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Neuro–Magnetic Resonance Imaging in Hand, Foot, and Mouth Disease: Finding in 412 Patients and Prognostic Features

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Purpose: The aims of this study were to describe the neuroimaging findings in hand, foot, and mouth disease and determine those who may provide prognosis.

Material and Methods: Magnetic resonance imaging scans in 412 severe hand, foot, and mouth disease between 2009 and 2014 were retrospectively evaluated. The patients who had the neurological signs were followed for 6 months to 1 year. According to the good or poor prognosis, 2 groups were categorized. The incidence of lesions in different sites between the 2 groups was compared, and multivariate analysis was used to look for risk factors.

Results: The major sites of involvement for all patients with percentages were the medulla oblongata (16.1%), spinal anterior nerve roots (12.4%), thoracic segments (11.1%), brain or spinal meninges (8.3%), and so on. There were 347 patients (84.2%) with good prognosis and 65 (15.8%) with poor prognosis in the follow-up. There was a significantly higher rate of lesions involving the cerebral white substance, thalamus, medulla oblongata, pons, midbrain, and spinal cord in the group with poor prognosis. Multivariate analysis showed 2 independent risk factors associated with poor prognosis: lesions located in the medulla oblongata ($P < 0.015$) and spinal cord ($P < 0.001$) on magnetic resonance imaging; the latter was the most significant prognostic factor (odds ratio, 29.11; $P < 0.001$).

Conclusions: We found that the distribution patterns for all patients mainly involved the medulla oblongata, spinal anterior nerve roots, thoracic segments, and brain or spinal meninges. Our findings suggested that

patients with lesions located in the medulla oblongata and spinal cord may be closely monitored for early intervention and meticulous management. For children with the symptom of nervous system, they are strongly recommended for magnetic resonance examination.

Key Words: hand, foot, and mouth disease, prognostic factors, magnetic resonance imaging, brain stem, spinal cord

Abbreviations: HFMD—hand, foot, and mouth disease, EV71—enterovirus 71, CAV—coxsackievirus A, MRI—magnetic resonance imaging

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Hand, foot, and mouth disease (HFMD) is a common disease that mainly occurs in children, caused by many kinds of viruses, including echovirus, enterovirus 71 (EV71), coxsackievirus A (CAV), and so on. As the most frequent etiologic agents, EV71 and CAV16 have caused several outbreaks in Mainland China and Hongkong,^{1–4} and the number of HFMD cases has been increasing rapidly year by year. The cumulative total of reported cases in China reached nearly 1.9 million in 2013 and 2.7 million in 2014, with an era of unprecedented large-scale outbreaks in the Asia Pacific area.^{5,6}

Most of the HFMD is characterized by flulike symptoms such as rash on the hands, feet, and buttocks; mouth ulcers; or vomiting and diarrhea. However, there are still some most severe cases of HFMD, and most of these cases are caused by EV71 infections—as a highly neurotropic virus, it can result in central nervous system (CNS) complications, including aseptic meningitis, encephalitis, acute flaccid paralysis, and Guillain-Barré syndrome.^{7–10} So magnetic resonance imaging (MRI) acquisition is important for patients with EV71 infection to reveal the location of lesions and select the potential severe cases with poor prognosis, which is needed to provide support for early medical intervention. Previous studies, largely from China, have been performed to identify risk factors associated with severe HFMD^{11–18} by baseline clinical and experimental results, but there is lack of MRI acquisition and follow-ups.

In this study, we aim to review MRI characteristics of the severe HFMD using a multivariate approach to compare the prognosis of different lesion sites and identify whether lesion location may aid in predicting prognosis based on a large cohort with follow-up.

MATERIALS AND METHODS

Study Subjects

The patients are from 2 units: Guangzhou Women and Children's Medical Center and Guangdong General Hospital. Because of the retrospective nature of the study, informed consent was

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waived. This study was approved by the regional ethics committee of the 2 hospitals.

