Transmission of Seasonal Outbreak of Childhood Enteroviral Aseptic Meningitis and Hand-foot-mouth Disease

This study was conducted to evaluate the modes of transmission of aseptic meningitis (AM) and hand-foot-mouth disease (HFMD) using a case-control and a case-crossover design. We recruited 205 childhood AM and 116 HFMD cases and 170 non-enteroviral disease controls from three general hospitals in Gyeongju, Pohang, and Seoul between May and August in both 2002 and 2003. For the case-crossover design, we established the hazard and non-hazard periods as week one and week four before admission, respectively. In the case-control design, drinking water that had not been boiled, not using a water purifier, changes in water quality, and contact with AM patients were significantly associated with the risk of AM (odds ratio [OR]=2.8, 2.9, 4.6, and 10.9, respectively), while drinking water that had not been boiled, having a non-water closet toilet, changes in water quality, and contact with HFMD patients were associated with risk of HFMD (OR=3.3, 2.8, 6.9, and 5.0, respectively). In the case-crossover design, many life-style variables such as contact with AM or HFMD patients, visiting a hospital, changes in water quality, presence of a skin wound, eating out, and going shopping were significantly associated with the risk of AM (OR=18.0, 7.0, 8.0, 2.2, 22.3, and 3.0, respectively) and HFMD (OR=9.0, 37.0, 11.0, 12.0, 37.0, and 5.0, respectively). Our findings suggest that person-to-person contact and contaminated water could be the principal modes of transmission of AM and HFMD.

Key Words : Meningitis, Aseptic; Hand, Foot and Mouth Disease; Disease Transmission; Waterborne Infection; Enterovirus; Epidemiology

INTRODUCTION

Enteroviral infection is a pediatric infectious disease with a wide spectrum of clinical syndromes including mild respiratory infections, hand-foot-mouth disease (HFMD), herpangina, myocarditis, and aseptic meningitis (AM). In temperate zones, enteroviral infection has strong seasonality, being most common during summer. During the epidemic season, AM is one of the major causes of morbidity in a community, accounting for most of the acute beds occupied in the pediatric ward. More than 80% of the known etiology of AM occurs via enteroviruses. Although AM has a fairly good prognosis, children who have contracted AM are recommended to be admitted to the hospital as it is sometimes, although rarely, is accompanied by death or lethal sequelae such as encephalitis or status epilepticus (1).

It has been estimated that the attack rate of AM was 275 per 100,000 children during outbreaks in Korea (2, 3), and the nationwide incidence of aseptic meningitis among children under 15 yr of age was 3.48 per 1,000 per year (2, 3). The incidence and outbreak of AM shows cyclic fluctuations with outbreak every 3 or 4 yr, with the annual incidence in 1997 being 8.44/1,000 and that in 2000 being 0.79/1,000 (2, 3). AM outbreaks have seasonal variations since they are seasonally dependent in the temperate zone, with AM being most prevalent between May and July (4-6). AM spreads in a community within a very short period of time after detection of the index case (7).

Direct contact via the fecal-oral route with patients who have clinical or subclinical AM symptoms is the principal transmission route of AM (8, 9); however, given its strong seasonal pattern of outbreak in a community (2), direct trans-
mission is not a compatible mode of transmission in a community outbreak. Other modes of transmission including the foodborne and waterborne route should be sought during investigations of the transmission of AM (10). However, few studies have been conducted to evaluate the mode of transmission in a community except for episodic common-vehicle outbreaks. Knowledge of the major mode of transmission of AM can provide a key basis for prevention of the enteroviral infection in a community (11).

The authors assume that waterborne transmission may play an important role in community-based outbreaks (2). We also assume that AM and HFMD, the two most common enteroviral diseases, may have similar modes of transmission (5, 12).

To investigate this issue, evaluation of the risk factors associated with individual patients in a community collected over a long time period is necessary. Although a case-control study is a general approach for evaluation of risk factors associated with infectious diseases, combined use of a case-crossover study will provide insight into the time-dependent exposures of an individual. Therefore, this study was conducted to investigate the mode of transmission of the two enteroviral diseases, AM and HFMD, in communities by applying case-control and case-crossover designs simultaneously.

