

**For Clinicians:
Diagnosing Acute Flaccid Myelitis (AFM)
in the United States**

Last updated November 30, 2015

Slide 1 notes

This presentation provides background information on acute flaccid myelitis in the United States. Slides include information about the clinical presentation, investigation of cases that occurred in the US during 2014, and envisioned activities moving forward, including detailed instructions on how clinicians can help with ongoing surveillance efforts.

This presentation is intended to give an overview of AFM, summarize the investigation in the United States in 2014, and emphasize the importance of identifying and reporting cases of AFM.

The primary audience for this presentation is clinicians.

ACUTE FLACCID PARALYSIS AND ACUTE FLACCID MYELITIS

Acute Flaccid Paralysis (AFP)

- AFP is an “umbrella” term used to characterize syndrome
- AFP covers a number of clinical entities:
 - Myelitis
 - Peripheral neuropathy
 - Myopathy
 - Others...
- The lesion may be anywhere along the neuraxis from lower motor neuron onward.

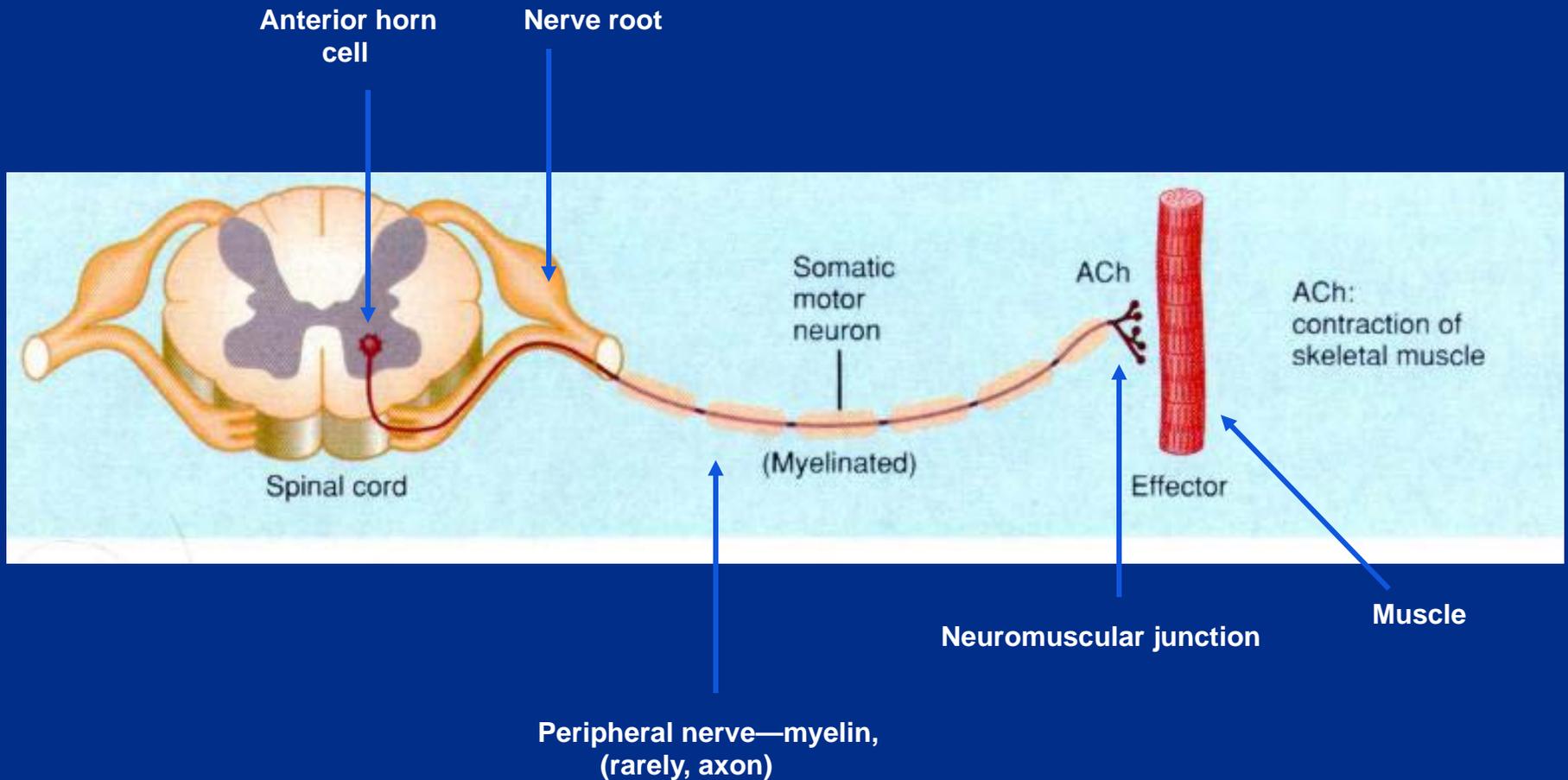
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Acute flaccid paralysis is an umbrella term used to describe a syndrome characterized by the acute onset of weakness of the limbs, as well as sometimes trunk or facial muscles. As the name suggests, the affected limbs are flaccid in tone, and deep-tendon reflexes are generally decreased or absent.

