Enterovirus 71-Induced Brainstem Encephalitis and Myelitis: MRI Findings in Eight Cases

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Learning objectives

The purpose of our educational exhibit is to:

• Review eight different cases of children with enterovirus-related brainstem encephalitis and myelitis.
• Describe the clinical manifestations and neurological symptoms.
• Describe the most common brain and spine MRI findings.
Background

Hand, foot, and mouth disease (HFMD) is a common viral disease, caused by many kinds of viruses, including enterovirus 71 (EV71), coxsackievirus A (CAV), coxsackievirus B (CBV), and echovirus (Echo).

EV71 and CAV16 belong to the family Picornaviridae, which is characterized by a single positive-strand genomic RNA known to have a high mutation rate caused by low-fidelity replication and frequent recombination. EV71 was first isolated between 1969 and 1972 during an outbreak in California. EV71 viruses are classified into three genotypes - A, B, and C - and genotypes B and C are further divided into five subgenotypes based on their VP1 gene sequences.

EV71 and CAV16 are the most frequent etiologic agents causing outbreaks of HFMD. HFMD usually affects children below the age of 10 years, mainly those in the range of 1-5 years. The clinical presentations are usually mild and include fever and blister-like eruptions in the mouth and/or skin rashes on the hands and feet, with recovery taking only a short time. Previous data have shown that EV71 has also been associated with several clinical syndromes: acute flaccid paralysis mimicking paralytic poliomyelitis, bulbar and brainstem encephalitis, the Guillain-Barre# syndrome, and rapidly fatal pulmonary edema and hemorrhage.

Deaths usually occur within 6-24 hours after admission because the disease rapidly progresses to the critical stage. Hence, early diagnosis of enterovirus 71 infection with neurologic involvement and prompt, appropriate management is important.
Findings and procedure details

We analysed retrospectively clinical and imaging data from eight cases of children (age range from 1 to 4 years old) with enterovirus-induced brainstem encephalitis and/or myelitis who were hospitalized in our Paediatric Intensive Care Unit from June 1st, 2016 to September 1st, 2016.

CLINICAL AND LABORATORY FINDINGS

All patients underwent:

- Anamnesis and physical examination.
- Cerebrospinal fluid (CSF) biochemical analysis.
- Detection of enterovirus nucleic acid by PCR in CSF and nasopharyngeal and rectal swab.

The main clinical manifestations were fever, maculopapular lesions and blisters on the hand, foot, mouth and buttocks. On the day of admission, 7 patients (88%) had a body temperature ≥ 39ºC.

Neurological symptoms in the early stage included:

- Tremor (5 cases).
- Drowsiness (3 cases).
- Ataxia (2 cases).
- Irritability (2 cases).
- Loss of strength in the lower limbs (1 case).

Biochemical analysis of CFS showed mononuclear pleocytosis (# 200 µl) in 4 cases (50%) with a mean level of glucose of 61 mg/dl.

EV71 detection was conducted with nasopharyngeal and rectal swab and CSF collected from the patients, using polymerase chain reaction (PCR). The results were:

- CSF → Negative in all cases.
- Rectal swab → Positive in 8 cases (100%).
- Nasopharyngeal swab → Positive in 4 cases (50%).

All patients had a complete recovery of their symptoms, with a mean time admitted in the Paediatric Intensive Care Unit of 9 days, with only two cases spending more than 10 days in the hospital.
MRI PROTOCOL

MRI scans were performed on a 1.5 Tesla system.

- **Brain MRI:** The protocol included the following sequences: Sagittal 3D T1-weighted images, axial and coronal T2-weighted images, axial spectral presaturation with inversion-recovery and fluid-attenuated inversion recovery (SPIR-FLAIR) images and axial diffusion weighted images (DWI).
- **Full spine MRI:** Most cases included full spine T2-weighted sagittal images, cervical spine T1-weighted sagittal images and axial T2-weighted cervical spine images. However, in some cases other sequences were acquired, for instance, STIR or DWI.

BRAIN MRI FINDINGS:

MRI distribution of EV71 brainstem encephalitis:

Although EV71 encephalitis is a type of viral encephalitis, its characteristic imaging features are different from the other common viral infections. Knowledge of the typical MR imaging findings of EV71 encephalitis is crucial for guiding diagnosis.

All the patients showed abnormalities on the MRI scans. The most common location was the dentate nucleus (Fig. 1). The dentate nucleus is the largest and most lateral of the cerebellar nuclei, located medially within each cerebellar hemisphere, just posterolateral to the forth ventricle. It is as a undulating semi-circular structure with the opening facing the midline. In our study the dentate nuclei were affected bilaterally on 6 patients (75%).

