Original Investigation

Acute Flaccid Myelitis of Unknown Etiology in California, 2012-2015

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IMPORTANCE There has been limited surveillance for acute flaccid paralysis in North America since the regional eradication of poliovirus. In 2012, the California Department of Public Health received several reports of acute flaccid paralysis cases of unknown etiology.

OBJECTIVE To quantify disease incidence and identify potential etiologies of acute flaccid paralysis cases with evidence of spinal motor neuron injury.

DESIGN, SETTING, AND PARTICIPANTS Case series of acute flaccid paralysis in patients with radiological or neurophysiological findings suggestive of spinal motor neuron involvement reported to the California Department of Public Health with symptom onset between June 2012 and July 2015. Patients meeting diagnostic criteria for other acute flaccid paralysis etiologies were excluded. Cerebrospinal fluid, serum samples, nasopharyngeal swab specimens, and stool specimens were submitted to the state laboratory for infectious agent testing.

MAIN OUTCOMES AND MEASURES Case incidence and infectious agent association.

RESULTS Fifty-nine cases were identified. Median age was 9 years (interquartile range [IQR], 4-14 years; 50 of the cases were younger than 21 years). Symptoms that preceded or were concurrent included respiratory or gastrointestinal illness (n = 54), fever (n = 47), and limb myalgia (n = 41). Fifty-six patients had T2 hyperintensity of spinal gray matter on magnetic resonance imaging and 43 patients had cerebrospinal fluid pleocytosis. During the course of the initial hospitalization, 42 patients received intravenous steroids; 43, intravenous immunoglobulin; and 13, plasma exchange; or a combination of these treatments. Among 45 patients with follow-up data, 38 had persistent weakness at a median follow-up of 9 months (IQR, 3-12 months). Two patients, both immunocompromised adults, died within 60 days of symptom onset. Enteroviruses were the most frequently detected pathogen in either nasopharynx swab specimens, stool specimens, serum samples (15 of 45 patients tested). No pathogens were isolated from the cerebrospinal fluid. The incidence of reported cases was significantly higher during a national enterovirus D68 outbreak occurring from August 2014 through January 2015 (0.16 cases per 100,000 person-years) compared with other monitoring periods (0.028 cases per 100,000 person-years; \( P < .001 \)).

CONCLUSIONS AND RELEVANCE In this series of patients identified in California from June 2012 through July 2015, clinical manifestations indicated a rare but distinct syndrome of acute flaccid paralysis with evidence of spinal motor neuron involvement. The etiology remains undetermined, most patients were children and young adults, and motor weakness was prolonged.
With the elimination of wild poliovirus in populations throughout most of the world, the clinical syndrome of acute flaccid paralysis due to spinal motor neuron injury has largely disappeared from North America. It was not until the more recent emergence of West Nile virus in Israel, Europe, and North America and enterovirus A71 in Southeast Asia and Australia that acute flaccid paralysis has reappeared with appreciable frequency. The syndrome also has been rarely associated with other viruses, including enterovirus D68.9,10 Despite occasional case reports, the absence of centralized public health surveillance for non–polio acute flaccid paralysis in the United States has precluded accurate incidence estimates, thereby limiting the ability to distinguish potential disease outbreaks from the natural fluctuation inherent in rare phenomena.11

Since 1998, the California Department of Public Health (CDPH) has maintained a passive surveillance program for potentially infectious undiagnosed neurological conditions.12,13 In the fall of 2012, the CDPH received 3 separate reports of acute flaccid paralysis cases with evidence of spinal motor neuron injury.14 No such cases had been reported to the program during the preceding 14 years.15 No etiology was identified and epidemiological and laboratory investigation did not implicate poliovirus. In response to these unusual case reports, the CDPH implemented enhanced surveillance for similar cases with the goal of characterizing observed cases and identifying possible etiologies. This program was implemented more than 2 years prior to a US outbreak of an enterovirus D68–associated respiratory illness (August 2014-January 2015), which also coincided with a spike in acute flaccid paralysis cases throughout North America.9,10,16

We summarize reported cases and report the minimum statewide incidence of acute flaccid myelitis, which encompasses a subset of acute flaccid paralysis cases with predominantly gray matter myelitis, irrespective of etiology. This clinical syndrome has been previously referred to as poliomyelitis or polio-like,2–4,6,7 reflecting its similarity to the clinical and radiological features of paralytic poliovirus infections.