Between January 2009 and December 2014, 1172 patients with virus culture–confirmed HFMD were enrolled. Four hundred twenty were given a diagnosis of severe HFMD, of which 3 who did not undergo MR scan and then 5 who had neurological signs at discharge and thus were lost to follow-up were excluded. Finally, a total of 412 patients were included in the study. Hand, foot, and mouth disease was confirmed by sequence analysis performed on stool, rectal swab, throat swab, or cerebrospinal fluid specimens. The severe case is determined on the basis of the Chinese guideline for HFMD diagnosis and treatment (Chinese Ministry of Public Health, revised in 2010).¹⁹ A severe case was defined as having two of the following clinical manifestations: (1) continuous high fever for more than 3 days; (2) symptoms of nervous system, such as weakness, vomiting, irritability, and so on; (3) abnormal white blood cell count; (4) high blood glucose level; and (5) poor blood circulation of the limbs.

Data Collection

The patient records were retrospectively examined for primary set of data, and data were composed of demographic characteristics (age and sex), clinical symptoms, MRI result, outcomes at discharge and during the period of neurologic follow-up, admission and discharge dates, and length of hospital stay.

MR Scan

Most MR scans were performed using a 1.5-T MRI (GyrosanAchieva 1.5 T; Philips Healthcare, Best, the Netherlands) equipped with an 8-channel head coil. The scanning parameters were set as follows: T1WI (repetition time/echo time [TR/TE], 593/15 milliseconds), T2WI (TR/TE, 3720/100 milliseconds), fluid-attenuated inversion recovery (FLAIR) images (TR/TE, 11000/140 milliseconds; range of inversion times, 2400 milliseconds), and enhanced T1WI (TR/TE, 488/15 milliseconds). The remaining MR examinations were performed using a 1.5-T MRI (Signa Excite HD; GE Healthcare, Milwaukee, Wis) equipped with an 8-channel head coil. The scanning parameters were set as follows: T1WI (TR/TE, 400/11 milliseconds), T2WI (TR/TE, 4300/100 milliseconds), FLAIR images (TR/TE, 8400/120 milliseconds; range of inversion times, 2100 milliseconds), and enhanced T1WI (TR/TE, 500/20 milliseconds). All images for all sequences were 5-mm thick with an interslice gap of 1.0 mm. The matrix size was 256 × 256, and the field of view was 18 cm. The contrast agent for enhanced scan was gadopentetate dimeglumine (Bayer, Germany), injected at a dose of 0.1 mmol/kg. Uncooperative children were given chloral hydrate enema (0.5 mL/kg) sedative before the examination.

Imaging Analysis

All MRI examinations were reviewed by 2 neuroradiologists, in consensus, with full knowledge of the patients' clinical findings and history. The sites of lesions were assessed systematically on each MRI examination at the following locations: brain or spinal meninges, cerebral cortex and subcortex white substance, basal ganglia, callosum, thalamus and cerebellum, midbrain, pons, medulla oblongata, spinal cord (cervical, thoracic, and lumbar segments), and spinal nerve roots. At each site of lesions, the presence of signals on T1WI, T2WI, FLAIR, and enhanced T1WI was recorded. A positive lesion is defined as hypointense signal on T1WI, hyperintense signal on T2WI and FLAIR, or an enhancement on enhanced T1WI.

Definitions

Poor prognosis was defined as patients who died or had neurological sequelae in the duration of hospital stay and the neurological sequelae did not disappear during 3 to 12 months of follow-up. Neurological sequelae were defined as handicaps or disabilities when performing daily activities or mental regression. Muscle strength was measured by Lovett method, ranging from grades 0 to V, with decreased muscle strength defined as grades 0 to IV. To record neurological sequelae, all subjects were physically and neurologically examined by pediatric neurologists.

