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Clinical and neuroimaging features of enterovirus71 related acute flaccid paralysis in patients with hand-foot-mouth disease

Feng Chen[1], Jian-Jun Li[1*], Tao Liu[2], Guo-Qiang Wen[2], Wei Xiang[3]

[1]*Department of Radiology, People's Hospital of Hainan Province, Haikou, PR. China*
[2]*Department of Neurology, People's Hospital of Hainan Province, Haikou, PR. China*
[3]*Department of Pediatrics, People's Hospital of Hainan Province, Haikou, PR. China*

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ABSTRACT

Objective: To investigate clinical and neuroimaging features of enterovirus71 (EV71) related acute flaccid paralysis in patients with hand-foot-mouth disease. **Methods:** Nine patients with acute flaccid paralysis met the criterion of EV71 induced hand-foot-mouth disease underwent spinal and brain MR imaging from May 2008 to Sep 2012. **Results:** One extremity flaccid was found in four cases (3 with lower limb, 1 with upper limb), two limbs flaccid in three cases (2 with lower limbs, 1 with upper limbs), and four limbs flaccid in two cases. Spinal MRI studies showed lesion with high signal in T2-weighted images (T2WI) and low signal T1-weighted images (T1WI) in the spinal cord of all nine cases, and the lesions were mainly in bilateral and unilateral anterior horn of cervical spinal cord and spinal cord below thoracic 9 (T9) level. In addition, the midbrain, pons, and medulla, which were involved in 3 cases with brainstem encephalitis, demonstrated abnormal signal. Moreover, spinal cord contrast MRI studies showed mild enhancement in corresponding anterior horn of the involved side, and strong enhancement in its ventral root. **Conclusions:** EV71 related acute flaccid paralysis in patients with hand-foot-mouth disease mainly affected the anterior horn regions and ventral root of cervical spinal cord and spinal cord below T9 level. MR imaging could efficiently show the characteristic pattern and extent of the lesions which correlated well with the clinical features.

1. Introduction

Hand-foot-mouth disease (HFMD) was an epidemic disease usually caused by several enterovirus, and the susceptible population were mainly infant and young children. Most of their symptoms are mild, with painful vesicular lesions on the hands, feet, mouth and tongue, and mild fever. Fewer patients developed aseptic meningitis, encephalitis, acute flaccid paralysis, respiratory infection, and myocarditis *et al*[1,2]. Some critically ill patients have quick progression and are easy to die. The enterovirus which caused HFMD included enterovirus71 (EV71), coxsackie virus, and some serum type of ECHO virus, EV71 is considered to be the dominant pathogen of severe complications. EV71 has been considered to cause poliomyelitis-like paralysis in several studies since 1975, but it is a benign course with different epidemiology and therapy method compared with poliomyelitis. The widely used MR imaging has shown EV71 related brain stem encephalitis, and spinal cord MR imaging was reported to specifically involve both anterior horn cells of the cord and ventral roots, however, more details are needed to describe characteristic changes in the spinal cord, especially correlated with clinical features. In this study, we used the MR imaging to demonstrate the characteristic changes of brain and whole spinal cord in HFMD with AFP complication and correlate the clinical finding to the MRI characteristics.

2. Materials and methods

2.1. Study population

Participants in this study consisted of 9 infants and young

*Corresponding author: Jian-Jun Li, People's Hospital of Hainan Province 570311, China.
E-mail: cjr.lijianjun@vip.163.com
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children (5 male, 4 female, age from 4 months to 27 months, mean age 16 months) who met the criteria for HFMD with AFP. They all were admitted our institution for treatment from May 2008 to Sep 2012. Their throat swab, stool and cerebrospinal fluid were tested positive of EV71 DNA at two to four days after fever. AFP was indicated in these patients when there were acute onset of flaccid muscle weakness and lack of reflex in one or several limbs.

