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Outbreak of vertigo in Wyoming: possible role of an enterovirus infection

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SUMMARY

An epidemiologic investigation was conducted to characterize and evaluate the possibility of a viral aetiology of an outbreak of acute vertigo in Hot Springs County, Wyoming, during autumn 1992. Case-finding identified Hot Springs County residents who sought medical attention for new onset vertigo during 1 August, 1992–31 January 1993. Thirty-five case-patients and 61 matched controls were interviewed and serum specimens were obtained during January 1993. Case-patients were more likely than controls to report symptoms (e.g. fatigue, sore throat, fever, diarrhoea) of antecedent acute illness. Case-patients did not have a significantly greater prevalence or mean titre of IgG antibodies to respiratory syncytial virus, parainfluenza viruses, Epstein–Barr virus, and cytomegalovirus than controls. Serologic evidence of recent enterovirus infection (IgM antibodies) was found for 74% of case-patients compared with 54% of controls ($P < 0{\cdot}05$), suggesting a possible association between vertigo and enterovirus infection. Future studies are needed to define the role of enteroviruses in inner-ear diseases.

INTRODUCTION

Epidemic vertigo is varyingly described as vestibular neuronitis or neuritis, acute labyrinthitis, or collectively as acute vestibulopathy. It is characterized by a single sudden attack of vertigo lasting days to weeks, without cochlear involvement [1, 2]. This type of vertigo differs from that in Meniere's disease, which is characterized by recurrent but intermittent episodes of vertigo attacks lasting minutes to hours, with cochlear involvement [1]. Mixed forms of inner-ear disease that do not clearly belong in either category, such as recurrent labyrinthitis, have also been described [3–7].

Although a viral aetiology for vertigo of peripheral origin (i.e. acute vestibulopathy) has long been suggested in the literature [5, 6, 8–11], it has never been clearly established. Similarly, clusters of vertigo (i.e. epidemic vertigo) suggesting an infectious ideology have been reported [1, 12–16], but none of these studies successfully identified a cause of the illness. Laboratory animal studies have shown that certain commonly circulating viruses, such as influenza A virus, can cause damage to the inner ear [17–19]; however, no clinical studies have demonstrated that natural infection with such viruses can cause vertiginous inner-ear diseases in humans. Other viruses, such as rubella virus, mumps virus and cyto-

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megalovirus (CMV), are known to cause deafness [19], but no study has linked these viruses to inner-ear diseases in adults. Studies of case series of patients from general or otology clinic practices have shown that many of these patients had either an upper respiratory tract infection preceding the onset of vertigo, serologic evidence of acute viral infection, or recent activation of latent viruses [2, 6, 20–22]. However, only one of these studies [22] included an appropriate control group to establish the background prevalence of these infections so that an association between the presence of viral antibodies and vertigo could be determined; however, this study, which suggested human spuma retrovirus as a cause of sudden hearing loss, has recently been retracted [23].

In the autumn of 1992, an apparent outbreak of acute vertigo cases occurred in Hot Springs County, Wyoming. Initial reports from the local hospital stated that *c.* 1% of the county's population of *c.* 5000 people had visited their family practitioner for complaints of vertigo during the autumn. Here, we report the results of the epidemiologic and laboratory-based study we conducted during January 1993 to characterize the vertigo illness, document the outbreak, identify risk factors, and ascertain the possibility of a viral aetiology.

METHODS

Study design

Case definition and case ascertainment

Vertigo was defined as the sensation of a spinning motion of self or the environment. A case-patient was defined as any resident of Hot Springs County with new onset of vertigo that prompted medical attention during the 6-month period between 1 August 1992 and 31 January 1993. We excluded patients whose vertigo we judged to have been potentially caused by a preexisting chronic condition (e.g. cervical disease, neurological disorders, strokes, metabolic disorders, tumours or malignant hypertension).

An extensive search for vertigo case-patients in Hot Springs County was conducted. They were identified by the four local family practitioners who provided all primary health care in Hot Springs County, through advertisements run in the local newspaper during the month of January, and from records of anti-vertigo drug prescriptions (meclizine and scopolamine patches) completed between 1 January 1992 and 15 January 1993, at the four local pharmacies. We reviewed the medical charts of all identified potential case-patients and selected those who possibly fulfilled the case definition. We then asked these patients to complete a questionnaire and donate a blood specimen for serologic studies.