Statistical Analysis

The 2 groups were categorized according to the good or poor prognosis. Student *t* test was used to analyze continuous variables of the 2 groups based on results from the normality test and homogeneity test of variance. We used the χ^2 test to analyze dichotomous variables. After a univariate analysis had been performed for all possible factors, a multiple logistic regression analysis was conducted to examine the adjusted odds ratios (ORs) for those significant factors in the univariate analysis. All statistical analyses were performed using SPSS version 19.0 software. *P* < 0.05 was considered to be statistically significant.

RESULTS

Clinical Characteristics

Of those 412 cases who were investigated, 289 were men, and 123 were women, with the ratio of 2.35; mean age was 22.7 ± 12.4 months (range, 1 month to 12 years). There are 11 outpatient cases and 401 hospitalized cases. The length of stay ranged from 3 to 30 days, and 56 cases were admitted into the pediatric intensive care unit. Three hundred sixteen cases (76.7%) were confirmed to be infected by the EV71 virus, 72 were positive for CAV 16, and the remaining 24 were positive for other echovirus.

MRI Characteristics

All 412 patients had undergone the brain MRI, 124 patients had undergone the spine MRI at the same time, and 52 cases had reexamination of MRI. One hundred seventy-four cases (42.2%) showed positive lesions located in different sites on MRI (Fig. 1).

Ninety-three cases (22.6%) presented with abnormal signal intensities in the brain stem (Figs. 2, 3). Of the 93 cases, 86 (94.5%) were located in the dorsal brain stem, 78 only involved 1 site of the brain stem, and 13 involved 2 sites or more. Sixty-six involved the medulla oblongata (Fig. 2), 29 involved the pons, and 18 involved the midbrain (Fig. 3). Sixty cases (11.3%) had abnormal signals on the spinal cord (Fig. 4); 58 cases (96.7%) affected the anterior horn regions, and 2 affected the whole spinal cord. Twenty-two of 60 both involved the brain stem and spinal cord. Fifty-one cases showed spinal anterior nerve roots enhancement (Fig. 5); 28 of 51 cases both involved spinal cord abnormal signal intensity and corresponding spinal anterior nerve roots enhancement. Of those 60 cases, 45 only involved 1 site of the spinal cord, and 15 involved 2 sites or more. Forty-two involved thoracic segments, with most cases in the inferior thoracic segments; 23 involved cervical segments; and 15 involved lumbar segments. Thirty-four manifested brain or spinal meninges enhancement. There are 21 cases who had abnormal signal intensity in the cerebrum and cerebellum, including 6 that involved the cerebral cortex, 11 that involved the cerebral white substance (Fig. 6), 5 that

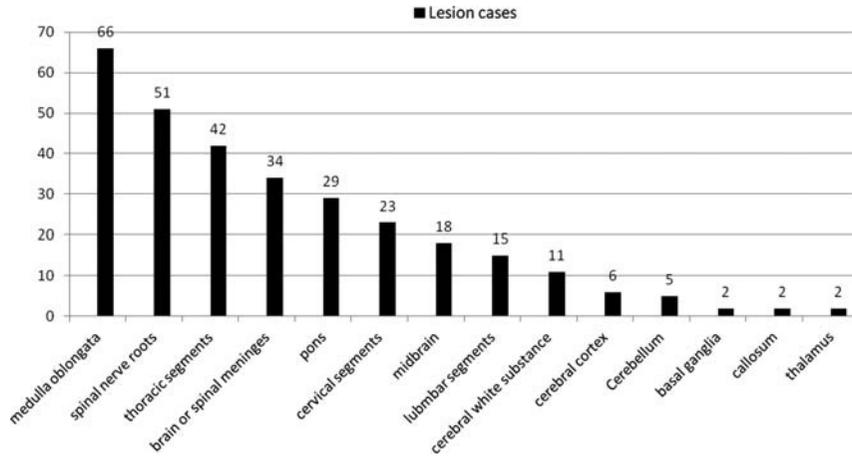


FIGURE 1. Cases involving different sites on MRI.

involved the cerebellum, 2 that involved the basal ganglia, 2 that involved the callosum, and 2 that involved the thalamus. Of the 21 cases, 16 only involved 1 site, and 5 involved 2 sites or more.