AFP covers many clinical entities including myelitis, peripheral neuropathy, myopathy, Guillain-Barré syndrome (GBS), toxic neuropathy, and muscle disorders.

Patients presenting with AFP have lesions that can appear anywhere along the axis of the central nervous system from the lower motor neuron (anterior horn cell), out to the nerve root, peripheral motor nerve, the neuromuscular junction, or the muscle itself.

Areas of the Spinal Cord Affected by AFP



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This is a diagram illustrating the locations of lesions that can result in AFP, starting with the lower motor neuron (anterior horn cell) within the gray matter of the spinal cord (the part containing nerve cells), the nerve roots, the peripheral motor nerve, the neuromuscular junction, and then finally the muscle itself. Disease processes that affect one or more of these structures can result in AFP.

Acute Flaccid Myelitis (AFM)

- AFM is characterized by a sudden onset of weakness in one or more arms or legs.
- AFM is the term used to describe the cases that were occurring during summer/fall 2014 in the United States
 - Several cases of AFM initially described in California in 2012
- Specifically involves gray matter (neurons) of the spinal cord
- It is identical in clinical presentation to the illness caused by poliovirus
- AFM is most commonly associated with poliovirus, but may be caused by numerous other viral pathogens:
 - non-polio enteroviruses,
 - flaviviruses (West Nile virus, Japanese encephalitis virus),
 - herpesviruses,
 - adenoviruses

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Since the ongoing successes at eliminating wild-type polio from most of the world, this syndrome has become exceedingly rare. GBS is now the leading cause of AFP worldwide. Because 'poliomyelitis' connotes infection with poliovirus and none of the specimens from recent cases with this 'polio-like' illness tested positive for poliovirus,, we decided to use the term 'acute flaccid myelitis', or AFM, to describe the cases that we were seeing in the summer / fall of 2014.

Several cases of AFM were described in California in 2012 in the course of their ongoing encephalitis surveillance, and each year, several cases of AFM will be recognized. However, during the summer / fall of 2014, the United States witnessed a large number of AFM cases involving many states, distinctly clustered in space and time. Initially noted in Colorado, ongoing national surveillance indicated that cases were occurring throughout the country.

AFM specifically involves the gray matter, or motor neurons, of the spinal cord.

AFM is identical in clinical presentation to the illness caused by poliovirus and affects the same region of the spinal cord

AFM is also most commonly associated with poliovirus but there may be other causes from different viral pathogens including: non-polio enteroviruses (for example enterovirus (EV) 71), flaviviruses like West Nile virus or Japanese encephalitis virus, herpesviruses, and adenoviruses.

