

[ORIGINAL ARTICLE]

Clinical Characteristics of Epidemic Myalgia Associated with Human Parechovirus Type 3 during the Summer of 2019

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Abstract:

Objective Epidemic myalgia associated with human parechovirus type 3 (EM-HPeV3) is characterized by severe muscle pain and weakness on the limbs and trunk with a fever. No outbreak of EM-HPeV3 has been reported since 2016, and its clinical characteristics have not been sufficiently clarified. We herein report a series of EM-HPeV3 cases during the summer of 2019 and clarify the clinical characteristics of EM-HPeV3.

Methods The diagnosis of EM-HPeV3 was established when the patients met both of the following criteria: (1) Patients developed severe muscle pain and weakness with a fever within a week, and those symptoms resolved within a month; and (2) HPeV3 was detected in either a throat swab or fecal specimen of the patient by polymerase chain reaction. We reviewed the medical records of these patients retrospectively.

Results Seven patients met the criteria (6 men and 1 woman, age 34 to 47 years old). Myalgia was observed on the thigh, lower legs, upper arms, and forearms in seven, five, two, and five patients, respectively. Four patients showed distal dominant weakness on the arms, while none of the patients showed proximal dominant weakness on the arms. Of the six patients examined, five showed reduced tendon reflexes on all four limbs. One patient showed slight myogenic change and increased insertion activities on needle electromyography.

Conclusion We observed seven cases of EM-HPeV3 during the summer of 2019. Reduced tendon reflexes and distal dominance of muscle pain and weakness on the arms are considered its distinct clinical features.

Key words: human parechovirus type 3, HPeV3, epidemic myalgia, myositis

(Intern Med 59: 1721-1726, 2020)

(DOI: 10.2169/internalmedicine.4416-20)

Introduction

During the summer of 2008, patients with a fever and severe muscle pain were frequently observed in Yamagata, Japan, and were diagnosed with epidemic myalgia (1). Mizuta et al. isolated human parechovirus type 3 (HPeV3) from those patients afterward (1). Subsequently, outbreaks of epidemic myalgia associated with HPeV3 (EM-HPeV3) were observed in that area in 2011, 2014, and 2016 (2-4).

Epidemic myalgia, which is caused by coxsackie B virus, was initially recognized in the 1930s (5). It is also called

Bornholm disease, and it usually manifests with chest and abdominal muscle pain with a fever (5). EM-HPeV3 causes severe pain and weakness in the four limbs accompanied by a fever and sore throat, which develops after a few days (4). Since this disease differs from Bornholm disease regarding the major pathogen and the site of pain (5), some clinicians call this disease as HPeV3-associated myalgia/myositis (6).

HPeV3 infection is prevalent in several areas of Japan and other countries (7, 8). However, most of the published reports of EM-HPeV3 are derived from a single group of researchers in Yamagata, and other reports on EM-HPeV3 concern only a small number of cases (9). Furthermore, no

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Received: January 1, 2020; Accepted: February 26, 2020; Advance Publication by J-STAGE: April 16, 2020

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Table 1. Clinical Characteristics of the Seven Patients with Epidemic Myalgia Associated with Human Parechovirus Type 3.

