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NEUROLOGICAL INFECTIOUS DISEASES

Acute Flaccid Paralysis and Enteroviral Infections

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Abstract

Purpose of Review The focus of this review is on enterovirus (EV)-associated acute flaccid paralysis (AFP) due to spinal cord anterior horn cell disease. Emphasis is placed on the epidemiology, pathogenesis, diagnosis, treatment, and outcome of AFP caused by polioviruses, vaccine-derived polioviruses, EV-D68, and EV-A71.

Recent Findings Since the launch of The Global Polio Eradication Initiative in 1988, the worldwide incidence of polio has been reduced by 99.9%, with small numbers of poliomyelitis cases being reported only in Afghanistan, Pakistan, and Nigeria. With the planned phaseout of oral polio vaccine, vaccine-associated poliomyelitis is also expected to be eliminated. In their place, other EVs, chiefly EV-D68 and EV-A71, have emerged as the principal causes of AFP. There is evidence that the emergence of EV-D68 as a cause of severe respiratory disease and AFP was due to recent genetic virus evolution. Antiviral medications targeting EV-D68, EV-A71, and other EVs will likely be available in the near future. An effective EV-A71 vaccine has been developed, and preliminary investigations suggest an EV-D68 vaccine could be on the horizon.

Summary The eradication of poliomyelitis and vaccine-associated poliomyelitis is near, after which other EVs, presently EV-D68 and EV-A71, will be the principle viral causes of AFP. Moving forward, it is essential that EV outbreaks, in particular those associated with neurologic complications, be investigated carefully and the causal strains identified, so that treatment and prevention efforts can be rapidly developed and implemented.

Keywords Acute flaccid paralysis · Acute flaccid myelitis · Enterovirus D68 · Enterovirus A71 · Poliovirus · Poliomyelitis · Vaccine-derived poliovirus

Introduction

Since the launch of The Global Polio Eradication Initiative in 1988, the worldwide incidence of poliomyelitis has been reduced by 99.9%, with small numbers of cases being reported only in Afghanistan, Pakistan, and Nigeria [1]. Furthermore, with the planned phaseout of oral polio vaccine (OPV), vaccine-associated paralytic poliomyelitis is also expected to be eliminated in the near future [2]. With the near-elimination of polioviruses (PVs) and vaccine-derived polioviruses (VDPVs) from the globe, other enteroviruses, chiefly enterovirus-D68 (EV-D68) and EV-A71, have emerged as the principle causes of EV-associated acute flaccid paralysis (AFP).

AFP is a clinical syndrome, of diverse etiology, characterized by the rapid onset of muscle weakness that progresses to maximum severity over days to a few weeks [3]. Acute flaccid myelitis (AFM) is a subset of AFP in which injury to the anterior horn cell of the spinal cord is presumed to be present. The focus of this review is on AFP/AFM associated with EV infection. The definition of AFP and AFM and the clinical presentation of EV-associated AFP/AFM are described first. The epidemiology, pathogenesis, microbiologic diagnosis, treatment, and prevention for individual pathogens, chiefly PV, EV-D68, and EV-A71, are then discussed, followed by emerging trends in treatment and prevention.

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Acute Flaccid Paralysis/Myelitis

Definitions

The World Health Organization (WHO) defines AFP as the sudden onset of paralysis/weakness in any part of the body in a child younger than 15 years of age. This definition was designed for poliomyelitis surveillance purposes and, as such, is deliberately broad, capturing not only cases of flaccid myelitis (spinal cord disease) but also cases of polyradiculopathy (Guillain-Barré syndrome), toxic neuropathy, and muscle disorders.

In response to the outbreak of EV-D68-associated AFP in the USA and Canada in 2014, the CDC developed a case definition for the identification of AFP cases in whom the etiology was due to injury to the anterior horn cell of the spinal cord (AFM) [4]. Confirmed AFM was defined by the presence of acute focal limb weakness and magnetic resonance imaging (MRI) evidence of predominantly gray matter lesion(s) spanning one or more spinal cord segments. Those with acute focal limb weakness and cerebrospinal fluid (CSF) pleocytosis (> 5 cells/mm^3) were categorized as probable cases. In contrast to the WHO definition for AFP, no age limitation was included in recognition of observed cases of AFM throughout the lifespan. Henceforth in this review, AFP/AFM will be used to refer to EV-associated anterior horn cell disease, in part because of the predominant use of AFP in the literature, and in part in recognition that the primary site of injury for EV-associated AFP is the anterior horn cell of the spinal cord.

Neurologic Manifestations

The abrupt onset of limb weakness that progresses over a period of 2–4 days should raise the suspicion for EV-associated AFP/AFM, although the differential diagnosis is broad and includes abnormalities anywhere along the neuraxis, including the brain, spinal cord, the anterior horn cell, nerve, muscle, and neuromuscular junction (Table 1) [3]. Clinical features that may help distinguish AFP/AFM from disorders affecting other parts of the neuraxis include the asymmetric nature of the paralysis, the presence of pain in the affected limb, and the absence of sensory manifestations or bladder and bowel dysfunction. Pain in the affected limb as well as paresthesia or hyperesthesia are prominent in both poliomyelitis and EV-D68-associated AFP/AFM [5, 6, 7••, 8, 9••, 10•, 11•]. During the 2014 EV-D68 outbreak in North America, limb pain was observed in 40–69% of cases, while numbness or paresthesia was seen in 20–45% (Table 2) [7, 8, 9••, 10, 11•]. In poliomyelitis, bladder paralysis is distinctly uncommon in children but may be seen in about 25% of adults [6]. Reported rates of bowel or bladder dysfunction in EV-D68-associated AFP/AFM cases varied from none to a high of 51% [7, 10, 11, 12••].