Clinical Outcomes

The patients who had the neurological signs at discharge should be followed for 6 months to 1 year. There were 347 patients (84.2%) with good prognosis and 65 (15.8%) with poor prognosis in the follow-up. Of those 65 cases, there were 7

(10.8%) who died of cardiopulmonary failure, 37 (56.9%) with decreased muscle strength, 7 with convulsion, 5 with pavor in the sleep, 3 with facial nerve paralysis, 2 with left eye movement disorder, 1 with salivate, 1 with nystagmus, 1 with difficulty swallowing, and 1 with ataxia.

Risk Factors for Poor Prognosis

Four hundred twelve patients were divided into 2 groups based on good or poor prognosis. Compared with the group with

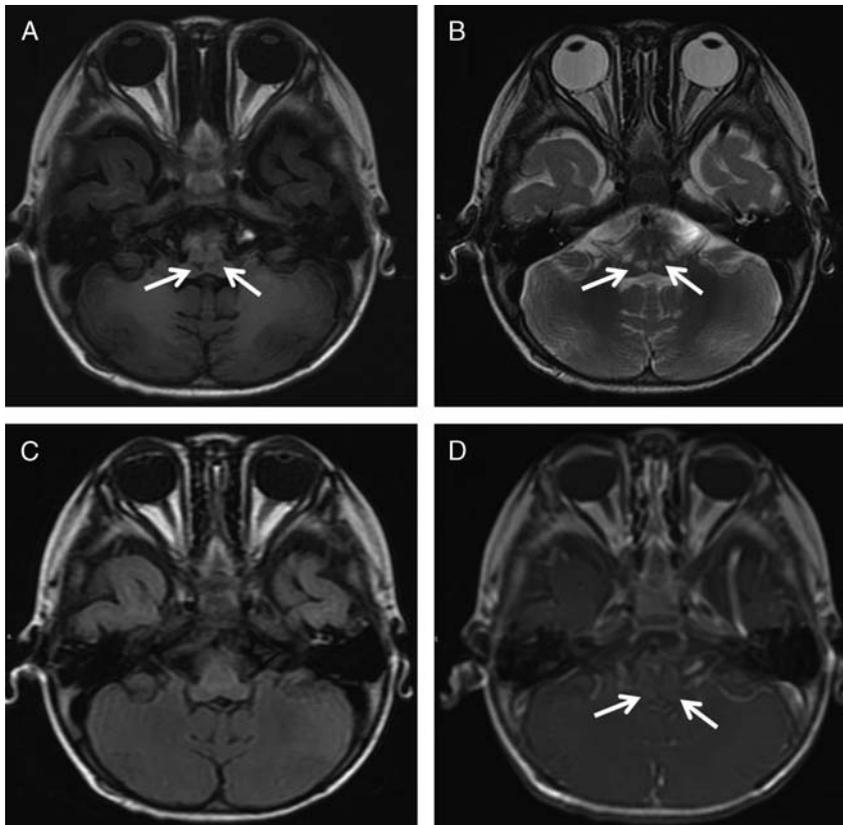


FIGURE 2. A 23-month-old girl having EV71 with poor prognosis. A, T1WI shows remarkable bilateral hypointense signal on the posterior portion of medulla oblongata (arrows). B, T2WI demonstrates high signal intensity (arrows). The lesions were obscure on FLAIR (C) and showed slight enhancement on contrast-enhanced T1WI (D).

