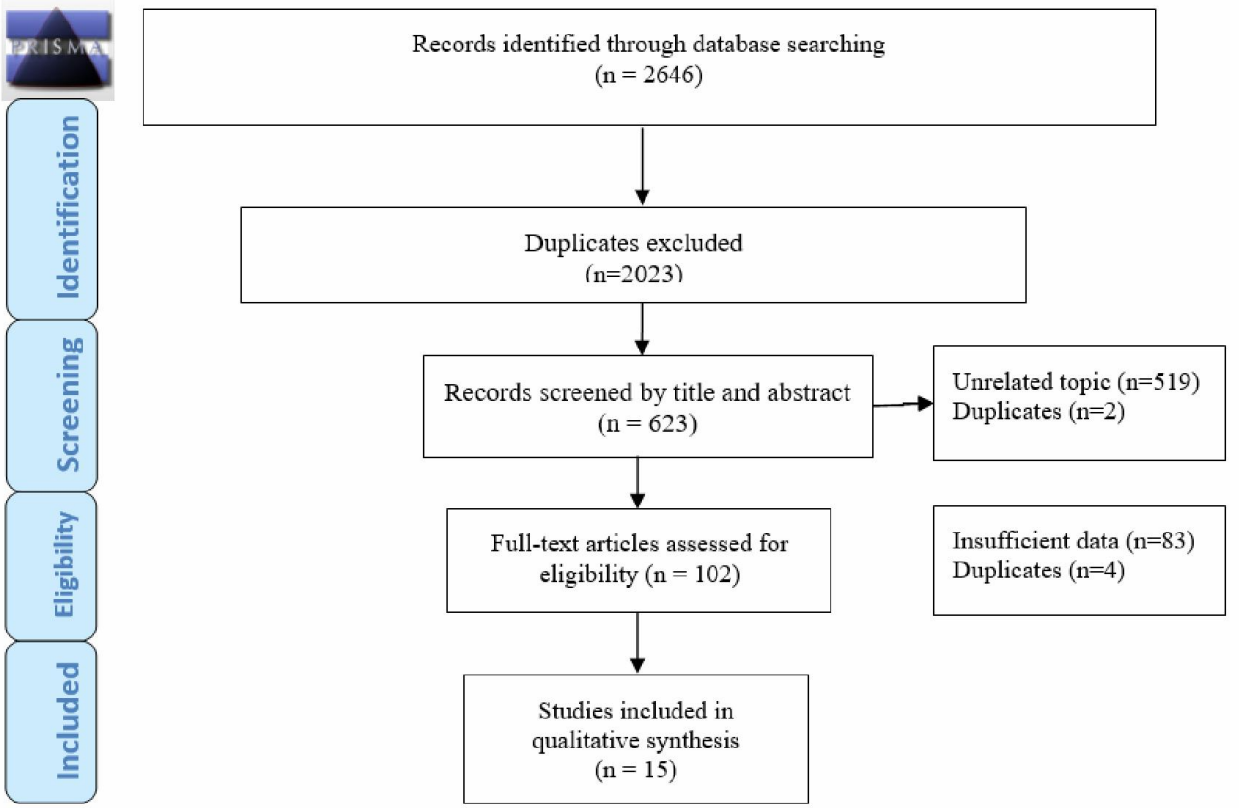

Figure-1: PRISMA 2009 Flow Diagram of study enrolment for systematic review

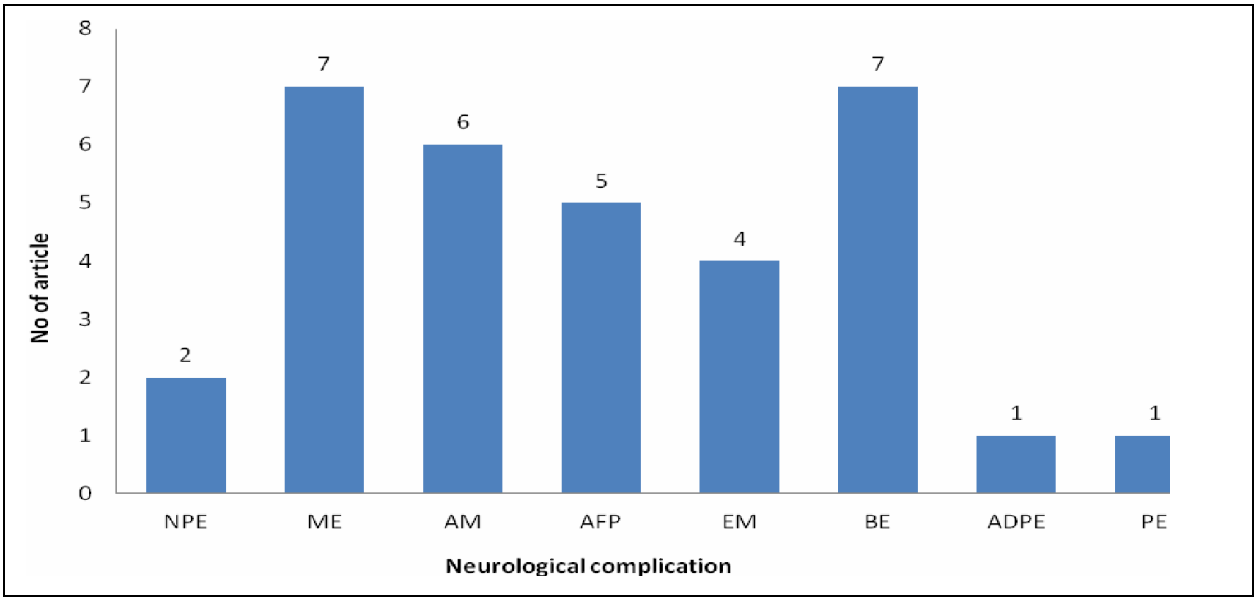

Figure-2: Number of articles reported each neurological complication.