Table 1 Differential diagnosis of acute flaccid paralysis with no cranial nerve involvement or encephalopathy

Acute myelopathy
Transverse myelitis
Cord compression (paraspinal or epidural abscess, tumor, hematoma)
Anterior horn cell
Poliomyelitis
Vaccine-associated paralytic poliomyelitis
Non-polio enteroviruses
Other viruses (Japanese encephalitis virus, West Nile virus, European tick-borne encephalitis virus, etc.)
Polyradiculoneuropathy
Guillain-Barré syndrome
Peripheral neuropathy
Infection-related: diphtheria, tick bite paralysis, Lyme disease, relapsing fever
Chemical ingestion-related: poisonous plants (ripe fruit of *Karwinskia humboldtiana* [wild cherry], *Gloriosa superba* [climbing lily]; chemicals [lead, arsenic, thallium]; medications [colchicine, aminoglycosides])
Neuromuscular junction
Myasthenia gravis
Botulinum toxin
Tetanus toxin
Animal toxins (snake venom, dart poison frog, puffer fish tetrodotoxin)
Organophosphate poisoning
Muscle disorders
Polymyositis
Myositis (viral)
Hypokalemic periodic paralysis
Weakness associated with critical illness

Information derived in part from reference [3]. The presence of cranial nerve involvement/bulbar signs or encephalopathy should prompt investigation for focal brain abnormalities

The distribution of weakness may vary by etiology. PV and VDPV typically affect proximal muscle groups more than distal ones and most commonly involve the lower limbs [5, 6]. Involvement of one leg is the most common followed by one arm, less often multiple limbs [6, 13]. EV-D68-associated AFP/AFM, on the other hand, is more commonly associated with upper extremity weakness [7, 9, 10, 11•, 14•]. Physical examination findings in EV-D68-associated AFP/AFM include variable weakness (mild (4/5 strength) to complete (0/5 strength) paralysis) and decreased muscle tone and accompanying areflexia or hyporeflexia in the affected limb(s) in 81–88% (Table 2) [7••, 9••, 11•]. Similar to PV, EV-A71-associated AFP/AFM affects the lower limbs more often than the upper limbs, but unlike PV, the weakness is usually mild, and in 60–80%, it is restricted to a single limb [15, 16•, 17, 18].

Brainstem and supratentorial involvement occurs in a significant minority of individuals with PV-, EV-D68-, and EV-

Table 2 Clinical manifestations and CSF and MRI findings for three AFP/AFM cohorts during 2014 outbreak in the USA and Canada

	CDC ($n = 120$)	California ($n = 59$)	Canada ($n = 25$)
Demographics			
Age (years)	7.1 (IQR 4.8, 12.1)	9.0 (IQR 4.0, 14.0)	7.8 (0.8–15.0)[a]
Sex (% male)	59	56	64
Prodrome			
Any (%)	90	92	88
Fever (%)	64	80	60
Respiratory (%)	81	71	88
Gastrointestinal (%)	–	64	–
Neurologic symptoms and signs			
Limb weakness			
Upper limb (%)	77	73	72
Lower limb (%)	65	–	68
1 limb affected (%)	30	9	36
2–3 limbs affected (%)	–	42	44
4 limbs affected (%)	–	49	20
Cranial nerve dysfunction (%)	28	27	25
Sensory involvement (%)	21	44	4
Areflexia or hyporeflexia (%)	81	–	88
Altered mental status (%)	11	22	4
CSF findings[b]			
Pleocytosis (> 5 cells/μL) (%)	81	74	91
Leukocyte count (cells/μL)	44 (IQR 12, 93)	41 (IQR 5, 99)	46 (0–156)
Percent lymphocytes	74% (46, 89)[a]	71%[c]	88% (0–96)[a]
Elevated CSF protein (> 45 mg/dL) (%)	48	48	28
Protein (mg/dL)	43 (IQR 34, 60)	44 (IQR 29, 70)	28.5 (19–527)[a]
MRI abnormalities			
Spinal cord gray matter (%)	–	95	–
Nerve root enhancement (%)	34	20	72
Anatomic involvement			
Cervical (%)	87	–	84
Thoracic (%)	80	–	56
Conus medullaris/cauda equina (%)	47	–	52
Virus detection in respiratory tract			
Enterovirus-D68	20% (11/56)	22% (9/41)	29% (9/24)
Non-D68 enterovirus/rhinovirus[d]	21% (12/56)	7% (7/41)	29% (9/24)

Information derived from references [7••, 9••,10•,11•]. The CDC study [9••] included 24 of the subjects from the California study [10•]

[a] Range

[b] CSF was predominantly lymphocytic in most patients; CSF glucose is normal in all cases

[c] Range not provided

[d] CDC site: rhinovirus ($n = 9$), enterovirus 71 ($n = 1$), enterovirus C105 ($n = 1$), untypeable ($n = 1$); California site: coxsackievirus B3 ($n = 2$), coxsackievirus A6 ($n = 1$), unknown ($n = 3$); Canada: rhinovirus ($n = 5$), enterovirus A71 ($n = 1$), coxsackievirus B2 ($n = 1$)

A71-associated AFP/AFM. Bulbar poliomyelitis, most often involving cranial nerves IX and X manifested as dysphagia, dysarthria, dyspnea, or pooling of secretions, develops in 5–35% of cases [6, 19]. Similarly, approximately 25% of those with EV-D68-associated AFP/AFM experienced cranial nerve involvement, most often presented as facial weakness, dysphagia, and diplopia [9••, 11•]. Altered mental status is uncommon, having been observed in 11% of cases reviewed by the CDC and even fewer in the Canadian cohort [9••, 11•]. EV-A71-associated AFP/AFM may occur in isolation or together with brainstem encephalitis or encephalomyelitis [16•, 17, 20, 21].

Systemic Features

Systemic clinical features for selected EV strains are depicted in Table 3. Additional detail is also provided in individual pathogen sections below.

Cerebrospinal Fluid, Electromyography, and Neuroimaging Findings

CSF findings are non-specific, consisting of mild to moderate lymphocytic pleocytosis, normal or elevated CSF protein, and normal glucose [5–8, 9••, 11•, 14•, 17, 30, 31]. Virus detection in the CSF is uncommon and is discussed in more detail in the sections devoted expressly to individual pathogens.

Electromyographic features of PV-, EV-D68-, and EV-A71-associated AFP/AFM are similar. Findings indicative of acute motor axonal neuropathy, such as reduced compound motor action potential amplitude, reduced recruitment of motor unit potentials, and denervation of affected muscles, are characteristic [7••, 10•, 11•, 14•, 16•, 32, 33].

