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SCIENTIFIC LETTERS

Infection outbreak due to an enterovirus causing severe neurological complications in a tertiary hospital☆,☆☆

Brote de infección por enterovirus causantes de afectación neurológica grave en un hospital terciario

Dear Editor:

Enterovirus (EV) frequently causes outbreaks of infection in children in spring and summer. Although it usually produces mild illness, there are also cases with severe neurologic involvement (encephalitis, rhombencephalitis, acute flaccid paralysis and autonomic dysfunction with pulmonary oedema) that may cause lifelong sequelae or death. The serotypes associated with the most severe cases are A71 and D68.[1–6] We describe the cases of the patients admitted to a tertiary care hospital in Madrid in May 2016 following the outbreak of EV infection with severe neurologic involvement in Catalonia in the same year.[1]

We conducted a prospective descriptive study of the clinical and epidemiological characteristics, the diagnostic tests performed and the outcomes of patients admitted with suspected EV infection and severe neurologic symptoms (Table 1).

We analyzed 11 cases, of which 10 were confirmed, defined as presenting with acute neurologic manifestations of encephalitis, rhombencephalitis and/or acute paralysis with compatible findings on MRI examination and detection of enterovirus by PCR analysis of a nasopharyngeal or rectal swab sample in the absence of evidence of a different aetiological agent. One was a probable case, suspected based on compatible clinical manifestations and results from diagnostic tests, but without microbiological confirmation.

All the patients were previously healthy. The median age was 26 months (interquartile range [IQR], 22–32) and there was a predominance of the female sex (6/11). We did not find an apparent epidemiological association between the different cases. The symptoms at onset were irritability (11/11), fever (10/11) and skin and mucosal involvement (8/11). Neurologic symptoms developed a median of 3 days after the onset of systemic symptoms (IQR, 2–4), and the most common were ataxia (11/11), somnolence (10/11), tremors (9/11) and myoclonus during sleep (7/11). Only 2 patients had symptoms of brainstem involvement, while flaccid paralysis was initially suspected in 1 (due to areflexia and need for mechanical ventilation) but eventually ruled out due to the quick resolution of symptoms within 24 h. Four patients were admitted to the PICU due to dysautonomia and cardiac dysfunction.

All patients underwent a lumbar puncture, and subsequent examination of the sample revealed pleocytosis in the cerebrospinal fluid in 9 out of 11 patients, with lymphocytic predominance in 7. A MRI scan was performed in 10 patients, revealing rhombencephalitis in 8 (associated with myelitis in 7) and isolated myelitis in 2 (Fig. 1). Since a high proportion of patients presented with somnolence and irritability, an encephalogram (EEG) was performed in 10, revealing slow wave activity in 9. The results of 9 brainstem auditory evoked response tests in patients with manifestations or MRI evidence of brainstem involvement and the 3 electromyograms performed in patients with significant spinal cord involvement were normal.

Enterovirus was detected in rectal swab samples (10/11) and nasopharyngeal swab samples (5/9) by PCR (GeneXpert®) in our hospital, and subsequently typed in samples submitted to the Centro Nacional de Microbiología. It was not detected in cerebrospinal fluid (CSF) or blood samples in any patient. The most frequent serotype was A71 (5/10), while serotype D68 was not detected in any case. The 10 patients classified as having moderate illness (significant somnolence) or severe illness (clinical manifestations or neuroimaging evidence of brainstem or spinal cord involvement) received early intravenous immunoglobulin (IVIG) therapy (within 24–48 h from admission) in adherence with the treatment protocol applied in previous outbreaks.[1,2] All of them received IVIG (1 g/kg/day for 2 days), combined with administration of boluses of IV methylprednisolone (30 mg/kg/day for 3 days) in patients with severe disease. Only patients admitted to the PICU received fluoxetine (0.3 mg/kg/day), which was prescribed off-label on account of its in vitro activity and had no clear beneficial effects.

Two of the patients with severe disease had immediate sequelae that resolved after 3 months, and all patients remained asymptomatic at 12 months' followup. The diagnostic tests repeated during followup included 4 EEGs that showed normalization of wave patterns and 2 MRI scans, of which 1 was unremarkable and 1 had features indicative of persistent myelitis.

