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SHORT REPORT
Epidemic myalgia and myositis associated with human parechovirus type 3 infections occur not only in adults but also in children: findings in Yamagata, Japan, 2014

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SUMMARY

We previously reported an association between human parechovirus type 3 (HPeV3) and epidemic myalgia with myositis in adults during summers in which an HPeV3 outbreak occurred in children. However, this disease association has not yet been reported elsewhere. We have since continued our surveillance to accumulate data on this disease association and to confirm whether myalgia occurs in children as well as adults. Between June and August 2014, we collected 380 specimens from children with infectious diseases. We also collected clinical specimens from two adult and three paediatric patients suspected of myalgia. We then performed virus isolation and reverse-transcription–PCR using the collected specimens. We detected HPeV3 in 26 children with infectious diseases, which we regarded as indicating an outbreak. We also confirmed HPeV3 infection in all patients suspected of myalgia. In particular the symptoms in two boys, complaining of myalgia and fever, closely matched the criteria for adult myalgia. Based on our findings from 2008, 2011 and 2014, we again urge that clinical consideration be given to the relationship between myalgia and HPeV3 infections during HPeV3 outbreaks in children. Furthermore, our observations from 2014 suggest that epidemic myalgia and myositis occur not only in adults but also in children.

Key words: Adult, child, HPeV3, myalgia, myositis.

Human parechovirus (HPeV) is a positive-sense, single-stranded RNA virus belonging to the genus *Parechovirus* of the family Picornaviridae [1, 2]. There are 16 types of HPeV (HPeV1-16), in which types 1 and 2 were formerly classified in genus *Enterovirus* [1, 2]. HPeV3 was first isolated from a stool specimen of a 1-year-old Japanese girl with transient paralysis, high fever and diarrhoea in 1999, and serological and virological studies have suggested that HPeV3 infections occur in early infancy before age 5 years [2–4]. In young infants, HPeV3 has been detected in association with mild diseases, such as

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respiratory, and gastrointestinal illness, and erythematous disease, as well as with serious diseases, such as meningitis, encephalitis and neonatal sepsis [2–9]. Previous studies have also indicated that outbreaks of HPeV3 infections in children occur in the summer season every 2–3 years [5–8].

We first reported an outbreak of epidemic myalgia associated with HPeV3 infection in adults during the summer of 2008 in Yamagata, Japan [10]. Further, we again observed sporadic cases of myalgia in association with HPeV3 infection in adults in the summer of 2011, which coincided with the next observed outbreak of HPeV3 in children in Yamagata [7]. Based on our findings from 2008 and 2011, we postulated that when an outbreak of HPeV3 infections occurs within a community, the HPeV3 tends to infect entire households, including the parents of infected children, and a number of these affected adults exhibit symptoms of myalgia [7, 10]. To confirm this hypothesis, we have been waiting for the publication of supporting evidence from areas other than Yamagata. Unfortunately, a search of the PubMed site on 27 August 2015 under the terms 'myalgia' and 'parechovirus' failed to identify any papers related to the topic. Furthermore, the findings described in our paper were recently referred to as an 'unusual outbreak' [2]. These facts appear to indicate that the notion of an association between myalgia with HPeV3 infection has not yet been established. In fact, the only relationships described for epidemic myalgia in the latest medical textbooks are those for group B coxsackieviruses, echoviruses, and group A coxsackieviruses [1]. Our current plan is to continue our surveillance of HPeV3 infections in children as well as that of epidemic myalgia in adults to accumulate additional data to confirm whether this phenomenon is repeated in Yamagata. On the other hand, the question has arisen as to whether myalgia occurs only in adults. We shared this question with local paediatricians, neurologists, and laboratory technologists and challenged them to identify cases of suspected myalgia in children in Yamagata. Subsequently, in the summer of 2014, we observed another HPeV3 outbreak in children in combination with cases of myalgia not only in adults but also in children, which we describe herein.

As part of our contribution to the National Epidemiological Surveillance of Infectious Diseases (NESID), Japan outlined in the Infectious Diseases Control Law, we collected 368 nasopharyngeal swabs as well as six cerebrospinal fluid (CSF) and six stool ($n = 380$) specimens from patients at paediatric clinics between June and August 2014. Of these specimens, 293 (77·1%) were from patients aged <5 years, 51 (13·4%) from patients aged 5–9 years, 20 (5·3%) from patients aged 10–14 years, eight (2·1%) from patients aged >14 years and eight (2·1%) from patients of unknown age. The clinical diagnoses for these patients were as follows: upper respiratory infections (137, 36·1%), lower respiratory infections (86, 22·6%), herpangina (64, 16·8%), viral exanthema (15, 3·9%), and others (44, 11·6%). Specimens were sent to the Department of Microbiology, Yamagata Prefectural Institute of Public Health and virus isolation was carried out as part of our routine surveillance using a microplate method with six cell lines mainly targeting respiratory viruses such as influenza virus, parainfluenza virus, human metapneumovirus, respiratory syncytial virus, enterovirus, rhinovirus, and adenovirus [11]. As isolation of HPeV3 is difficult using the microplate method, virus isolation, reverse transcription–polymerase chain reaction (RT–PCR) for the detection of HPeV3 and sequence analysis were performed independently as described previously [7, 10]. The remainder of each specimen was stored at −80 °C. Sequence data were registered under GenBank accession numbers LC043114–LC043128.