AFM CASES IN THE UNITED STATES

Emergence of AFM in the United States, 2014

- **On September 12, 2014 CDC was notified of 9 children with:**
 - Focal extremity weakness, cranial nerve dysfunction or both
 - MRI: multi-level gray matter lesions of the spinal cord, brainstem, or ventral nerve roots
- Radiology, neurology, infectious disease, pediatric teams had very rarely encountered similar cases in the past
- A large number of cases of respiratory illness due to EV-D68 were happening at the same time
- CDC assisted with case investigations, along with local clinicians and the Colorado Department of Public Health and Environment

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AFM first came to CDC's attention in 2014 when CDC was notified on September 12, 2014 of 9 children presenting with:

Focal extremity weakness, cranial nerve dysfunction or both AND

An MRI with gray matter lesions involving multiple segments of the spinal cord, brainstem, or ventral nerve roots

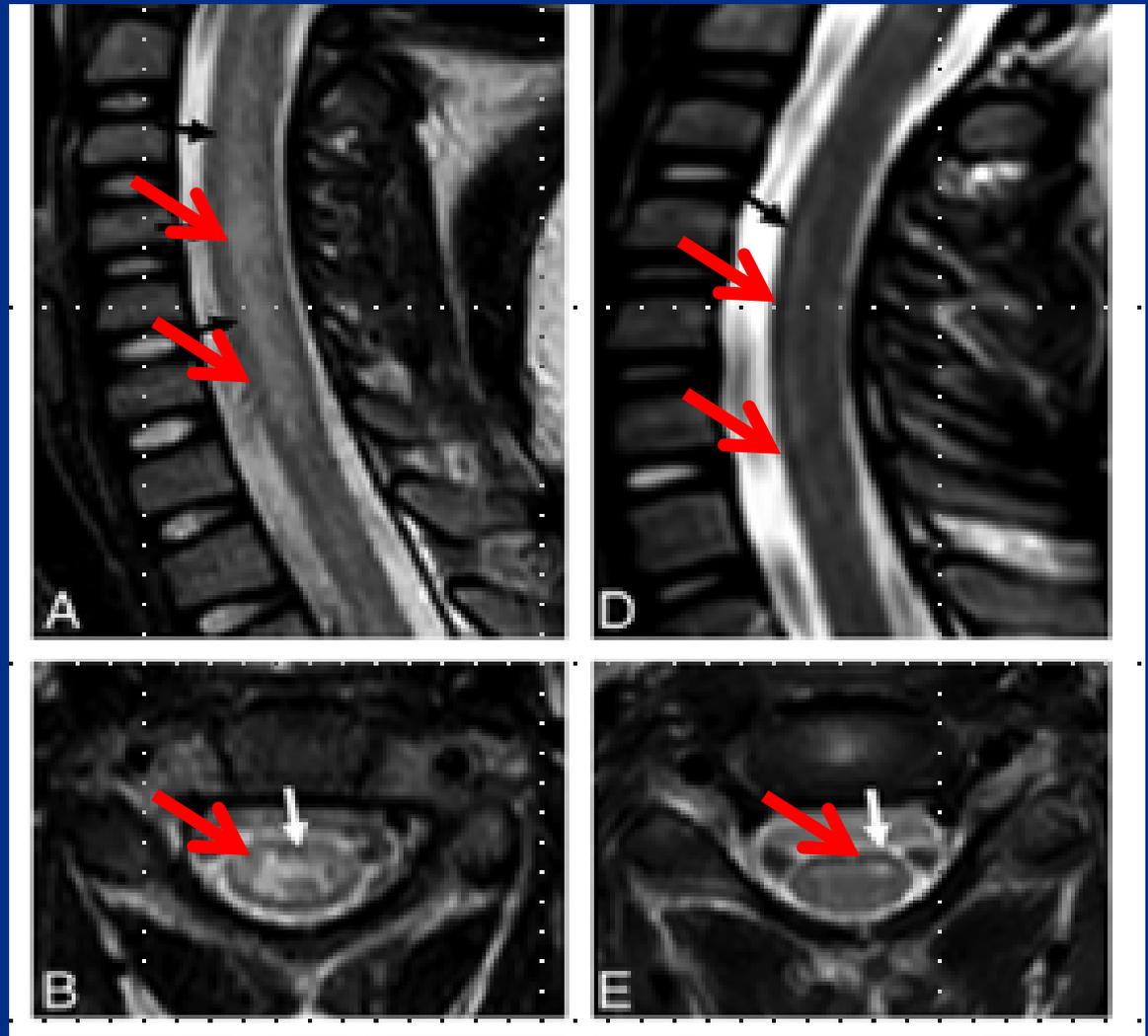
Specialist treating these patients had stated that they had very rarely encountered similar cases in the past

A large number of cases of respiratory illness due to EV-D68 were happening at the same time

Because of the severity of the clinical presentation of the early cases, and presumed rarity of this syndrome, CDC was invited to assist with case investigations along with local clinicians and the Colorado Department of Public Health and Environment.