There is a relative paucity of data on MRI findings in poliomyelitis because of the near-eradication of polio prior to widespread availability of MRI. In the limited reports that are available, the main findings consisted of hyperintense lesions in the anterior horn cell region of the spinal cord on T2-weighted images [34–36]. MRI abnormalities of EV-D68- and EV-A71-associated AFP/AFM are similar and include single, or more often multiple, spinal cord gray matter T2 signal abnormality lesions of variable length, gadolinium enhancement of cord lesions, and nerve root enhancement [7••, 9••, 10•, 11•, 15, 16•, 17, 21•, 37••, 38]. An important minority also have cortical, subcortical, midbrain, pons, medulla, thalamus, basal ganglia, or cerebellar lesions (Fig. 1) [7••, 9••, 10, 11•, 17, 21•, 37••].

Table 3 Salient epidemiologic and systemic clinical features of acute flaccid paralysis/acute flaccid myelitis (AFP/AFM) for selected EV serotypes

Virus	Prodrome	Second-phase illness	General comments	Selected references
PV, VDPV	• Typically mild illness with 1 or more of fever, listlessness, headache, sore throat, vomiting[a] • Duration usually 1–3 days	• Interval between prodrome and second phase usually 3–4 days • Fever, headache, neck stiffness, vomiting, myalgia, localized hyperesthesia or paresthesia, muscle spasm or fasciculation	• Biphasic course in children; in adults, prodrome tends to be prolonged with paralysis developing more gradually • Any age, predominantly children	[5, 6]
EV-D68	• Fever, nasal congestion, cough, sore throat	• Median interval between prodrome onset and second-phase illness is 5 days • Fever, headache, stiff neck, myalgia	• Any age, predominantly children (median age 7–9 years)	[7••,8, 9••, 10•, 12••, 14•]
EV-A71	• HFMD, herpangina[b]	• Paralysis onset 2–6 days after the start of prodromal illness • Myoclonic jerks, tremor, ataxia, or other symptoms of concurrent brainstem encephalitis may be seen	• Predominantly infants (median age 1–2.5 years)	[15, 17, 18]
EV-D70[c]	• Hemorrhagic conjunctivitis, fever, duration up to 5 days	• Latent period of 10–21 days between prodrome and paralysis onset • Fever, malaise, myalgia for 4–5 days prior to paralysis onset	• Predominantly adults • 2–2.5:1 male predominance	[22–25]
CV-B1–B6[c]	• Coryza, cough, pharyngitis, vomiting, diarrhea, or headache with or without fever	• Interval of 1–30 days between prodromal symptoms and paralysis • No specific recrudescence of systemic symptoms reported	• Predominantly children (90%, ≤ 5 years of age)	[26]
CV-A7[d]	• Not well described	• Fever, vomiting, meningeal irritation	• Almost exclusively children ≤ 3 years of age • 2:1 male predominance	[27, 28]
EV-C105	• Cough, rhinorrhea within 2 weeks of paralysis onset	• Fever, fatigue, headache, myalgia starting 4 days prior to paralysis	• Case report of a 6-year-old girl (during 2014 EV-D68 outbreak in the USA)	[29]

Only studies that provided clinical information on cases are included

CV-B coxsackievirus B; *HFMD* hand, foot, and mouth disease; *PV* poliovirus; *VDPV* vaccine-derived poliovirus

[a] The absence of cough, nasal congestion, or rhinorrhea is characteristic

[b] HFMD and herpangina can also be caused by other EV-A strains including CV-A (CV-A2–8, CV-A10, CV-A12, CV-A14, and CV-A16); neurologic disease with these viruses is much less common, however

[c] The evidence specifically implicating anterior horn cell disease as the cause of AFP is limited in these cases; the relatively long interval between conjunctivitis and paralysis in EV-D70-associated cases is potentially consistent with a post-infectious, perhaps immune-mediated, process; in three fatal cases associated with CV-B infection, pathology did not demonstrate anterior horn cell abnormalities [26]

[d] Pathologic studies were deemed similar to those associated with poliomyelitis in one report [28]

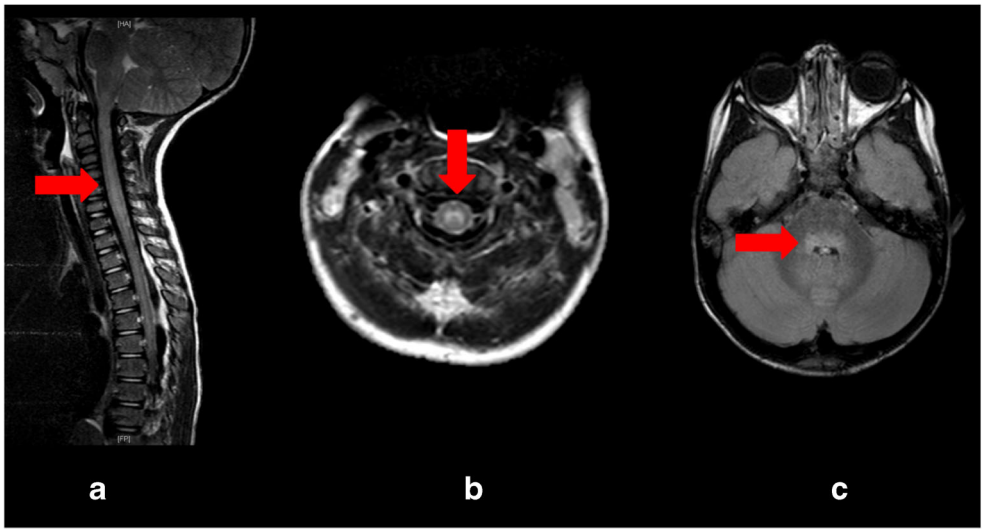

Fig. 1 MRI images from a child with EV-D68 AFM. **a** Sagittal T2-weighted image of the cervical spine demonstrating longitudinally extensive bright signal in the spinal cord. **b** Axial T2-weighted image of the cervical spine in the same child, demonstrating gray matter predominance of abnormal signal. **c** Axial T2 flair image showing hyperintense signal of the dorsal pons in a child with AFM.