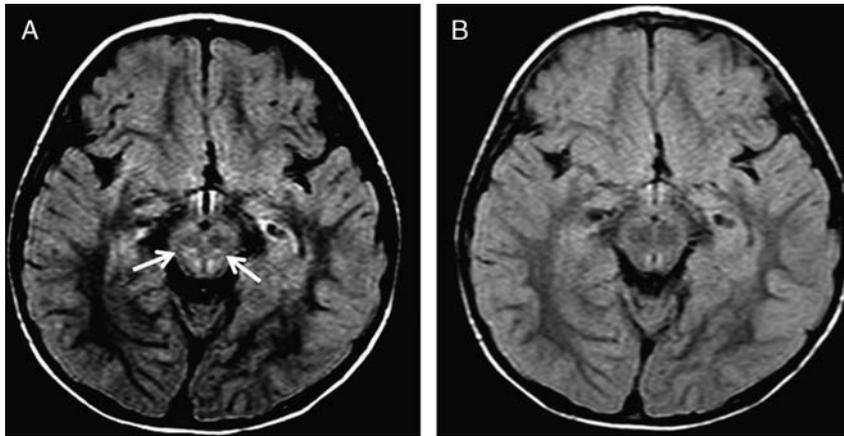


FIGURE 3. A 26-month-old boy having EV71 with good prognosis. Initial FLAIR (A) reveals symmetrical hyperintense signal on the midbrain (arrows); after 6-month follow-up, the lesions had disappeared (B).

good prognosis (Table 1), there was a significantly higher rate of lesions involving the cerebral white substance ($P = 0.011$), thalamus ($P = 0.006$), medulla oblongata ($P < 0.001$), pons ($P = 0.004$), midbrain ($P = 0.006$), and spinal cord ($P < 0.001$) in the group with poor prognosis. After screening for clinical and laboratory parameters by using multivariate analysis (Table 2), we identified 2 risk factors that may predict poor prognosis: lesions located in the medulla oblongata ($P < 0.015$) and spinal cord ($P < 0.001$). Lesions involving the spinal cord on MRI was the most significant prognostic factor after multiple logistic regression analysis (OR, 29.11; $P < 0.001$).

DISCUSSION

During the outbreak of HFMD caused by EV71, CNS infections are common and may lead to severe neural injury or even

death. Therefore, MRI is crucial for the early detection of the locations of CNS involvement, which is helpful for timely management. Recent studies surveying risk factors for severe HFMD have emerged^{11–18} mainly from China, but the severe cases is determined on the basis of the Chinese guideline for HFMD diagnosis and treatment (Chinese Ministry of Public Health, revised in 2010),¹⁹ which is on the basis of many clinical manifestations and lack of MRI data.

As the outbreak of HFMD was caused by EV71 in China,^{2,20} in our study, EV71 was the predominant virus in 76.7% cases. Enterovirus 71 possesses strong neurotropism and retrograde axonal transport in neuron cells,²¹ resulting in brain and spinal cord infection. This is the same with our results: we found that the brain stem is the most common site of lesions; 93 cases (22.6%) presented with abnormal signal intensities in the brain stem, followed by