Identification of control-patients

For each vertigo case-patient, matched controls were selected by alphabetically searching the medical records of the family practitioners, beginning with the case-patient's chart, for the next three patients who were within 5 years of age and of the same sex as the case-patient. These persons were contacted and asked to participate in the study and were disqualified as controls if they had a history of recent or recurrent dizziness or vertigo. The search protocol for matched controls continued until at least one control was successfully enrolled for each case-patient in the study. All interviews and blood specimen collections were completed during the last 2 weeks of January 1993.

Interviews

The patient questionnaire included questions about demographics, the character of vertigo episodes, history of symptoms of acute illness during a 4-week period prior to their first vertigo episode, current use of prescription medication, and chronic health problems during the preceding 10 years. Some questions addressed potential environmental exposures, including recent (within the same 4 weeks) participation in local outdoor activities (e.g. mountaineering and bathing in the hot springs of Thermopolis), contact with children in home or at work, exposure to other people with vertigo, and exposure to allergens. Each control completed a similar questionnaire, excluding the questions regarding vertigo symptoms. For comparison, controls were asked about symptoms of acute illness and behavioral risk factors for the same 4-week period that the matched case-patient had indicated in his or her interview. Questionnaires were administered by two of us (L.S., A.S.K.) and a calendar was used as a reference for recalling symptoms and activities.

Serology and other laboratory specimens

Blood specimens were centrifuged within a few hours of collection and the sera shipped on wet ice to the Centers for Disease Control and Prevention (CDC)

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for serological studies. A second (convalescent-phase) blood specimen was obtained from one acutely ill patient. Serologic enzyme-linked immunosorbent assays (ELISAs) were done for a panel of viruses that might have been associated with this outbreak, including enteroviruses, respiratory syncytial virus (RSV), parainfluenza virus types 1 and 3, cytomegalovirus (CMV), and Epstein–Barr virus (EBV).

Enteroviruses

Enteroviruses constitute a large and heterogenous group of viruses (e.g. coxsackieviruses and echoviruses) that are most prevalent in the late summer and early fall. Considerable serologic cross-reactivity is known to occur between members of this group of viruses. A recently developed pan-enterovirus IgM ELISA was used to screen for evidence of recent enterovirus infection. This assay was adapted from a previously described capture ELISA [24], based on substitution of the detection system with Coxsackie B6 as antigen and biotinylated anti-Coxsackie B6 monoclonal antibody 505-2G-6A-8D as detector antibody. A positive result was defined as a $\geqslant 2$ SD elevation above the mean of the optical densities for the negative controls [24], and typically indicates recent infection with an enterovirus [25–27].

The pan-entero IgM assay is highly specific for infection by enteroviruses. In earlier studies, the assay has been positive in $> 95\%$ of the specific acute infections documented by isolation studies [25]. Furthermore, infections with other viruses such as hepatitis A virus, measles virus, RSV and parvovirus B19 do not induce antibodies that are detectable by this enterovirus IgM assay [27, and CDC, unpublished data].

Due to the extensive serologic cross reactivity, the Coxsackie B6 IgM assay cannot distinguish between infection by particular enteroviruses, but is useful as a screening test for the presence of unspecified enterovirus IgM (a pan-enterovirus test) [27 and CDC, unpublished date].

RSV and parainfluenza virus types 1 and 3

We tested for specific IgG antibodies to RSV and parainfluenza virus types 1 and 3 in sera by indirect ELISA, using a modification of standard methods [28]. In addition, case-patients were tested for specific IgM antibodies to RSV using a modification of an indirect EIA assay [29].

CMV and EBV

To detect antibodies specific to EBV, we used the EBV capsid antigen (VCA) IgG-antibody assay [30]. The IgG antibody level indicates the presence and activity level of this virus. Specific antibodies to CMV were detected by an IgG enzyme immunoassay [31]. The CMV antibody level detected by this method indicates a combination of presence and activity level of this virus.

Human spumavirus

We tested a subset of vertigo patients for evidence of spumavirus DNA in lymphocytes. The methods and results of this study were reported earlier [32].

Influenza virus

Influenza titres were not measured; Interviews with local public health and medical personnel and available regional laboratory data indicated that there was no documented influenza activity in Wyoming during the peak months of the vertigo outbreak (October and November).

Virus isolation

For both patients who had new-onset vertigo during January 1993, a nasal and throat swab specimen was collected in Stuart transport medium and sent to CDC overnight at room temperature.