Figure 1: Characteristic MRI Findings

A, B. Sagittal and axial images demonstrating hyperintensity of the entire central gray matter of the thoracic spinal cord; on axial imaging, demonstrating characteristic 'H' shape pattern.



D, E. Sagittal and axial images demonstrating T2 hyperintensity confined to the left anterior horn cells (best demonstrated in E).

*From Maloney JA et al. Am J Neuroradiol 2015;36(2):245-50

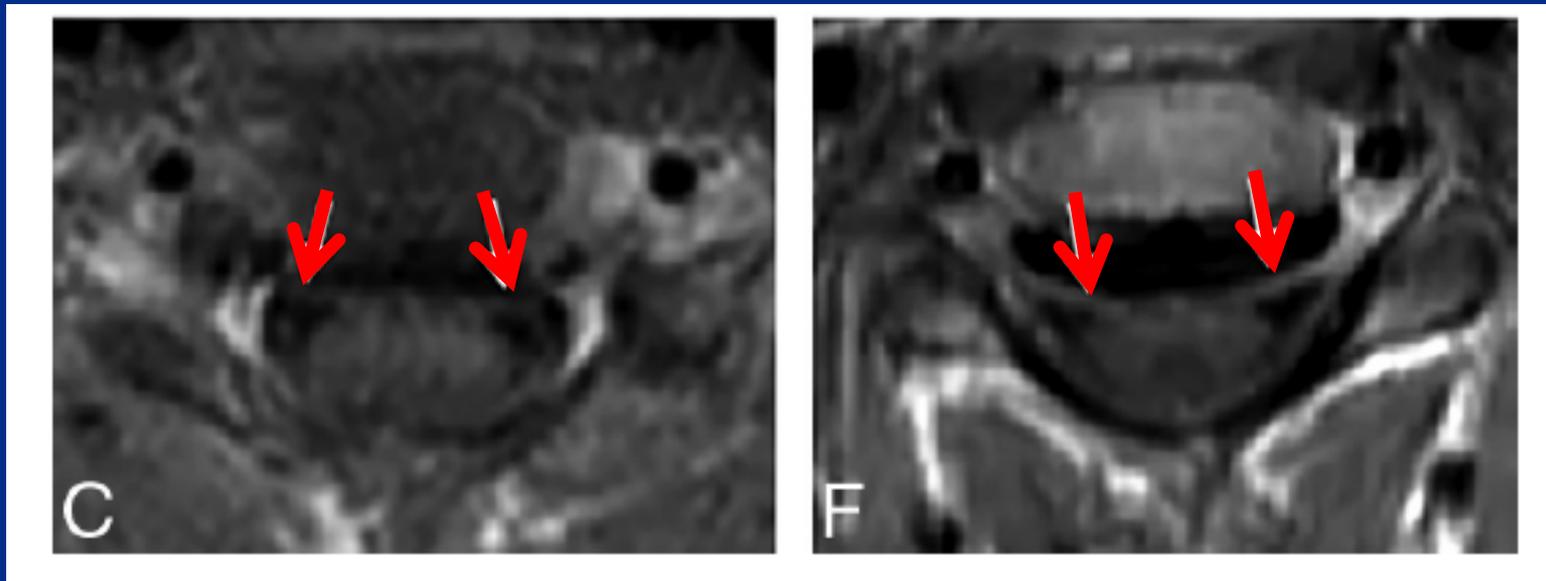
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These MRI images provide examples of the characteristic MRI findings among cases presenting with AFM in Colorado during August – October 2014.

Panels A and B present sagittal and axial images to demonstrate the hyperintensity of the entire central gray matter of the thoracic spinal cord (as indicated by the arrows in panel A) and the characteristic “H” shape pattern often seen (indicated by the red arrow in panel B).

Panels D and E present the sagittal and axial images demonstrating T2 hyperintensity that is confined to the left anterior horn cells. This is best demonstrated in panel E, indicated by the red arrow.