MATERIALS AND METHODS

Case-control design

AM and HFMD cases and non-enteroviral disease (NEVD) controls were recruited from two general hospitals with 200-400 beds located in mid-sized cities in southeast Korea (Gyeongju and Pohang) and one hospital with 700 beds located in a large city (Seoul) during two seasons, 2002 and 2003. AM cases were defined as confirmed AM patients among those admitted to the hospital who met the three following criteria: 1) symptoms of meningitis such as fever and meningeal signs, 2) negative bacterial culture in the laboratory, and 3) positive test of enteroviral RNA through reverse transcription polymerase chain reaction (RT-PCR) of either cerebrospinal fluid (CSF), a fecal specimen, and/or a throat smear. HFMD cases were defined as those with a clinical syndrome of mild fever, painful oral lesions and rash, sores, or blisters on the body. NEVD controls were patients who were admitted to the hospitals with diagnoses of diseases that were unrelated to enteroviral diseases such as respiratory infectious diseases, except those from enteroviral origin, enteritis of bacterial origin, or other surgical diseases including herniotoy. All study subjects were selected as children less than 15 yr of age. Of the eligible population, we interviewed 215 AM cases, 127 HFMD cases, and 192 NEVD controls. We excluded subjects admitted during the non-seasonal outbreak (between September and April) who constituted only a small proportion (5.4%) of the AM cases. Finally, 205 AM, 116 HFMD cases and 170 NEVD controls were selected. This study was approved by the institutional review board of Dongguk University Gyeongju Hospital and informed consent was obtained from all subjects.

By structured questionnaire, we collected information regarding demographic characteristics such as age at admission and sex, as well as other environmental and lifestyle risk factors such as residential area upon examination, month of admission, boiling of drinking water, use of water purifier, drinking water supply, water used in cooking and toilet usage. We also evaluated events and/or changes in life style one month prior to hospital admission such as eating shellfish, changes in water quality including color, taste, or smell, and the presence of precipitation or floating materials in the water, as well as contact with AM, HFMD, common cold, or enteritis patients. Additionally, we collected information regarding measles-mumps-rubella (MMR) vaccination history within the previous two months to take into account the minimal incubation period following this vaccination (13) and to rule out the possibility of adverse effect of MMR vaccination since the vaccination may cause enteroviral infection or encephalitis (14, 15).

When a subject was admitted to the hospital during the study period, a research nurse recorded the date of admission to the hospital and handed the questionnaire to the subjects’ parents. Within two days, the nurse collected the questionnaire and interviewed the parents for information that was not provided. We reviewed all the patients’ medical charts to confirm the diagnosis in order to decrease misclassification bias.

Case-crossover design

Only AM and HFMD cases were selected for the case-crossover design (N=205, 116, respectively). Information collected for the case-crossover design was primarily designed to delineate the subject’s unusual events in detail and/or changes in life style at weekly intervals for the one month prior to admission. Possible indicators for contact with clinical or subclinical AM or HFMD patients were contact with AM and HFMD cases and being admitted to or visiting a hospital. Possible indicators for virus-contaminated drinking water were changes in color, taste, or smell, and the presence of precipitates or floating materials in the water. Possible indicators for direct skin or mucosal contact with virus-contaminated water were use of public saunas and swimming pool and presence of a skin wound. Possible indicators for drinking water in places other than home were eating out, going shopping, going for a picnic, and going to amusement parks. Although the incubation period of enterovirus infection is usually between the 3rd and 7th day after contact (16), some studies demonstrated a longer incubation period for AM of up to 15 days (17). Therefore, the first week (1-7 days) prior to admission was established as the hazard period and the
fourth week (22–28 days) prior to admission was considered to be the non-hazard period. Subjects were classified into two categories that were exposed to any modes of transmission during the hazard and non-hazard period.

