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Acute flaccid myelitis in Switzerland – association with enterovirus D68

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Summary

Poliomyelitis-like acute flaccid myelitis associated with enterovirus D68 (EV-D68) has emerged globally during the past decade. Here we describe the first documented case reported from Switzerland, and a second, suspected case occurring in temporal association. AFM occurs primarily in children, is usually heralded by a febrile, respiratory prodrome followed by acute-onset, usually asymmetrical, limb weakness with some predilection for the upper extremities, and respiratory muscle compromise in one third of reported cases. There is no specific therapy and the majority of cases result in permanent neurological sequelae. A comprehensive diagnostic workup and timely reporting to the health authorities are essential. Surveillance of respiratory and stool samples for EV-D68 and other neurotropic enteroviruses is in place in several European countries and warrants consideration in Switzerland. This could entail the extension of the poliomyelitis surveillance program of the Federal Office of Public Health by monitoring and enteroviral typing of respiratory samples from patients with acute flaccid paralysis.

Background

The term acute flaccid myelitis was created by the US Centers for Disease Control and Prevention (CDC) in 2014 to describe patients, usually children, with acute onset of acute flaccid limb weakness of unknown aetiology without and with lesions in grey matter of the spinal cord [1]. Since then, enterovirus type D68 (EV-D68) has emerged as the major driver of this poliomyelitis-like disease in many regions of the world [2, 3] including Europe, where circulation was first described in detail in 2014 [4]. Several hundred cases have now been reported worldwide [2].

First isolated in 1962 in the USA from respiratory specimens [5], EV-D68 enters the body by way of the respiratory tract, which is unusual for an enterovirus and resembles the rhinoviruses [6]. EV-D68 was later found to cause epidemics of acute respiratory disease, usually in a biennial pattern with peak activities in the late summer [7] and autumn of even-numbered years [8, 9]. The first cases of acute flaccid myelitis were reported from California in 2012 [10]. An outbreak in Colorado in 2014 established a spaciotemporal connection between cases of acute flaccid myelitis and the circulation of EV-D68[11]. Subsequent studies established a firm link between EV-D68 and acute flaccid myelitis. This clinical manifestation is thus typically heralded by a prodromal illness of the respiratory tract [12], followed by acute-onset, severe weakness of one or more extremities with some predilection for the upper limbs [2, 13]. Weakness is usually asymmetrical, but symmetrical disease also occurs. These features reflect spinal disease of the anterior horn or, less frequently, of the brainstem motor nuclei and usually result in persistent motor disability similar to poliomyelitis [2, 13].

Some European countries saw an out-of-phase activity of EV-D68 in the autumn of 2019 [14]. Most unusual, however, was the complete absence of the expected wave in 2020. This was attributed at least in part to the population-wide non-pharmaceutical interventions implemented to curb the COVID-19 pandemic, which largely suppressed the circulation of enteroviruses in general [15, 16]. However, a new wave of EV-D68 infections was reported in many European countries in the autumn of 2021. Although cases of acute flaccid myelitis were not observed in one survey [17], we report two cases, with EV-D68 recovered from one patient, and a non-speciated enterovirus in the other, occurring in the late autumn of 2021. To our knowledge, this is the first report of EV-D68-associated acute flaccid myelitis in Switzerland.

Case reports

The air distance between the two patients' places of residence was 90 km. They or their close family members did not knowingly spend time with each other or in the same geographic vicinity.

Patient 1

Patient 1 was a 9-year-old, previously healthy, male child with his immunisations up to date including the vaccines against poliomyelitis and tick-borne encephalitis. He came down with low-grade fever, rhinorrhoea and a sore throat in early November 2021. No other family member was