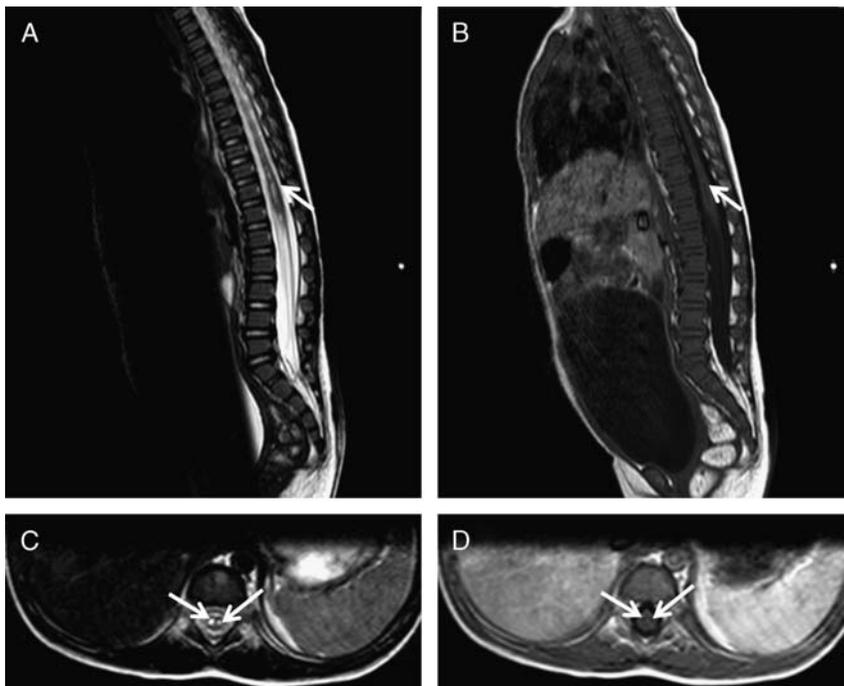


FIGURE 4. A 16-month-old boy having EV71 with poor prognosis. He manifested decreased muscle strength in his bilateral lower limbs in the follow-up. A, Sagittal T2WI reveals high signal intensity in the inferior thoracic segments (arrows). B, T1WI demonstrates slightly low signal intensity (arrows). Axial images showed hyperintense symmetrical lesions in the anterior horn regions on T2WI (C) and T1WI (D).

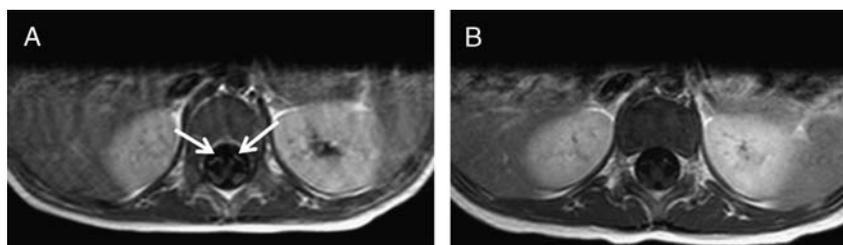


FIGURE 5. A 19-month-old boy having EV71 with good prognosis. He manifested bilateral lower limb weakness during hospitalization. Initial image (A) showed bilateral spinal anterior nerve roots enhancement (arrows); after 8-month follow-up, the lesions had disappeared (B), and the symptom also disappeared.

the spinal cord. Another theory is that EV71 is a more virulent strain of enterovirus and more prone to induce viremia, which is assumed to be related to the occurrence of complications.²²

The strengths of this study are the relatively large study population and use of MRI characteristics, which is more objective, to predict the prognosis of severe HFMD based on follow-up. In our

TABLE 1. Comparison of Groups With Good Prognosis Versus Poor Prognosis

Variables	Good Prognosis (N = 347), n (%)	Poor Prognosis (N = 65), n (%)	<i>t</i> / χ^2	<i>P</i>
Brain or spinal meninges				
0	320 (92.2)	58 (89.2)	0.646	0.422
1	27 (7.8)	7 (10.8)		
Cerebral cortex				
0	342 (98.8)	63 (96.9)	1.412	0.241
1	4 (1.2)	2 (3.1)		
Cerebral white matter substance				
0	341 (98.6)	60 (92.3)	9.034	0.011*
1	6 (1.4)	5 (7.7)		
Cerebellum				
0	344 (99.1)	63 (96.9)	2.235	0.178
1	3 (0.9)	2 (3.1)		
Basal ganglia				
0	346 (99.7)	64 (98.5)	1.771	0.291
1	1 (0.3)	1 (1.5)		
Callosum				
0	345 (99.4)	65 (100)	0.376	1.000
1	2 (0.6)	0 (0)		
Thalamus				
0	347 (27.2)	63 (13.6)	10.729	0.006*
1	0 (0)	2 (86.4)		
Medulla oblongata				
0	301 (86.7)	46 (70.8)	12.480	<0.001*
1	46 (13.3)	19 (29.2)		
Pons				
0	330 (94.5)	55 (94.6)	8.215	0.004*
1	19 (5.5)	12 (5.4)		
Midbrain				
0	336 (96.8)	58 (89.2)	7.567	0.006*
1	11 (3.2)	7 (10.8)		
Spinal cord				
0	323 (93.1)	29 (44.6)	103.362	<0.001*
1	24 (6.9)	36 (55.4)		
Spinal nerve roots				
0	303 (87.3)	58 (89.2)	0.184	0.693
1	44 (12.7)	7 (10.8)		