Statistical analysis

A chi-square test and Fisher’s exact test were used to evaluate the group differences between cases and controls. Missing data under 5% of frequency were imputed to the code of reference level in a variable that shifts risk of AM or HFMD towards the null hypothesis. To determine the AM or HFMD risk associated with each mode of transmission in the case-control design, we estimated the adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) by unconditional logistic regression analysis adjusted for age, residential area at examination, and month of admission. We also estimated the risk of AM or HFMD in the case-crossover design, and compared the exposure status during the hazard and non-hazard periods using the ORs (95% CIs) via the conditional logistic regression model. All analyses were conducted by SAS 9.1.

RESULTS

Age, residential area at examination, month of admission among the AM cases, and the age and residential area among the HFMD cases and NEVD controls were significantly different (Table 1).

Table 1. Selected characteristics of AM	extsuperscript{1} cases, HFMD	extsuperscript{1} cases and NEVD	extsuperscript{4} controls

| Characteristics                  | NEVD	extsuperscript{4} controls (n=170) | AM	extsuperscript{1} cases (n=205) | P value	extsuperscript{4} | HFMD	extsuperscript{1} cases (n=116) | P value	extsuperscript{4} |
|---------------------------------|----------------------------------------|-----------------------------------|----------------------------|-------------------------------------|----------------------------|
| Age (yr)                        |                                        |                                   |                            |                                     |                            |
| 0-3                             | 95 (55.9)                              | 38 (18.5)                         | <0.001                     | 62 (53.4)                           | <0.001                     |
| 4-6                             | 36 (21.2)                              | 51 (24.9)                         | 0.35                       | 24 (20.7)                           | 0.35                       |
| 7-12                            | 23 (13.5)                              | 51 (24.9)                         | 9.03                       | 13 (11.2)                           | 9.03                       |
| 13-15                           | 16 (9.4)                               | 65 (31.7)                         | 17 (14.7)                  |                                     |                            |
| Sex                             |                                        |                                   |                            |                                     |                            |
| Male                            | 105 (61.8)                             | 136 (66.3)                        | 0.35                       | 66 (56.9)                           | 0.12                       |
| Female                          | 65 (38.2)                              | 69 (33.7)                         |                            | 50 (43.1)                           |                            |
| Residential area of examination |                                        |                                   |                            |                                     |                            |
| City 1 (mid-sized city)         | 130 (76.5)                             | 135 (65.9)                        | <0.001                     | 115 (53.7)                          | <0.001                     |
| City 2 (mid-sized city)         | 29 (17.1)                              | 30 (14.6)                         |                            | 98 (45.8)                           |                            |
| City 3 (big city)               | 11 (6.4)                               | 40 (19.5)                         | 1 (0.5)                    |                                     |                            |
| Month of admission              |                                        |                                   |                            |                                     |                            |
| May                             | 34 (20.0)                              | 83 (40.5)                         | <0.001                     | 43 (37.1)                           | 0.88                       |
| June                            | 31 (18.2)                              | 76 (37.1)                         |                            | 48 (41.4)                           |                            |
| July                            | 59 (34.7)                              | 30 (14.6)                         |                            | 17 (14.7)                           |                            |
| August                          | 46 (27.1)                              | 16 (7.8)                          |                            | 8 (6.9)                             |                            |

*Non-enteroviral diseases (NEVD) controls unrelated to enteroviral diseases, such as respiratory infectious diseases and enteritis of bacterial origin, and other surgical diseases; 
\textsuperscript{4}Aseptic meningitis (AM); \textsuperscript{1}Hand-foot-mouth disease (HFMD) controls; \textsuperscript{4}P values for the difference between AM cases and NEVD controls; \textsuperscript{4}P values for the difference between HFMD cases and NEVD controls.
Changes in water as a possible indicator for virus-contaminated drinking water was related to a significantly increased risk for AM and HFMD (OR=8.0, [95% CI=1.1-64.0] and OR=11.0, [95% CI=1.2-72.9], respectively). Of the possible indicators for direct skin contact with virus-contaminated water, having a skin wound was associated with AM as well as HFMD risk (OR=2.2, [95% CI=1.1-4.9] and OR=12.0, [95% CI=1.6-92.3], respectively). Of the possible indicators for drinking water in places other than home, eating out and going shopping were associated with both AM and HFMD risks (OR=22.3, [95% CI=7.0-71.0] and OR=3.0, [95% CI=1.0-9.3] for AM risk; OR=37.0, [95% CI=5.1-269.5] and OR=5.0, [95% CI=1.9-13.1] for HFMD risk, respectively).

