An Outbreak of Aseptic Meningitis Due to Echovirus 30 in a High School Baseball Club—Possible Role of Severe Exercise for a High Attack Rate

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Abstract

In September 2008, an outbreak of aseptic meningitis caused by echovirus 30 occurred in Ota City, Gunma. Among the 26 people hospitalized, 17 were members of a high school baseball club. The attack rate within the club was as high as 40%. The other 9 patients were either their families or close relatives of the baseball club members, indicating the outbreak was confined to a limited community. Although numerous outbreaks of echoviral meningitis have been reported worldwide, those with such a high attack rate within a limited community are rare. Severe physical exercise in a hot temperature could be associated with this high attack rate.

Key words: echovirus, enterovirus, meningitis, outbreak, transmission, attack rate

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Introduction

Viral meningitis is the most common type of meningitis (1, 2). Its exact annual incidence in Japan is unknown, but approximately 50,000 people per year are hospitalized in North America (3). Although etiological agents are not determined in many cases, enterovirus is the most frequent agent when identified, ranging from 30 to 83% (1, 4).

Enteroviruses are single-strand RNA virus, and more than 60 serotypes are known (5). Some serotypes have strong association with meningitis, though others seldom cause it. Echovirus 30 (E30) is among them one of the most frequently identified causative agents (2, 6, 7). There have been many reports of E30 meningitis epidemics, but most were of open community outbreaks (3, 8-21). The attack rate was, therefore, quite low. We found only a few reports of E30 meningitis outbreaks in limited communities, but one was of co-infection with other enteroviruses (22) and others were of a lower attack rate (23-27). In September 2008, we

encountered an outbreak of E30 meningitis in a limited community. Most patients belonged to a baseball club, and about 40% of the club members needed to be hospitalized. Here, we report this outbreak and discuss the possible mechanism of this extraordinarily high attack rate.

Case Report

A 15-year-old boy with no remarkable past disease history was admitted to our hospital in early September, 2008, complaining of fever, headache, and vomiting which lasted for 4 days (patient 1 in Table 1). He belonged to a high school baseball club, and had been doing well till September 1. No close friends or relatives had febrile illness before he became sick. In spite of fever and severe headache, no consciousness disturbance or focal neurological deficits were confirmed. There also were no physiological abnormalities other than mild tachycardia presumably associated with the fever. Of note was that he showed no definite neck stiffness. Mild leukocytosis (13,000/ μ L) was found and the C-reactive

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Table 1. Patients of Viral Meningitis Admitted to Our Hospital

patient No.	sex	age	onset date	admission date	discharged date	relation with the baseball club
1	M	15	9/2	9/5	9/8	club member, brother of patient 2 and 8
2	F	7	9/6	9/8	9/11	sister of patient 1 and 8
3	M	15	9/6	9/9	9/15	club member
4	M	15	9/6	9/12	9/15	club member
5	M	16	9/6	9/12	9/15	club member
6	M	16	9/7	9/8	9/13	club member
7	M	15	9/7	9/10	9/15	club member
8	M	17	9/8	9/9	9/13	brother of patient 1 and 2
9	M	16	9/8	9/10	9/15	club member
10	F	8	9/8	9/11	9/13	cousin of patient 1, 2 and 8
11	M	15	9/8	9/11	9/15	club member
12	M	16	9/9	9/11	9/15	club member
13	M	16	9/10	9/16	9/20	club member
14	M	17	9/11	9/11	9/17	club member
15	M	16	9/12	9/16	9/18	brother of a club member
16	M	18	9/13	9/14	9/16	brother of a club member
17	M	16	9/14	9/14	9/18	classmate of patient 6 and 14
18	M	17	9/14	9/16	9/20	classmate of patient 6 and 14
19	M	17	9/14	9/18	9/21	club member
20	F	33	9/16	9/17	9/19	mother of a friend of patient 2 and 3
21	M	9	9/17	9/18	9/24	brother of patient 8

protein (CRP) level was elevated (1.64 mg/dL). As meningitis was suspected, we performed a lumbar tap study. The results of cerebrospinal fluid (CSF) analysis were as follows: initial pressure, 220 mmH₂O; cell count, 88 cells/ μ L (85% polymorphonuclear cells: PMN); protein, 57 mg/dL; glucose, 47% of blood glucose level. No bacterial growth was confirmed in the CSF. His brain CT scanning showed no abnormal findings (not shown).

We suspected viral meningitis, but ceftriaxone sodium was intravenously given because PMN predominance in the CSF made it difficult to rule out bacterial meningitis. Fever, headache, and emesis gradually subsided, and the antibiotic was discontinued two days later because the benign clinical course further suggested viral meningitis. He became afebrile, and went home three days after admission.