Case	Sex	Age (y)	Season	Peak (d)	Resolution (d)	CK (IU/L)	CRP (mg/dL)	NCS	nEMG	Tendon reflexes	MRI (STIR)	Fever	Other symptoms	Family history	Throat	Feces
1	M	32	June	3	22	409	1.11	Normal	ND	Reduced	Normal	(+)	Pubic pain, Leg dysesthesia	Child, boy, runny nose	(+)	ND
2	M	47	June	2	10	849	0.6	ND	ND	ND	ND	(+)	ND	Child, HFMD	(+)	ND
3	F	38	June	3	14	961	0.63	Decreased SNAP on the sural nerve	Normal	Reduced	ND	(+)	Stomatitis Throat discomfort	9mo, boy, rash, runny nose	(-)	(+)
4	M	34	June	4	10	1,605	2.13	ND	ND	Normal	Muscle, Fascia	(+)	Sore throat	1y, runny nose, cough	(-)	(+)
5	M	46	July	4	9*	952	1.33	Normal	Slightly Myogenic	Reduced	Muscle, Fascia	(+)	(-)	15y, cough, fever	(+)	(+)
6	M	42	July	2	11	338	0.76	Normal	ND	Reduced	Normal	(+)	Pubic pain, Throat discomfort	3y, 8mo, girl, HFMD	(-)	(+)
7	M	38	July	4	ND	259	0.36	Normal	ND	Reduced	ND	(+)	Pubic pain Joint pain	Infant, runny nose	(-)	(+)

*With steroid therapy. Peak and resolution indicate the number of days after the onset of any symptom. Throat and feces indicate the result of HPeV3 examination for throat swab and fecal specimen by polymerase chain reaction.

y: year, d: day, ND: not described, NCS: nerve conduction study, SNAP: sensory nerve action potential, nEMG: needle electromyography, HFMD: hand-foot-and-mouth disease

case reports regarding this disease have been published from countries outside of Japan.

We herein report seven adult cases of EM-HPeV3 encountered during the summer of 2019. We investigated the clinical characteristics of these patients and compared their clinical characteristics with those in the reported literature.

Materials and Methods

We retrospectively investigated the clinical characteristics of EM-HPeV3 patients who visited the neurology department 1) of the symptoms resolved within a month; and 2) HPeV3 was detected in either a throat swab or fecal specimens collected from patients by polymerase chain reaction (PCR). Reverse transcription PCR (RT-PCR) was performed using a primer pair to detect the VP1 region of HPeV. The HPeV-positive PCR product was purified and directly sequenced by performing a dye terminator method and subsequently classified based on the genotype of HPeV (10). Clinical data were collected from the patients' medical records.

The study protocol was reviewed and approved by the Institutional Review Board of the Japanese Red Cross Medical Center and conducted in accordance with the Declaration of Helsinki.

Results

Seven patients met the inclusion criteria, and their clinical data are presented in Table 1. First, we will describe the clinical course of a representative case.

Representative case (Case 5 in Table 1)

The patient was a 46-year-old man. In early July, he developed a fever and muscle pain in all four limbs and his trunk four days before admission. Three days before admission, his fever resolved, but his muscle pain and weakness worsened, and he experienced difficulty walking and writing letters. Finally, he could hardly rise from his bed in the morning on the day of admission due to muscle pain and weakness. On admission, his body temperature was normal, and his throat was reddish. He had severe myalgia on his forearms and thighs that worsened when using and grasping his muscles. He had proximal dominant weakness on his legs but distal dominant weakness on his arms. His grip strength decreased to 10 kg and 16 kg for the right and left hands, respectively. Deep tendon reflexes were reduced in all four limbs, except for both Achilles tendon reflexes. He had no sensory impairment in his limbs. A blood test revealed that the white blood cell count was within the normal range (5,390/ μ L), but the platelet count was decreased to 6.9

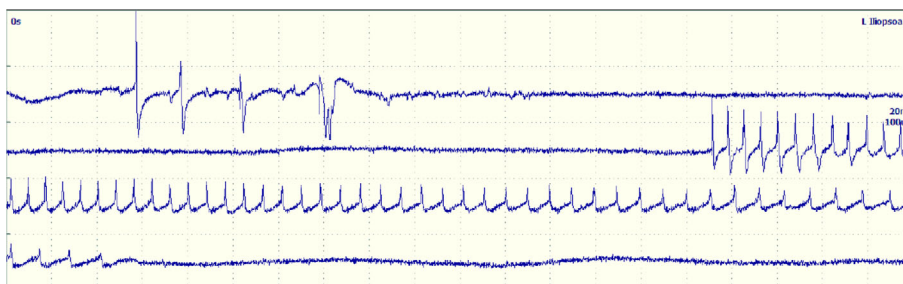


Figure 1. At rest, increased insertion activity was observed on needle electromyography in case 5.