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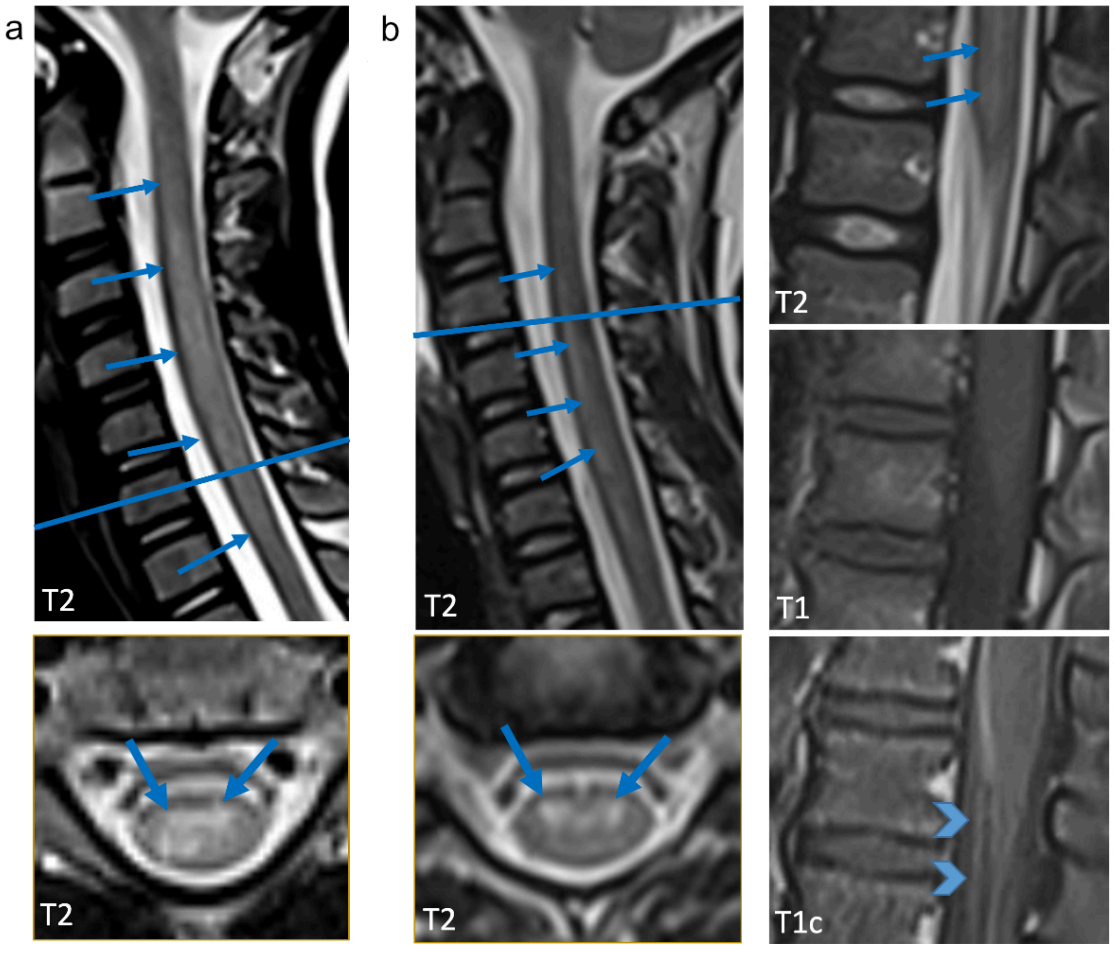
ill, but he mentioned a similar illness among some of his classmates. Two days later he noticed complete inability to move his right arm and complained of orthostatic dizziness. On admission to the hospital, he was fully alert. His body temperature was 38.0°C. Heart rate, respiratory rate and transcutaneous O_2 saturation were 92–145 bpm, 28/minute and 90–92%, respectively. General physical examination revealed mild pharyngeal redness, productive cough and mild jugular retractions, but was otherwise normal. Neurologically, he showed a near total flaccid palsy of his right arm with no ability to execute visible movements in his right shoulder and upper arm (muscle strength M0–1 on a conventional five-point scale [18]) and with limited function in his right hand and wrist (M2–3). There was no neck stiffness, no sensory impairment and no bladder dysfunction. Magnetic resonance imaging (MRI) revealed a contiguous T2-hyperintense lesion predominantly within the grey matter of the spinal cord reaching from the craniocervical junction to thoracic vertebra 1, indicative of myelitis (fig. 1, panel a).

The cervical spinal cord was swollen but did not show contrast enhancement. His laboratory data are listed in table 1. Enterovirus polymerase chain reaction (PCR) testing from both cerebrospinal fluid (CSF) and stool were negative, but enterovirus PCR on a nasopharyngeal swab was positive. Sanger sequencing following reverse RNA transcription of a viral genomic region located between the VP4 and the VP2 capsid proteins [19] later identified EV-D68. Shotgun metatranscriptomic sequencing (Illumina® MiSeq, Nextera Flex, 2 × 150 bp, 300 cycles) [20] of the total extracted RNA revealed the presence of few reads (5/4,528,656 reads), which nonetheless unambiguously identified EV-D68 (bootstrap 100%) [21] in two recovered regions (316 bases of 5'UTR, and 132 bases of the capsid protein 1A of VP4; data not shown), covering in total 6.1% of the EV-D68 reference genome sequence AY426531.1. Based on the initial assumption of an immune-mediated inflammatory process, he received high-dose intravenous methylprednisolone, followed by plasmapheresis and intravenous immunoglobulin replacement (table 1). There was no neurological improvement. He was otherwise stable except for