### DISCUSSION

In this case-control and case-crossover design for AM and HFMD, modes of transmission associated with an increased risk were non-boiling of drinking water, change in water quality within one month prior to admission, contact with AM patients, eating shellfish, changes in water quality, contact with HFMD patients, contact with URI** patients, and MMR** vaccination within past 2 months.
Table 3. The association between mode of transmission and risk of AM* and HFMD† using a conditional logistic regression model in a case-crossover design

| Possible indicators | Life-style changes between hazard period (1 week prior to admission) and non-hazard period (4 weeks prior to admission) | AM* cases | HFMD† cases |
|---------------------|------------------------------------------------------------------------------------------------|------------|-------------|
|                     |                                                                                               | No.¹ (a¹/b¹) | OR (95% CI) | P value | No.¹ (a¹/b¹) | OR (95% CI) | P value |
| Contact with clinical or subclinical AM* or HFMD† patients | Contact with AM* cases | 205 (18/1) | 18.0 (2.4-134.5) | 0.01 | 116 (0/0) | – |
|                     | Contact with HFMD† cases | 205 (5/0) | – | – | 116 (9/1) | 9.00 (1.7-71.0) | 0.001 |
|                     | Being admitted to or having visited a hospital | 205 (42/6) | 7.0 (3.0-16.5) | 0.001 | 116 (37/1) | 36.99 (5.1-269.5) | 0.001 |
| Drinking contaminated water | Changes in water quality | 177 (8/1) | 8.0 (1.1-64.0) | 0.04 | 101 (11/1) | 11.0 (1.2-72.9) | 0.03 |
| Direct skin contact with contaminated water | Use of public saunas | 205 (5/1) | 5.0 (0.6-42.8) | 0.14 | 116 (13/7) | 1.9 (0.7-4.7) | 0.19 |
|                     | Swimming in a pool | 205 (9/4) | 2.3 (0.7-7.3) | 0.18 | 116 (3/1) | 3.0 (0.3-28.8) | 0.34 |
|                     | Presence of a skin wound | 205 (20/9) | 2.2 (1.1-4.9) | 0.04 | 116 (12/1) | 12.00 (1.56-92.3) | 0.02 |
| Drinking water in places other than home | Eating out | 206 (67/3) | 22.3 (7.0-71.0) | 0.00 | 116 (37/1) | 37.0 (5.1-269.5) | 0.001 |
|                     | Going shopping and eating | 205 (12/4) | 3.0 (1.0-9.3) | 0.05 | 116 (25/6) | 5.0 (1.9-13.1) | 0.01 |

OR (95% CI) of the use of a purifier was not estimated because we surveyed monthly changes and not the weekly changes.

*Aseptic meningitis (AM); †Hand-foot-mouth diseases (HFMD); Total number of cases for analysis; ‡Subjects exposed to risk factor in the hazard period only (1 week prior to admission); ††Subjects exposed to risk factor in the hazard period only (4 weeks prior to admission).

events with the same disease (AM or HFMD), drinking water in places other than home (eating out and going shopping), and direct skin contact with potentially contaminated water such as having a skin wound. Not using a water purifier was only associated with the risk of AM, whereas the use of unsanitary toilets was associated with HFMD risk.

Studies have shown that drinking unpurified water was a cause of AM outbreak (10, 18, 19). Our findings of an increased risk among subjects who did not use a water purifier and who did boil drinking water strongly suggest that AM infection in a community is related to drinking water. Furthermore, increased risk in subjects who experienced changes in drinking water within one week prior to admission directly implicated potentially contaminated water as the principal mode of transmission for both AM and HFMD. In some studies, enteroviruses such as Coxsackie virus and adenovirus have been isolated from both water supply facilities and tap water (20, 21). Although our results could not offer direct evidence of enterovirus-contaminated water contact, it is still possible that the virus-contamination of drinking water may also be the mode of transmission for the outbreak of AM and HFMD.

