IDCases 17 (2019) e00549

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Acute flaccid myelitis associated with enterovirus D68 in a non-epidemic setting

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ARTICLE INFO

Article history:
Received 5 April 2019
Received in revised form 30 April 2019
Accepted 30 April 2019

Keywords:
Acute flaccid myelitis
Enterovirus D68

ABSTRACT

Acute flaccid myelitis (AFM) is a recently defined clinical disease accompanied by the national outbreak of enterovirus D68 (EV-D68) in the United States during the late summer/fall of 2014; 258 cases of EV-D68 and 59 cases of AFM were reported in Japan during the late summer/fall of 2015. Subsequently, there have been no epidemics of AFM or EV-D68. However, we encountered a patient who had AFM associated with EV-D68 in 2017. This is the first case of AFM caused by EV-D68 after the 2015 epidemic, and the only reported case in 2017. This report indicates that AFM caused by EV-D68 can arise even in non-epidemic situations. If a patient presents with paralysis, AFM caused by EV-D68 should be included in the differential diagnosis, regardless of the absence of an epidemic of EV-D68 infection.

Introduction

There was an epidemic of acute flaccid myelitis (AFM) in the United States during the late summer/fall of 2014, and enterovirus D68 (EV-D68) was suspected as a possible cause [1]. In Japan, cases of acute flaccid paralysis (AFP) in children were reported during the late summer/fall of 2015 [2]. Moreover, there was an outbreak of EV-D68 during this period, suggesting that the two outbreaks may be linked [2]. A guideline (Guidelines for Surveillance, Clinical Practice, and Testing of Acute Flaccid Paralysis) was prepared to facilitate diagnosis of this illness [3]. No cases of AFM or EV-D68 were reported in Japan in 2016–2017. However, in 2017, we encountered a patient with AFM. In this case, magnetic resonance imaging (MRI) and polymerase chain reaction findings suggested EV-D68 was the causative agent [4]. This is the first reported AFM case associated with EV-D68 since the 2015 outbreak in Japan, occurring in a non-outbreak setting.

Case report

A 2-year-old boy presented with AFP involving both legs after displaying upper respiratory symptoms. He was previously healthy and had been fully vaccinated, in accordance with the Japanese Child vaccination program, including the polio vaccine. Initially developing a fever and cough, he began to demonstrate light-headedness when walking on the third day and was unable to walk or sit; he developed oliguria by the fourth day, thus precipitating admission to our hospital (day 4 of illness). Clinical analyses of blood, urine, and cerebrospinal fluid (CSF) performed on admission (Table 1) revealed mononuclear pleocytosis. Spinal MRI and myelography (Fig. 1a) revealed no obvious bleeding or vascular disease. Notably, extensive longitudinal lesions existed, but they were overlooked on the day of hospital admission.

Brain MRI revealed no abnormality. The course of treatment and order of tests performed post-admission are shown in Fig. 2. Based on the clinical diagnosis of Guillain-Barré Syndrome (GBS) or AFM, the patient was started on treatment with gamma-globulin (2 g/kg) and steroid pulse therapy (methylprednisolone 30 mg/kg/day) on day 4 of illness. Samples (pharyngeal swab, cerebrospinal fluid,

Abbreviations: AFM, acute flaccid myelitis; AFP, acute flaccid paralysis; EV-D68, enterovirus D68; GBS, Guillain-Barré Syndrome; MRI, magnetic resonance imaging; MMT, manual muscle testing.

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https://doi.org/10.1016/j.idcr.2019.e00549

Table 1
Findings of clinical tests on admission. CSF collected on the day of admission showed pleocytosis. For virus polymerase chain reaction, we examined EV (including EV-D68) and poliovirus for all specimens. EV-D68 was detected in the nasopharyngeal swab collected on day 5.

Blood			Rapid test	
WBC	8880	/μL	Influenza	negative
Lymph	31.1	%	RSV	negative
Neut	61.6	%	Mycoplasma	negative
RBC	488	/μL		
Hb	11.3	g/dL	Nerve conduction velocity examination	
Ht	35.8	%	Decrease in amplitude in the left tibial nerve	
Plt	21.3 × 10*4	/μL	F wave negative	
ALB	4.2	g/dL		
CK	39	IU/L	Antibody test	
AST	28	IU/L	Anti-GQ1b IgGAb	negative
ALT	12	IU/L	Anti-GM-1 IgGAb	negative
LDH	248	IU/L		
Cr	0.26	mg/dL	Virus PCR	
UA	3.9	mg/dL	Pharyngeal swab	EV-D68 positive
BUN	11.2	g/dL	Blood/urine/CSF/stool	negative
Glu	127	mg/dL		
Na	136	mEq/L		
K	3.9	mEq/L		
Cl	103	mEq/L		
Ca	9.1	mg/dL		
CRP	0.02	mg/dL		
Urine				
pH	6			
Blood	(-)			
Protein	(-)			
Glucose	(-)			
RBC	<1	/HPF		
WBC	1∼4	/HPF		
CSF				
Appearance	clear			
Cellularity	87	/μL		
Monocytes	95	%		
Protein	34	mg/dL		
Glucose	76	mg/dL		

