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A First Case of Acute Flaccid Myelitis Related to Enterovirus D68 in Belgium: Case Report

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Enterovirus · Acute flaccid palsy · Motor deficit · Spinal cord · Case report

Abstract

Introduction: We describe the first case of acute flaccid myelitis (AFM) related to enterovirus D68 (EV-D68) infection in Belgium. The clinical and radiological presentation of AFM associated with EV-D68 although well described currently remains a challenging diagnosis. Through this interesting clinical case, we aimed to review the differential diagnosis of acute flaccid palsy in a child and discuss the specific point of interest related to AFM. ***Case Presentation:*** We present the case of a 4-year-old girl with a torticollis associated with an acute palsy of the right upper limb. The magnetic resonance imaging revealed an increased T2 signal intensity of the entire central gray matter of the cervical cord with involvement of the posterior brainstem. A polymerase chain reaction (PCR) conducted on a nasopharyngeal swab was found positive for EV-D68. The definition of AFM proposed by the Center for Disease Control and Prevention (CDC) is an acute-onset flaccid weakness of one or more limbs in the absence of a clear alternative diagnosis and the radiological evidence of gray matter involvement on an MRI picture, and our case fits these two criteria. A prompt and detailed workup is required to distinguish this emergent disease from other forms of acute flaccid palsy. The functional prognosis of AFM is poor, and there are no evidence-based treatment guidelines so far. ***Conclusion:*** AFM is an emerging pathology that requires the attention of pediatricians to quickly rule out differential diagnoses and adequately manage the patient. Further research is needed to optimize treatments, improve outcomes, and provide scientifically based guidelines.

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Introduction

Acute flaccid myelitis (AFM) is an acquired spinal cord disorder that mostly affects preschoolers and is characterized by acute flaccid weakness of one or several limbs. Magnetic resonance imaging (MRI) reveals a spinal cord lesion largely restricted to the gray matter [1].

Recent publications have outlined the relationship between outbreaks of enterovirus D68 (EV-D68) infections and AFM [2]. We aimed to describe the first pediatric case of AFM related to EV-D68 reported in Belgium, which had the particularity of being combined with an A71 infection. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535316).

Case Report

A previously healthy 4-year-old girl presented with an acute paralysis of the right upper limb. The patient was fully vaccinated including vaccination against poliomyelitis. She first complained of pain in the right arm and the next morning developed a weakness in the right arm with torticollis. Clinical findings revealed irritability, poor neck control, and proximal paralysis with areflexia of the right upper limb (MRC score 0/5). Ataxia or cranial nerve dysfunctions was not observed. A mild upper respiratory tract infection with fever was reported approximately 10 days before the episode.

The initial head computed tomography scan was unremarkable. The blood test showed mild inflammatory signs, i.e., sedimentation rate 30 mm/h, C-reactive protein (CRP) < 0.5 mg/L, and normal leukocyte count. Serological tests for *Borrelia*, Epstein-Barr virus, and cytomegalovirus were all negative.

The cerebrospinal fluid (CSF) showed 28 red-blood cells/mm^3, 250 white-blood cells/mm^3, glucose level of 87 mg/dL, and protein level of 35 mg/dL. Both bacteriology and a polymerase chain reaction (PCR) panel for meningo-encephalitis in CSF (FilmArray testing for *Steptococcus pneumoniae, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis*, herpes simplex viruses 1 and 2, varicella zoster virus, enteroviruses, and *Cryptococcus neoformans*) returned negative results.

MRI of the brain and spinal cord revealed increased T2 signal intensity of the central gray matter of the cervical cord extending from C2 to C7, along with involvement of the posterior brainstem (Fig. 1). This peculiar MRI pattern was strikingly similar to that described in previous outbreaks of viral myelitis caused by enterovirus A71 (EV-A71), EV-D68, and poliomyelitis [3–5]. More specifically, the restriction of signal abnormalities to the central gray matter along with the lack of supratentorial lesions allowed us to rule out other possible diagnoses, such as acute disseminated encephalomyelitis or neuromyelitis optica spectrum disorder (NMOSD).

A nasopharyngeal aspirate identified both EV-D68 and human-herpes virus 6, while a PCR of the stools revealed the presence of EV-A71. The optic fundus was normal, ruling out the diagnosis of NMOSD. The diagnosis of AFM was confirmed using clinical and radiological criteria fulfilled [6].