Abbreviations: NPE (Neurogenic pulmonary oedema), ME (Meningoencephalitis), AM (Aseptic meningitis), AFP (Acute flaccid paralysis), EM(Encephalomyelitis), BE (Brainstem encephalitis), ADPE (Autonomic dysregulation with pulmonary oedema), PE (Parencephalitis).

DISCUSSION

Qualitative hospital-based data from 6 countries between 1999 and 2018 were integrated. The qualitative analysis included 15 studies and 1043 children. Although we found that the proportion of boys was higher than girls among patients with neurological complications.[20,21] Nevertheless, a meta-analysis consisted of 19 studies concluded that gender was not a risk factor while young age was a risk factor, consistent with other studies.[8,22,23] Most of the children were <5 years of age.[7]

Meningoencephalitis in patients caused by EV71 showed symptoms like seizure, convulsion, myoclonus and low consciousness. Intravenous immunoglobulin is commonly used to treat patients with meningoencephalitis.[3] A study conducted in Iran on genotyping of EV71 among meningoencephalitis patients found that genotype C was the prevalent genotype.[24] According to previous studies, sub genotype C4a is predominantly involved in severe infections and case fatalities.[21,22,25–27] The primary clinical features of aseptic meningitis included fever, vomiting, headache, and seizure, which appeared soon after infection.[20]

The most frequent neurological complication involving CNS is brainstem encephalitis, caused by EV71 and appeared in the form of ataxia, tremor, myoclonus, oculomotor dysfunction, and bulbar palsy.[28–31] Treatment of brainstem encephalitis is mainly focused on the direct treatment of viral infections and systemic inflammatory response after infection. IVIG and glucocorticoids can alleviate the incidence of neurological sequelae among these patients.[32]

Reported symptoms with Encephalomyelitis patients were fever, rashes, tachypnoea, loss of consciousness, vomiting, seizure, limb weaknesses, and lethargy.[33] A large cohort study demonstrated that children suffered from EV71 encephalomyelitis had generally unimpaired long-term cognitive function except in case of defects consisting cerebellar dysfunction in only 10.2% of children with encephalomyelitis.[33,34]

Patients who had neurogenic pulmonary oedema usually presented with tachycardia, tachypnoea, or apnoea, as well as hypotension or undetectable blood pressure.[28] Neurogenic pulmonary oedema associated with EV71 was first documented in the Asia-pacific region.[35,36] Due to the high mortality associated with neurogenic pulmonary oedema, early aggressive treatment such as mechanical ventilation and supportive therapy is recommended to improve chances of recovery.[28] In addition to pre-regular pressure ventilation and strict control of liquid intake, administration of Milrinone is an effective treatment for NPE, as it can regulate the sympathetic nervous system and alleviate the production of IL-13, thus significantly slow down heart rate, decrease white blood cell and platelet count.[37] In case of neurogenic pulmonary oedema, rapid rehydration can worsen pulmonary oedema; adopt a slow recovery method by appropriately reducing the amount and speed of fluid resuscitation to help prevent aggravation of pulmonary oedema.

Leading pathogen reported by several outbreaks worldwide with AFP is EV71.[38] Damage to the motor neuron in the anterior horn of the spinal cord caused by EV71 appeared in the form of paralysis.[20,26,36,39] Acute flaccid paralysis has been treated with high corticosteroid alone or in combination with IVIG.[40–43]

The aetiological agent detected in patients with parencephalitis is EV71, with symptoms such as fever, headache, rashes, vomiting, disturbance in consciousness, ataxia and treatment provided was supportive and glucocorticoids therapy.[3,44]

Some of the limitations will also be accounted in for this systematic review: Only a limited number of papers met the inclusion criteria. Most of the selected studies showed pooled results and some patients developed multiple neurological complications, so it was difficult to specifically correlate each symptom, pathogen or treatment to each neurological complication. We could not include any paper about vaccine partly because of the fact that most studies on vaccines were animal-based studies or in-vitro studies and partly due to the vaccine's focus on HFMD prevention rather than treating its neurological complication. All the included studies are case series with their own restrictions. We found and investigated only hospitalized patient, hence our result may not be generalized to the primary care setting, therefore, to validate and crosscheck data elucidated in this review, prospective studies with a large number of patients are required.

CONCLUSION

This data might be useful for future investigation and development of therapeutic strategies for neurological complications related to HFMD. Children seen with fatal neurological diseases that can cause permanent disability pose a serious diagnostic and therapeutic challenge. Reliable methods of predicting development of HFMD and its neurological complication and its risk of disease progression are still lacking. The role of other non EVA71 EVs such as CVA16 or Echoviruses could be investigated further for potential consideration as a new aspect of vaccine development to prevent HFMD and its harsh complications. Administration of IVIG, methylprednisolone, Mannitol and other

supportive therapies in time and rationally might avoid disease aggravation and enhance the rate of successful rehabilitation in HFMD patients with neurological complication. Evidence based clinical practice guidelines for early detection and treatment would significantly help the management of these devastating neurological complications.

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