whole blood, stool, and urine) were collected on days 4 and 5 of illness and stored at −70 °C for further analysis.

By day 8 of illness, the patient showed ischuria and dyschezia. He was unable to raise both shoulders and showed decreased motor function in both hands (right hand: manual muscle testing level 3 (MMT3), left hand: MMT2). There was no further progression of these symptoms. On day 21 of illness, a review of T2-weighted MRI from the day of admission by an experienced radiologist revealed extensive longitudinal lesions in the entire spine, predominantly in the central gray matter; smooth linear enhancement of the anterior cauda equina nerve roots was also observed (Fig. 1a). The patient was therefore diagnosed with AFM, based on the weakness of his legs, CSF pleocytosis, and MRI findings. On day 27 of illness, the T2-weighted spinal MR image was re-examined; the spinal cord lesions tended to be well-defined and were bilaterally confined to the anterior horns. Anterior dominant enhancement of the cauda equina was observed on the second MRI (Fig. 1b).

On the day of discharge (day 35 of illness), the patient's right and left hands had recovered to MMT4 and MMT3, respectively, and urinary retention was improved; however, weakness of the legs remained. After discharge, the polymerase chain reaction result for the throat swab collection on day 5 of illness was positive, which indicated the presence of EV-D68. No other pathogen (including poliovirus) was detected in samples from the patient. We therefore diagnosed him with EV-D68-associated AFM. At 1 year after discharge, motor function showed improvement to MMT5 for his upper limbs and MMT3 for his lower limbs. He is able to sit without support and has begun to use devices to assist with scoliosis that was acquired after AFP. He continues to undergo rehabilitation.

Discussion

AFM affects a subset of patients with AFP who have gray matter predominant lesions in the spinal cord, suggestive of myelitis and anterior horn involvement as the cause of their paralysis [5]. In addition to polio, EV-A71 and D68 have been reported as causative viruses of AFM [6–9]. In Japan, the nationwide alert and guideline during the 2015 EV epidemic among children led to widespread recognition of the association between EV and AFM among physicians and the public health community in all medical institutions [3].Although the causal role of EV-D68 in AFM outbreaks is strongly suspected, patients who developed AFM during the epidemic of EV-D68 showed low EV-D68 infection rates: EV-D68 was detected in <20% of all pharyngeal fluid swabs, although this was higher than the detection rate observed in other sample types including CSF, whole blood, stool, and urine [2]. In the United States, among the respiratory specimens assessed for 56 patients, 11 (20%) nasopharyngeal/oropharyngeal specimens were positive for EV-D68 and 12 (21%) were positive for other enteroviruses/rhinoviruses [1].

To improve diagnosis, Tanaka-Taya et al. [3] recommended that clinicians cryopreserve (−70 °C) the five acute-phase-collected samples (pharyngeal swab, cerebrospinal fluid, whole blood, stool, and urine) and collect acute and convalescent paired serum samples. As recommended [3], the five acute-phase collected samples in this case were cryopreserved at −70 °C and pharyngeal fluid swabs were collected on days 4 and 5; these methods improved diagnosis. Moreover, the initial day 4 sample of pharyngeal fluid swabs was negative with CODEHOP PCR [10]; however, EV-D68 was detected from a pharyngeal sample collected on day 5 with a different in-house nested PCR assay