The patient was initially treated with high-dose corticosteroids (30 mg/kg/day for 4 days); however, there was no clinical improvement. Second-line treatment with intravenous immunoglobulins (500 mg/kg/day for 4 days) resulted in slight motor improvement.

At 4 days, repeated medullary MRI showed a clear regression of the lesions (Fig. 1), and cerebrospinal pleocytosis decreased (41 white-blood cells/mm^3 including 97% lymphocytes). In parallel, the patient underwent intensive physiotherapeutical rehabilitation.

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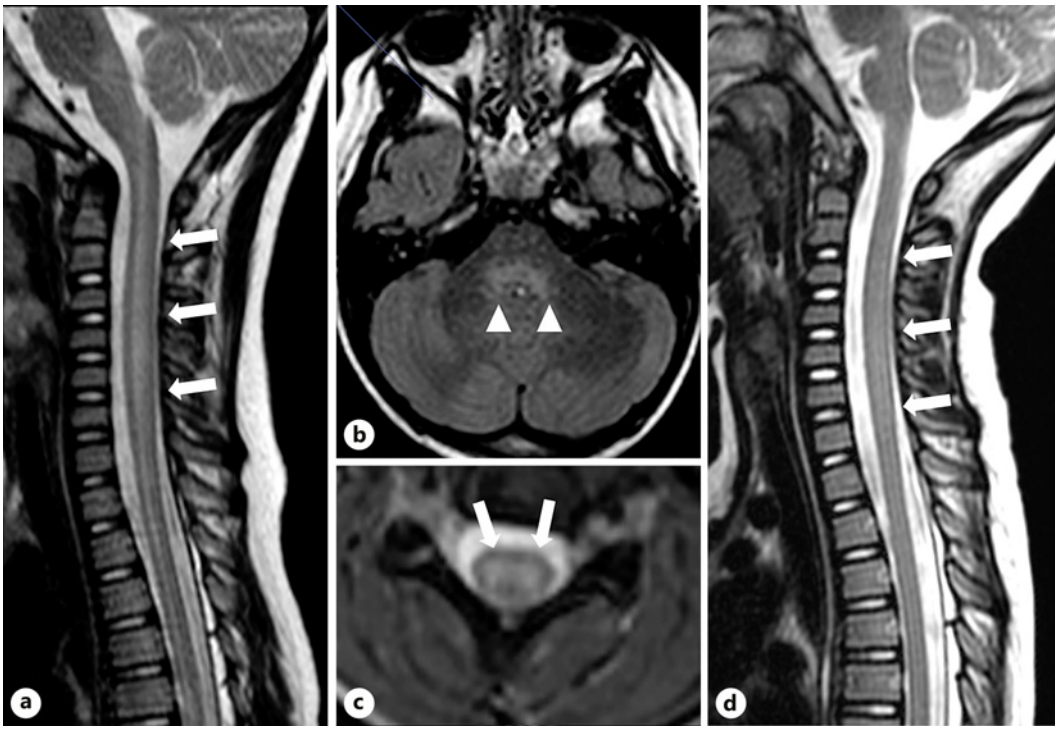

Fig. 1. MRI findings at admission (**a–c**) and follow-up (**d**). **a** Sagittal T2-weighted image shows longitudinally extensive increased signal intensity and moderate swelling of the cervical spinal cord (arrows). **b** Axial T2 FLAIR-weighted image shows increased signal intensity of the dorsal pons (arrows). **c** Axial gradient-recalled echo (GRE) T2-weighted image at the level of C4 demonstrates ill-defined increased signal intensity of entire central gray matter with sparing of peripheral white matter (arrows). **d** MRI of the spinal cord after 4 days treatment shows near-complete regression of signal abnormalities (arrows).

At 3 months after disease onset, due to an unelectable F-wave, a motor nerve conduction study suggested a motor involvement in the cubital nerve and electromyography (EMG) showed rare fibrillation potentials in the deltoid (motor unit action potential was not studied due to sedation). Detailed sensory nerve conduction study of the right upper limb was strictly normal.