Typical EV71 brainstem encephalitis lesions located at the dorsal junction region of the medulla oblongata (Fig. 2) and pons (Fig. 3) appear as a longitudinal patch, although similar findings are found in polio and coxsackievirus infections. In our study, four cases showed lesions in the tegmentum of the pons and in two cases lesions were demonstrated at the medulla oblongata. When the disease involves the posterior portion of the medulla oblongata, the dorsal nuclei of the vagus nerve, the medial longitudinal fasciculus, the reticular formation, and the nuclei of the solitary tract may be affected.

Three patients had abnormalities in the midbrain, specifically at the cerebral peduncles (Fig. 4), with one case affecting also the periaqueductal grey matter (Fig. 5). If the pons and midbrain are involved, the nuclei of cranial nerves III, IV, VI, VII and IX may be affected.
Supratentorial lesions were also demonstrated, although only two patients showed lesions affecting the thalamus asymmetrically, with a higher signal intensity on the left thalamus (Fig. 6) and in one case globus pallidus was affected bilaterally (Fig. 7).

According to the literature, typical locations primarily involved with infection include the posterior portion of the brainstem and spinal cord, while the bilateral dentate nuclei of the cerebellum, bilateral putamina and thalami are rarely involved. However, in our study the dentate nuclei were the primary location of rhombencephalitis.

**MRI signal intensity:**

Brainstem encephalitis lesions on plain T1-weighted images showed, in most cases, an isointense signal (Fig. 8). Whereas, in two patients hypointense T1 signals were demonstrated in the dorsal brainstem (Fig. 9) and the thalamus.

FLAIR has been reported to be more sensitive than T2WI in detecting encephalitic lesions, nevertheless, we found that the sensitivity of FLAIR was not superior to T2WI in detecting EV71 lesions (Fig. 10). This result is similar to most reports, possibly due to the fact that the EV71 encephalitis frequently involves the brainstem, whereas other viral encephalitis usually involve the cortical and subcortical white matter.

During the acute stage of EV71 encephalitis, T2WI revealed hyperintense areas that were not seen on T1WI reflecting acute inflammation of brain tissue (Fig. 8).

Diffusion weighted images were also acquired. DWI is widely used to evaluate various diseases involving the brain and spinal cord, and its role in other conditions, including infection, has been increasingly explored. More recent reports in the literature indicate that DWI can be useful in the early diagnosis of the neurological complications associated with CNS infections. In our study none of the lesions showed restricted diffusion (Fig. 11). This lack of restricted diffusion helped to exclude acute infarction and vasculitis, and therefore a poorer prognosis.

**SPINE MRI FINDINGS**

**MRI distribution of EV71 myelitis:**

Acute viral myelitis can present as acute flaccid paralysis (AFP) or neurologic dysfunction due to involvement of the white matter. Acute flaccid paralysis is due to cytolytic infection.
of anterior horn cells usually caused by polioviruses-1, -2, and -3, CAV and CBV, EV71, and flaviviruses, including West Nile virus.

EV71 infections have been associated with poliomyelitis-like paralysis in several outbreaks worldwide since 1975, and EV71 is considered one of the leading causes of AFP now that poliomyelitis has been nearly eradicated.

In our study six patients (75%) had signal abnormalities in the cervical spine (Fig. 12) and one patient in the conus medullaris (Fig. 13). The range of cervical myelitis involved from C1 to D1 and all the patients had C4 and C5 levels affected. The abnormalities were seen in the grey matter with a diffuse (Fig. 14) or anterior horns distribution (Fig. 15). Solitary posterior horns affection was not encountered.

**MRI signal intensity:**

All of our cases with myelitis had an engorgement of the affected spine levels, better seen on sagittal images, and T2 hyperintense signal (Fig. 16).

In T1-weighted images, there was a spine signal hypointensity (at the same levels as the T2 hyperintense signal) in just one patient (Fig. 17). Therefore, isointensity on T1-weighted images (Fig. 18) was the most common finding.

In spite the fact that six patients had signal and morphologic abnormalities in the cervical spine, only one case had spine neurological symptoms such as loss of strength in the limbs.

Again, no restricted diffusion was detected, but nevertheless only three spine MRIs had a DWI sequence on the protocol.
Fig. 1: Female, 12 months old. Axial SPIR-FLAIR shows bilateral hyperintense signal on the dentate nuclei (red arrows).