Figure 2: Characteristic MRI Findings



- C. Axial image of thoracic spinal cord demonstrating absence of nerve root enhancement
- F. Axial image of thoracic spinal cord with enhancement of nerve roots

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These MRI findings present additional examples (taken from some of the cases in Colorado) of the characteristic MRI findings among cases with AFM.

Panel C demonstrates axial images of the thoracic spinal cord where nerve root enhancement is absent (indicated by the red arrows).

In contrast, panel F illustrates the axial image of the thoracic spinal cord with enhancement of the nerve roots (indicated by the red arrows)

MRI Findings in Children with Acute Flaccid Paralysis and Cranial Nerve Dysfunction Occurring during the 2014 Enterovirus D68 Outbreak

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ABSTRACT

BACKGROUND AND PURPOSE: Enterovirus D68 was responsible for widespread outbreaks of respiratory illness throughout the United States in August and September 2014. During this time, several patients presented to our institution with acute flaccid paralysis and cranial nerve dysfunction. The purpose of this report is to describe the unique imaging findings of this neurologic syndrome occurring during an enterovirus D68 outbreak.

MATERIALS AND METHODS: Patients meeting a specific case definition of acute flaccid paralysis and/or cranial nerve dysfunction and presenting to our institution during the study period were included. All patients underwent routine MR imaging of the brain and/or spinal cord, including multiplanar T1, T2, and contrast-enhanced T1-weighted imaging.

RESULTS: Eleven patients met the inclusion criteria and underwent MR imaging of the brain and/or spinal cord. Nine patients presented with brain stem lesions, most commonly involving the pontine tegmentum, with bilateral facial nerve enhancement in 1 patient. Ten patients had longitudinally extensive spinal cord lesions; those imaged acutely demonstrated involvement of the entire central gray matter, and those imaged subacutely showed lesions restricted to the anterior horn cells. Ventral cauda equina nerve roots enhanced in 4 patients, and ventral cervical nerve roots enhanced in 3, both only in the subacute setting.

CONCLUSIONS: Patients presenting with acute flaccid paralysis and/or cranial nerve dysfunction during the recent enterovirus D68 outbreak demonstrate unique imaging findings characterized by brain stem and gray matter spinal cord lesions, similar to the neuroimaging findings described in previous outbreaks of viral myelitis such as enterovirus 71 and poliomyelitis.

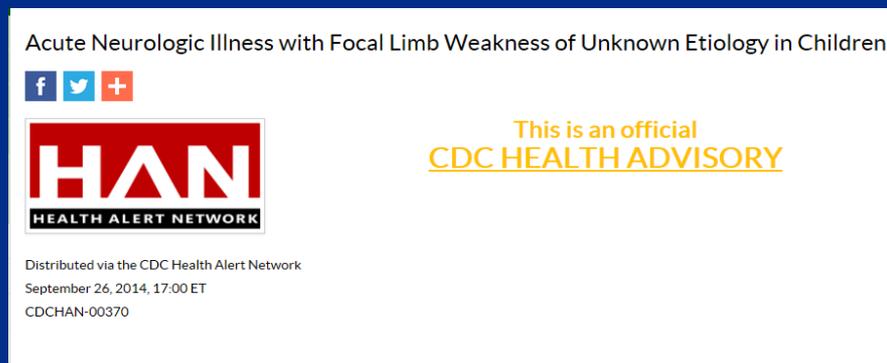
ABBREVIATIONS: AFP = acute flaccid paralysis; EV-D68 = enterovirus D68; EV-71 = enterovirus 71

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A manuscript describing the MRI findings among the children with AFM in Colorado during 2014 was published in November 2014.

Was Colorado the only state experiencing cases of AFM?

- On September 26, 2014, CDC sent out a national call for cases of AFM to determine extent of problem



- **Case definition proposed for national reporting:**
 - Acute onset focal limb weakness, AND
 - Predominant gray matter lesions on spinal MRI,
 - Persons \leq 1 years of age,
 - Occurring on or after August 1, 2014

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Colorado was the first state to identify a cluster of cases of AFM. But was this occurring in other states?

To determine the extent of the problem, CDC released an official Health Advisory through the Health Alert Network on September 26, 2014 requesting that states with patients meeting the case definition for AFM report them to CDC.