Enterovirus Taxonomy and Biology

Human EVs consist of at least 80 genetically distinct non-enveloped, positive sense, single-stranded RNA viruses within the *Enterovirus* genus (*Picornaviridae* family) [39•, 40]. The original classification of serologically distinct EVs as PV (3 serotypes) [1–3], coxsackievirus A (CV-A; 23 serotypes), coxsackievirus B (CV-B; 6 serotypes), and echoviruses (28 serotypes) was based on antigenic characteristics, disease pattern in experimentally infected animals, and differences in tissue culture effects, with EVs identified later being designated as new EVs (4 serotypes) [39•, 40]. More recently, human EVs have been categorized according to genetic diversity into four species, designated A, B, C, and D (Table 4) [39, 40]. The serotype designation within species has been retained.

Polio Viruses and Vaccine-Derived Polioviruses

PVs are classified as wild-type polioviruses (WTPVs), oral polio vaccine viruses (OPVVs), and VDPVs. AFP/AFM can be caused by both WTPVs and VDPVs.

Vaccine-associated paralytic poliomyelitis is due to infection with VDPVs, strains characterized by enhanced neurovirulence acquired through mutation, principally in the

Table 4 Human enteroviruses and association with acute flaccid paralysis

Species	Serotypes	Serotypes associated with AFP[a]
A	CV-A2, CV-A2, CV-A3, CV-A4, CV-A5, CV-A6, CV-A6, CV-8, CV-A10, CV-A12, CV-A14, CV-A16 EV-71, EV-76, EV-89, EV-90, EV-91, EV-92, EV-114, EV-119, EV-120, E-121	CV-A7 (CV-A2, CV-A4, CV-A6, CV-A14, CV-A16) EV-A71 (EV-A76, EV-119)
B	CV-A9, CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, CV-B6 E-1 (includes E-8), E-2, E-3, E-4, E-5, E-6, E-7, E-9 (includes CV-A23), E-11, E-12, E-13, E-14, E-15, E-16, E-17, E-18, E-19, E-20, E-21, E-24, E-25, E-26, E-27, E-29, E-30, E-31, E-32, E-33 EV-69, EV-73–75, EV-77–88, EV-93, EV-97, EV-98, EV-100, EV-101, EV-106, EV-107, EV-111	CV-A9, CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, CV-B6 E-6, E-7, E-9 (E-1, E-2, E-3, E-11, E-12, E-13, E-14, E-18, E-19, E-20, E-21, E-24, E-25, E-27, E-29, E-30, E-33)
C	PV-1–3, VDPV CV-A1, CV-A11 (includes CV-A15), CV-A13 (includes CV-A18), CV-A17, CV-A19, CV-A20, CV-A22, CV-A24 EV-C95, EV-C96, EV-C99, EV-C102, EV-C104, EV-C105, EV-C109, EV-C113, EV-C116, EV-C117, EV-C118	PV-1, PV-2, PV-3, VDPV (CV-A20, CV-A21) (EV-C105)
D	EV-D68, EV-D70, EV-D94, EV-D111	EV-D68, EV-D70 (EV-D94)

Information obtained in part from references [39, 40] and from http://www.picornaviridae.com/enterovirus/enterovirus.htm

AFP acute flaccid paralysis, *CV-A* coxsackievirus A, *CV-B* coxsackievirus B, *E* echovirus, *EV* enterovirus, *PV* poliovirus, *VDPV* vaccine-derived poliovirus

[a] Information obtained in part from references [6, 22–26, 29, 41–49]. Strains with relatively strong association with AFP are shown without brackets, and those with less consistent association or more recently described ones are shown in brackets

5′ non-translated region of the original OPVV strain genome [50••, 51, 52]. VDPVs are classified as circulating if there is evidence of transmission in the community (cVDPV), as immunodeficiency-associated if isolated from persons with an immunodeficiency (iVDPV), or as ambiguous if the source is unknown (aVDPV).

Epidemiology

WTPV circulation is currently restricted to a few areas in Afghanistan, Pakistan, and Nigeria [1, 50••]. Of the three WTPV strains, only WTPV1 continues to circulate—during 2016 and 2017 combined, 58 WTPV1 cases were detected in Afghanistan ($n = 26$), Pakistan ($n = 28$), and Nigeria ($n = 4$) [1]. WTPV2 was declared globally eradicated in September 2015, and the last isolate of WTPV3 was detected in Nigeria in November 2012 [1, 50••].

The incidence of vaccine-associated paralytic poliomyelitis (VAPP) is approximately 4.7 per million live births [51]. The highest risk is seen after receipt of the first dose, in either the recipient or their close contacts and in individuals who are immunocompromised. Approximately 85% of VAPP is due to cVDPV2 [50••]. In 2015 and 2016 combined, a total of 14 cases of AFP due to cVDPV2 were reported in Nigeria, Guinea, Pakistan, and Myanmar [2]. In 2017, 96 cases were detected (74 in Syria and 22 in the Democratic Republic of Congo) [2]. The most recent cases of VAPP due to cVDPV1 and cVDPV3 were reported in 2015–2016 in Laos, Madagascar, and Ukraine and in 2013 in Yemen, respectively [2].

Pathogenesis

PV infection is transmitted predominantly by the fecal oral route [6, 52]. Initial virus replication in the gastrointestinal tract, upper respiratory tract, and lymph nodes is followed by minor viremia and reticuloendothelial tissue infection [6, 52]. In about 95% of cases, the virus is contained at this stage, type-specific immunity is established, and no symptoms develop. In 4–8%, virus replication in the reticuloendothelial tissues is followed by major viremia, most often manifested as abortive poliomyelitis [6]. Non-paralytic aseptic meningitis develops in 1–2% of cases and paralytic poliomyelitis in approximately 0.1% of cases [6, 52].

The mechanisms through which PVs enter the central nervous system (CNS) have not been fully elucidated but likely involve both retrograde axonal transport and hematogenous spread [6, 52–54]. The classic pathology consists of neuronal destruction and an inflammatory infiltrate composed of neutrophils, macrophages, and lymphocytes, predominantly affecting the anterior horn cells of the spinal cord and motor nuclei of the pons and medulla and, to a lesser extent, neurons of the motor cortex [55].

