Outcome of paediatric acute flaccid myelitis associated with enterovirus D68: a case series

AMIR KIROLOS | KATE MARK | JAY SHETTY | NANDITA CHINCHANKAR | CATHERINE MCDougall | PAUL EUNSON | JANET STEVENSON | KATE TEMPLETON | NHS LOTHIAN EV-D68 ASSOCIATED AFM STUDY GROUP*

1 Directorate of Public Health and Health Policy, National Health Service, Lothian, Edinburgh; 2 National Health Service, Lothian, The Royal Hospital for Sick Children, Edinburgh; 3 Department of Child Life and Health, University of Edinburgh, Edinburgh; 4 Department of Virology, National Health Service, Lothian, Royal Infirmary Edinburgh, Edinburgh, UK.

Correspondence to Jay Shetty, Royal Hospital for Sick Children – Paediatric Neurosciences, Edinburgh EH9 1LF, UK. E-mail: jay.shetty@ed.ac.uk

*See Appendix S1 (online supporting information) for names and affiliations of the NHS Lothian EV-D68 Associated AFM Study Group.

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Enterovirus D68 (EV-D68) is an emerging infection associated with acute flaccid myelitis (AFM). Cases of AFM associated with EV-D68 infection have increased in recent years and the evidence for a causal link is growing. However, our understanding of the epidemiology, clinical features, prognosis, and neurological sequelae of EV-D68 requires ongoing surveillance and investigation. We report five cases of AFM in previously typically developing children (2–6y) from South East Scotland during September and October 2016 after infection with EV-D68 (all detected in the nasopharyngeal aspirates). All cases presented with significant neurological symptoms, which were severe in two cases requiring intensive care support because of respiratory paralysis. At 18-month follow-up, two cases remain ventilator-dependent with other cases requiring ongoing community rehabilitation. These cases represent one of the largest reported paediatric cluster of AFM associated with EV-D68 in Europe. The epidemiology and clinical information add to the knowledge base and the 18-month outcome will help clinicians to counsel families.

METHOD

After one case of AFM associated with EV-D68 infection presented to the Royal Hospital for Sick Children Edinburgh on September 10th, 2016, a multidisciplinary incident management team was convened to investigate and set up monitoring for further possible cases. A clinical alert was sent to paediatric services throughout Scotland to be aware of potential cases of AFM associated with EV-D68 infection and to report all possible cases to the incident management team.

Possible case

Person presenting with AFM in Scotland from September 10th, 2016 without other identified cause.
Confirmed case

Person presenting with AFM in Scotland from September 10th, 2016 with laboratory confirmed EV-D68.

Parents of cases were interviewed using a trawling questionnaire (Appendix S2, online supporting information) based on recall and covered exposures within 4 weeks before onset of symptoms. All confirmed cases were managed by paediatric neurology and intensive care specialists at the Royal Hospital for Sick Children, Edinburgh.

Clinical investigations included brain and spine magnetic resonance imaging (MRI), electrophysiological studies, cerebrospinal fluid analysis, and virology testing (stool samples, throat swabs and nasopharyngeal aspirates [NPA] for a panel of viruses including EV-D6) using real time polymerase chain reaction. Stool specimens were all tested for the presence of polio virus. Fairly extensive neuroinflammatory investigations were carried out in the first two cases and not done in subsequent cases as the diagnosis became more apparent.

All children were regularly followed up by paediatric neurology, respiratory, physiotherapy, occupational therapy, speech and language therapy, psychology, and dietetic teams over the following 18 months. Data on this follow-up period were extracted from clinical records.

Parents gave written consent for the use of anonymized data for investigation and dissemination. NHS Lothian Caldicott Guardian’s approval was obtained for data storage and dissemination.

RESULTS
Clinical presentation and epidemiology

All confirmed cases were residents within the South East Scotland region. Figure 1 displays the chronology of onset of prodromal and neurological symptoms for this cluster. From the questionnaires, there were no common sources (food, environmental exposures, recent travel, and previous direct contact with each other) identified. All children had received age-appropriate vaccinations, including inactivated polio vaccine. Their prodromal illness, clinical presentation, neurological weakness, investigations, treatment, and progress have been detailed in Table I. All presented with asymmetric flaccid weakness of varying severity, severe pain, three with bulbar involvement, and the two severely affected cases required intubation and respiratory support.

Investigations

All confirmed cases had EV-D68 detected from NPA samples after their admission. Two tested positive for EV-D68 on throat swab. However, in one case repeated throat swabs were negative and only confirmed on NPA. Viral typing confirmed EV-D68 B3 lineage. Faecal testing for polio was negative in all cases.

All children had a brain and spinal MRI and demonstrated an abnormal high T2 signal in the spinal cord grey matter (Fig. 2). Three of these cases showed high T2 signal particularly in the cervical spinal cord, with one case having entire cord involvement. Four of the children also showed signal abnormality in the dorsal pons and medulla. Cerebrospinal fluid results showed an elevated white cell count with a predominantly lymphocytic picture, negative for EV-D68 and negative for other viruses or bacteria.