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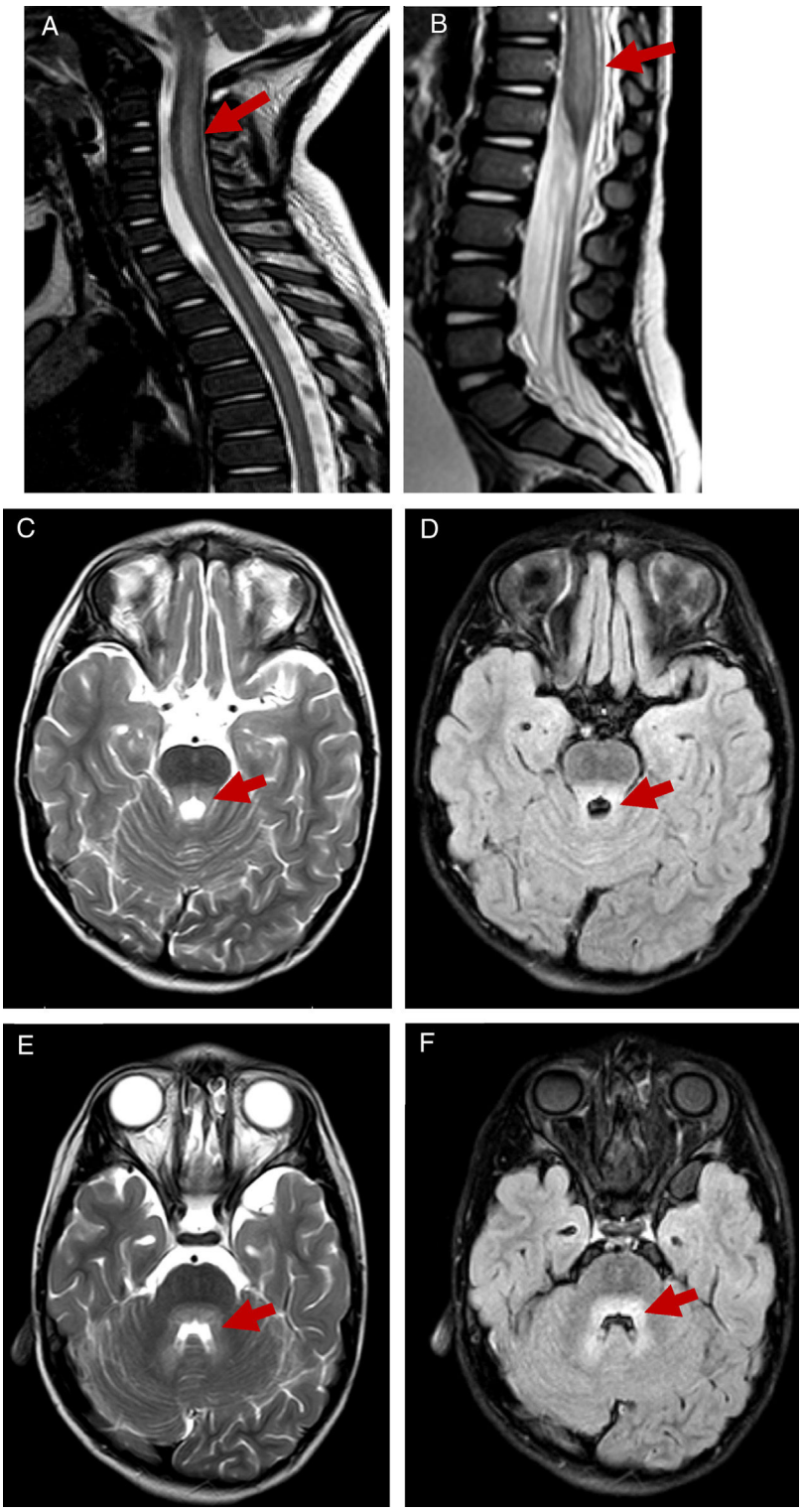

Figure 1 T2-weighted and FLAIR MR images showing hindbrain involvement with myelitis. T2-weighed images showing hyperintensity on at the level of the cervical spine until segment C6 in patient 2 (A) and significant thickening of the conus medullaris in patient 4 (B). Hyperintensity on T2-weighted and FLAIR MR images at the level of the posterior pons and surrounding the fourth ventricle in patient 2 (C–F).

In conclusion, we present a group of cases of EV infection with neurologic involvement linked in time, in which the most frequent type of involvement was rhombencephalitis. The clinical presentation was similar to the one described in other studies.[1–3] The serotype detected most frequently was A71. As happened in the outbreak in Catalonia, while the initial presentation of some of the patients was severe, none died and all had favourable outcomes with no sequelae,[1] which was not the case in other countries.[2,3,6]