Methods

In August 2012, the CDPH implemented passive, voluntary statewide surveillance for acute flaccid myelitis cases of unknown etiology. The CDPH requested case reporting by local health jurisdictions and clinicians. A case was defined as a patient with acute onset of flaccid weakness in 1 or more limbs and evidence of a spinal gray matter lesion on magnetic resonance imaging (MRI) or on electrodiagnostic studies (eg, electromyogram) consistent with anterior horn cell damage in a patient admitted to a California hospital or treated at a clinic between June 1, 2012, and July 31, 2015. Patients meeting criteria for Guillain–Barré syndrome, West Nile virus infection, stroke, myasthenia gravis, or botulism were excluded.

Cases reported retrospectively from June and July 2012 were investigated and included if they met the case definition. In California, data collected and analyzed for the investigation of reportable diseases, including unusual diseases, such as acute flaccid myelitis, are exempt from institutional review board approval per Title 17, §2500 of the California Code of Regulations. These data collection activities also were reviewed by the US Centers for Disease Control and Prevention Human Subject Protection Program and were considered nonresearch. Nonetheless, the CDPH maintains an ongoing institutional review board protocol for its Neurologic Surveillance and Testing Program, which covers surveillance activities and similar investigations related to neurological illnesses.

Detailed medical record data were obtained from clinicians and abstracted with a standardized case abstraction tool. Anonymized summaries of patient data, including MRI and electromyogram reports, were reviewed by a neurologist (K.V.) and an infectious disease epidemiologist (P.A. or C.A.G.) trained in case ascertainment to determine if patients met the case definition determined by the CDPH. If the 2 reviewers disagreed, a second neurologist’s opinion (E.W.) was sought. Data were extracted and summarized from official MRI reports. Three clinicians (K.V., E.W., and J.B.S.) reviewed the MRI reports for several patients under their care.

Clinicians involved in the ongoing care of patients were queried for assessments of motor function during clinical follow-up. Full motor recovery was defined as a score of 5 of 5 on the Medical Research Council’s scale for testing muscle strength and function or by a statement from the treating physician specifying full strength in the patient’s affected limbs. Demographic characteristics of patients, including race and ethnicity, were abstracted from medical records to identify epidemiological patterns.

Clinical specimens obtained via throat and nasopharyngeal swabs, stool and rectal swabs, acute serum sampling, and collection of cerebrospinal fluid were requested for all cases. Infectious agent testing was performed by the CDPH Viral and Rickettsial Disease Laboratory and the University of California, San Francisco, Viral Diagnostics and Discovery Center. Briefly, testing methods used polymerase chain reaction for enterovirus VPI and 5′-UTR gene coding regions,17,18 as well as next-generation sequencing.19 Further details are provided in the Methods in the Supplement.

Enterovirus testing was completed on at least 1 sample of every specimen type received for each patient. If a specimen tested positive, viral subtyping was completed on all specimens with sufficient residual volume. Additional infectious disease testing was done on a case-by-case basis, and was dependent on sample availability and the infectious agent testing already completed at the hospital, commercial laboratory, or both. A national enterovirus D68 outbreak occurred from August 2014 through January 2015 (dates independently demarcated by an official US Centers for Disease Control and Prevention outbreak investigation),15 with cases observed throughout California.