2.2. Methods

All MRI examinations were performed using 1.5 Telsa scanner (GE Signa 1.5 T Twinspeed /Excite Ⅱ) with 8 channel Head Coil and 4 channel Spine Coil. The sequence parameters included two parts: for brain scanning, axial T1WI_FlAIR (TR 1 800 ms, TE 24 ms, TI 750 ms, flip angle 90 °, voxel size 0.8 mm×1.15 mm), axial T2WI (TR 3 000 ms, TE 100 ms, flip angle 90 °, voxel size 0.6 mm×0.8 mm), axial FLAIR (TR 8 002 ms, TE 129 ms, TI 2 000 ms, flip angle 90 ° voxel size 0.8 mm×1.15 mm), were used with slice thickness 5 mm and gap 0.5 mm; for spinal cord scanning, sagital T1WI (TR 750 ms, TE 20 ms, flip angle 90 °, voxel size 0.8 mm×1 mm), sagital T2WI (TR 3 600 ms, TE 100 ms, flip angle 90 °, 0.8 mm×1 mm), axial T2WI (TR 3 000 ms, TE 120 ms, flip angle 90 °, voxel size 0.8 mm×1 mm) were used with slice thickness 3 mm and gap 0.3 mm. Contrast Gd-DTPA was applied in three patients with 0.1 mmol/kg.

3. Results

3.1. Clinical findings

All nine patients were with fever in variable degree (one case from 37 ℃ to 38 ℃, five cases from 38 ℃ to 39 ℃, three cases more than 39℃), and skin rash were found in all nine cases with or without oral herpes before or after fever. Among the nine cases, four cases showed one flaccid limb (3 with lower limb, 1 with upper limb), three cases showed two flaccid limbs (2 with lower limbs, 1 with upper limbs), and four flaccid limbs found in two cases, and all these nine cases are without sense defect, three of the nine cases with brainstem encephalitis had disturbance of conscious, myoclonus, tremor and ataxia *et al*.

3.2. MRI

Spinal cord MR imaging indicated that there were long strip high signal on T2WI and low signal on T1WI in cervical spinal cord (Figure 1A, 2A) and below T9 level on sagital images and on axial images, there were low signal on T1WI and high signal on T2WI in bilateral or unilateral anterior horn (Figure 1B, 2B). In the 5 cases with bilateral limbs weakness there was abnormal signal in bilateral anterior horn, and in 3 cases with brainstem encephalitis there was punctate abnormal low signal on T1WI and high signal on T2WI in pons, medulla, and midbrain (Figure 1C, 2C, CF). With Contrast Gd-DTPA, there were obvious enhancement in ventral root (Figure 1D, 2D) and mild enhancement in medulla and anterior horn (Figure 2E). After therapy and recovery, the size of lesion was smaller in posterior brainstem (Figure 2G).

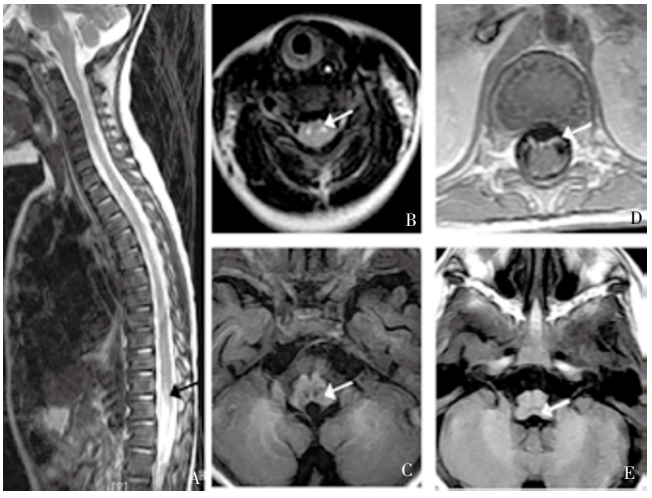

Figure 1. Changes of MRI of case No.1 before and after treatment.
A: Sagital plane T2WI of spinal cord before treatment; B: Axial plane T2WI of cervical spinal cord before treatment; C: Axial plane T1WI of medulla before treatment; D: Axial plane contrast-enhanced axial T1-weighted image before treatment; E: Axial plane T1WI of medulla after treatment.