The patient was discharged after 8 days of hospitalization and was subjected to an intensive rehabilitation program. She partially recovered muscle strength, but 3 years later, proximal paresis of the right arm persisted with atrophy of the shoulder muscles.

Discussion

Here, we describe a case of AFM in a 4-year-old girl who was tested positive for EV-D68. She first presented with right arm pain, followed by an acute proximal weakness in the context of a recent febrile upper respiratory infection.

Historically, the clinical presentation of AFM is known to be caused by another enterovirus, namely, poliovirus. This virus induces dysfunction or death of the anterior horn cells, causing symptoms of acute flaccid paralysis; however, the exact pathomechanism is still not well understood [7].

The Center for Disease Control and Prevention (CDC) proposed the definition of AFM in 2014 after a large EV-D68 outbreak in the USA. This was formerly labelled "polio-like" myelitis or Hopkins disease. Since then, an increase in AFM cases associated with EV-D68 has been observed worldwide [8].

In Belgium, EV-D68 has been isolated in the respiratory tract since 2014, with an increasing incidence in 2018; however, no associated case of AFM has been described so far [9].

Since 2014, cases of AFM have been reported in the USA with peaks every 2 years, from late summer to early fall. A similar evolution was expected in Belgium [10].

The diagnostic criteria for AFM were updated by the CDC in 2019, based on clinical and radiological data. The main clinical finding was the acute onset of flaccid limb weakness. The acute timeframe is important because paralysis usually progresses within 4 days, sometimes with bulbar involvement and paresis of the respiratory muscles [3, 10]. The MRI findings are longitudinally extensive involvement of spinal cord gray matter and rhombencephalitis affecting the dorsal brainstem in patients in whom gray matter involvement from other causes have been ruled out (i.e., malignancy, vascular disease, or anatomic abnormalities [6]).

The pathogenesis is not well understood, but a strong correlation between AFM and EV-D68 infection has been established. This is supported by neurotropism of the virus, which takes a retrograde axonal route. The hypotheses are either direct viral aggression or a post-infectious inflammation in the motoneuron, which is now the preferred theory [7].

Viruses other than poliovirus or EV-D68 are known to be associated with AFM, such as flaviviruses (Zika virus and West Nile virus), adenoviruses, and other enteroviruses. EV-A71, in particular, was responsible for several recent epidemics of AFM, but the presentation seems slightly different from that in our case [11].

Indeed, patients with EV-A71 are likely to present with hand, mouth, and foot syndromes, irritability, signs of meningitis or encephalitis, ataxia, and autonomic instability. Compared with EV-D68, children with AFM associated with EV-A71 seem to have a milder weakness and a better outcome [12, 13]. Interestingly, our patient was positive for EV-D68, from nasopharyngeal aspirate and EV-A71, from stools.

We could not sequence the EV-D68 for comparison with the EV-A71; however, regarding the typical clinical course, EV-D68 is most likely responsible for the symptomatology of the patient. The recommended investigations in the case of AFM include blood and CSF analysis, MRI of the brain and spinal cord with and without gadolinium, optic fundus examination to rule out NMOSD, and EMG and nerve conductions (Table 1).

AFM is characterized by fibrillation potentials, reduced recruitment of motor unit potentials, and low response amplitudes of compound muscle action potentials, without sensory abnormalities. These signs can appear from 1 or 2 weeks and persist for several months after the onset of symptoms [8, 14]. In the present case report, the electroneuromyographic data supported proximal denervation with normal motor and sensory nerve conduction velocity; however, the F-wave disappeared from the ulnar nerve. This was consistent with a second motor neuron injury.

Initial intensive management is required, using cardiorespiratory monitoring, given the risk of bulbar lesions and respiratory failure. Mechanical ventilation has been reported in up to 44% of the patients in the US [10]. Treatment is mainly supportive because there is neither a specific treatment nor a vaccine or clear guidelines for a therapeutic approach in the acute phase [8, 10].

Intravenous immunoglobulin is currently the first recommended treatment in several studies [8]. It has been administered alone or in combination with other treatments, with variable clinical responses. Indeed, if some patients show an improvement in neurological deficits or at least stabilize, others do not respond at all [7, 15].