Our study shows that contact with an AM or HFMD patient is a strong risk factor with very high ORs when compared to water-related risk factors. However, the population attributable risk of direct contact should be much lower than that of the waterborne sources because the proportion of children with contact history is lower than 10% of the total cases among study subjects. Considering that the incubation period of enteroviral diseases is one or two weeks, infection through common vehicle exposure is a more plausible explanation of the primary mode of transmission of the community cases during the outbreak season. In addition, our study supports the results of previous studies that contact with potentially contaminated water, such as direct skin or mucosal contact through bathing and swimming, and environments of unsafe water, could be other modes of AM transmission, in addition to direct contact with patients (17, 22-24).

The case-crossover design, developed by Maclure (25), requires information only from cases (26). This design has the advantage of enabling adjustment of confounding factors since the cases themselves serve as the controls during the non-hazard period (27). This design has proven useful for the identification of time-dependent risk factors of diseases or health effects within a short time frame from exposure to outcome (27, 28). In our case-crossover design, factors possibly related to direct contact with patients infected by enterovirus and drinking or skin contact with virus contaminated water were significant or marginally significant. In addition, a recent study reported that the case-crossover design was useful for confirming the risk of acute adverse events of aseptic meningitis after receiving MMR vaccination. In this study, the results of the case-crossover study were similar to those of the case-control study (13).

We included the MMR vaccination history as a risk factor of AM or HFMD due to differential classification of AM or HFMD by enteroviral infections and meningitis or encephalitis based on the adverse effects of MMR vaccination (13-15). MMR vaccination history was not associated with AM or HFMD risks in our results; thus, we could not rule out the possibility of AM development related to MMR vaccination.

In this study, the presence of contact history with patients of AM or HFMD was associated with a highly increased risk of AM and HFMD. We collected additional information regarding substitutes of person-to-person contact, such as the number of family members, number of rooms in the residence, number of rooms per one person to measure the spatial den-
sity, and the number of children taken to nursery care among pre-schoolers. However, none of these variables were associated with the risk of AM and HFMD.

This study had some limitations. The number of cases and controls between small city/count and large city was significantly different, which suggests that there are differences in the quality and quantity of the water supply and socioeconomic conditions among the three areas. However, those conditions were determined by the geographic location of the study subjects and differed among areas. Therefore, we included residential area at examination as a covariate to reduce misclassification bias. Information regarding the frequency and quantity of water consumption was not collected. Although changes in water quality consisted of many variables such as changes in color, taste, and smell, and the presence of precipitation or floating materials in the water, we did not collect specific data regarding water quality measurement. Thus, our results may be subject to misclassification bias. Our definition of HFMD cases and NEVD controls was defined according to clinical diagnosis. We also selected a group of HFMD cases who had equal opportunity for exposure to enteroviruses. Additionally, the results from both our case-control and case-crossover designs were consistent. Our study subjects represent all controls were attributed to non-enteroviral origin and that all controls were attributed to non-enteroviral origin. However, this bias can act towards the null and underestimate the effect size.

Nevertheless, this study has several strengths. Misclassification bias was minimized since AM cases were defined by serological or virological evidence of infection rather than by clinical diagnosis. We also selected a group of HFMD cases who had equal opportunity for exposure to enteroviruses. Additionally, the results from both our case-control and case-crossover designs were consistent. Our study subjects represent most of the AM cases in a community during outbreak season. Our results regarding risk factors suggest water contamination as a common mode of disease transmission in community cases.

Our findings demonstrate that viral contamination of water could be a potential risk factor for AM and HFMD, even though person-to-person contact history is the most important risk factor. Therefore, the practice of boiling drinking water and use of a water purifier at home are considered to be effective means of protecting against AM and HFMD. Maintenance of a high level of sanitation of public saunas and swimming pools and avoidance of the use of such places for those who have skin wounds is recommended. A nationwide surveillance and quality control of drinking water sources are also needed. An effective water control strategy for AM and HFMD could reduce childhood morbidity (29) as well as national medical expense (1).

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