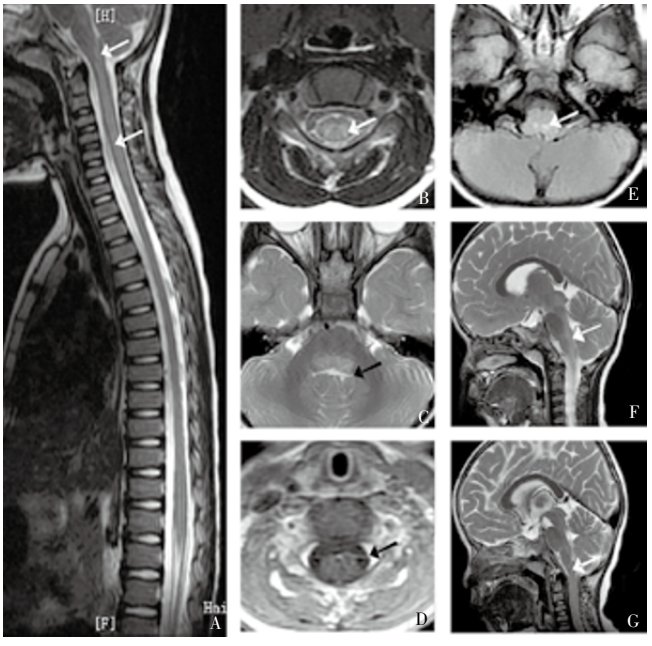

Figure 2. Changes of MRI of case No.2 before and after treatment.
A: Sagital plane T2WI of spinal cord before treatment; B: Axial plane T2WI of cervical spinal cord before treatment; C: Axial plane T1WI of pons before treatment; D: Axial plane contrast-enhanced axial T1-weighted image of cervical spinal cord before treatment; E: Axial plane contrast-enhanced axial T1-weighted image of medulla before treatment; F: Sagital plane T2WI of brainstem before treatment; G: Sagital plane T2WI of brainstem after treatment.

3.3. Follow up result

The patients' recovery order begun with the fingers and toes' joints or wrist and ankle joint, but proximal muscle strengthen and muscle tone is slowly recovered. After 4 weeks, three cases HFMD with AFP in single lower limb could be better recovered to muscle strengthen III or Ⅳ level. Another three cases with bilateral limbs or single upper limb weakness could be recovered to muscle strengthen I-Ⅱ level. Two cases with quadriplegia, upper limbs' muscle strengthen was recovered to Ⅱ Level and the lower limbs' muscle strengthen to III or Ⅳ level in one case, in the other case upper limbs' muscle strengthen was recovered to III or Ⅳ Level and the lower limbs' muscle strengthen to Ⅱ level. Three cases with brainstem encephalitis, the MRI findings showed that lesion was recovered and the size of the lesion was smaller than the previous, with improved tendon reflex and muscle tension.

4. Disscussion

4.1. Epidemiologic feature of EV71 related HFMD

Since 1974, Schmidt *et al* firstly identified EV71 from patients with encephalitis in California, there were several outbreaks and epidemics in the world[3-5]. From 1972 to 1973, in 1986 and 1999 there were EV71 outbreaks in Australia, most of severe critical patients had neurological damage including aseptic meningitis, brainstem encephalitis, AFP *et al*, some patients even had severe respiratory symptoms[6]. In the recent years, there was on the rise for EV71 infection. In 1998, there was a pandemic HFMD in Taiwan with 129 106 infected cases, 405 children among them had severe complications including aseptic meningitis, encephalitis, pulmonary edema and pulmonary haemorrhage, and 78 dead cases were caused by pulmonary edema or haemorrhage with 91 percent dead cases less than five year old, among which the EV71 accounted 48.7% in virus identified[7]. AFP in EV71 related HFMD was of different ratio, in 1973 Japan outbreaks it was reported to be 2%, in 1975 Bulgaria 7.4%, in 1977 New York 17%, in 1978 Hungary 4%, from 1988 to 1990 Brazil 58%, in 1998 Taiwan 10%.