Incidence estimates were generated using SAS version 9.3 (SAS Institute Inc). Other figures and relevant statistics were generated using GraphPad Prism version 6.0 (GraphPad Software Inc). We used a 2-tailed Mantel-Haenszel χ2 test
Results

The CDPH evaluated available clinical information for more than 220 reported cases to determine if they met the case definition, including requesting medical records on 124 patients; of these, 59 met the case definition. Reasons for exclusion included alternate diagnoses to explain symptoms (eg, Guillain-Barré syndrome), clinical features not meeting case criteria (eg, absence of flaccid weakness), and symptom onset outside California or the specified time frame.

Two reviewers (K.V. and either P.A. or C.A.G.) agreed on the classification for 58 of the 59 cases; the remaining case was triaged to a third reviewer (E.W.) who recommended inclusion. Of the 59 cases described, 23 have been previously reported (5 in Roux et al,14 23 in Ayscue et al,20 and 10 in Greninger et al).21

Demographic features of the 59 cases appear in Table 1. Median age was 9 years (interquartile range [IQR], 4-14 years). Only 9 patients were older than 21 years (eFigure 1 in the Supplement). Patients resided in 27 of the 58 counties in California and there was a broad geographic distribution (eFigure 2 in the Supplement); no spatial clustering of cases was noted.

Clinical Features

Most patients (n = 44) had no known comorbidities prior to symptom onset (Table 1). Asthma was the most common comorbidity (n = 11); 3 patients had an immunocompromised status. In the 31 days prior to weakness onset, the majority of patients (n = 54) experienced a prodromal illness with either respiratory (n = 42) or gastrointestinal (n = 38) symptoms, or both types of symptoms (Table 2).

At the time of neurological symptom onset, patients reported recent fever (n = 47), limb myalgia (n = 41), headache (n = 29), neck stiffness (n = 20), mental status changes (n = 13), or a mix of these. During the course of neurological illness, many patients experienced neurogenic bowel or bladder manifestations (n = 30), focal paresthesia (n = 21), or both.

Severity of neurological nadir ranged from weakness in 1 limb (n = 5) to quadriplegic (n = 29), often with respiratory failure requiring mechanical ventilation (n = 20), cranial nerve palsies (n = 16), or both. Upper limb weakness was present in the majority of cases (n = 43). Subjectively, patients appeared to progress from normal strength to neurological nadir acutely, generally over the course of a few hours to a few days.

Limb weakness did not always progress to complete paralysis and often varied in severity from limb to limb. Sensory deficits were documented in 26 patients (eResults in the Supplement). The most common diagnoses at time of discharge were transverse myelitis (n = 23), infectious or postinfectious myelitis (n = 15), and Guillain-Barré syndrome (n = 4).

Electromyogram and MRI Report Features

All 59 patients had at least 1 spinal MRI report available for review and abstraction. Representative MRIs appear in Figure 1. Abstracted data from MRI reports are summarized in Table 2 (as well as in the eResults and in eFigure 3 in the Supplement). Spinal cord lesions extended 3 or more vertebral segments in length in most patients (n = 53) and commonly affected the cervical cord (eFigure 3). Findings from MRIs relative to onset of weakness are described in the eResults. Three patients had no spinal cord lesions reported, but had clinical and electromyogram features meeting the case criteria. Nine patients had full electromyogram reports available (eTable 1 in the Supplement).

Among 48 patients with brain MRI reports available (Table 2), most (n = 33) had no supratentorial lesions. When lesions were reported, they tended to affect cortical (n = 6) and subcortical (thalamus, n = 4; caudate, n = 2) gray matter structures. Sinus or mastoid inflammation was reported in 9 of the 48 patients, all occurring within 3 days of weakness onset. No optic nerve or chiasm lesions were reported.