Figure 1: Representative sagittal and axial T2w images are shown (a: patient 1, 9.3-year-old old boy; b: patient 2, 7.1-year-old girl) as well as T1w images with and without contrast agent (b). Cervical myelitis with increased T2 signal is present in both children (arrows), in the boy only in the cervical spinal cord (a), in the girl additionally in the lumbar spinal cord (b). On the axial slice predominant involvement of the grey matter is evident (arrows point to anterior horns). In b (second column) sagittal T1w images show enhancement of the cauda equina and anterior nerve root enhancement (arrow heads).Representative sagittal and axial T2w images are shown (a: patient 1, 9.3-year-old old boy; b: patient 2, 7.1-year-old girl) as well as T1w images with and without contrast agent (b). Cervical myelitis with increased T2 signal is present in both children (arrows), in the boy only in the cervical spinal cord (a), in the girl additionally in the lumbar spinal cord (b). On the axial slice predominant involvement of the grey matter is evident (arrows point to anterior horns). In b (second column) sagittal T1w images show enhancement of the cauda equina and anterior nerve root enhancement (arrow heads).



episodes of mild blood pressure instability and was discharged home after 18 days. Six months later and after intense outpatient rehabilitation he regained some function in his right hand and wrist (M3–4), but the near complete palsy of his upper right arm persisted.

Patient 2

Patient 2 was a 7-year-old, previously healthy girl, whose illness started with fever above 39.0°C, rhinorrhoea and cough. No other family members had similar symptoms. Five days later and after the fever had subsided, her parents noted an abnormal gait, weakness of her left arm and speech difficulties. On admission, her temperature was 36.9°C. Heart rate, respiratory rate and transcutaneous O_2 saturation were 102 bpm, 29/minute and 100%, respectively. Her general physical examination was normal. Neurologically, she showed bilateral paralytic disease. Assessment of muscle weakness revealed a patchy distribution with marked weakness in her left shoulder (M3) and mild weakness in her legs (M4, right proximal and left distal leg). There was no neck stiffness, no sensory impairment and no bladder dysfunction. MR1 revealed multilevel T2-hyperintense myelitis, affecting the grey matter of the spinal cord with contrast enhancement in the anterior horns of the grey matter. Additionally, there was leptomeningeal enhancement (fig. 1, panel B). Her laboratory data are listed in table 1. Microbiological tests were negative for enterovirus by PCR from both CSF and stool, but enterovirus PCR was positive in a nasopharyngeal swab. Both partial sequencing of the enteroviral VP4/VP2 region [19] and shotgun metatranscriptomic sequencing were unsuccessful in identifying EV-D68 or another enterovirus type molecularly. Her treatment consisted of intravenous high-dose methylprednisolone, followed by intravenous immunoglobulin (table 1). Her gait abnormality and speech disturbance disappeared within several days, but her left shoulder weakness persisted for several weeks. On her last follow-up visit 6 months after the onset of her illness, she had completely recovered.

Discussion

The clinical manifestations in our two patients were prototypical for EV-D68-associated acute flaccid myelitis. They consisted of a febrile respiratory prodrome, followed by rapid-onset asymmetric motor weakness, moderate CSF pleocytosis and T2-hyperintense, longitudinally extensive spinal cord grey matter disease on MRI. Major differential diagnoses, such as Guillain-Barré syndrome, demyelinating disease, other infectious causes or spinal stroke were ruled out using appropriate laboratory (table 1) and neuroimaging studies (fig. 1) and by the subsequent clinical course. Although the differentiation between inflammation and stroke by MRI may be difficult, CSF pleocytosis in both cases clearly established an inflammatory process.