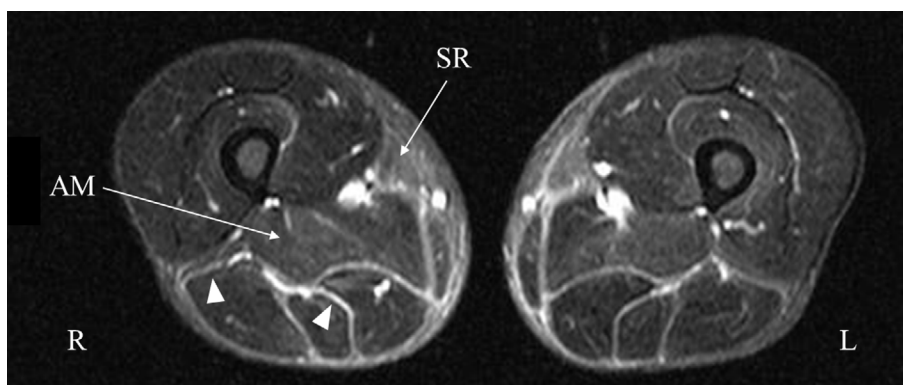


Figure 2. Skeletal muscle magnetic resonance imaging (MRI) of the thighs on short-tau inversion recovery (1.5 tesla; TR: 4013.33, TE: 70) in case 5. MRI revealed segmental distribution of high signal intensities on the adductor magnus muscle and sartorius muscle in the bilateral thighs. Thickening of the fascia (arrowhead) was also observed on MRI. AM: adductor magnus muscle, SR: sartorius muscle

$\times 10^4/\mu\text{L}$, the C-reactive protein (CRP) was slightly elevated to 1.33 mg/dL, and the creatine kinase (CK) was elevated to 952 IU/L.

A routine nerve conduction study (NCS) showed no abnormality, including in the F wave. Needle electromyography on the left iliopsoas muscle revealed slightly rapid recruitment and increased insertion activity (Fig. 1), but neither a positive sharp wave nor fibrillation potential was observed. Muscular magnetic resonance imaging (MRI) revealed patchy hyperintense lesions on his thigh muscles, and a thickened fascia was noted on short-tau inversion recovery (STIR) imaging (Fig. 2). His 16-year-old son had had an upper respiratory infection one week before he developed the abovementioned symptoms. At first, Guillain-Barré syndrome (GBS) was suspected because of the reduced deep tendon reflexes and the distal dominance of the symptoms on the upper limbs.

However, we also considered epidemic myalgia based on the severe myalgia, lack of antecedent infection, normal findings on an NCS, and implications of inflammation on the muscle and fascia, as confirmed by needle electromyography and MRI. Because he strongly requested medication to relieve his myalgia, we administered 20 mg of prednisone per day on the first and second hospital day under the assumption that inflammation of the muscle and fascia was the main pathology of this disease. His muscle pain

started to significantly decrease from the second hospital day, and the grip strengths of his right and left hands were 23 and 18 kg, 30 and 24 kg, and 32 and 24 kg on the second, third, and fourth day, respectively.

He was discharged on the fourth hospital day. His muscular symptoms resolved 2 days after discharge. HPeV3 was detected by PCR in the throat swab and fecal specimen.

Seven cases of epidemic myalgia associated with human parechovirus type 3

The 7 patients were 6 men (85.7%) and 1 woman (14.3%), ranging in age from 34 to 47 years old, with a median age of 38 years old. The disease onset was distributed between June and July. The muscle pain and weakness peaked within 2 to 4 days from the onset and resolved within 2 to 3 weeks. Six patients developed their symptoms in Tokyo, while one patient (case 5) who had been on a business trip to Tokyo developed his symptoms in Fukuoka Prefecture, which is over 800 km west of Tokyo.