Cerebrospinal Fluid Specimen Features

Eighty-two cerebrospinal fluid specimens were reported from 58 patients. Median time to first lumbar puncture was 2 days (IQR, 0-3 days) after onset of weakness. When all lumbar punctures were considered, pleocytosis (white blood cell count >5/μL) was present in 43 patients and protein level was elevated.
Table 2. Symptoms and Clinical Features of Acute Flaccid Myelitis Cases of Unknown Etiology in California, June 2012 Through July 2015

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Cases (N = 59)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Concurrent or prodromal illness</td>
<td>54 (92)</td>
</tr>
<tr>
<td>Fever &gt;38°C</td>
<td>47 (80)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>42 (71)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>38 (64)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (10)</td>
</tr>
<tr>
<td><strong>Neurological symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Limb weakness or paralysis</td>
<td>59 (100)</td>
</tr>
<tr>
<td>Upper limbs affected</td>
<td>43 (73)</td>
</tr>
<tr>
<td>1 limb affected</td>
<td>5 (9)</td>
</tr>
<tr>
<td>2 or 3 limbs affected</td>
<td>25 (42)</td>
</tr>
<tr>
<td>4 limbs affected</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Limb myalgia</td>
<td>41 (69)</td>
</tr>
<tr>
<td>Headache at onset of neurological symptoms</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Sensory deficit on neurological examination</td>
<td>26 (44)</td>
</tr>
<tr>
<td>Neurogenic bowel or bladder</td>
<td>30 (51)</td>
</tr>
<tr>
<td>Focal paresthesia</td>
<td>21 (36)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Respiratory insufficiency requiring intubation</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>13 (22)</td>
</tr>
<tr>
<td><strong>Hospital course</strong></td>
<td></td>
</tr>
<tr>
<td>Received intravenous immunoglobulin</td>
<td>43 (73)</td>
</tr>
<tr>
<td>Received intravenous steroids</td>
<td>42 (71)</td>
</tr>
<tr>
<td>Received plasmapheresis</td>
<td>13 (22)</td>
</tr>
<tr>
<td><strong>Diagnostic Studies</strong></td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>(n = 58)</td>
</tr>
<tr>
<td>Pleocytosis (white blood cell count &gt;5/μL)</td>
<td>43 (74)</td>
</tr>
<tr>
<td>Protein elevation (&gt;45 mg/dL)</td>
<td>28 (48)</td>
</tr>
<tr>
<td>White blood cell count, median (IQR), /μL</td>
<td>41 (5-99)</td>
</tr>
<tr>
<td>Protein level, median (IQR), mg/dL</td>
<td>44 (29-70)</td>
</tr>
<tr>
<td>Neuroimaging of brain</td>
<td>(n = 48)</td>
</tr>
<tr>
<td>No supratentorial lesions</td>
<td>33 (69)</td>
</tr>
<tr>
<td>Sinus or mastoid inflammation</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Type of lesion</td>
<td></td>
</tr>
<tr>
<td>Subcortical white matter</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Cortical gray matter</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Thalamic</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Caudate</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Neuroimaging of spine</td>
<td></td>
</tr>
<tr>
<td>T2 hyperintensity of spinal gray matter</td>
<td>56 (95)</td>
</tr>
<tr>
<td>Lesion &gt;3 vertebral lengths</td>
<td>53 (90)</td>
</tr>
<tr>
<td>Spinal cord edema</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Spinal gray matter lesion enhancement</td>
<td>23 (39)</td>
</tr>
<tr>
<td>Spinal nerve root enhancement</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Nerve root thickening or clumping</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Paraspinal muscle edema or enhancement</td>
<td>6 (10)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

* Data are expressed as No. (%) unless otherwise indicated.

** Onset within 31-day period prior to limb weakness.

(-45 mg/dL) in 28 patients (Table 2). Among the 42 patients with pleocytosis at the time of the initial lumbar puncture, 41 had white blood cell differential data reported with a predominance of lymphocytes (n = 29), neutrophils (n = 9), monocytes (n = 2), or mixed (n = 1) (eFigure 4 in the Supplement).

**Treatment and Outcome**

The majority of patients received intravenous steroids (n = 42), intravenous immunoglobulin (n = 43), plasma exchange (n = 13), or a combination of these at some point during the course of their initial hospitalization for acute flaccid paralysis (Table 2). The data did not allow for systematic assessment of treatment response; however, an acute improvement in motor function was rarely reported after patients received treatment.