In the latest textbook, Bornholm disease, which is best known as epidemic pleurodynia, is defined as an acute febrile illness with myalgia, especially involving the chest and abdomen, but without muscle weakness. The recognized causative agents of this disease, which has occurred both as an epidemic and sporadically in various locations, include coxsackievirus B virus as well as other enteroviruses [12]. However, as we discussed previously, none of the patients with epidemic myalgia associated with HPeV3 infection showed chest or abdominal pain, instead showing muscle weakness and myalgia involving mainly the proximal muscles of the arms and legs as well as symptoms of the common cold such as fever and a sore throat [7, 10]. Furthermore, our previous analyses of laboratory findings suggested that the disease is an acute myositis associated with HPeV3 infection [10]. The typical epidemic myalgia and myositis associated with HPeV3 infection in adults can, therefore, be defined as an acute febrile illness with myalgia and muscle weakness, especially involving the proximal muscles of the arms and legs. However, since we had no experience regarding children, we sought to identify a patient demonstrating possible muscle disorders including myalgia and muscle weakness. Two adult

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Table 1. *Patients with suspected myalgia and myositis associated with HPeV3 infection in Yamagata, Japan in 2014*

Cases ($n = 5$)	Age, yr/sex	Illness onset date (duration of hospital admission)	Main clinical symptoms	Detection of HPeV3			Laboratory test results
				Throat swab	Stool	Serum	
Case 1	9/M	7 July (9–14 July)	Myalgia, fever, sore throat	Isolation (+), RT–PCR (+)	Not done	RT–PCR (–)	CPK 3,719 IU/l (high), myoglobin 1127 ng/ml (high)
Case 2	2/M	5 Aug. (7–11 Aug.)	Not standing, diarrhoea	Isolation (–), RT–PCR (+)	Isolation (–), RT–PCR (+)	Not done	
Case 3	12/M	5 Aug. (8–12 Aug.)	Myalgia, fever, diarrhoea	Isolation (–), RT–PCR (+)	Isolation (+), RT–PCR (+)	Not done	
Case 4	44/M	9 Aug. (12–19 Aug.)	Myalgia, weakness, fever, stomatitis	Isolation (–), RT–PCR (+)	Isolation (–), RT–PCR (+)	RT–PCR (–)	CPK 874 IU/l (high)
Case 5	30/F	16 Aug. (no admission)	Myalgia, weakness, fever	Isolation (+), RT–PCR (+)	Not done	RT–PCR (–)	CPK 522 IU/l (high)

CPK, Creatinine phosphokinase.

patients, who visited the Department of Neurology, Yamagata Prefectural Central Hospital, were clinically suspected of typical myalgia associated with HPeV3 infection on the basis of fever, myalgia and muscle weakness (Table 1, cases 4 and 5). Apart from these adult cases, three children were also clinically suspected of myalgia (Table 1, cases 1–3). Case 1 was a 9-year-old boy who complained of generalized myalgia, fever and sore throat. Case 2 was a 2-year-old boy who presented with diarrhoea. He showed a disinclination to stand and irritation when the doctor examined his lower limbs at the outpatient clinic. The doctor suspected myalgia or ataxia and referred him to the reference hospital. Case 3 was a 12-year-old boy who presented with fever and diarrhoea and was clinically diagnosed with polymyositis. Clinical specimens were collected from each of the above patients between days 2 and 5 after the onset of illness and sent to the Department of Microbiology, Yamagata Prefectural Institute of Public Health for the detection of HPeV3 as described above.

This work was approved by the ethics committees of Yamagata Prefectural Central Hospital (No. 64) and Yamagata Prefectural Institute of Public Health (YPIPHEC H26–03). Informed consent was obtained from the patients (or their guardians) whose details are described herein.

During the study period, we detected the HPeV3 genome in 26 children aged <6 years using RT–PCR and isolated HPeV3 strains from eight specimens using the LLC-MK2 cell line. We succeeded in detecting the HPeV3 genome in all specimens from which the virus was isolated. Of the 26 HPeV3-positive children, we detected viruses other than HPeV3 in 16 specimens, including coxsackievirus type A4 in 10, parainfluenza type 3 in two, and human metapneumovirus, adenovirus type 2, adenovirus type 3 and echovirus type 11 in one case each. Excluding these 16 cases, the clinical diagnosis based on the most common symptom was viral exanthema in four (40%) cases, followed by upper respiratory infection in two (20%), herpangina in two (20%), sepsis-like illness in one (10%), and glossitis in one (10%).