Clinical Features

Clinical syndromes of PV infection, due to WTPVs or VDPVs, include abortive poliomyelitis, aseptic meningitis, spinal paralytic poliomyelitis, bulbar paralytic poliomyelitis, and polio encephalitis [5, 6]. Abortive poliomyelitis is a mild febrile illness sometimes accompanied by headache, sore throat, anorexia, or vomiting that typically lasts 1–3 days. The aseptic meningitis due to PV is also a benign self-limited illness. Polio encephalitis is rare, occurs predominantly in infants, and is typified by altered consciousness and seizures.

Paralytic poliomyelitis classically follows a biphasic course [5, 6]. Two to five days after resolution of the prodromal illness (symptoms as for abortive poliomyelitis), fever accompanied by symptoms of meningeal irritation (headache, neck stiffness, and vomiting) and severe myalgia (sometimes accompanied by localized hyperesthesia or paresthesia, muscle spasms, or fasciculations) develop. The onset of muscle weakness follows 1–2 days later.

The risk of paralytic poliomyelitis is increased by strenuous exercise, skeletal muscle injury, receipt of an intramuscular injection in the preceding 2–4 weeks, and in the case of bulbar poliomyelitis, prior tonsillectomy [6]. Intramuscular injections in the month prior to OPV administration can also enhance the risk of VAPP [56].

Microbiologic Diagnosis

PVs and VDPVs are rarely detected in the CSF. In immunocompetent subjects, the virus can be isolated from the respiratory tract for about a week into illness and from the stool for up to 3–4 months after resolution of symptoms. As part of global eradication efforts, it is essential that all clinical PV isolates be characterized by genomic sequencing in a reference laboratory as WTPVs, OPVVs, or VDPVs [6, 50].

Treatment and Prevention

The treatment of paralytic poliomyelitis is primarily supportive. Bed rest during the acute phase may reduce the risk of paralysis extension [6]. Mechanical ventilation for respiratory compromise, nutritional support, and robust physiotherapy and occupational therapy rehabilitation once progression of paralysis has stopped are important.

The Polio Eradication and Endgame Strategic Plan consists of four pillars: (1) PV detection and transmission interruption, (2) strengthening immunization systems and OPV withdrawal, (3) finalizing long-term biocontainment requirements, and (4) transition planning once PV eradication has been achieved [57]. In 2016, subsequent to the elimination of WTPV2, 155 countries and territories switched from trivalent OPV to bivalent OPV, containing OPV1 and OPV3, and introduced

inactivate polio vaccine (IPV). Stockpiling of OPV2 was implemented in order to respond to cVDPV2 cases and outbreaks. A key element of the "end game" moving forward will be robust ongoing clinical and environmental surveillance and maintenance of high levels of immunity in the population [50••, 57].

Enterovirus D68

EV-D68 was first isolated in culture from the oropharynx of children hospitalized with acute lower respiratory tract infections associated with wheezing and radiographic evidence of pneumonia in 1962 [58]. At that time, it was labeled as the "Fermon virus" after the first strain recovered, later receiving the designation EV-68 and, finally, after its classification in species D of the genus *Enterovirus*, as EV-D68. The large outbreak of EV-D68-associated severe respiratory disease and AFP/AFM in 2014 in the USA and Canada brought it to the forefront [8, 9, 10•, 11•, 14, 30]. The evidence in support of EV-D68 as a cause of AFP/AFM is relatively strong, with six of the nine Bradford-Hill criteria for causality being fully met and two others being partially met [59••].

Epidemiology

Prior to 2005, EV-D68 was rarely implicated as a cause of disease in the USA, with only 26 confirmed cases between 1970 and 2005 [60]. However, beginning in 2007, small outbreaks of EV-D68-associated respiratory tract infection were increasingly being reported in the USA and around the world [61]. Clusters of EV-D68-associated respiratory illness were observed among hospitalized patient in Georgia and Pennsylvania in 2009 and in Arizona in 2010 [61], and over a 5-year period between 2009 and 2013, EV-D68 accounted for 4.3% of respiratory tract isolates in the National Enterovirus Surveillance System (NESS) [62]. Similar outbreaks, totaling 699 patients, were also reported between 1970 and 2013 in Europe, Africa, and Southeast Asia [63•].

In the summer and fall of 2014, a large outbreak of EV-D68-associated severe respiratory illness and increased incidence of AFP/AFM, primarily affecting children, occurred in the USA and Canada, with smaller clusters observed in multiple European countries, China, and Taiwan [63•]. Between September and December 2014, there were 1153 cases of severe respiratory illness and 120 cases of AFP/AFM attributed to EV-D68 in the USA [9••, 63•]. In three Canadian provinces, Ontario, Alberta, and British Columbia, there were 268 documented pediatric hospitalizations due to EV-D68 during September 2014 [64]. Of 25 cases of childhood AFP/AFM reported nationwide in Canada between July 1 and October 31, 2014, seven had EV-D68 detected in the respiratory tract [11•].

Similar to other EVs, the peak incidence of EV-D68 disease occurs in the late summer to early fall, between August and October in the Northern Hemisphere. In the Southern Hemisphere, the peak incidence is during fall and early winter months. Transmission is primarily from person to person by direct or indirect exposure to respiratory droplets.

Pathogenesis

EV-D68 shares many properties with rhinoviruses, including enhanced replication at 33 °C rather than 37 °C and acid lability, which likely explain its propensity for the respiratory tract rather than the gastrointestinal tract [65]. Binding to upper respiratory tract epithelium is mediated by the interaction of virus capsid components with α-2–6-linked sialic acids [66]. Neuron-specific intercellular adhesion molecule 5 (ICAM-5) is a cellular receptor for EV-D68, which may play a role in facilitating neuroinvasion [67]. There are currently six EV-D68 clades (A1, A2, B1, B2, B3, C, and D), of which clade B1 was implicated in the 2014 North American outbreak [12••].

The worldwide emergence of EV-D68 in the last decade is likely related to virus genetic evolution over time [65, 68, 69]. Phylogenetic analysis of EV-D68 strains in the Netherlands showed rapid expansion in diversity in 2010, suggesting that antigenic drift combined with low-level community immunity has contributed to epidemic spread [68].