Data analysis

Data were analyzed using both matched and unmatched procedures. We matched cases with their selected controls when comparing illnesses and potential risk factors during the 4-week period preceding the onset of the case-patient's vertigo. Because questions about general health for the preceding 10 years covered the same period for all study participants and all blood specimens were collected at the same time, strict matching between cases and controls was less critical for analysis of these data. For the unmatched analyses, we took the more general approach of stratifying by sex and age (younger than 20 years, 20–39 years and 40 years and older). Both the matched and stratified analyses for dichotomous outcomes were performed using an exact version of the Mantel–Haenszel test [33]. Antibody titres for CMV and EBV were analysed using the stratified Wilcoxon rank sum test. ELISA optical densities for

enterovirus, RSV, and parainfluenza virus types 1 and 3 were evaluated using the analysis of variance.

RESULTS

Case finding and ascertainment

Of 71 patients identified as candidates for the study, 17 were excluded because their vertigo occurred prior to August 1992, 9 had other medical conditions that could explain their vertigo, 4 had not sought medical attention, 2 failed to describe a spinning sensation in their questionnaire, 2 had moved from Wyoming, and 2 declined to participate in the study. The remaining 35 persons met the case definition and were enrolled as case-patients in the study.

The number of new-onset vertigo cases peaked during October and November (19 of the 35 case-patients had their first episode during these 2 months). November was the peak month for the number of persons purchasing anti-vertigo prescription drugs at the four local pharmacies (21 persons in November compared with an average of 8 persons per month during January through July, 1992; $P < 0{\cdot}001$ by Poisson distribution) (Fig. 1).

Demographic and clinical characteristics of vertigo patients

Of the 35 case-patients, 24 (69%) were female and the median age was 41 years (range 7–83 years). All were Caucasian, reflecting the racial distribution in Hot Springs County. For 22 of the 35 case-patients, the attending physician had noted one or more symptoms suggesting an acute viral illness at the time of their first visit for vertigo. The combinations of symptoms differed among patients, but included fever, headache, fatigue, congestion, diarrhoea, sore throat, earache, rhinorrhoea, facial pressure, cough and dyspnoea. Most case-patients (83%) had a vertiginous diagnosis in their medical record. For the remaining six patients, their physician remembered diagnosing them with vertigo and prescribing meclizine or scopolamine patches, but the consultation was not mentioned in their medical records; for these patients, the onset of illness was determined by the self-reported date. At the time of their first vertigo visit, 4 patients had nystagmus, 6 had no objective nystagmus, and the remaining 25 patients had no reference to nystagmus in their medical charts. Three case-patients were referred to an otolaryngologist and two were hospitalized. Audiograms and tympanograms done for nine arbitrarily selected case-patients in January 1993 as part of this investigation confirmed that these patients had normal hearing and middle ear function.

Typically, the vertigo patient reported feeling fine in the evening and waking up the next morning with a vigorous spinning sensation. These attacks were debilitating for most patients: 50% (17/34) reported being unable to perform their normal work routine or being totally incapacitated; 65% (20/31) reported missing work for an average of 2 days (range 1–5 days). Twenty percent (6/30) reported one single episode of vertigo (where the spinning sensation lasted days to weeks), while 80% (24/30) reported having had several episodes between August 1992 and January 1993 (the spinning sensation lasted less than 1 h for 73% [16/22] of these patients). Forty-seven percent (14/30) reported being dizzy between attacks with sudden changes in position. Most case-patients (32/35) belonged to different households. The remaining three case-patients were from the same household and had vertigo within 2–5 days of each other. A fourth member of the household had vertigo episodes for several years and was excluded from this study. Two of the three related case-patients reported a preceding or concurrent febrile illness with various respiratory or gastrointestinal symptoms.

In addition to the spinning sensation specified by our case definition, all case patients reported problems with balance, and 74% reported nausea associated with their vertigo episodes. The majority of the case patients also reported one or more cochlear symptoms, such as tinnitus (54%), a sensation of temporary hearing loss (66%), or fullness or pressure in one or both ears (68%) associated with vertigo episodes.