Categorical variables are shown as number of patients (percentage).

**P* < 0.05.

TABLE 2. Risk Factors for Poor Prognosis of HFMD

	<i>df</i>	β	SE	OR (95% CI)	Wald χ^2	<i>P</i>
Spinal cord	1	2.92	0.42	29.11 (12.86–65.89)	65.39	<0.001
Medulla oblongata	1	1.19	0.55	5.56 (2.84–7.76)	15.86	<0.015

CI indicates confidence interval.

study, we identified 2 independent risk factors associated with poor prognosis, including lesions located in the medulla oblongata and spinal cord.

Our findings showed that the dorsal medulla oblongata is the most common site of lesion, followed by the pons. We found that lesions that involved the dorsal medulla oblongata increased the risk of poor prognosis. It might be related to damage of respiratory center, which will cause pulmonary edema—once the pulmonary edema occurs, the prognosis is worse. Chang et al²³ suggested that lesions in the CNS are caused by EV71 neurotropism and may lead to neurogenic pulmonary edema. This theory is consistent with our observation that all cases with pulmonary edema were induced by medulla oblongata damage, and all the deceased patients

died of neurogenic pulmonary edema. Neurogenic pulmonary edema can develop very rapidly after CNS insult, and death may occur within minutes.²⁴ Although the incidence of other 2 locations, including the pons and midbrain, was significantly higher in the group with poor prognosis, they were not independent risk factors. We observed that most of these lesions were reversible in the reexamination of MRI, and the patients with clinical symptoms could completely disappear in the follow-up.

In this study, we found that lesions involving the spinal cord on MRI was the most significant risk factor (OR, 29.11; $P < 0.001$). Lesions in the regions of the anterior horn cell of the spinal cord explain the poliomyelitis-like paralysis in our patients, and the symptom did not disappeared in the following 6 months to