Neurovirulence potential may also have evolved relatively, recently. In phylogenetic analysis, 11 EV-D68 isolates associated with the 2014 AFP/AFM outbreak were shown to belong to an evolutionary cluster, clade B1, estimated to have emerged approximately 4.5 years earlier [12••]. Five of six coding polymorphisms observed in the clade B1 polyprotein were also present in neuropathogenic EV-D70 or PVs [12••]. Another report noted that most B1 subclade viruses associated with AFP/AFM during the 2014 outbreak had 21 unique amino acid substitutions, 12 of which contained the same residues observed at equivalent positions in PV, EV-D70, and EV-A71 [70•].

Pathologic and experimental evidence of anterior horn cell injury following EV-D68 infection is emerging. Diffuse T lymphocyte infiltrates and neuronophagia involving the motor nuclei of the anterior spinal cord was observed in a fatal case of EV-D68 encephalitis involving a previously healthy 5-year-old boy [71]. Flaccid paralysis with pathologic evidence of motor neuron loss in the anterior horns has been demonstrated in mice following experimental infection with EV-D68 strains from the 2014 outbreak, but not with infection with earlier strains, including the Fermon strain [72••].

Clinical Features

EV-D68 is predominant a respiratory pathogen. Disease spectrum varies from uncomplicated upper respiratory tract

infection to severe bronchiolitis and pneumonia with respiratory failure and need for mechanical ventilation [30, 63, 68]. Children with underlying respiratory illnesses, particularly asthma, are at increased risk of severe respiratory disease [30, 63•, 68, 73]. There is a slight male predominance among those hospitalized with EV-D68 infections.

A respiratory or febrile prodrome is observed in the approximately 90% of patients with ED-D68-associated AFP/AFM (Table 2). The median interval between the prodromal illness and the onset of limb weakness is 5 days (IQR 3, 9) [9••]. Many patients experience an improvement in prodromal symptoms prior to the onset of weakness [7••, 10•, 14]. As in poliomyelitis, the onset of limb weakness is associated with the recurrence of fever, headache, and pain in the affected limb, neck, or back [7••, 10•, 14•].

Microbiologic Diagnosis

Detection of EV-D68 relies almost exclusively on PCR testing of respiratory tract samples, stool, and CSF. Similar to PV and EV-A71, EV-D68 is only rarely detected in the CSF [9••, 60, 71], likely due to very low viral load [21•, 31]. The pickup rate from serum or stool samples is also low [9••, 10•, 12, 14•]. Respiratory sample testing offers the highest yield—during the 2014 outbreak, EV-D68 was detected in respiratory specimens of approximately 20–30% of patients with AFP/AFM [9••, 10•, 11•]. Samples taken more than 7 days after respiratory symptom onset are rarely positive—in the CDC study, 8 of 11 EV-D68-positive results were from samples obtained within a week of respiratory symptom onset [9••].

Treatment and Outcome

As with poliomyelitis, the mainstay of management is supportive, consisting of mechanical ventilation when there is impairment of respiratory muscles or inability to protect the airway, nutritional support, and physiotherapy and occupational therapy rehabilitation support [7••].

There is no proven effective treatment for EV-D68-associated AFP/AFM. Immune-modulating treatments, including high-dose intravenous corticosteroids, intravenous immune globulin (IVIG), and plasmapheresis, were used in many patients during the 2014 outbreak without clear benefit [7••, 9–11]. The antiviral agent pocapavir was used in a small number of children, also with no evidence of benefit [12••, 14•]. Human IVIG containing high levels of broadly neutralizing anti-EV-D68 antibodies was beneficial in reducing the severity of AFP/AFM in a mouse model of EV-D68 infection [72••]. The authors hypothesized that the lack of benefit of IVIG observed during the 2014 outbreak may have been due to low titers of anti-EV-D68 antibody.

The short-term prognosis for full recovery is poor. Of the 56 of 120 cases with follow-up information in the CDC cohort (median 4.2 months [range 0.8–7.5]), only three reported complete recovery of strength; 14% were fully dependent on caregivers, 68% had functional impairment requiring support for some activities, and 18% reported being fully functional [9••]. Of the 21 of 25 children with follow-up information in the Canadian cohort, 2 fully recovered, the remainder showing persistent deficits (median Expanded Disability Status Scale (EDSS) of 3). No deaths were reported in these two cohorts. It should be emphasized that the long-term outcome of these patients has not been reported and will require ongoing study.

Enterovirus A71

Epidemiology

EV-A71 was first isolated from patients with CNS disease in the late 1960s in California [74]. During the subsequent two decades, small clusters of EV-A71-associated hand, foot, and mouth disease (HFMD); aseptic meningitis; encephalitis; and AFP/AFM were reported in the USA, Europe, Australia, and Japan [31]. Outbreaks in Bulgaria in 1975 with 705 reported cases and in Hungary in 1978 with 323 laboratory-confirmed cases were noteworthy for the high rates of neurologic disease, including AFP/AFM, and deaths [75].

The largest reported outbreaks have occurred in Asia. The first of these, which involved 2628 cases of HFMD and 34 deaths, occurred over a 3-month period in Malaysia in 1997 [31, 76]. In 1998, an epidemic involving 129,106 cases of HFMD or herpangina, 405 cases of severe disease, and 71 deaths (91% of whom were children aged ≤ 5 years of age) occurred in Taiwan [20]. Between 2008 and 2012, over seven million cases of HFMD were reported in China, of which 267,942 (3.7%) were laboratory-confirmed and 2457 (0.03%) were fatal [77••]. Among microbiologically proven cases, EV-71 was implicated in 45% of mild, 80% of severe, and 93% or fatal cases [77••].

Studies from Malaysia, Japan, and Taiwan suggest cyclical epidemics occur every 2–3 years [78–81]. Sentinel surveillance from Sarawak, Malaysia, demonstrates EV-A71 epidemics occurring every 3 years, concurrent with HFMD disease activity, with peak incidence occurring between April and July [79]. In Taiwan, epidemic peaks occurred annually during the summer months, but severe disease peaked every 2–3 years [82]. In China, disease peaks occur annually in June in northern regions and biannually in May and October in southern regions [77••].