The CK values of all of the patients were elevated, ranging from 259 to 1,605 IU/mL with a median value of 849 IU/L. The CRP values of all of the patients were slightly elevated, ranging from 0.36 to 2.13 mg/dL. Stool specimens were obtained from five patients, and HPeV3 was positive in all of these patients. Throat swab samples were positive for the virus in three of the seven patients.

Table 2. Muscle Strength and Pain of Patients with Epidemic Myalgia Associated with Human Parechovirus Type 3 Infection.

Case	Grip strength rt/lft (kg)	MRC score									Muscle pain			
		Deltoid	Biceps	Triceps	FE	FF	Iliopsoas	Quadriceps	TA	GC	Upper arms	Forearms	Thighs	Lower legs
1	ND	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(3, 3)	(4, 4)	(5, 5)	(5, 5)		(+)	(+)	(+)
2	24.0/22.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	(+)	(+)	(+)	
3	13.5/11.5	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(4, 4)	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(+)		(+)	(+)
4	ND	(4, 4)	(4, 4)	(4-, 4-)	(4, 4)	(3, 3)	(3, 3)	(3+, 3)	(5, 4)	(5, 5)			(+)	(+)
5	10.0/16.0	(5, 5)	(4+, 4+)	(5, 5)	(5, 4+)	(4, 4)	(3, 3)	(3+, 3+)	(5, 5)	(5, 5)		(+)	(+)	
6	29.0/31.0	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(4, 4)	(5, 5)	(5, 5)	(5, 5)		(+)	(+)	(+)
7	27.0/28.0	(5, 5)	(5, 5)	(5, 5)	(5, 5)	(4, 4)	(4, 4)	(5, 5)	(5, 5)	(5, 5)		(+)	(+)	(+)

mMRC score: modified British Medical Research Council score, FE: finger extensor muscles, FF: finger flexor muscles, TA: tibialis anterior, GC: gastrocnemius, ND: not described, rt: right, lt: left

Of the six patients whose tendon reflexes were evaluated, five showed reduced tendon reflexes in all four limbs. However, of these five patients, the Achilles tendon reflexes were normal in four. Of the five patients in whom an NCS was performed, one (case 3) showed decreased sensory nerve action potentials in both sural nerves. The other four showed no abnormalities, including for the F wave.

All patients developed a fever in their courses. Throat discomfort or pain was observed in three patients. Three of the six men reported groin pain in their courses. Aside from that, however, different patients experienced abnormal sensation in the lower limbs, stomatitis, and joint pain. All patients had contact with their children, who subsequently developed some symptoms indicative of a viral infection, such as a fever, runny nose, and cough, and two children were diagnosed with hand-foot-and-mouth disease in other hospitals. However, none of their family members developed any muscle symptoms.

Table 2 shows the patients' muscle symptoms. All patients had muscle pain on their limbs and trunk when they visited our department. Cases 1, 2, 5, and 6 experienced difficulty writing letters because of the pain and a decreased grip strength, and cases 1, 2, 4, and 5 experienced difficulty walking because of their leg pain and weakness. Patients usually showed muscle weakness on the limbs and trunk, with modified British Medical Research Council scores of 3 to 4 (11). In most patients, limb weakness exhibited proximal predominance on the legs, but the finger flexor, which reflects grip strength, was more severely affected than the upper arms. Muscle pain was spontaneous and usually exacerbated by grasping those muscles. Regarding their extremities, all of the patients experienced pain in the thighs, and five patients experienced pain in the lower legs. In addition, five patients experienced pain in the forearms, while upper arm pain was observed in only two patients.