EV-D68-associated acute flaccid myelitis occurs mainly in children. EV-D68 circulates throughout all regions of the world [22] and most individuals encounter it at some point in their lifetime. In Europe, recent seroprevalence studies from the Netherlands [23] and the UK [24] indicate that primary infection with this pathogen occurs early in life. Reinfections by different strains may be common later in life [25]. Data from Switzerland are scanty, but the isolation of EV-D68 from Swiss patients has recently been reported [25, 26]. Most infections solely induce an acute respiratory syndrome, but EV-D68 is – or has recently become [27] – neurotropic and has clearly been linked to acute flaccid myelitis epidemiologically [10], virologically [28], immunologically [29] and in animal models [30]. This is corroborated by evidence from autopsy material from a deceased child with acute flaccid myelitis, showing EV-D68 RNA and protein in anterior horn motor neurones of the spinal cord [31]. The predilection for the paediatric age group may indicate that neurological disease preferentially complicates primary infection rather than reinfection in later life.

We failed to find reports on EV-D68-associated acute flaccid myelitis from Switzerland. Indeed, it is a rare clinical entity and may not have occurred previously in this country as the role of EV-D68 in its pathogenesis has only emerged during the last decade. Alternatively, cases did occur, but were not reported or were missed because of lack of awareness or negative test results. In fact, searching for EV-D68 is quite challenging both in epidemiological surveillance and in clinical practice. First, EV-D68 replicates preferentially in the respiratory rather than the gastrointestinal epithelium. Stool PCR and culture are mostly negative. Routine surveillance of poliomyelitis eradication, which has been in place in Switzerland for many years in accordance with WHO recommendations, focuses on syndromic surveillance of acute flaccid paralysis and laboratory testing of stool specimens (https://www.spsu.ch/en/home). It is thus likely that EV-D68 is missed. Second, clinicians may tend to focus their search for a causative pathogen in cases of acute flaccid myelitis on CSF studies. Unfortunately, CSF enteroviral PCR and CSF metagenomic next-generation sequencing are virtually always negative in acute flaccid myelitis [12, 32, 33], which may have hampered its association with EV-D68 for many years. Rather, the odds of detecting EV-D68 are best in nasopharyngeal material collected during the first few days of illness [2]. Third, routine virological testing in clinical practice does not identify specific enterovirus types. Nasopharyngeal PCR or immunofluorescence [34] testing usually consists of combined detection of enterovirus and rhinovirus species. Single or multiplex CSF PCR may detect enterovirus spp., but do not identify the enterovirus types involved. Thus, a clinical suspicion of AFM should be communicated to the clinical virologist to ensure appropriate testing using type-specific PCR or sequencing for identification of EV-D68. This should be done in a timely manner, because knowledge of the presence of EV-D68 may obviate therapeutic interventions that are expensive, ineffective and potentially harmful.

There is currently no established treatment for acute flaccid myelitis and the majority of patients suffer from persistent motor sequelae [13]. Corticosteroids and plasmapheresis administered to our two patients have no role in acute flaccid myelitis and were given based on the hypothesis of a non-infectious inflammatory process before EV-D68 could be identified. Also, there is currently no evidence for a beneficial effect of intravenous immunoglobulins, although recent evidence from a mouse acute flaccid myelitis model demonstrated that early administration of

Table 1:
Clinical, laboratory, radiology findings and management of two cases with acute flaccid myelitis. Clinical, laboratory, radiology findings and management of two cases with acute flaccid myelitis.