Case-control study

Risk factors

The 35 case-patients were successfully matched with 61 control persons (1–3 controls per case-patient). Case-patients were significantly more likely than controls to report one of the following symptoms of a recent acute viral illness (fever, weakness or lethargia, fatigue, sore throat, diarrhoea, and a general feeling of 'getting the flu') (Table 1). In contrast, case-patients and controls were similarly likely to report recent episodes of otitis media or sinusitis. The most commonly reported chronic ailments, such as a history of allergies, chronic ear infections, migraine, car sickness and hypothyroidism, were not significantly

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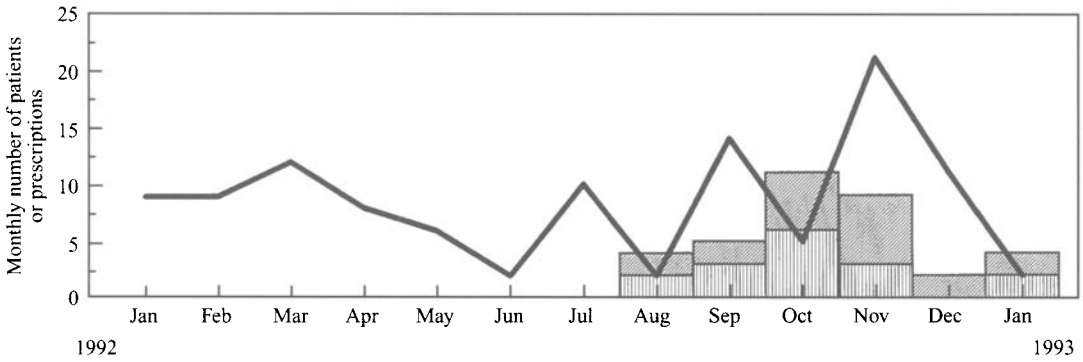

Fig. 1. The number of new-onset vertigo case-patients, 1 August 1992–31 January 1993, and the number of new prescriptions of antivertigo drugs filed, 1 January 1992–15 January 1993. ▥, Number of patients without tinnitus; ▨, number of patients with tinnitus; ——, number of prescriptions.

Table 1. *Comparison of self-reported prevalence of (1) symptoms of acute illness and prescription medication use* at the time of first vertigo episode, and (2) chronic illness during last 10 years, for 35 vertigo patients and 61 controls in Hot Springs County, Wyoming, January 1993*

Characteristic	% prevalence† and (number of patients)		Strength of association	
	Cases ($n = 35$)	Control ($n = 61$)	Matched odds ratio	*P*-value
Symptoms of acute illness				
'A feeling of getting the flu'	54 (19)	16 (10)	5·6	< 0·001
Fatigue	54 (19)	26 (16)	5·5	< 0·01
Sore throat	37 (13)	10 (6)	5·3	< 0·01
Fever	23 (8)	7 (4)	5·0	< 0·05
Weakness or lethargy	23 (8)	5 (3)	6·8	< 0·05
Diarrhoea	20 (7)	7 (4)	5·9	0·05
Acute ear infection/ache	20 (7)	11 (7)	2·0	0·3
Acute sinus infection	23 (8)	23 (14)	1·0	0·90
Chronic illnesses				
A history of allergies	23 (8)	31 (19)	0·6	0·5
Chronic ear infections	6 (2)	5 (3)	1·0	0·6
Chronic sinus infections	14 (5)	13 (8)	1·1	0·8
Migraine headaches	37 (13)	23 (14)	2·3	0·2
Car sickness	37 (13)	25 (15)	2·1	0·4
Hypothyroidism	14 (5)	5 (3)	7·3	0·13
Prescription medication use‡	63 (22)	41 (25)	2·3	0·07

* During a 4-week period prior to the onset of vertigo indicated for the case-patient for each matched pair.

† When analyzing the interview data, 'uncertain' was interpreted as symptom not present.

‡ One or more prescription of any kind was analyzed against no regular prescriptions.

associated with vertigo; however, case-patients were more likely than controls to have used regular prescription medication (Table 1). We found no significant differences between the proportions of case-patients and controls who said they had recently been mountaineering, flying, exposed to allergens, or had contact with children in home or the workplace (data not shown). Bathing in the local hot springs mineral baths during the recent 4 week period, however, was reported by significantly fewer case-patients than controls (6% compared with 27%; $P = 0·01$).

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Serology

Enteroviruses

Of the case patients, 77% (27/35) were positive for enterovirus IgM, compared with 56% (46/61) of the controls ($P = 0{\cdot}04$ by exact Mantel–Haenszel test). For one acutely ill patient, serum samples were obtained on the 2nd and 16th day after his first vertigo episode in mid-January. Concurrent with the vertigo episode, which lasted 3 days, this patient had onset of an acute illness with a fever (102 °C), a sore throat, headache, and other symptoms lasting about 1 week. Both serum samples were positive for enterovirus IgM.