On the same day when patient 1 was discharged, a 7-year-old girl (patient 2 in Table 1) and a 16-year-old boy (patient 6 in Table 1) came to our hospital complaining of similar symptoms as patient 1. Patient 2 was a sister of patient 1, and her symptoms had started soon after those of her brother. Patient 6 was a member of the baseball club to which patient 1 belonged, and the symptoms had appeared a few days after those of patient 1. As patient 2 and 6 showed meningeal irritation signs, they were diagnosed as meningitis. As the results of CSF study were compatible with viral meningitis, they were hospitalized and treated with non-steroidal anti-inflammatory drugs and intravenous antiemetics. They showed a benign clinical course, and were discharged several days later (Table 1).

As shown in Table 1, many patients were admitted to our hospital under the diagnosis of viral meningitis thereafter.

More than half of the patients belonged to the baseball club. Other patients, though not a club member, had evidence of direct or indirect contact with the baseball club members who became sick. Patient 17 and 18 were classmates of patient 5 and 14. By interviewing, it became evident that their seats were close in a classroom and had shared drink bottle. Patient 20 did not seem to have contact with other patients, but her daughter showed symptoms of viral meningitis; her daughter was a close friend of patients 2 and 10, and likely caught viral meningitis of the same etiology.

Five more baseball club members were admitted to other hospitals under the diagnosis of viral meningitis. Among 43 club members, therefore, 17 people became hospitalized. According to the manager of the club, all other baseball club members who were not hospitalized also experienced headache and fever; if we consider these people as having meningitis, the attack rate increases to 100%. On the other hand, no patients of viral meningitis came to our hospital in the same season after patient 21. According to the local public health center, no cases of aseptic meningitis were reported thereafter. We can suppose that this epidemic was stamped out promptly, without extending to an open community outbreak.

Symptoms and signs as well as the results of laboratory data of the patients admitted to our hospital are summarized in Table 2. As the medical record or CSF data were insufficient, those of patients who admitted to other hospitals were not included. The results of data analysis were essentially compatible with previous reports, which will be discussed later. Several patients underwent electroencephalography and brain imaging studies, but no patients showed abnormal

Table 2. Symptoms, Signs and Laboratory Data of the Hospitalized Patients

symptoms		CSF	
headache	100%	initial pressure (mmH2O)	216.4±43.6
fever	100%	cells (/μL)	108.9±114.0
emesis	90.5%	percentage of PMN (%)	59.7±28.9
diarrhea	9.5%	protein (mg/dL)	33.8±16.2
throat pain	23.8%	glucose (% of blood glucose)	55.5±7.8
signs		blood	
Jolt accentuation	87.5%	WBC (/μL)	10205±2157
neck stiffness	60.0%	CRP (mg/dL)	1.65±1.72
Kernig sign	23.5%		

CRP=C reactive protein; CSF=cerebrospinal fluid; PMN=polymorphonuclear cells; WBC=white blood cell

Table 3. Detection of E30 RNA or Neutralizing Antibody against E30

Patient No. in Table 1	CSF	pharyngeal swab
2	+	NE
3	+	NE
4	NE	+
6	+	NE
7	+	+
8	+	NE
9	+	+
10	+	+
11	+	+
12	+	+
13	-	NE
14	+	+
17	-	NE

CSF=cerebrospinal fluid; E30=echovirus 30; NE=not examined

findings (not shown). We sent CSF and/or pharyngeal swab of several patients to Gunma prefectural infection control center to identify the causative agent. In the prefectural infection control center, serotype-specific viral RNA and antibody were investigated. As summarized in Table 3, clinical samples of 11 among 13 patients revealed evidence of E30 infection. As no other causative agents were identified, we supposed that this outbreak was caused merely by E30.

Discussion

Isolation of virus in a cell culture was the traditional method to identify the causative agent of viral meningitis, but it usually has low sensitivity and therefore was replaced by indirect methods such as nucleic acid or serotype-specific antibody detection (28). As serotype-specific nucleic acid and/or antibody were confirmed from many clinical samples, we can consider that this outbreak was caused by E30. There were some reports of aseptic meningitis outbreaks with simultaneous involvement of plural enterovirus sero-

types (22, 29), but the cluster reported is likely due only to E30; the serotype-specific diagnostic reliability of RNA is quite high (28), and absence of other serotypes in 19 samples from 13 patients (Table 3) excluded the possibility of co-infection.

E30 is one of the most common causative agents of aseptic meningitis (30). In the United States, it accounted for 8.2% of aseptic meningitis from 1970 to 2001 (2). It sometimes causes epidemics of meningitis, some of which involves a whole nation (3, 8, 9), a province or city (10-21), or a limited community (22-27). It is transmitted person to person by the oral-fecal route, but contamination in open water plays an important role in open community epidemics (20). As for the outbreak reported here, direct person to person transmission was the sole mode of propagation; we could verify the fact of direct contact in all cases (Table 1).