The case definition proposed for national reporting included the following: A patient with acute onset of focal limb weakness AND predominant gray matter lesions on spinal MRI, in a person 21 years of age or younger, occurring on or after August 1, 2014

How AFM Cases Are Reported and Confirmed

- State health departments report suspected cases using standardized CDC forms
- Cases are confirmed by a CDC neurologist
- Different types of specimens are submitted to CDC for testing to try and identify etiology:
 - CSF (cerebrospinal fluid)
 - Serum/plasma/whole blood
 - NP (nasopharygeal) swab/aspirate/wash
 - Stool

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During the national investigation of AFM in the United States, which started August 1, 2014 and continues through the present:

State health departments report suspected cases of AFM to CDC using a standardized form developed by CDC.

When case reports are received at CDC, one of 2 CDC neurologists determines whether the patient meets the case definition.

Several different types of specimens are requested and submitted to CDC for testing to try and identify an etiology for AFM. The specimens requested and submitted include: cerebrospinal fluid (CSF), nasopharyngeal (NP) swabs, aspirates, or wash, serum, plasma, or whole blood, and stool (to rule out polio).

SUMMARY OF 2014 AFM CASE INVESTIGATION

Summary of Findings - Epidemiology

- **From August 2014- June 2015**
 - 120 confirmed cases
 - 118/119 (99.2%) hospitalized
 - 34 states

- **Demographic characteristics**
 - Age: median 7.2 years (range 5 months - 20 years)
 - Sex: Male: 72 (60%); Female: 48 (40%)

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The next several slides present a summary of the findings from the CDC investigation from August 2014 through June 2015.

A total of 120 confirmed cases were reported from 34 states. Almost all cases were hospitalized.

The median age of cases was 7.2 years with a range of 5 months to 20 years and cases were predominantly male.

Summary of Findings* – Clinical

- **Notable clinical characteristics on presentation:**
 - Antecedent respiratory or febrile illnesses: 92 (77%)
 - Number of limbs affected:
 - 29% had only one limb affected
 - 48% had asymmetric limb weakness
 - 24% had quadriplegia
 - Neurologic findings:
 - Any cranial nerve signs: 34 (28%)
 - Facial weakness, ophthalmoplogia, dysarthria / dysphagia, etc
 - Evidence of brain involvement uncommon
 - Altered mental status: 13 (12%)
 - Seizures: 5 (4%)
 - CSF pleocytosis (≥ 5 white blood cells/mm³): 89 (74%)

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Some of the notable clinical characteristics on presentation of illness included:

77% of cases had an antecedent respiratory and/or febrile illness

29% of cases had only one limb affected while an additional 47% had asymmetric limb weakness; 24% of patients had all limbs affected (quadriplegia)

Some of the neurologic findings of the cases included:

28% of cases had any cranial nerve signs (including such things as facial weakness, ophthalmoplegia, and dysarthria)

Evidence of supratentorial (brain) involvement were uncommon; 12% had altered mental status (e.g., lethargy, disorientation, behavioral changes), and 4% had seizures.

Importantly, 74% had CSF pleocytosis, which is defined as 5 or more white blood cells per cubic millimeter, an important indicator of CNS inflammation.

Notable MRI abnormalities among cases with AFM

- **Spinal cord lesions largely restricted to gray matter**
 - Ventral (anterior horn) cells most commonly involved
 - Some cases have entire central gray matter involved, producing characteristic “H” pattern on axial images
 - Ventral and dorsal nerve roots may demonstrate signal abnormality
 - Cord lesions often involve multiple vertebral levels, spanning multiple cervical/thoracic levels
 - Conus medullaris and cauda equina involvement frequently noted
- **Spinal cord lesions frequently characterized by hyperintensity on T2- and FLAIR weighted sequences and hypointensity on T1-weighted images**

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MRI abnormalities noted among the cases of AFM reported during 2014 include the following:

Spinal cord lesions largely restricted to gray matter

Ventral (anterior horn) cells most commonly involved

Some cases have entire central gray matter involved, producing characteristic “H” pattern on axial images

Ventral and dorsal nerve roots may demonstrate signal abnormality

Cord lesions often involve multiple vertebral levels, spanning multiple cervical/thoracic levels

Conus medullaris and cauda equina involvement frequently noted

Spinal cord lesions frequently characterized by hyperintensity on T2- and FLAIR weighted sequences and hypointensity on T1-weighted images

Notable MRI abnormalities among cases with AFM (cont'd)

- **Brainstem lesion involvement has been demonstrated**
 - Lesions involving cranial nerve nuclei in brainstem with pons frequently affected
- **Cauda equina involvement has been noted in some patients as well**
- **Gadolinium enhancement frequently noted**

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In some cases, lesions were also observed in the brainstem, specifically in the nuclei of various cranial nerves, which would correlate with the findings of cranial nerve dysfunction.