4.2. Pathological changes and pathogenesis in AFP of EV71 related HFMD

EV71 and polio virus are of the enterovirus with same infected region including: dorsal nucleus of vagus nerve, medial longitudinal fasciculus, medial longitudinal fasciculus and nucleus tractus solitarily in dorsal medulla; abducens nerve nucleus, facial nerve nucleus, glossopharyngeal nerve nucleus in dorsal pons; red nucleus, substantia nigra and nucleus of trochlear nerve in the middle part of midbrain; putamen, thalamus and anterior horn of spinal cord *et al*. The pathological studies proved that the above regions have their specificity[8,9]. In 1975 Bulgaria epidemic period, autopsy in the dead case showed spinal cord involved[10]; In 1978 Hungary, autopsy demonstrated inflammatory lesion in dorsal brainstem and anterior horn of spinal cord[11]; in 1997 Malaysia EV71 epidemic period, it showed similar inflammatory response in the medulla, pons and midbrain[12]. These responses included: perivascular cuffing predominantly by mononuclear cells, neuronal degeneration and necrosis with neuronophagia; and the presence of conspicuous microglial nodules. All these changes were mainly in the gray matter; pyramidal tract in the pons did not showed the above inflammatory response.

The mechanism of central nervous system (CNS) damaged by EV71 was not clear, but oral administration EV71 could cause persistent viremia and increased permeability in the blood brain barrier, but low level of virus count indicated that Hematogenous dissemination was not the dominant way of impairing CNS. Chen *et al*[13] used immunohistochemistry methods to detect antigen of EV71 in the infected mice, and showed that after 6 hours the EV71 antigen could be seen in small intestine; 24 hour later in the thoracic spinal cord; 50 hour later in cervical spinal cord and lumbar spinal cord; 78 hours later, in brainstem. This showed that Virus could be transmitted fast and massively replicated which could explain that EV71 related brain and spinal cord infection lead to pernicious development. Most of neural cells in CNS were degeneration and necrosis, then, were finally replaced by the inflammatory cell, but ischemic changes could not be seen in the normal region without inflammatory infiltration and hippocampus, thalamus *et al* which is susceptible to anoxia. The above results indicated EV71 had obviously neurotropism, and the lesion was not ischemic cause. Wong *et al*[14] based on the characteristic of the EV71 related CNS damage predicted that EV71 disseminated into the central nerve system mainly through nervous system especially motion nerve and this mechanism resulted in different damage regions compared with other virus related encephalitis. Moreover, the inflammatory cell infiltration leaded to occlusive vasculitis, and nucleus in gray matter which could not tolerate hypoxic-ischemic changes leaded to regional ischemic damage. This was possible mechanism of nucleus damage in gray matter for EV71 related

encephalomyelitis[15].