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**Fig. 2:** Female, 23 months old. Axial SPIR-FLAIR depicts a signal hyperintensity in the dorsal portion of the medulla oblongata (yellow arrow).

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Fig. 3: Same patient as Fig. 2, axial TSE T2-weighted (T2WI) shows a hyperintense signal in the pontine tegmentum (red arrow) extending through the medial portion of the middle cerebellar peduncles.

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Fig. 4: 2 y.o. female. Axial SPIR-FLAIR demonstrates a signal hyperintensity in both midbrain's cerebral peduncles (red arrows).

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Fig. 5: Female, 23 months old. Axial TSE T2WI shows hyperintense signal in the periaqueductal grey matter of the midbrain (yellow arrow).

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Fig. 6: 2-year-old female. Axial SPIR-FLAIR depicts a dorsal left thalamus signal hyperintensity (red arrow).

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**Fig. 7:** 2-year-old male. Coronal TSE T2WI shows a hyperintense signal in the internal globus pallidus bilaterally (red arrows).

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Fig. 8: 12-month-old female. Left: axial 3D T1-weighted (T1WI), no signal abnormalities are detected; Right: axial SPIR-FLAIR of the same patient depicts a hyperintense signal in the dorsal pons (red arrow). Signal hyperintensity is also noted in both cerebellar dentate nuclei.

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**Fig. 9:** Male, 4-year-old. Left: axial 3D T1WI demonstrates hypointense signal at the dorsal portion of the pons (yellow arrow); Right: axial SPIR-FLAIR of the same patient shows signal hyperintensity at the same level of the dorsal pons (red arrow).

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**Fig. 10:** 2-year-old male. Left: axial TSE T2WI. Right: axial SPIR-FLAIR. Signal hyperintensity is demonstrated at the dorsal pons extending through both middle cerebellar peduncles, without differences in the extent of the lesions between both sequences.

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**Fig. 11:** 23-month-old female. Left: axial SPIR-FLAIR shows a signal hyperintensity in the dorsal pons (red arrow). Right: axial diffusion weighted (DWI) of the same patient shows no restricted diffusion in the pontine tegmentum.

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Fig. 12: Male, 4 years old. Sagittal TSE T2WI demonstrates a hyperintense signal (yellow arrow) in the cervical spinal cord extending from C1 level to C5.

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**Fig. 13:** 23-month-old female. Sagittal TSE T2WI demonstrates an engorgement and a signal hyperintesity at the conus medullaris spinal cord level (yellow arrow).

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Fig. 14: 4-year-old male. Axial Fast Field Echo (FFE) T2WI shows a signal hyperintensity affecting both the anterior and the posterior horns (yellow arrows) of the cervical spinal cord.

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Fig. 15: 12-month-old female. Axial FFE T2WI depicts a hyperintense signal in the affecting right anterior horn (red arrows) of the cervical spinal cord.

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Fig. 16: Male, 2 years old. Sagittal TSE T2WI demonstrates a hyperintense signal and engorgement of the cervical spine, from the C1 level to C6 (red arrow).

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Fig. 17: 2-year-old male. Left: sagittal TSE T2WI depicts a signal hyperintensity in the cervical spine that extends from C1 level to D1 (red arrow); Right: sagittal TSE T1WI of the same patient shows signal hypointensity (yellow arrow) at the same spinal cord levels as the left image.

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**Fig. 18:** 4-year-old male. Left: sagittal TSE T2WI demonstrates a signal hyperintensity of the cervical spinal cord, from C1 level to C5 (red arrow). Right: sagittal TSE T2WI of the same patient showed no signal abnormalities.

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Conclusion

The characteristic lesion locations of EV71 brainstem encephalitis were in the bilateral dentate nuclei of the cerebellum, the posterior portions of the medulla oblongata and pons, and also may have involved the cerebral peduncles and the most central part of the midbrain. Some were in the thalami, and the globus pallidus.

Primary locations of EV71 myelitis was the cervical spine, with all cases affecting the C4 and C5 levels. Only one case had non-cervical spine MRI signal abnormalities, with lesions demonstrated in the conus medullaris.

Under adequate cardiopulmonary support, all patients had a complete recovery of their symptoms.

MRI scans can provide important information for clinical assessment and monitoring of treatment of the disease. MR imaging is particularly useful in the early detection of spinal cord and root lesions and should be helpful in excluding other surgically treatable causes of acute limb paralysis in children.
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