Treatment

One case did not receive any treatment other than supportive care and made excellent recovery. No significant improvement in clinical symptoms were observed after use

![Figure 1: Timeline of symptom onset or confirmed cases of acute flaccid myelitis associated with enterovirus D68 infection. (Colour figure can be viewed at wileyonlinelibrary.com).](image-url)
Table 1: Characteristics of confirmed cases of EV-D68 with associated acute flaccid myelitis and clinical features at 18mo follow-up

| Clinical details | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|------------------|--------|--------|--------|--------|--------|
| Age at onset, y  | 2      | 5      | 4      | 6      | 2      |
| Sex              | Male   | Male   | Female | Female | Male   |
| Medical history  | Mild asthma | None | None | None | CMPi |
| Prodromal symptoms | Fever, earache, reduced appetite (5) | Fever, headache, malaise, pyrexia (4) | Fever, headache, vomiting (2) | Yes | Fever, coryza (7) |
| Asymmetric severe flaccid limb weakness | Yes | Yes | Yes | Yes | Yes |
| Limb weakness | UL>LL | LL>UL | UL>LL | UL>LL | LL>UL |
| Cranial nerve involvement | Yes | No | Yes | Yes | No |
| Bulbar symptoms | Yes | No | Yes | Yes | Yes |
| Reduced or absent reflexes | Yes | Yes | Yes | Yes | Yes |
| Autonomic symptoms | Yes | No | Yes | Yes | No |
| Severe pain | Yes | Yes | Yes | Yes | Yes |
| MRI cord abnormality (location) | Yes (C2-C7) | Yes (C2-C7) | Yes (movement artefact) | Yes (C2-C7) | Yes (entire cord, maximum T1–T2) |
| MRI abnormality of pons and medulla | Yes | No | No | Yes | Yes |
| EV-D68 polymerase chain reaction detection | NPA (+) Throat swab (–) CSF (–) Stool (–) | NPA (+) Throat swab (–) CSF (–) Stool (–) | NPA (+) Throat swab (–) CSF (–) Stool (–) | NPA (+) Throat swab (–) CSF (–) Stool (–) | NPA (+) Throat swab (–) CSF (–) Stool (–) |
| Electromyography (left biceps) | Increased insertional activity, frequent fibrillations, no voluntary activity | Not performed | Not performed | Increased insertional activity, widespread fibrillations. Two discrete complex repetitive discharges. No spontaneous activity | Not performed |
| Nerve conduction studies | Normal sensory Reduced CMAP | Not performed | Not performed | Normal sensory Early CMAP | Not performed |
| Treatment | None IVIG, Steroids | IVIG | IVIG | IVIG, steroids | No |
| Respiratory support | Yes (long-term invasive ventilation) | No | No | Yes (long-term invasive ventilation) | No |
| Intensive care support | Prolonged | No | No | Prolonged | Short term |
| Hospital stay (d) | 376 | 67 | 125 | 278 | 62 |
| At 18mo follow-up | | | | | |
| Mobility | | | | | |
| Speech | Walking short distances | Normal | Normal | Almost normal mobility | Walking short distances |
| Swallow | Normal | Normal | Normal | Almost normal | Almost normal |
| Weakness | Significant proximal upper limb (asymmetric) with muscle wasting | Significant lower limb proximal weakness (asymmetric) | Mild distal unilateral lower limb weakness affecting gait (asymmetric) | Yes | Significant proximal upper limb (asymmetric) with muscle wasting |
| Shoulder dislocation | Yes | No | No | Yes | Yes |
| Scoliosis | Yes | Yes | Yes | Yes | Yes |
| Head tilt | Yes | No | No | Yes | Yes |
| Breathing | Tracheostomy and ventilatory support during sleep | Normal | Normal | Tracheostomy and ventilatory support during sleep | Normal |

CMAP, compound muscle action potential; CMPi, cow’s milk protein intolerance; CSF, cerebrospinal fluid; EV-D68, enterovirus D68; IVIG, intravenous immunoglobulin; LL, lower limb; MRI, magnetic resonance imaging; NPA, nasopharyngeal aspirate; UL, upper limb.
Treatment with antihypertensives was commenced in the two most severely affected cases to control hypertension. All five children required significant input from a multidisciplinary therapy team to manage limb and truncal weakness. Gabapentin was used to control pain with good effect. Clinical psychologists were involved in supporting the children and their families.

**Clinical outcome at 18 months**

Clinical progress at 18 months post admission is summarized in Table I. Recovery for affected cases was most significant in the first 12 months; however, they continued to show improvement even beyond this time. One child had recovered almost fully with only mild lower limb weakness and a mild gait abnormality persisting. Two of the most severely affected required long-term home ventilation and were able to manage short periods without ventilation during the day while awake. Both children can feed orally with varying degrees of improvement in bulbar function. The autonomic dysfunction suffered during the early part of their admission resolved fully and antihypertensive therapy stopped. Limb pain lasted 6 months.

Persisting limb weakness and loss of function was predominantly in the lower limbs for two children and in the upper limbs for three children. Despite improvements, there has been persisting proximal limb weakness with muscle wasting in one or more proximal limbs in all cases apart from one. These four cases have been referred for evaluation for nerve transfer. We could not reliably use any standardized functional scoring system because of their unique pattern of weakness and adaptation. Unlike other motor disorders there seems to be persisting regeneration in some muscle groups.