In some cases, there was prominent involvement of the cauda equina, the very end of the spinal cord, probably contributing to the profound leg weakness seen in some patients.

In those cases in which gadolinium was administered, enhancement was frequently observed, again a finding indicative of active inflammation.

Summary of Findings* - Laboratory Testing

- **All specimens tested by:**
 - Enterovirus (including poliovirus), EV-D68
 - Adenovirus PCR
 - Herpesviruses PCRs
 - Arbovirus serology
- **If negative for above pathogens:**
 - Pathogen Discovery (“pan-viral” assays, Next Generation Sequence)

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For laboratory testing, all specimens were tested using single-plex PCR assays for enteroviruses, including poliovirus, and EV-D68. We additionally did specific single-plex PCR assays for adenovirus, herpesviruses, as well as arbovirus serology.

Over time, since the yield on the specific testing for adenoviruses, herpesviruses, and arboviruses was low, we continued to do pan-enteroviral PCR as well as single-plex testing, but for the rest of the pathogens CDC's Pathogen Discovery laboratory was engaged where pan-viral assays, which screen for 12 different viral families simultaneously was performed; additionally, Next generation sequencing was performed on a subset of well-timed specimens.

Summary of Findings* - Laboratory Results

- EV-D68 identified in 10/55 (18%) respiratory specimens[^]
- EV-D68 not identified in any serum or stool specimens
- No arboviruses identified in any specimens
- Some serum specimens tested positive for other viruses but no single virus/virus family was consistently identified

[^] EV-D68 identified in 1/54 (2%) CSF specimens. CSF specimen was bloody so unable to determine whether virus present in blood or CSF.

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Results from the extensive laboratory testing conducted at CDC demonstrated:

EV-D68 was identified in 18% of respiratory specimens.

*However, only 1 CSF specimen out of 54 specimens tested identified EV-D68— of note, the CSF specimen was bloody so it was difficult to determine whether the virus was present in blood or CSF.

EV-D68 was not identified in any serum or stool specimens.

No arboviruses were identified in any specimens.

Although some serum specimens tested positive for other viruses, no single virus or virus family was consistently identified.

The Bottom Line. . .

- Cooperation from clinicians, including the child neurology community, in reporting cases was essential for this investigation and assistance is greatly appreciated
- Strong temporal association between EV-D68 respiratory outbreak and apparent increase in AFM cases
- Despite extensive testing:
 - 18% AFM cases with evidence of EV-D68 from non-sterile site*
- Temporal association, but no ‘smoking gun’

* >50 CSF specimens tested for EV-D68 by rRT-PCR; one positive (and this specimen questionable due to large # of red blood cells in CSF [contamination])

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Based on the results from the investigation through June 2015,

Cooperation from clinicians in reporting cases of AFM was essential for the investigation and your assistance is greatly appreciated.

A strong temporal association between the national EV-D68 respiratory outbreak and the apparent increase in AFM cases was noted.

But despite extensive laboratory testing, only 18% of AFM cases had evidence of EV-D68 from non-sterile sites.

And of the more than 50 cases with CSF specimens tested for EV-D68, only 1 positive was identified but there are caveats with those results because the specimen is questionable due to the large number of red blood cells in CSF. This specimen was likely contaminated so it is challenging interpreting the results.

So, although a temporal association was identified, there is no smoking gun.

HOW YOU CAN HELP

**BE VIGILANT FOR CASES OF AFM AND
REPORT SUSPECTED CASES TO YOUR
LOCAL/STATE HEALTH DEPARTMENT**

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As clinicians, how can you help with surveillance efforts?