When comparing the enterovirus serology results for vertigo patients with a first onset of vertigo during the first 3 months (August–October 1992) with those patients who had their first vertigo episode during the last 3 months (November 1992–January 1993), the prevalence of enterovirus IgM positivity is elevated in the latter group (65% *vs.* 87% of case patients, OR = 3·5) but this was not significant ($P = 0{\cdot}14$).

To explore the differences in serologic results further, we compared the seropositivity rates for case- and control-groups separately by age and sex. Among males, 91% (10/11) of the case-patients were seropositive, compared with 47% (8/17) of the controls ($P = 0{\cdot}02$). Among females 70% (16/23) of the case-patients were seropositive compared with 57% (24/42) of the controls ($P = 0{\cdot}3$). Examining the differences by age, we found that the statistically significant difference overall in serologic results reflected primarily the higher seropositivity rate for case-patients in the 20- to 39-year-old age group (6/6 compared with 5/13 controls, $P = 0{\cdot}02$). We also addressed whether enterovirus IgM seropositivity was associated with cochlear involvement among the case-patients. Among those reporting tinnitus, 88% (14/16) were seropositive compared with 67% (12/18) of those without tinnitus ($P = 0{\cdot}15$ by Fisher exact test). The pattern for pressure or fullness in one or more ears was similar: 78% (18/23) of those reporting pressure compared with 73% (8/11) of those not reporting pressure ($P = 0{\cdot}52$ by Fisher exact test).

Other viral serology

The mean IgG optical densities were similar among case-patients and controls for RSV ($P = 0{\cdot}28$), parainfluenza virus type 1 ($P = 0{\cdot}78$), and parainfluenza virus type 3 ($P = 0{\cdot}34$). All case-patients were negative for IgM antibodies to RSV (except for one patient whose specimen had a high background signal and therefore could not be interpreted). In the EBV assay, 88% of the case-patients and 90% of the controls had VCA IgG antibodies ($P = 0{\cdot}99$); the median antibody titre was 60 among the case-patients compared with 160 among the controls ($P = 0{\cdot}32$ by the Wilcoxon test stratified by age and sex). In the CMV assay, 62% of case-patients were found to have positive titres of CMV antibodies compared with 61% of controls ($P = 0{\cdot}99$); the median titre was 1630 for the case-patient group compared with 2500 for the controls ($P = 0{\cdot}06$ by stratified Wilcoxon test). Of five arbitrarily chosen patients tested for human spumavirus, none were positive (upper 95% confidence limit for infection rate = 45%).

Virus isolation from acutely ill patients

Nasal/throat swabs for viral isolation were obtained from two case-patients (an 11-year-old girl and a 38-year-old-man) at the time of their first vertigo episode in January 1993. Both patients also had symptoms of a febrile illness: the child had gastrointestinal symptoms and the man had respiratory symptoms. Virus isolation attempts were unsuccessful.

DISCUSSION

We have documented the occurrence of an outbreak of acute vertigo in Hot Springs County, Wyoming. Both the case ascertainment through local family practitioners and the local pharmacies' sales records of anti-vertigo drugs demonstrated an unusually high incidence of new-onset vertigo during late fall of 1992 in this community of 5000 residents. Based on the number of vertigo case-patients identified during the peak months of October and November, 1992, at least 0·4% of the population was affected during this time. Because the investigation was done in January 1993, well after the observed peak of the epidemic, and because we included only vertigo patients who originally had sought medical care, we believe our assessment of the magnitude and the timing of the outbreak was not biased by the attention the outbreak investigation received in Hot Springs County.

Due to the retrospective nature of this outbreak investigation, acute-phase serologic samples were not available for the majority of case-patients, making paired serologic analysis or individual diagnoses of specific viral infection impossible. Instead, we compared the case-patients as a group with the control

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subjects with respect to the IgG antibody titres obtained from the convalescent-phase sera for selected viruses. It is expected that, as a group, a population with a recent reactivation or new infection with a virus would have higher IgM or IgG titres than the control group; therefore, we considered a significant difference in the number of case-patients and controls who were above the cut-off for recent infection (or a significantly elevated mean titre among the cases compared to the controls, when a cut-off value was not available) to be serologic evidence of an association with vertigo and infection.