Previous records of E30 meningitis demonstrate that almost all cases showed headache and fever (4, 31), followed by vomiting (60-90%) (4, 15, 31), diarrhea (11%) (4, 14), and rash (3-9%) (4, 14, 31). One report from China (32) showed that more than half of the patients developed encephalitis, but all other case reports demonstrated a good outcome. The present cases showed similar results, but no patients showed skin lesions (Table 2). About 24% of patients complained of throat pain, which was again compatible with previous reports (4, 14). Despite that meningeal irritation signs seem to be the prerequisite for the diagnosis of meningitis, the present cases revealed that not all patients showed all meningeal signs (Table 2). Previous reports (4, 31) also showed that neck stiffness was confirmed only in 70% cases, and therefore, we should not exclude meningitis even when meningeal irritation signs are absent. Among the three meningeal irritation signs investigated here, Jolt accentuation signs showed the highest sensitivity (Table 2), which is compatible with a previous report (33). When a patient with a possible diagnosis of meningitis is encountered, the Jolt accentuation test is of great importance.

Although PMN predominance in CSF (Table 2) seems atypical for viral meningitis, previous reports also showed similar result (4, 14, 21, 30). The present cases further suggested that PMN predominance in CSF does not necessarily

mean bacterial meningitis. The number of cells and protein level in CSF tended to be lower in enterovirus meningitis than in herpes virus meningitis (31). In our cases, however, they greatly differed from case to case (cell count, 0 to 370/ μ L; protein level, 10 to 77 mg/dL), which made it difficult to speculate causative agents only by CSF pleocytosis or protein increase. In addition, the degree of inflammation in CSF did not indicate the severity of disease.

Many people remain asymptomatic when infected by enterovirus (7, 34). Even if symptomatic infection occurs, enterovirus usually causes only mild febrile illness; less than 5 % of people with symptomatic enterovirus infection develop meningitis (34, 35). Therefore, most outbreaks of enterovirus meningitis involve relatively small number of people compared to those with possible virus exposure. It is difficult to calculate the attack rate in open community outbreaks, but it is quite low. In an outbreak of E30 meningitis in southern Taiwan, for example, 38 people showed symptoms of meningitis (4). In an outbreak of northwest England also, only 38 people contracted meningitis. Two-hundred fifteen people suffered from meningitis in Kassel and neighboring countries in 2001, but the number of patients was very small when we take the total population within the area into account. As transmission occurs in a different way from that of limited community outbreaks, the viral load for each people might be lower in open community epidemics. When we discuss attack rate of meningitis epidemics, therefore, we need to distinguish limited community outbreaks from open-community ones.

Among the 43 members of the baseball club related to our case, 12 people were admitted to our hospital, 5 people to other hospitals, and all other people showed fever and headache even though they did not visit hospitals. When we define the attack as having fever and headache, the attack rate of meningitis within the baseball club reached 100%. When we count the hospitalized patients only, the attack rate was 40%. This is quite high when compared to previous reports of limited community E30 meningitis outbreaks. Faustini et al. reported a cluster of E30 meningitis among students who swam in a school pool, but the attack rate was 11% (27). Child-care centers sometimes became the place of outbreaks, but the attack rate ranged from 3 to 13% (23-25, 29). Only 24% of people with serological evidence of recent E30 infection showed symptoms in one study (23). A report

with the highest attack rate we found was an outbreak within travelers to Mexico; 88% people showed fever and emesis, and 50% became hospitalized (22). However, this outbreak was brought about not only by E30 but also by other enteroviruses such as coxsackievirus A1 and A5. When we consider the outbreak caused by E30 only, our case had an extraordinarily high attack rate.

The reason for this high attack rate is not simple. The amount of virus each patient was exposed to might have been so large so as to cause clinically evident symptoms. However, the relation of virus load and symptom appearance has not been established in viral meningitis; virus replicate in host cells promptly, and whether the pathogen cause disease or be eliminated depends not only on virus load. After entering the host, enterovirus initially replicates in the oropharynx. The best temperature for enterovirus to replicate is 37°C, and condition with lower temperature is unsuitable to cause viremia (5). This may be one of the reasons enterovirus meningitis is prevalent in hot seasons. Even if the temperature is not sufficiently high, the condition may become good for enterovirus when the host exercises and body temperature rises. In our cases, club members undertook physically severe training, and this might have played some roles in the evolvement of meningitis. Indeed, the previous report also revealed that the time spent for swimming correlated with the occurrence of clinically apparent meningitis (20, 22). In poliomyelitis also, which is caused by one of the enteroviruses, hard physical exercise often preceded establishment of paresis (36). Moreover, experimental data also demonstrates that exercise in the early phase of enterovirus infection makes the disease severe. In the animal model of murine poliomyelitis, the degree of exercise correlated with the severity of paresis (37). Cardiac muscle damage caused by coxsackie virus, that is one of the enteroviruses, that was augmented by exercise (38). Not only virus replication but also immunomodulation might be implicated in this exercise-induced exacerbation (39, 40); the number of T lymphocytes in the damaged tissue was changed by exercise (41, 42). It is thus believed that severe exercise makes the disease more severe in enteroviruses infection (6). The high attack rate of viral meningitis outbreak in Ota City, Gunma, might be brought about because of the hard training in the baseball club in hot temperature.

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