Two children experienced neurological symptom onset during brief courses of oral steroids for asthma-like symptoms; one of these children tested positive for enterovirus D68. Two patients received pocapavir through a US Food and Drug Administration emergency investigational drug protocol for whom recommended weight-adjusted dosing was used; no change in clinical status was noted.

The degree of motor recovery varied but most patients remained weak during the extended follow-up period (Table 3). Among 45 patients with clinical data available, 38 had persistent weakness at a median follow-up of 9 months (IQR, 3-12 months); complete motor recovery was reported in only 7 patients, 6 of whom achieved full recovery within 3 months of symptom onset. No neurological relapses were reported.

Two individuals, aged 55 and 73 years, died within 60 days of neurological symptom onset. Both of these patients had serious preexisting conditions, including immunosuppression (human immunodeficiency virus and AIDS; chronic myelogenous leukemia).

**Infectious Agent Testing**

The state laboratory received biological specimens from 45 of 59 patients. Delayed reporting prevented submission of specimens for the remaining 14 cases. Laboratory test results are summarized in Table 4 and in eTable 2 in the Supplement. An infectious agent was detected in 20 patients, 15 of whom had an enterovirus species detected in at least 1 specimen source (eg, nasopharyngeal swab, serum sample, stool swab). Testing from 9 patients yielded sequencing consistent with enterovirus D68 (1 patient was also positive for coxsackievirus A16), whereas testing from the remaining patients who were positive for enterovirus yielded sequencing consistent with coxsackievirus B3 (n = 2), coxsackievirus A6 (n = 1), and insufficient samples for further subtyping (n = 3).

Enteroviruses were most commonly isolated from a nasopharyngeal swab specimen (n = 13), stool specimen (n = 6), and serum sample (n = 2). Five patients had enteroviruses detected in more than 1 specimen source; only 1 patient was simultaneously positive for more than 1 subtype. No viruses were isolated from cerebrospinal fluid. The timing of sample collection is described in the eResults in the Supplement.
Figure 1. Sagittal and Axial Magnetic Resonance Imaging (MRI) of the Spinal Cord From Representative Patients in This Case Series

Spinal cord MRI typically revealed longitudinally extensive (>3 vertebral bodies) T2 hyperintense lesions affecting spinal gray matter with relative sparing of adjacent white matter (A-J), although various accompanying radiological features were also observed. In some patients, lesions traversed the entire cord with a stable, symmetric appearance (arrowhead in A), whereas other patients demonstrated patchy, asymmetric lesions affecting discrete segments of the cord (arrowheads in B and C). In other patients, subtler lesions (white arrowhead in D) were observed adjacent to more severely affected segments manifesting cord edema (black arrowhead in D). Brainstem lesions were occasionally observed (white arrowheads in C and D) and often correlated with cranial nerve weakness. Although certain lesions appeared to affect dorsal as well as ventral gray matter, the lesions were typically more prominent within the ventral gray matter (G and J), consistent with the location of the spinal motor neurons. Axial sequences revealed spinal lesions that included a “snake eyes” or “owl eyes” appearance highlighting the bilateral ventral horns (F and J), increased T2 signal highlighting the majority of the spinal gray matter (G), unilateral lesions of the ventral horns (H and I), lesions affecting both spinal gray matter and adjacent white matter (I). A distended bladder was observed (white arrowhead in part E) in association with edematous lesions of the conus (black arrowhead in E) in a child with lower limb paralysis. Brainstem and cord lesions are consistent with descriptions of similar cases reported in Colorado in 2014. The black arrowheads in the sagittal images (A-E) demarcate the approximate anatomic level of the associated axial images (F-J, respectively).
Temporal Trends
Epidemiological data by month and year of focal neurological symptom onset appear in Figure 2. The incidence of cases occurring during the US enterovirus D68 outbreak (August 2014-January 2015; 0.16 cases per 100,000 person-years) was significantly higher than during other monitoring periods (0.028 cases per 100,000 person-years; \( P < .001 \)), as well as during the same months in 2012 and 2013 (0.029 cases per 100,000 person-years; \( P < .001 \)).