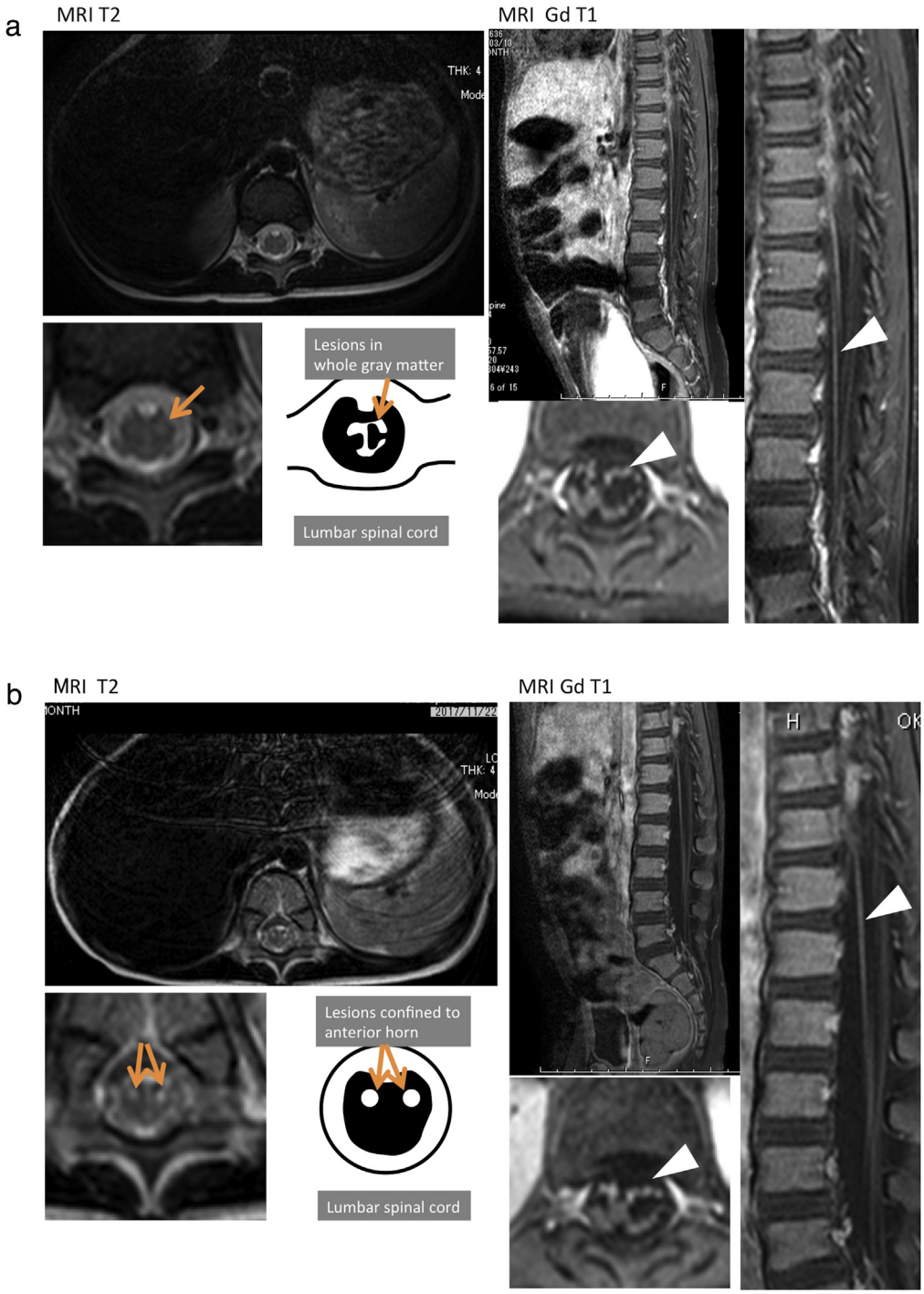

Fig. 1. a) Spinal magnetic resonance imaging (MRI) scan obtained on the day of admission (day 4).
T2-weighted images of the lumber spinal cord show that longitudinal lesions are ill-defined and involve the central gray matter (arrow). Gadolinium-enhanced T1-weighted images show abnormal enhancement of the cauda equina, predominantly in the ventral roots (arrowheads). b) Spinal magnetic resonance imaging (MRI) scan obtained on day 27.
In this second MRI scan, spinal lesions appeared to have become well-defined and were confined to the anterior horn (arrow). The anterior dominant enhancement of the cauda equina remained (arrowheads).

[11]. Due to the limited sample volume, it was difficult to apply both PCR assays to all samples. Our in-house PCR method [11] was considered to be more sensitive for EV-D68.

