Clinical Severity of Influenza-like Illness due to Coxsackievirus/Echovirus: A Case-Series Analysis

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1 Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD; 2 Naval Medical Center, San Diego, CA; 3 Madigan Army Medical Center, Tacoma, WA; 4 Madigan Army Medical Center, San Antonio, TX; 5 Walter Reed National Military Medical Center, Washington, DC; 6 Dinformatics Laboratories, Huntsville, AL; 7 Clinical and demographic information, and a nasopharyngeal swab was collected at baseline (day 0). Participants returned on subsequent days for follow-up visits and swabs were collected. Participants were asked to monitor symptoms throughout the study and to complete a daily symptom diary which was reviewed at each visit. The presence and severity of symptoms were recorded either by self-report (diary) or interview as: 0 (none); 1 (mild: not changing activity or requiring medical care); 2 (moderate: requiring medical care); and 3 (severe: incapacitating, unable to perform normal activities, requiring bed rest and/or medication). Participants were trained by research personnel on the definitions of each score. Swabs were tested for influenza virus by real-time reverse transcription polymerase chain reaction (RT-PCR) at the Naval Health Research Center (San Diego, CA).

A target-enriched multiplex PCR (TEM-PCR) panel for 13 bacterial and 10 viral respiratory pathogens was developed by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter Agency Agreement [Y1.A1.G0072] to Uniformed Services University of the Health Sciences. The Naval Health Research Center, San Diego, CA; 9 Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda MD.

Methods

• Since 2009, we enrolled otherwise healthy military personnel and beneficiaries into an ongoing, longitudinal study of influenza-like illness (ILI) at the military treatment facilities across the continental United States (Figure 1).

• Eligibility. Patients presenting for care <72h after the onset of ILI, defined as fever (temperature of 100.4°F or greater at the time of evaluation, or by self-report) and sore throat or one of the following respiratory symptoms: cough, sputum production, shortness of breath, or chest pain. Patients with underlying medical conditions were excluded.

• Clinical and demographic information, and a nasopharyngeal swab was collected at baseline (day 0). Participants returned on subsequent days for follow-up visits and swabs were collected. Participants were asked to monitor symptoms throughout the study and to complete a daily symptom diary which was reviewed at each visit. The presence and severity of symptoms were recorded either by self-report (diary) or interview as: 0 (none); 1 (mild: not changing activity or requiring medical care); 2 (moderate: requiring medical care); and 3 (severe: incapacitating, unable to perform normal activities, requiring bed rest and/or medication). Participants were trained by research personnel on the definitions of each score. Swabs were tested for influenza virus by real-time reverse transcription polymerase chain reaction (RT-PCR) at the Naval Health Research Center (San Diego, CA).

• A target-enriched multiplex PCR (TEM-PCR) panel for 13 bacterial and 10 viral respiratory pathogens was developed by Dinformatics Laboratories, LLC (Huntsville, AL). The platform relies upon nested multiplex PCR to provide the initial target enrichment and super primers to amplify and label the PCR products. The viral respiratory pathogens on the panel include: adenovirus, coxsackievirus/echovirus, bocavirus, coronavirus, human metapneumovirus, rhinovirus, influenza A/B, parainfluenza, and respiratory syncytial virus.

• We measured presence of a symptom at any severity level (mild, moderate, severe): further stratified comparisons were based on moderate/severe versus none/mild, and severe versus mild/moderate/severe. Composite measures were the sum of individual symptom scores in the following categories: (1) lower respiratory symptoms: cough, breathing difficulty, hoarseness and chest pain; (2) upper respiratory symptoms: sneeze, runny nose, sore throat and sneezing; (3) systemic symptoms: chill, muscle ache, headache and fatigue; (4) total symptom scores: sum of the above three categories.

• Statistical analyses were performed using SAS (Version 9.3, SAS Institute, Cary, NC) and R Package (version 3.1.3 for Windows). The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences (DCDP-045).

Results

• From 2009-2014, a sample of 898 cases with ILI were tested for viral respiratory pathogens using Diatherix multiplex respiratory pathogen panel. Of these, 89 (9.9%) had detection of coxsackievirus/echovirus. Children were more likely to have CVEV detection compared to adults (14.7% vs. 8.0%, p<0.01).

• Forty-six (51.7%) cases with CVEV had co-detection of other viral respiratory pathogens, including human rhinovirus (78%), human metapneumovirus (13%), RSV (13%), coronavirus (9%), and parainfluenzairus (4%).

• Proportion of CVEV detection increased in March and was high in late spring and summer, while detection of influenza virus peaked in winter season (Figure 2). We examined characteristics associated with coxsackievirus/echovirus (CVEV) detection and compared clinical severity of CVEV patients to influenza patients to understand the relative impact of such pathogens.

Conclusions

• Overall, CVEV represented a small proportion of ILI and was prevalent in post-influenza season.

• CVEV causes more severe upper respiratory tract symptoms in both adults and children, but less severe systemic symptoms compared to influenza virus.

• Studies of severe ILI among adults should assess the contribution of CVEV, especially in the post-influenza season.

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