The incidence of cases occurring during the full surveillance period was 0.049 cases per 100,000 person-years. Enterovirus D68 was identified in 2 patients in November 2012 and in 7 patients during August 2014 through January 2015; all had symptom onset during the US enterovirus season (considered late summer and fall).22

Discussion
In response to sentinel case reports in mid-2012, California implemented statewide surveillance for acute flaccid paralysis cases manifesting injury to spinal motor neurons, with efforts spanning a period before, during, and after the 2014 North American outbreak of enterovirus D68. Acute flaccid myelitis has been occurring in California since at least 2012, affecting primarily children, and commonly resulting in prolonged weakness. The relatively selective localization to the spinal motor neurons with subsequent denervation and limited motor recovery suggest direct neuronal injury in a pattern that appears clinically and radiologically similar to infections with poliovirus, enterovirus A71, West Nile virus, and a handful of other viral agents.

To our knowledge, we report the first modern estimates of morbidity and minimum incidence of this syndrome in California. Our analysis indicates a significant increase in reported acute flaccid myelitis cases in California during August 2014 through January 2015, coinciding with the US enterovirus D68 outbreak and a cluster of acute flaccid myelitis cases in children reported by the Children’s Hospital Colorado.15,23,24 Although we isolated enterovirus D68 from respiratory specimens, serum samples, stool specimens, or a mix of these, from 9 patients, we did not detect enterovirus D68 or any other virus in the cerebrospinal fluid of affected individuals.

The etiology of acute flaccid myelitis cases in our series remains undetermined. Although the syndrome described is largely indistinguishable from poliomyelitis on clinical grounds,25 epidemiological and laboratory studies have effectively excluded poliovirus as an etiology. Alternatively, transverse myelitis, which has a presumed autoimmune etiology, is clinically and radiologically distinct, typically manifesting spastic weakness, sensory deficits in relative proportion to the...
Trends in Acute Flaccid Myelitis in California, 2012-2015

Original Investigation Research

 severity of weakness, absence of spinal gray matter predominance, lower likelihood of longitudinal extension, a more favorable response to steroids or plasma exchange, and often a more favorable recovery.26-28

To the best of our knowledge, all previously identified acute flaccid myelitis cases with a definitively proven etiology have had an infectious origin.8 The clinical, radiological, laboratory, and seasonality patterns in our case series are reminiscent of the acute flaccid myelitis and encephalitis syndromes that have been observed during outbreaks of enterovirus species, such as enterovirus A71 and poliovirus.3,8 The decrease in case incidence since January 2015 appears consistent with a larger, nationwide trend.16 This pattern may reflect reduced viral transmission after the outbreak, consistent with the periodic outbreaks observed for many enteroviruses, or may result from diminished virulence of the virus or viruses responsible.

Even when a specific infectious etiology is not identified, clinical suspicion of an infectious agent represents a crucial distinction in the early triage of clinical care and treatment decision, particularly when treatment strategies for similar clinical syndromes (eg, transverse myelitis) often call for immune modulation or suppression. The majority of patients in our series received some form of therapeutic intervention, although treatments were often administered after the weakness had stabilized and discernable improvements were rarely reported. The deaths of 2 patients with preexisting immunosuppression as well as the onset of paralysis in 2 children receiving oral steroids for asthma-like exacerbations suggest that immunosuppressive treatment regimens for patients with acute flaccid myelitis should be considered cautiously.