Using this approach, we found an association between vertigo and serologic evidence (IgM) of recent enterovirus infection. The high background seroprevalence of 54% in the control group is consistent with that expected in a community with recent enterovirus activity. In general, *c.* 15–60% of adults are enterovirus IgM seropositive. The major factors that determine the prevalence in a given population are geographical location, time of year, previous enterovirus activity in the area and the age structure (CDC, unpublished surveillance data). It is possible that only a small proportion of persons recently infected with an enterovirus capable of causing vertigo would exhibit this symptom. For comparison, in an echovirus 30 outbreak in a daycare centre, the majority of the parents and children (60% and 75% respectively) were enterovirus IgM positive, whereas only a small fraction had aseptic meningitis (18% and 3% respectively) [25].

The finding of a borderline elevated prevalence of enterovirus IgM seropositivity in patients with a more recent onset of vertigo is consistent with the enterovirus IgM antibody titre decreasing over time, with a half life of about 6 months (CDC, unpublished data). While the enterovirus IgM seropositive prevalence rates were higher for both male and female case-patients than for their respective controls, only the rates for male case-patients were statistically significantly elevated. Although this apparent gender difference might be due to chance and the relatively small numbers of subjects in the study, it might also reflect a true greater strength of the association for males. It is possible, for example, that males as a group had more severe symptoms than females, and thus, indirectly the case-definition was more specific for males, since it required a visit to a physician.

We did not attempt serologic testing for specific enterovirus antibodies because no virus was isolated from the patients, and public health surveillance data for circulating enterovirus strains in Wyoming at the time of the vertigo outbreak were not available. Based on the serology results alone, the extensive cross-reactivity between antigens and antibodies to various enteroviruses prohibits identification of the enterovirus that caused the elevated IgM titres detected in sera from the majority of case-patients. Since Coxsackie B6 virus is relatively rare [34], it is most likely the heterotypic response, indicating infection with an unspecified enterovirus, that is detected in our study. We failed to identify the enterovirus that caused the elevated IgM titres in the vertigo patients, as enteroviruses can be isolated from throat and nasal samples for only a relatively short time following infection and can be difficult to culture [35]. Stool specimens, which may be positive for enteroviruses for a longer period, were not obtained from these patients.

Our ability to identify specific signs and symptoms and risk factors associated with vertigo was limited by the timing of the investigation and the sketchy nature of the medical records. Further, study participants were asked to recall symptoms and activities that had occurred as much as 6 months earlier; this factor introduced the possibility that case-patients, with their more clearly defined time reference, recalled symptoms more accurately than did the controls. Despite this potential bias toward spurious associations, we did not identify any environmental risk factors associated with being diagnosed with vertigo. Bathing in the local mineral waters was actually found to be negatively associated with vertigo and may reflect that ill case-patients were less likely to engage in outdoor bathing.

The majority of the vertigo case-patients reported a clinical picture that was unusual for epidemic vertigo. Many reported cochlear symptoms (e.g. tinnitus, a sensation of temporary hearing loss or ear pressure) that have not previously been reported with acute vestibulopathy or epidemic vertigo. The clinical picture presented by many of these case-patients (i.e. cochlear symptoms and recurrent vertigo episodes of < 1 h) is more compatible with symptoms of a Meniere's-like illness. Since most enterovirus infections are mild or asymptomatic [36], the absence of more serious symptoms associated with enterovirus infection among vertigo patients, such as meningitis, pleurodynia, herpangina or hand-foot-mouth syndrome, is not inconsistent with our hypothesis.

To our knowledge, this investigation is the first study in which serologic evidence of a viral infection

was associated with vertigo. Our data suggest that recent infection with one or more unspecified enteroviruses may have contributed to the occurrence of this vertigo outbreak. In support of this finding, an association with a recent enterovirus infection, based on the same pan-enterovirus IgM assay, was also found in a study of a vertigo outbreak that occurred in a work place in Atlanta in 1994 (where serologic results from 21 persons with self-reported symptoms of vertigo were compared with serologic results from 51 colleagues without these symptoms) [37].

While our study has suggested a possible association of vertigo and enterovirus infection, the retrospective nature of the outbreak investigation and the failure to isolate a virus made it impossible for us to obtain strong or definite evidence of a role of enteroviruses in vertiginous illnesses. Future investigations of the aetiology of epidemic vertigo should consider enteroviruses as a possible aetiologic agent, and include collection and culturing of stool and throat specimens of patients during the early phase of illness. This approach may lead to the identification of a particular enterovirus that causes vertigo.

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