**DISCUSSION**

The confirmed cases in this cluster were linked in time, place, and person and presented to hospital with significant neurological symptoms within a 2-week period. No clear hypothesis for a common environmental exposure was identified in this cluster based on recall of parents or guardians. After the presentation of this cluster we retrospectively retested all throat swabs and NPAs for EV-D68 which had previously tested positive for enterovirus. This retrospective testing found 59 samples between July and October 2016 were positive for EV-D68. These were in a select population of those presenting to hospital, mostly children with respiratory symptoms; however, these positive samples indicate wider circulation of EV-D68 in South East Scotland during this time. The baseline clinical data of those children reported to have EV-D68 without AFM did not identify any potential risk factors for AFM apart from the fact that the AFM cohort were much younger.

The age of presentation, pattern of limb weakness, bulbar involvement, cerebrospinal fluid results, MRI findings, and nerve conduction studies are like other reported case series.8–11,13 Two cases with autonomic involvement with severe hypertension and evidence of end organ damage during acute presentation had not been reported before. There was no association between steroid treatment and subsequent hypertension. One case developed worsening respiratory function after the use of general anaesthetic during lumbar puncture. It is not possible to determine whether this was exacerbated by use of anaesthesia, but we advise caution with use of general anaesthetic for suspected cases in future. We wanted to carry out follow-up MRI studies and we delayed this to avoid general anaesthesia. NPA was found to be the investigation which most consistently identified EV-D68 infection even when the throat swab was negative.
Different treatments (intravenous immunoglobulin, steroids, etc.) have been used in acute settings and the benefits of these treatments are not well understood. Although the numbers are small, one case in our cohort made almost full recovery without any treatment. Further studies are needed to establish the benefits of these treatments.

Long-term outcome is variable and in our cohort all children can walk, talk, and feed with varying degrees of persistent neurological deficits at 18-month follow-up. Permanent proximal limb weakness with muscle wasting was present in four cases with varying severity. There seems to be continued improvement even at 18 months and rehabilitation in community settings with psychological support should be provided for future affected cases.

Recent developments have shown that infection with EV-D68 can cause AFM in murine models and the virus has been isolated from the spinal cord of infected mice. The short duration of prodromal illnesses before onset of acute neurology favours pathogenesis through direct destruction of the nerve by the virus. Direct or indirect association of viruses with neuro-inflammation disorders (N-methyl-D-aspartate, multiple sclerosis, Guillain-Barre syndrome, etc.) are rare but have been increasingly recognized. It is important to try to understand the susceptibility in those affected. This is a case series and hence there are limitations. There is an urgent need for a coordinated, cooperative, international approach to monitoring this emerging infection globally, particularly as cases of AFM associated with EV-D68 infection emerge in other regions out with North America and Europe.

CONCLUSIONS

Cases of AFM associated with EV-D68 present with short prodromal illness, asymmetric limb weakness, bulbar involvement, severe pain, and some autonomic involvement in previously typically developing children, confirmed by MRI and EV-68 viral isolation. This condition has a devastating effect on the physical and mental health of the child and family, and there is a lack of any prevention or treatment for complications. There are significant resource implications for health care services; not only in the provision of intensive care but also for long-term home ventilation and community rehabilitation. Further research should be targeted at the prevention of infection as well as understanding and preventing serious sequelae of AFM aiming to minimize complications. To achieve these goals, a global coordinated response from researchers, clinicians, virologists, and public health officials is required to understand and ultimately prevent this infection and its potential severe neurological sequelae. It is imperative that we act now as outbreaks of EV-D68 and reports of cases of AFM associated with infection become more common.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: NHS Lothian EV-D68 associated AFM study group.

Appendix S2: Parent interview trawling questionnaire.

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El enterovirus D68 (EV-D68) es una infección emergente asociada con mielitis flácida aguda (MFA). Los casos de MFA asociados con la infección por EV-D68 han aumentado en los últimos años y la evidencia de un vínculo causal está creciendo. Sin embargo, nuestra comprensión de la epidemiología, las características clínicas, el pronóstico y las secuelas neurológicas del EV-D68 requiere una vigilancia e investigación continuas. Presentamos cinco casos de MFA en niños con desarrollo típico (2 a 6 años) del sureste de Escocia durante septiembre y octubre de 2016 después de la infección con EV-D68 (todos detectados en los aspirados nasofaringeos). Todos los casos presentaron síntomas neurológicos significativos, que fueron graves en dos casos que requirieron apoyo de cuidados intensivos debido a la parálisis respiratoria. A los 18 meses de seguimiento, dos casos siguen siendo dependientes del ventilador, mientras que otros casos requieren una rehabilitación continua de la comunidad. Estos casos representan uno de los grupos pediátricos más grandes de MFA asociados con EV-D68 en Europa. La epidemiología y la información clínica se suman a la base de conocimientos y el resultado de 18 meses ayudará a los clínicos a asesorar a las familias.