The relative prominence of enterovirus D68 in our case series is unique compared with prior enterovirus surveillance reports in the United States and India. Nine of the 15 enteroviruses detected in this California population were typed as enterovirus D68. In contrast, the National Enterovirus Surveillance System in the United States typed 49,635 viruses from patients with any clinical manifestation between 1970 and 2005, but detected enterovirus D68 in only 26 cases, including 1 patient manifesting acute flaccid paralysis in 2005 who had enterovirus D68 detected in cerebrospinal fluid.29 Similarly, during surveillance for enterovirus species among patients with acute flaccid paralysis in Southwest India between 2009 and 2010, enterovirus D68 was completely absent among the 415 enteroviruses identified.30

A related report reveals that all sequenced enterovirus D68 strains from patients with acute flaccid myelitis in both California and Colorado correspond to a novel clade, which emerged approximately 4.5 years ago and shares homology with poliovirus and enterovirus 70.1 Historically, enterovirus D68 has manifested as a purely respiratory illness in the majority of patients and is rarely identified as an enterovirus; however, it may be misdiagnosed as rhinovirus due to substantial cross-reactivity in diagnostic testing.31 Since 2005, however, enterovirus D68 has been detected in the cerebrospinal fluid of at least 2 patients with acute flaccid paralysis.5,29 Interpreted together, these findings suggest the possibility of a broader manifestation of enterovirus D68 associated neurological illness than previously recognized.

Enterovirus D68 is unique among enteroviruses in that it shares features with rhinoviruses, causes respiratory illness, and is shed primarily from the respiratory tract.32,33 Although enterovirus D68 has been previously isolated from the cerebrospinal fluid of patients with acute flaccid paralysis,8,34 demonstrating a causal link between enterovirus D68 and acute flaccid myelitis, our case series is complicated by an inability to detect the virus in cerebrospinal fluid specimens. This difficulty in detection is nonetheless consistent with the experience of other enterovirus species, most notably polioviruses and enterovirus A71, which are rarely detected in the cerebrospinal fluid of similarly affected patients.35,36 Among patients in our case series, acute enterovirus D68 viremia was detected in 1 patient.1 Viremia appears to be a necessary
To our knowledge, the California surveillance program for acute flaccid paralysis is the first to use specific case criteria and report subsequent incidence data for the subset of paralysis cases attributable solely to acute flaccid myelitis and may serve as a guide for similar surveillance efforts in the future. Whether the cases reported across this surveillance period represent an increase from incidence prior to 2012 is unclear; however, a study of California children conducted from 1992 through 1998 did not identify any instances of spinal gray matter involvement in 245 identified cases of acute flaccid paralysis.

The paucity of preexisting incidence data for this syndrome is due partly to a lack of spinal imaging in prior eras of surveillance; however, problematic terminology may have also contributed to this knowledge gap. Indeed, the patients in our series were variably described by clinicians, epidemiologists, and others as having transverse myelitis, poliomyelitis, polio-like paralysis, Hopkins syndrome, or acute flaccid paralysis. These terms are often correctly applied yet remain unnecessarily vague or etiologically misleading. Acute flaccid myelitis offers an appropriately descriptive term for the syndrome.

Our study limitations include the voluntary nature of reporting, which probably underestimates the overall incidence of this syndrome. Our dependence on noncentralized interpretation of MRIs requires radiologists to both recognize and transcribe a potentially subtle or unusual radiographic pattern in the MRI report. Similarly, although we received biological samples for most patients, delayed sample acquisition likely contributed to a lower overall yield of testing for possible infectious agents.

In addition, our follow-up data are limited by the relatively high number of patients who were lost to follow-up, which may bias our clinical follow-up data toward more severe impairment. Both recent and historical experience suggest that not all strains convey the same degree of neurovirulence even within the same family of viruses, limiting our ability to generalize existing knowledge of enteroviruses to the reported cases. Ongoing surveillance efforts are required to understand the full and potentially evolving levels of infectious agent–associated morbidity and mortality.

Conclusions

In this series of patients identified in California from June 2012 through July 2015, clinical manifestations indicated a rare but distinct syndrome of acute flaccid paralysis with evidence of spinal motor neuron involvement. The etiology remains undetermined, most patients were children and young adults, and motor weakness was prolonged.

Critical revision of the manuscript for important intellectual content: Van Haren, Ayscue, Waubant, Clayton, Yagi, Glenn-Finer, Padilla, Strober, Aldrovandi, Wadford, Chiu, Xia, Harriman, Watt, Glaser.

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