Vascular lesions, AFM, and GBS have all been considered as potential causes of AFP. Vascular lesions [12] cause hemiplegia in children, but they were absent from brain and spinal MRI scans. Thus, AFM and GBS were considered; gamma-globulin and steroid pulse therapies, which are empirically used for AFM, were administered [1,2,13]. However, these treatments have not been proven efficacious [14]. GBS was suspected because of the progression of symptoms, but gamma-globulin was not effective; thus, we regarded it as an atypical GBS pattern. MR images from the day of admission were sent to a radiologist who is an expert in AFM; we obtained an accurate diagnosis of AFM on day 21 of

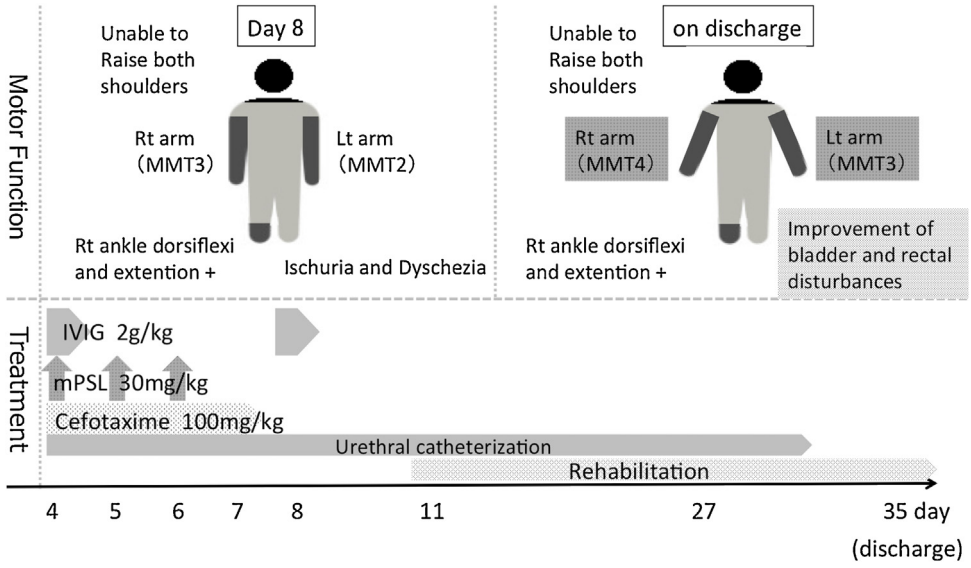

Fig. 2. Follow-up of motor function and treatment.
The upper part shows the development of motor function over time. The motor function of the upper limbs improved, but the weakness of the lower limbs remained. Rehabilitation continued after discharge from the hospital. The bladder and rectal disorders had improved before the discharge. The lower part shows the treatment course. Gamma globulin and steroid pulse were administered as shown.

illness. It should be noted that these cases may be missed if the clinician is not closely reviewing T2-weighted spinal cord images, as AFM is sufficiently rare and there are few opportunities to observe actual MRI findings, even among radiologists and pediatricians. Therefore, accurate interpretation of MR images by an experienced physician, such as a pediatric neuroradiologist, is critical [15].

The most important point of the present case is that, although there was no epidemic of AFM and EV-D68 in 2016/2017, we encountered a patient who had AFM associated with EV-D68. Later, the national pathogen surveillance team discovered that EV-D68 was present in Osaka and Hiroshima in October, suggestive of a small EV-D68 epidemic in western Japan. This suggests that there may be a low prevalence of EV-D68 in Japan, which is sufficiently low that it may be overlooked. For instance, researchers in the UK reported that since the EV-D68 test is not a standard screening method in clinical laboratories, milder cases may not be detected [16]. Further cases must be accumulated to support this point. This report emphasizes the importance of considering AFM caused by EV-D68 even in non-epidemic situations.

Author statement

Kazuki Hatayama wrote the initial draft of the manuscript and contributed to treatment of the patient.

Shinichiro Goto, Masato Yashiro, Tsuguto Fujimoto, Keiko Tanaka-Taya, and Masaru Inoue: drafted the manuscript and contributed to treatment of the patient. Tsuguto Fujimoto, Nozomu Hanaoka, and Tomoka Zuzan: contributed to the EV-D68 gene detection. Harushi Mori: contributed to collecting the images of spinal MRI scans. All authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

None.

Informed consent

Informed consent for the publication of this case report was obtained from the patient's parents.

Authorship

KH, SG, MY, TF, KT, and MI: drafted the manuscript and contributed to treatment of the patient. TF, NH, and TZ: contributed to the EV-D68 gene detection. HM: contributed to collecting the images of spinal MRI scans. All authors have read and approved the final manuscript.

Acknowledgements

We thank all those involved in this study including the Okayama Red Cross Hospital Laboratory and the Okayama City Health Center staff. This study was partly supported by the AMED research program on Emerging and Re-emerging Infectious Disease (grant No. 10104402, JP18fk0108004j0303) and the Health and Labor Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan (grant number H28-Shinkogyosei-Ippan-007).

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