Table 1 Summary of clinical characteristics, diagnostic tests, treatment and outcomes for each patient.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age (months)	25	49	26	22	29	32	25	48	14	11	26
Sex	Female	Male	Male	Female	Male	Male	Female	Female	Female	Female	Male
Systemic manifestations											
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Irritability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin and mucosal involvement	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hand-foot-mouth-like rash	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes
Enanthem	No	No	Yes	Yes	No	No	No	No	No	No	No
Neurologic manifestations											
Onset (days from onset of systemic symptoms)	7	3	2	2	3	4	5	3	1	2	3
Somnolence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Ataxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Leve
Myoclonus	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
Tremors	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Convulsive seizures	No	No	No	No	No	No	No	No	No	No	No
Flaccid paralysis	Yes	No	No	No	No	No	No	No	No	Initial suspicion	No
Involvement of cranial nerves III-XII	Yes	Yes	No	No	No	No	No	No	No	No	No
Dysautonomia											
Altered breathing pattern	Yes	Yes	No	No	No	No	No	No	No	Yes	No
Neurogenic pulmonary oedema	Yes	Yes	No	No	No	No	No	No	No	No	No
Cardiac dysfunction	Yes	Yes	No	No	No	No	No	No	No	No	No
High blood pressure	No	No	Yes	No	No	No	No	No	No	No	No
Brain and spine MRI	Involvement of hindbrain and spinal cord	Involvement of brainstem, medulla and cervical spinal cord	Cervical transverse myelitis	Involvement of cervical spine and conus medullaris	Involvement of dentate nucleus and spinal cord through segment D1	Possible but unclear hyperintensity at the level of the C3–C6 segments and periaqueductal white matter	Lesions in left thalamus and cerebral peduncles and cervical myelitis	Hyperintensity in cerebral peduncles, periaqueductal brain matter and cervical spine through segment C6	Tracer uptake in the cervical and dorsal spine and conus medullaris	Mild hyperintensity in dentate nucleus	Not performed
Enterovirus serotype	Nontypeable	A	A 71	A 71	A 71	A 71	B	–	Echo 32	Nontypeable	A 71
Treatment											
Days from onset of symptoms	8	5	4	3	4	6	7	7	3	4	No treatment
IVIG	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Corticoids	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Fluoxetine	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No
Outcome											
PICU stay (days)	Yes (12)	Yes (11)	Yes (2)	No	No	No	No	No	No	Yes (2)	No
Mechanical ventilation (days)	Yes (7)	Yes (7)	No	No	No	No	No	No	No	Yes (2)	No
Length of stay (days)	26	25	8	5	5	9	7	6	5	10	5
Early sequelae	Altered sleep and irritability	Tremors and irritability	No	No	No	No	No	No	No	No	No

CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; PICU, paediatric intensive care unit.

Given the potential severity of neurologic involvement in enterovirus infection and that an outbreak of this magnitude had not been described in Spain until 2016, we believe that reporting the cases occurred in our country is relevant. This could help identify similar cases earlier, improving the initial management (especially supportive care) of an infection that can lead to death in the first 24 h from the onset of neurologic symptoms.

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Self-monitoring treatment programme with oral vitamin K antagonists in paediatric patients☆

Programa de autocontrol del tratamiento anticoagulante oral con antagonistas de la vitamina K en pacientes pediátricos

To the Editor:

The increased survival of congenital heart diseases has led to an increase in the long-term use of oral anticoagulants (OACs) in children.[1] The most frequently used type are vitamin K antagonists, which are characterised by their narrow therapeutic margin and the need for frequent monitoring of the international normalised ratio (INR). Their management in children is complicated by problems inherent in this age group, such as inconsistent nutritional intake or infectious diseases.[1,2]

Treatment quality is assessed based on the time in therapeutic range (TTR), the percentage of time that the patient maintains an INR within the target range. While values of less than 60% are considered ineffective, greater values are associated with a decreased risk of bleeding episodes and thrombotic events.[1,3]

There is evidence that OAC self-management programmes achieve increases in TTR in children.[1,4,5] We present the first paediatric case series analysed in Spain to assess the impact of the introduction of an AOC therapy self-monitoring programme.

We conducted a retrospective cohort study between January 2015 and May 2017 in patients aged 1 to 17 years. Our aim was to compare the TTRs after the introduction of a self-monitoring programme with the TTRs achieved in the previous year.

We collected data for demographic variables, age, indication for OACs, target therapeutic range, INR values, frequency of monitoring, date of initiation of self-monitoring, incidence of thrombotic events or bleeding episodes and reasons for variations of INR above 5 or below 1.4.

After they agreed to participate in the study, children and their caregivers received training on the use of the following: CoaguChek® XS portable system (Roche Diagnostics), tables to guide self-dosing of AOCs, and an online platform (TAONet®) and a mobile application (TAONet® Me) to report results to health care providers in real time.

The TTR was estimated using the Rosendaal linear interpolation method, which reduces the impact of multiple INR values over a short period of time. Applying the methodology used in other studies, we calculated the TTR based on the exact target INR with the addition of a 0.2 unit margin on either side, as the dose is usually not adjusted when the INR remains within these values.[1,3] We assessed association by means of the Student's *t* test for paired samples after verifying that the data followed a normal distribution.

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