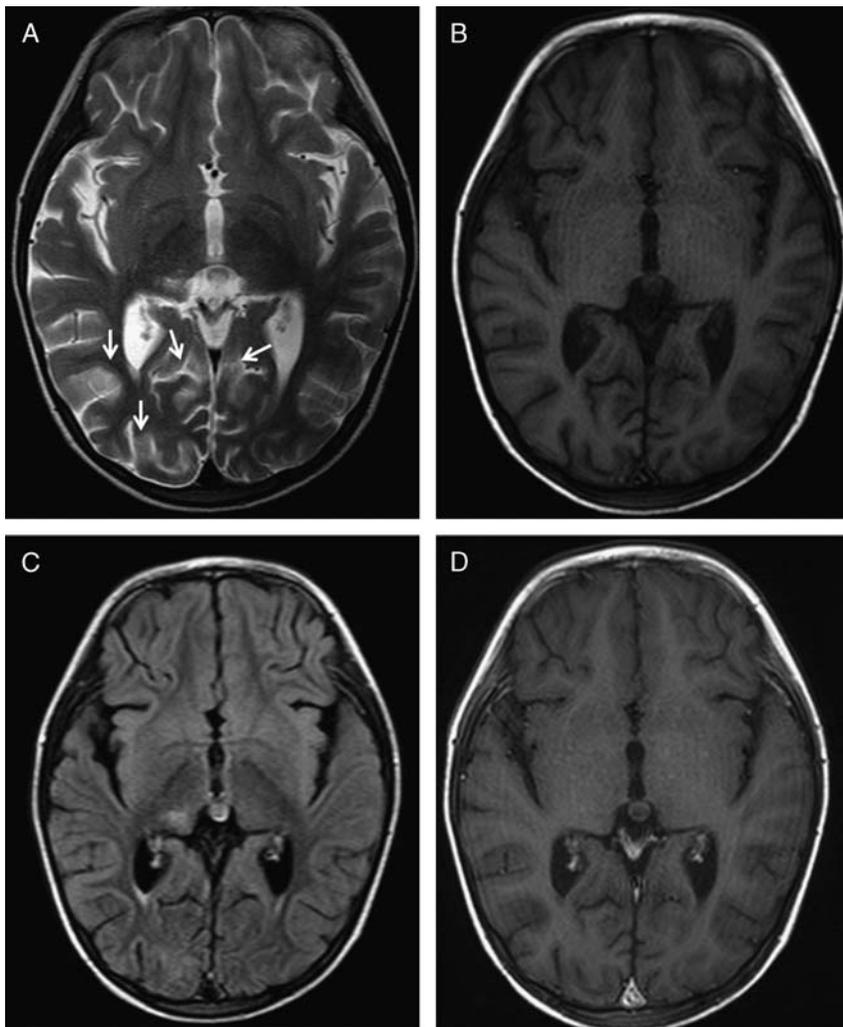


FIGURE 6. A 2-year-old boy having EV71. There are extensive lesions in the occipital cortex and the subcortical white matter on T2WI (A), which were difficult to identify on T1WI (B) and FLAIR (C), and contrast-enhanced transverse T1WI showed no enhancement (D).

1 year. It has been reported that 20% patients with encephalomyelitis had sequelae involving limb weakness and atrophy.²⁵ Chen et al²⁶ used immunohistochemistry methods to detect antigen of EV71 in the infected mice and showed that, after 6 hours, the EV71 antigen could be seen first in the small intestine, then subsequently in the spinal cord after 24 hours, and 78 hours later in the brain stem. Because the spinal cord is the first location, we suppose that the spinal cord damage may lead to pernicious development caused by the persistent viremia, so this may explain why lesions involving the spinal cord on MRI was the most significant prognostic factor. Damage in the ventral root can also cause limb weakness, but we found that only ventral root enhancement can easily disappear in the follow-up, and the symptom can also be absent. So we need MRI to identify the spinal cord damage and whether, for the dyskinetic disorder, early limb function exercise and rehabilitation nursing are required—the more timely, the more beneficial to patients' recovery.²⁷

Magnetic resonance imaging result and clinical feature showed high correlation; MRI could provide better sensitivity and specificity for the location of lesions. Our results showed that the clinical symptoms and MRI results have good consistency. When the lesions involve the posterior portion of the medulla oblongata, the vagus nerve, fasciculus longitudinalis medialis, and reticulate body might be affected, which leads to respiratory and circulatory dysfunction. If the posterior portion of the pons and mid-brain was involved, the nuclei of cranial nerves III, IV, VI, VII, and IX may often be damaged.

There are several limitations in this study. First, the conventional MRI may miss some lesions at the early stage; as reported in our previous study, diffusion weighted imaging seems to be more sensitive in detecting EV71 encephalitis than conventional MRI sequences at the acute stage,²⁸ but few of our patients had undergone diffusion weighted imaging. Furthermore, follow-up MRI was not carried out for every patient. Finally, we should explore the long-term follow-up of this cohort to determine the ultimate prognosis in the future.

In conclusion, our results suggest that children who have severe HFMD with lesions located in the medulla oblongata and spinal cord may be closely monitored for early intervention, especially children with spinal cord damage, and early rehabilitation treatment should be performed. The clinical symptoms and MRI results have good consistency; for the children with the symptom of nervous system, they are strongly recommended for MR examination.

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