Discussion

In the present study, we reported a total of seven patients with EM-HPeV3 who visited our department during the summer of 2019 and investigated the clinical characteristics

of these patients. Human parechoviruses are ribonucleic acid viruses of the genus parechovirus in the family *Picornaviridae* (12). HPeV3 was first isolated in 1999 from an infantile case of transient paralysis (13). HPeV3 usually causes mild respiratory or gastrointestinal symptoms, herpangina, and "hand-foot-and-mouth disease" in infants ≥ 3 months old and children (14, 15). However, it mostly causes severe symptoms in neonates, and the infected patients are diagnosed with sepsis-like syndrome, meningitis, and encephalitis (16). HPeV3 is detected in the stool and throat (10, 17), and it is transmitted either by the oral-fecal or respiratory route (18).

In Japan, a survey conducted in 2014 showed that the positivity of neutralizing antibody to individuals under 5 years old was 51.5% and increased with age up to 100% in the 15- to 19-year-old age group, fluctuating between 70% and 96% in older age groups (7). Another survey conducted in Australia, the Netherlands, and the United States showed a similar tendency, in which the antibody titer continued to increase in adolescent children and decreased below the level sufficient for protection in adults >30 years old (8). These observations support the fact that patients with EM-HPeV3 are typically between 20 and 50 years old, which is child-rearing age. Parents without sufficient antibodies may be infected by their young children. However, the reason why men are more likely to present with muscle symptoms than women has not been clarified yet.

Although HPeV3 infection is prevalent worldwide (7, 8), apart from Yamagata, reports of outbreaks of EM-HPeV3 are hardly reported. According to the Infectious Agents Surveillance Report from the National Institute of Infectious Diseases, Japan, outbreaks of HPeV3 infection among all age groups were observed in 2008, 2011, 2014, and 2016 throughout Japan, which was consistent with the cases of EM-HPeV3 reported in Yamagata (19). This suggests that undiagnosed EM-HPeV3 also existed during those times throughout Japan. Most of our patients lived in Tokyo, but one developed the disease in the Fukuoka Prefecture, which is more than 800 km west of Tokyo. We suspect that an outbreak of EM-HPeV3 occurred in 2019 and could have been observed anywhere in Japan. The lack of reported cases may be explained as follows: first, patients scarcely visit the hos-

Table 3. Comparison of Clinical Characteristics of Epidemic Myalgia Associated with Human Parechovirus Type 3, Influenza Myositis, Bornholm Disease, and Guillain-Barré Syndrome.

	EM-HPeV3	Influenza myositis ^a	Bornholm disease ^b	GBS ^c
Susceptible age, sex	20-50 years old, male	Children	Children >20-50 years old	Anyone
Prevailing season	Summer	Winter	Summer	Anytime
Period between infection and onset	1-3 days	1-18 days	1 day	3 days to 6 weeks
Period between onset and recovery	2-3 weeks	1 day to 1 month	6 days to 1 month	Months to years
Distribution	Limbs and trunk; distal on the arms (reduced grip strength), proximal on the legs	Legs (particularly calf muscles)	Chest or upper part of the abdomen	Limbs, trunk, and/or cranial nerves
CK	Slightly or moderately elevated	Moderately or remarkably elevated	Normal or slightly elevated	Normal or slightly elevated
NCS	Normal	ND	ND	Axonal or demyelinating neuropathy
Tendon reflexes	Normal or reduced	Mostly normal	ND	Reduced or absent
Associated organisms	HPeV3	Influenza A or B virus	Coxsackie B virus	<i>C. jejuni</i> , CMV, and other bacteria and viruses

a: based on combination of data from references (25, 26), b: based on data from reference (5), c: based on data from reference (22).

CK: creatine kinase, *C. jejuni*: *Campylobacter jejuni*, CMV: Cytomegalovirus, EM-HPeV3: epidemic myalgia associated with human parechovirus type 3, GBS: Guillain-Barré syndrome, NCS: nerve conduction study, ND: not described

pital and receive detailed examinations because EM-HPeV3 specifically affects working young men and is self-limiting; second, the detection of HPeV3 by RT-PCR is performed in few research institutes.