Continue to be vigilant for cases of AFM and report suspected cases to your local or state health department.

Imaging for Suspected Cases of AFM

- **Imaging should be guided by clinical presentation**
 - Because often multiple levels of the spinal cord are involved, imaging entire spinal cord is reasonable if patient is able to tolerate procedure
 - In patients with cranial nerve deficits, high cuts of brainstem should be considered
 - Axial and sagittal images are most helpful in identifying lesions
 - Some cases may present with some white matter involvement but for AFM cases, lesions are predominantly in gray matter

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Here are some guidelines for imaging patients suspected of having AFM. Imaging should be guided by clinical presentation.

If the patient is able to tolerate imaging of the entire spinal cord, that would be a reasonable approach as often multiple levels of the spinal cord are involved.

High cuts of brainstem should be considered in patients with cranial nerve deficits.

Axial and sagittal images are most helpful in identifying lesions

For patients with AFM, lesions are predominantly in the gray matter although some cases may present with some white matter involvement.

Next Steps

■ Surveillance

- Case definition modified from that used during investigation to better determine occurrence of AFM and to add sensitivity
- National standardized case definition adopted June 2015*
 - Confirmed case of AFM – a patient who has acute onset of focal limb weakness, AND an MRI showing a spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments.
 - Probable case of AFM - a patient who has acute onset of focal limb weakness, AND cerebrospinal fluid (CSF) with pleocytosis (white blood cell count >5 cells/mm³).
- CDC is partnering with several select state/local health departments to initiate establishment of surveillance for AFM
 - Surveillance important for determining rate of AFM, early identification and monitoring potential increases in AFM, and identifying potential causes, risk factors, and preventive measures or therapies.

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Moving forward, we would like to move towards establishing surveillance for AFM.

As part of surveillance, the CDC, in collaboration with the Council of State and Territorial Epidemiologists modified the case definition that was used during the 2014 investigation to better determine the occurrence of AFM and add sensitivity.

In June 2015, the updated case definition was adopted to provide a national standardized case definition for use in surveillance moving forward. This updated case definition has 2 categories for cases: confirmed and probable. A confirmed case is one with acute onset of focal limb weakness AND an MRI showing spinal cord lesion largely restricted to gray matter.

A probable case of AFM is a patient who has acute onset of focal limb weakness, AND has CSF pleocytosis

To help with surveillance efforts, CDC is partnering with several select state and local health departments to start establishing surveillance for AFM

Surveillance is important for determining baseline information of AFM, for early identification and monitoring potential increases in cases, identifying potential causes, risk factors, and possible preventive measures or therapies.

How to Report Suspected Cases of AFM

- **When a suspected case of AFM is identified:**
 - 1) Collect specimens for pathogen testing as early in course of illness as possible to increase chance of yielding etiology
 - Ideally on Day 1 of weakness and save specimens until determined if case definition met
 - Specimens to collect include: CSF, serum and/or whole blood, NP/OP swab, and stool for rule-out polio testing (www.cdc.gov/acute-flaccid-myelitis/hcp/instructions.html)
 - 2) Complete patient summary form – available at: www.cdc.gov/acute-flaccid-myelitis/hcp/data.html
 - 3) Send patient summary form to local/state health department who will then send form to CDC
 - 4) If case is meets case definition for AFM, send specimens to state health department for coordination of AFM testing at state and CDC

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The steps for reporting suspected cases of AFM are listed here. More details about how to submit specimens and case information are available on the CDC website listed here.

Your Role is Important

- **All clinicians involved in patient care of persons with AFM will be crucial to AFM surveillance activities**
 - General pediatricians, family physicians, nurse practitioners, infectious disease specialists, neurologists, radiologists, infection control practitioners, etc.
- **Opportunities for clinical community to assist in critically important public health response**
- **Opportunities for clinical community to assist in future important public health initiatives**

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This is a good opportunity for collaboration between the clinical community and public health.

All clinicians involved in the patient care of persons with AFM are critical to the success of AFM surveillance activities.

This collaboration can provide opportunities for the clinical community to assist with a critically important public health response and future important public health initiatives.

For additional information visit:

www.cdc.gov/acute-flaccid-myelitis

Contact CDC at: limbweakness@cdc.gov