Finding	Case 1	Case 2
Clinical symptoms and signs		
Gender	M	F
Age	9 years, 3 months	7 years, 1 month
Comorbidity	None	None
Vaccines received	Up to date including, polio and TBE	Up to date, including polio (not TBE)
Prodromal illness	Upper respiratory tract infection	Upper respiratory tract infection
Onset of paralysis	5 November 2021	17 December 2021
General manifestations on admission	Fever, pharyngitis, cough, jugular retractions	None
Neurological examination	Near total right arm palsy	Left shoulder and bilateral leg weakness
Haematology, chemistry, immunology, CSF [reference range]		
White blood cell count (G/l) [3.0–12.5]	8.34	9.65
Lymphocyte count (G/l) [1.00–8.00]	1.56	2.65
C-reactive protein (mg/l) [<5]	6	<3
ALT, AST, LDH, creatine kinase	Within normal limits	Within normal limits
Vitamin B12 (pmol/l) [145–569]	530	554
Serum IgG (g/l) [5.0–11.7]	11.7	7.37
Serum autoantibodies[1]	Negative	Negative
CSF white blood cell count (×10^6/l)	186	46
– Mononuclear cells	148	45
–Polymorphonuclear cells	38	1
CSF glucose (mmol/l) [3.33–4.44]	3.36	3.1
CSF protein (g/l) [0.20–0.40]	0.36	0.63
CSF lactate (mmol/l) [1.20–2.10]	1.89	2.80
CSF IgG intrathecal synthesis (%) [<10]	15	0
CSF IgA intrathecal synthesis (%) [<10]	0	0
CSF IgM intrathecal synthesis (%) [<10]	20	21
CSF autoantibodies (aquaporin-4; MOG)	Negative	Negative
Microbiology		
Nasopharyngeal swab direct immunofluorescence panel[2]	Negative	Negative
Nasopharyngeal swab for SARS-CoV-2 PCR	Negative	Negativ
Nasopharyngeal swab for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Bordetella pertussis* PCR	Negative	Not done
Nasopharyngeal swab for enteroviruses PCR	Positive	Positive
VP4/VP2 Sanger sequencing	EV D68	Unsuccessful
Shotgun metatranscriptomics	D68	Unsuccessful
CSF Biofire® multiplex PCR	Negative	Not done
CSF specific Enterovirus PCR	Negative	Negative
CSF specific HSV1/2 PCR	Not done	Negative
CSF Epstein-Bar virus PCR	Not done	Negative
CSF *M. pneumoniae* PCR	Not done	Negative
Serology panel I[3]	Negative	Negative
Serology panel II[4]	Positive	Positive
Stool molecular bacterial enteritis panel[5]	Negative	Not done
Stool enterovirus PCR and culture	Negative	Negative
Radiology		
Magnetic resonance imaging	see figure 1	
Therapy		
Methylprednisolone IV 30 mg/kg (days)	5	5
Plasmapheresis (days)	5	–
IV immunoglobulin 0.4 g/kg per day (days)	5	2
Outcome		
Neurological findings	Persistent proximal: right arm palsy	Complete recovery

ANCA: anti-neutrophil cytoplasmic antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMV: cytomegalovirus; CSF: cerebrospinal fluid; HHV: human herpes virus; IV: intravenous; LDH: lactate dehydrogenase; MOG:myelin oligodendrocyte glycoprotein; PCR: polymerase chain reaction; TBE: tick-borne encephalitis; VZV: varicella-zoster virus

[1] Rheumatoid factor IgA/IgM, PR3-ANCA, myeloperoxidase-ANCA, anti-phospholipase receptor A2; aquaporin-4; MOG. [2] Influenza A/B; respiratory syncytial virus A/B; parainfluenza; picornaviruses; adenovirus; human metapneumovirus (hMPV). [3] Herpes simplex virus 1+2 IgG, HHV-6 IgM (tested in patient 1 only), CMV IgM, VZV IgM, parvovirus B19 IgM (patient 1 only), *Bartonella henselae,Mycoplasma pneumoniae*, *Borrelia burgdorferi*. [4] CMV IgG, anti-Epstein-Barr virus-1 IgG, HHV-6 IgG, parvovirus B19 IgG (patient 2 only), VZV IgG. [5]*Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Aeromonas* spp., *Vibrio* spp., *Yersinia enterocolitica*.

a neutralising monoclonal antibody may improve paralytic outcome [35].

Because of its recent emergence as a neurotropic agent, monitoring of the clinical burden of EV-D68-associated acute flaccid myelitis in the population is paramount. This can be achieved by epidemiological surveillance, either specifically for EV-D68 or, preferentially, by general genomic surveillance of neurotropic enterovirus types circulating in the community, such as enterovirus A71. Such programmes have been implemented in several countries and provide us with what we currently know about EV-D68 in Europe [17, 36]. Enhanced efforts to generate genomic viral surveillance data should not be limited to influenza and SARS-CoV-2 but be extended to other microorganisms that pose emergent public health threats. This report illustrates that EV-D68 is one of them.

Conclusion

EV-D68-associated acute flaccid myelitis is an emerging health threat primarily for children. No host predisposing factors are known. This case report illustrates the classic clinical course of acute flaccid myelitis and the diagnostic approach needed to maximise the yield of EV-D68 in clinical specimens. This process must be initiated by the clinician who first sees a patient with acute flaccid paralysis of any possible cause. This report should also serve as a call to action for expanding genomic enterovirus surveillance in Switzerland.

Acknowledgment and ethics statement

The authors thank the patients and their families for their cooperation.

Bern University Hospital General Consent (GC) was granted by the patients' legal guardians for the use of routine clinical data in the medical record for research purposes and scientific publications. In addition, oral informed consent was obtained from the legal guardians as required by the University Hospital for case reports.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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