Pathogenesis

EV-A71 can be transmitted by the fecal-oral or through direct or indirect contact with respiratory droplets or fomites. Shedding of virus in the respiratory tract can persist for about

2 weeks and in stool for up to 3 months after infection [31, 83].

In contrast to PVs, virulence determinants for EV-A71 are poorly understood [78, 84••, 85•]. No significance differences in nucleotide sequence have been demonstrated between EV-A71 isolates from fatal and non-fatal cases [86, 87]. Higher rates of CNS disease observed with different EV-A71 strains, such as those seen with B5 strains compared to B4 strains in Sarawak, Malaysia, could be due to differences in virulence but could also be related to other factors such a pre-existing immunity, host susceptibility, and co-infections [88]. Scavenger receptor class B, membrane 2 (SCRAB2), present on many cell types including neurons, appears to be the main cellular receptor for EV-A71 [89].

There is evidence that host susceptibility contributes to EV-A71 infection and disease severity [78, 84••, 90, 91]. HLA-A33 is associated with an increased risk of EV-A71 infection, and its higher prevalence in certain Asian compared to Caucasian populations (17–33% compared to ≤ 1%) has been proposed as a factor contributing to the higher frequency of EV-A71 outbreaks in Asia compared to western countries [90]. HLA-A2 has been linked with an increased risk of EV-A71-associated cardiopulmonary failure [90], and genetic polymorphism in the chemokine ligand 2 (CCL2) has been linked to an increased risk of EV-A71 encephalitis in a Chinese population [91].

The mechanism of EV-A71 CNS invasion and pathogenesis of neurologic disease is incompletely understood [84••]. Autopsy studies of fatal EV-A71 cases have demonstrated intense inflammation consisting of perivascular cuffing, edema, necrosis, microglial nodules, and neuronophagia primarily in the spinal cord, brainstem, hypothalamus, medulla, pons, and midbrain [78, 84••, 92]. EV-A71 antigen staining is evident in the same regions, but most prominently in the anterior horn cells [92, 93]. EV-A71 has also been isolated or detected by immunohistochemistry or RT-PCR from brain tissue, particularly the brainstem and spinal cord, of fatal cases [94–96]. Taken together, these observations have led to the hypothesis that CNS invasion may occur by retrograde axonal transport [92]. Hematogenous spread and invasion of the CNS via a disrupted blood-brain barrier is also possible, though unproven [78, 84••].

Clinical Manifestations

EV-A71 and CV-A16 are the primary causes of HFMD and herpangina [31]. HFMD is characterized by fever; oral ulcers, mainly of the buccal mucosa and tongue; and a papulovesicular rash involving the palms and soles. Herpangina is a closely related exanthem, the hallmark of which is multiple painful oral ulcers on the soft palate, uvula, tonsils, and posterior oropharynx. In the vast majority of cases, both conditions are self-limited with symptom resolution occurring within a week of onset. The peak incidence is in children less than 5 years of age.

The incidence of severe disease, defined by high fever, vomiting, tachypnea, pulmonary edema or hemorrhage, myocarditis, or neurologic complications leading to hospitalization, is approximately 8.3 per 100,000 cases [20]. Neurologic complications have been observed in 10–30% of children hospitalized during HFMD epidemics in several Asian countries [20, 88, 97, 98]. Brainstem encephalitis with cardiorespiratory failure and pulmonary edema or hemorrhage, due to autonomic dysregulation, can be rapidly fatal and is the most feared complication [17]. Other neurologic complications, in addition to AFP/AFM, include aseptic meningitis, encephalomyelitis, transverse myelitis, and Guillain-Barré syndrome [16•, 17, 21, 31, 99]. Most children with CNS disease have features of HFMD or herpangina, but isolated CNS disease does occur in a small proportion of cases [17].

Microbiologic Diagnosis

Microbiologic diagnosis relies primarily on isolation of the virus in culture or its detection using molecular techniques [31, 100]. Detection of EV-A71 in the CSF, blood, urine, or vesicular fluid is superior to detection from non-sterile sites such as the oropharynx or stool in establishing causality, because the latter may represent resolved infection unrelated to current symptoms or incidental co-infection [31]. The overall yield from the CSF is low—in most studies, the virus was detected in < 30% of neurologic disease cases [21•, 31, 88, 98, 101, 102]. However, pickup rates may vary according to clinical syndrome; in one recent Australian study, EV-A71 was detected in the CSF of all encephalitis samples tested, but only 14% of those with other neurologic syndromes [21•].

Treatment and Outcome

General supportive management is similar to that for PVs and EV-D68.

Several retrospective comparative studies suggest that IVIG may be of benefit in reducing the risk of autonomic nervous system dysregulation and death in severe EV-A71 infections, if administered early [98, 103]. The WHO Guide to Clinical Management recommends IVIG for patients with HFMD associated with symptoms or signs of autonomic nervous system dysregulation or CNS disease other than aseptic meningitis [104]. For those with established cardiopulmonary failure, IVIG may be considered, if not previously given [104]. Significant reductions in levels of the pro-inflammatory cytokines IFN-γ, IL-6, IL-8, IL-10, and IL-13 have been observed after IVIG administration in children with brainstem encephalitis and pulmonary edema, suggesting that the beneficial effect of IVIG is immunomodulatory [105].

The long-term prognosis of EV-A71-associated AFP/AFM has not been extensively studied. In one prospective study of 142 children with EV-71-associated CNS disease and median follow-up of 2.9 years, 56% of those with AFP/AFM had residual unilateral limb weakness and atrophy [103]. Other studies have emphasized the relatively mild nature of the AFP/AFM and better outcome when compared to poliomyelitis [16•, 21•, 106]. In another retrospective study of 134 children with EV-A71-associated CNS disease, 80% (16/20) of those with isolated AFP/AFM had single limb involvement, and only 12.5% (3/24) of those with muscle weakness at admission had residual weakness at 6-month follow-up [16•].