4.3. Clinical features and MRI characteristic for EV71 related HFMD with AFP

With the program of eradicating the polio virus around the world, polio related AFP had been controlled, but EV71 had replaced polio virus to become the important neurotropic pathogen in the world[16]. We should pay attention to the predisposition which the EV71 caused different CNS damage in difference epidemic period. When the spinal cord was mainly involved, it was considered to be polio-like AFP; When the brain is mainly involved, it was thought to be brainstem encephalitis. This indicated that difference in virus strain and its various affinities[17]. MRI could provide better sensitivity and specificity for HFMD with AFP, MRI result and clinical feature showed highly correlation. Lesion in different level of the anterior horn and ventral root often caused limb motion damage, for cervical spinal cord damage, it will caused upper limb muscle flaccid paralysis; for the lower thoracic and lumbar spinal cord damage, it will cause lower limb muscle flaccid paralysis. When the damage included the cervical spinal cord and lower thoracic spinal cord aside with brainstem encephalitis, it increased probability of whole spinal cord involvement. Moreover, it helped us evaluate prognosis in this kind of patient. When there were severe damage to spinal cord and the efferent motor nerve, Prognosis of the patient may be worse. Follow up of the patient with AFP, the recovery in single lower limb flaccid paralysis could be faster, and the recovery in upper limb AFP and four limbs AFP was slow. If combined with brainstem encephalitis, the patient's prognosis is worse than the patient with simple AFP. If there were limb tremor, abnormal eye ball movement and other cranial nerve symptom, there should be some precaution to brainstem encephalitis. The presentation in the MRI may be fuzzy lamellar abnormal signal in the dorsal medulla and pons, or unilateral or bilateral localized punctate abnormal signal in the posterior brainstem. The presentation of brainstem encephalitis in the MRI may be different due to the progression of disease and severity of the illness, which need further study for improvement.

Few reports had been focus on the radiological features of EV71 related CNS damage, Malzberg *et al*[18] reported one case with EV71 related flaccid paralysis, in which there high signal on T2WI at C4-5 level. In 1989, Hayward *et al*[19] showed five cases with EV71 related poliomyelitis-like paralysis, two of which showed the damage in anterior horn of the spinal cord. Chen *et al*[20] reported that in 1998 Taiwan seven cases with EV71 related flaccid paralysis were thought to be the spinal cord damage, six cases showed abnormal signal in unilateral and bilateral anterior horn of the spinal cord, and three cases were undergone contrast enhancement study of which two cases were seen ventral root enhancement and one case was seen anterior root enhancement. When bilateral ventral root were involved, Guillain-Barre syndrome should be excluded which did not display lesion in the anterior horn and contrast enhancement in the nerve root, compared with EV71 related AFP. Clinical findings did not shown any sensory system damage in all nine cases, and the MRI finding neither detect any posterior horn and dorsal root involved. Among the nine cases, abnormal signal was generally seen in anterior horn disseminated different levels of the spinal cord, which characterized with cavity or patch, and in the five cases with contrast enhancement, the MRI finding are as following: two cases with bilateral anterior horn enhancement, one cases with bilateral ventral root enhancement, one case with bilateral anterior horn enhancement, and one case with no enhancement.

4.4. Differential diagnosis

There were multiple causes could lead to AFP which presented with acute onset of muscle weakness and functional impairment. The most common reason was poliomyelitis, Guillain-Barre syndrome, transverse myelitis, and metabolic disease *et al*. Both of EV71 and poliomyelitis belong to enterovirus with the same target region in CNS, however, the later often lead to sequel of limb dysfunction and worse prognosis. Moreover, EV71 related AFP in HFMD occurred at the onset of the virus infection and quickly rise to peak, and had the brainstem encephalitis at the same time which presented with myoclonus, tremor, and ataxia, which was absent in Poliomyelitis. Localized anterior horn damage was the main point for EV71 related AFP to differentiate from transverse myelitis, spinal cord neoplasm *et al*. When bilateral anterior horn involved, whether there was posterior horn involved was the key point for discriminate EV71 related AFP from Guillain-Barre Syndrome.

EV71 related AFP in HFMD is often seen in the child less than 2 years old, possible combined with brainstem encephalitis. Lesion was mainly in cervical spinal cord and spinal cord below T9; and anterior horn and ventral root of spinal cord were damaged. Follow up findings proved that EV71 related AFP in HMFD was reversible which depend on the size of the lesion and severity of disease. MRI could efficiently show the characteristic pattern correlated with

clinical findings and facilitate us to evaluate the prognosis.

Conflict of interest statement

We declare that we have no conflict of interest.

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