The benefits of corticosteroid treatment remain controversial. On the one hand, it should assist in the decrease of spine edema, but on the other hand, it would induce immune suppression. However, corticosteroids have never been associated with a negative outcome in

Table 1. AFM: recommended workup

Recommended examination	Alternative diagnoses
MRI of the brain and spinal cord	Typical feature of AFMs: increased T2 signal intensity of cervical cord central gray matter and dorsal brainstem
	Differential diagnoses: ADEM, NMOSD, other infectious etiologies
Electromyography, nerve conductions, repetitive stimulation studies	Guillain-Barré syndrome, neuropathies, mononeuritis multiplex, myasthenia gravis, Lambert-Eaton myasthenic syndrome, myopathies
Blood and serum analysis	CBC, electrolytes, LFT, ESR, CRP, CK
	Autoimmune antibody panel: ANA, dsDNA, ENA, ANCA, CCP, SSA, SSB, antiphospholipid, anticardiolipin, antithyroglobulin, complement levels, sedimentation rate
	Anti-AQP4, anti-MOG
	Acetylcholine receptor antibodies
	Consider chest CT, bronchoalveolar lavage, lymph node or bronchial biopsy if sarcoidosis suspected
	Viral serology: HIV-1/2, herpes viruses (HSV-1/2, VZV, EBV), enterovirus, adenovirus, West Nile virus, +/− Zika virus
	Bacterial serology, including *Borrelia burgdorferi* +/− *Corynebacterium diphteriae*, *Clostridium botulinum*
	Blood culture for bacteria and fungi
CSF analysis	Cell count, protein level, glucose, lactate, immunoelectrophoresis/electrofocusing, and cytology
	Anti-AQP4, anti-MOG
	Bacterial, mycobacterial, and fungal stains and cultures, VDRL
	Meningo-encephalitis panel, including HSV, VZV, enterovirus, EBV, CMV, HHV6, HIV, flaviviruses
	Antibodies for HTLV-I, *B. burgdorferi*, *M. pneumoniae*, *Chlamydia pneumoniae*
Respiratory pathogens multiplex PCR (nasopharyngeal swab or aspirate)	For enteroviruses
Gastro-intestinal PCR	For enteroviruses
Urine analysis	Porphobilinogen
Toxical screening	Toxic neuropathies
Optic fundus	For anti-AQP4/MOG-associated myelitis

ADEM, acute disseminated encephalomyelitis; HHV6, human-herpes virus 6; EBV, Epstein-Barr virus.

transverse myelitis, even in infectious cases, and patients may benefit from early anti-inflammatory therapy [16]. A recent publication outlined the potential benefit of fluoxetine as an antiviral therapy and this treatment certainly has to be studied [17]. There was no proven benefit for alternative therapies such as plasmapheresis, antiviral therapies,

interferon or biological treatment alone or combined [6, 18]. Currently, the functional prognosis of this disease is poor and rehabilitation treatments have to be studied, including surgical nerve transfers in some cases [19].

To conclude, we describe the first case of AFM related to EV-D68 in Belgium, with a severe clinical presentation that evokes well-known poliomyelitis. Accurate recognition and documentation of AFM are important to avoid under- or misdiagnosis. The diagnosis of this severe disease is complex because the virus is rarely isolated from the CSF but rather from the respiratory tract and stool samples. There is an urgent need for further investigation to develop prevention and treatment options for this severe and disabling disease with an increasing incidence [20].

Statement of Ethics

The parents of the patient provided their written informed consent for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors declare no conflicts of interest to declare.

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Author Contributions

RODESCH Marine: first author, writing the article based on the current literature and applied revisions from the other authors, and approval of the final version to be published. SCULIER Claudine: substantial contribution to the conception and design of the work and critically revising it thoroughly and approval of the final version to be published. LOLLI Valentina: substantial contribution to the conception of the work and critically revising it, in particular for the radiological points, choice and comments on the appropriate pictures, and approval of the final version to be published. REMICHE Gauthier, FRICX Christophe, and VERMEULEN Françoise: substantial contribution to the conception of the work and critically revising it and approval of the final version to be published. DELPIRE Iris: substantial contribution to the conception of the work, drafting some part of the work and reviewed literature, and approval of the final version to be published. CHRISTIAENS Florence: last author, substantial contribution to the conception and design of the work and critically revising it thoroughly, and approval of the final version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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