Other enteroviruses

Sporadic clusters of AFP/AFM, usually of lesser severity than that due to PVs, have been reported with many other EVs, including CV-A7; CV-A9; CV-B1 to B6; echoviruses 6, 7, and 9; and EV-D70 (Table 2) [22–29, 41–49]. AFP/AFM associated with EV-D70 and CV-A24 is often accompanied by acute hemorrhagic conjunctivitis [22–25, 44]. Those associated with CVs and echoviruses are typically associated with a non-specific respiratory or gastrointestinal symptoms or less often with HFMD or herpangina [26, 41–43]. EV-C105 is a newly described serotype that was implicated as the cause of right arm AFP/AFM and extensive gray matter hyperintensity on MRI in a previously healthy 6-year-old girl following a mild respiratory prodrome during the 2014 EV-D68 outbreak in the USA [29, 107, 108].

The significance of detecting non-polio EVs in the stool of children with AFP/AFM in the context of polio surveillance needs to be viewed with caution because EVs are ubiquitous and can be shed in stool for months after acquisition. In a large study in India, non-polio EVs, predominantly CV-B and echoviruses 7, 11, 12, 13, and 20, were detected not only in the stool of 27% of children with AFP/AFM but also in 34% of asymptomatic controls [48]. CV-A16 has often co-circulated with EV-A71 during HFMD outbreaks but has generally been associated with milder disease and has only rarely been associated with neurologic disease [20, 77, 97, 109].

Arboviruses

Several arboviruses, including Japanese encephalitis virus, West Nile virus (WNV), and European tick-borne encephalitis virus, have been linked with AFP/AFM that can be clinically indistinguishable from that due to PV and other EVs [110–115]. In the largest case series of childhood AFP/AFM due to Japanese encephalitis virus, a short febrile prodromal illness was followed by the rapid onset of severe asymmetric flaccid paralysis, more often of lower limbs [110]. A potentially distinguishing feature of AFP/AFM due to WNV is that it predominantly affects adults and is often associated with encephalitis or meningitis [112]. In a study of 32 cases of AFP/AFM due to WNV in the USA, the median age was 56 years, only two were children (15–19 years range), and 81% had concomitant encephalitis or meningitis [112]. Among 443 children with neuroinvasive disease from 1999 to 2007 in the USA, only 5 (1%) had isolated AFP/AFM [116]. Tick-borne encephalitis virus has occasionally been associated with a poliomyelitis-like syndrome characterized by proximal muscle weakness often with concurrent cranial nerve and diaphragm involvement [114].

Future directions

Antiviral Medications

There are a number of antiviral agents with potential activity against EVs at different stages of development [117•].

The capsid inhibitors, pleconaril, pirodavir, pocapavir, and vapendavir, are active against most rhinoviruses and EVs but do not appear to have good activity against EV-D68 [118, 119•]. Pleconaril showed promising results in treating neonatal EV infections [120], but unfortunately, it is not currently commercially available. Pirodavir exhibits some activity against EV-A71 [118]. Pocapavir reduced shedding of OPV in a randomized placebo-controlled trial and may play an important role in polio eradication efforts in the coming years [121•]. It has also been used in the treatment of neonatal EV infections [122].

In vitro susceptibility data indicate that rupintrivir, a C3 protease inhibitor, has potent activity against rhinoviruses and EVs [123], including EV-D68 and EV-A71 [119•], and is effective in treating EV-A71 infections in suckling mice [124]. After initial promising phase 1 and 2 clinical trials in humans in the mid-2000s [125, 126], the development of this drug was, however, discontinued but given current need and could potentially be revived.

Fluoxetine, a selective serotonin reuptake inhibitor, demonstrates good in vitro activity against EVs, including EV-D68 [118, 127–129], which appeared beneficial in the treatment of a 5-year-old boy with X-linked agammaglobulinemia and chronic EV encephalitis [130]. The concentration of fluoxetine in the brain is 20-fold higher than that in the serum, suggesting that this may be a good treatment option for CNS disease due to susceptible EVs [129]. However, fluoxetine treatment was of no benefit in improving motor outcomes in mice with EV-D68-induced AFP/AFM [72].

Ribavirin exhibits moderate in vitro activity against EVs, including EV-A71, and in an EV-A71-infected mouse model, it reduced mortality, morbidity, and subsequent paralysis

[131]. In vitro synergistic activity of ribavirin with the nucleoside analogue gemcitabine has been observed [132].

Vaccines

The success of polio vaccines should serve as a model for the prevention of serious disease due to other highly pathogenic EVs.

The response to EV-A71 has included the development of vaccines. Three large randomized, double-blind, placebo-controlled trials of inactivated whole virus C4 genotype EV-A71, alum-adjuvanted, vaccines administered to infants in China have demonstrated 90–97% reductions in HFMD [133••, 134••, 135••, 136•]. One of the trials demonstrated 100% efficacy in preventing EV-A71-associated hospitalizations (0 case in vaccine arm vs. 24 cases in placebo arm) and neurologic complications (0 case in vaccine arm vs. 8 cases in placebo arm) [133••]. Two of these vaccines have been licensed for use in China and are in commercial production [137]. A cost-effectiveness analysis of routine EV-A71 vaccination of infants in China, assuming a birth cohort of 15 million per year, suggests that over 600,000 cases of HFMD/herpangina and 435 deaths would be averted and that the vaccine would be cost-effective at current pricing [138]. The long-term efficacy and impact on virus evolution of these vaccines will need to be monitored carefully.

The need for an EV-D68 vaccine is uncertain at this stage. Nevertheless, it is noteworthy that a recombinant EV-D68 virus-like particle vaccine elicited potent serotype-specific neutralizing antibodies against EV-D68 in a mouse model [139, 140].

Conclusion

With the near-eradication of PV-related flaccid paralysis, EV-D68, EV-A71, and to a lesser extent, other EVs have emerged as the predominant causes of AFP/AFM. We have highlighted the growing knowledge related to these viruses, the poor prognosis of EV-associated AFP/AFM, and the lack of knowledge regarding treatment. Future research should focus on the following: (1) understanding the pathogenesis of AFP/AFM and defining virus strain-specific virulence determinants; (2) delineating host factors that predispose to neurological complications; (3) evaluating potential treatments, including antiviral agents; (4) vaccine development; and (5) determining the long-term outcome of EV-associated AFP/AFM.

Compliance with Ethical Standards

Conflict of Interest Drs. Ari Bitnun and E. Ann Yeh declare that they have no conflicts of interest related to this project.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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