A chief complaint of myalgia was observed in four patients (Table 1), of whom the adult patients (cases 4 and 5) complained of muscle weakness as well. Case 2 was unable to complain of myalgia as he was only aged 2 years. However, as he showed a reluctance to stand, became irritated when his parents changed his nappy and showed irritation when the doctor examined his lower limbs in the acute phase, we assumed

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that the child was experiencing muscle pain. We succeeded in detecting the HPeV3 genome from all patients suspected of myalgia, and were able to isolate HPeV3 from three patients (Table 1). Laboratory findings revealed inflammatory signs, such as elevated creatinine phosphokinase (CPK) levels, in three patients (cases 1, 4, 5) and increased myoglobin level in case 1. There were no other biochemical or X-ray findings to support the presence of inflammation.

Based on our experience in Yamagata in 2008 and 2011, we proposed that epidemic myalgia in adults might be associated with HPeV3 infections and their spread through the younger members of a community [7, 10]. However, this notion had not been supported by other studies until a recent report by Yamamoto *et al.* [13]. We have, therefore, encouraged neurologists and paediatricians in Yamagata to strengthen their surveillance of HPeV3 infections, particularly with regard to patients suspected of myalgia and myositis due to HPeV3, in order to accumulate data to support our hypothesis and resolve the associated questions.

According to the month-by-month detection of HPeV3 strains from public health laboratories throughout Japan, a total of 261 HPeV3 strains (June $n = 60$, July $n = 119$, August $n = 82$) were detected over the summer months in 2014 [14], indicating an outbreak of HPeV3 infections had occurred in children, not only in Yamagata, but also on a national scale. Based on our hypothesis, such a nationwide and/or community outbreak of HPeV3 in children is a necessary prerequisite for an outbreak of epidemic myalgia in adults [7]. As in 2008 and 2011, we identified two typical adult patients of child-rearing age, and succeeded in detecting HPeV3 in samples from these patients, as reported previously [7]. Furthermore, for the first time in our surveillance in Yamagata, a paediatric team identified three children with suspected myalgia and myositis. Of these, cases 1 and 3 clearly complained of myalgia and symptoms of the common cold, matching almost exactly the criteria for adult myalgia (Table 1). In case 1 in particular, elevated CPK and myoglobin levels suggested myositis, as observed previously in adult cases [7, 10]. These laboratory findings support the notion that epidemic myalgia can occur in children as well as in adults via myositis. Based on his reactions, we suspected that case 2 experienced pain in his lower limbs. The first isolation of HPeV3 in the world was from 1-year-old boy with infant paralysis, and an infant with a gait disorder was observed in Hiroshima in 2008 [3, 15]. Although we do not have sufficient evidence of myositis in these young children based on laboratory data, we speculate that HPeV3 infections can influence muscular function, even in young children on the basis of our findings for case 2 in 2014.

It is likely that the clinical course of myalgia varies on an individual basis from mild to severe. Case 3 in 2014 was primarily diagnosed with herpangina because of fever and throat inflammation. However, he could not get up due to severe muscle pain and was brought to the Department of Paediatrics at our institution, where he was suspected of polymyositis, Guillain–Barré syndrome or myalgia due to HPeV3. Laboratory findings for antinuclear factor and CSF excluded the possibility of polymyositis or Guillain–Barré syndrome. Interestingly, his younger brother experienced fever and pain in his lower limbs for 2 days at the end of July and his mother experienced myalgia in both lower limbs on 4–5 August. Since his younger brother and his mother had oral stomatitis as well, we suspected that they were also affected by HPeV3 and represent milder cases of myalgia. Case 4 initially visited his family doctor and an orthopaedic clinic because of muscle weakness and myalgia in all four limbs. He was then referred to the Department of Neurology at our institution, where he was suspected of having myositis. These experiences in Yamagata indicate that myalgia cases due to HPeV3 do not always visit an appropriate specialist, such as a neurologist or paediatrician, with sufficient knowledge and experience to accurately diagnose their condition.

In conclusion, our experiences in Yamagata in 2008, 2011 and 2014, as well as a recent report from Osaka, Japan [13], strongly suggest that clinical consideration should be given to the potential for myalgia and myositis to develop in cases of HPeV3 infection, not only in adults but also in children, in summer seasons when an HPeV3 outbreak occurs in a community every 2–3 years. Further, our experiences in Yamagata indicate that it is difficult to identify cases of myalgia and myositis associated with HPeV3 infection during outbreaks without active surveillance by specialists with an understanding of this disease. We hope our repeated reports will help clinicians to identify myalgia and myositis cases due to HPeV3 infection during future active surveillance.

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DECLARATION OF INTEREST

None.

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