Generally, patients with myositis show normal tendon reflexes because the muscle spindle is not affected from the start of the disease, and proximal weakness is also the typical finding (20, 21). Among two patients in whom needle electromyography was performed, one showed slightly rapid recruitment and increased insertion activity, indicating myogenic changes with increased excitability at the muscle membrane, on the iliopsoas muscle. MRI revealed the patchy distribution of hyperintense muscles and thickened fascia on STIR. Based on the previous report (4), we hypothesize that myositis and fasciitis are considered pathologies of this disease. However, reduced tendon reflexes and distal dominant weakness on the arms make it atypical for myositis.

Patients often visited our department and were suspected of having GBS because of the acute course of the disease, weakness of grip strength, and reduced tendon reflexes. However, GBS patients generally develop their neurological symptoms three days to six weeks after an incidence of gastrointestinal or upper respiratory viral infection and sometimes develop respiratory failure or cranial nerve disturbances, while EM-HPeV3 patients experience weaknesses at the same time or at latest a few days after developing common cold symptoms, and the symptoms resolve within a few weeks without respiratory or cranial nerve disturbances (22). Regarding the NCS findings, although previous reports have demonstrated a slightly decreased frequency of F wave in some cases, five of the six patients examined were normal (4). The other patient showed only an abnormal sural nerve amplitude. It is difficult to tell if the finding resulted

from this disease because we did not perform a follow-up NCS, but in any case, electrophysiological abnormalities only for the sural nerves are not typical findings in GBS patients (23).

A previous report also showed that EM-HPeV3 is associated with normal cerebrospinal fluid findings, which could be helpful in distinguishing GBS from EM-HPeV3 (4). Table 3 shows the clinical characteristics of EM-HPeV3 obtained from our cases and GBS.

In addition to HPeV3, there are several viruses known to cause myositis, myalgia, or rhabdomyolysis. Bornholm disease, which was called epidemic myalgia before the appearance of EM-HPeV3, commonly manifests with severe pain in the chest and abdominal muscles. Coxsackie B virus is the major cause of the disease (5). Influenza A and B viruses, which are the leading causes of respiratory infections, can also cause viral myositis (24-26). The viruses usually affect the calf muscle but may affect the whole body (25). Other viruses, such as dengue virus (27), herpes viruses, and human immunodeficiency virus, have also been reported (28). Table 3 depicts the clinical characteristics of EM-HPeV3, influenza myositis, and Bornholm disease. Although EM-HPeV3 can be differentiated from these viral infections by their clinical course, symptoms, and seasons, a virus examination is necessary to establish the exact diagnosis.

Whether EM-HPeV3 is caused by direct viral invasion or an immunologic process is unclear. The occurrence of muscle pain and other symptoms simultaneously indicates direct viral invasion by these viruses. Although a muscle biopsy has not been performed in any patients with this disease, there is a reported case of influenza virus having been isolated from muscle tissue (29).

Aside from the muscular symptoms, patients manifested a

fever, mild respiratory symptoms, and joint pains that are often observed in other viral infections. The mechanisms underlying the groin pain in half of our male patients were unclear, but orchitis or epididymitis was speculated, based on a previous report (4).

Conclusion

We herein report the clinical characteristics of seven patients with EM-HPeV3 who visited our department during the summer of 2019. To our knowledge, this 2019 outbreak of EM-HPeV3 was the first since its last epidemic in 2016, and it could be observed in other places in Japan. We evaluated the clinical characteristics of EM-HPeV3, including detailed assessments of the distributions of pain and weakness in the limb muscles. In our cases, weakness was distally dominant on the arms but proximally dominant on the legs, and muscle pain showed similar distributions. In addition to these characteristic distributions of muscle symptoms, reduced tendon reflexes, which were frequently observed, are considered distinct clinical features of this disease.

The authors state that they have no Conflict of Interest (COI).

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