CLINICAL RESEARCH STUDY

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Coronavirus and Other Respiratory Illnesses Comparing Older with Young Adults

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ABSTRACT

BACKGROUND: Study of human coronavirus and other virus-associated respiratory illnesses is needed to describe their clinical effects on chronically ill, older adults.

METHODS: A prospective study during 2009 to 2013 clinically assessed acute respiratory illnesses soon after onset and 3 to 4 weeks later in patients aged ≥60 years with chronic lung and heart diseases (group 1, 100 subjects) and healthy adults aged 18 to 40 years (group 2, 101 subjects). Respiratory secretions were tested for nucleic acids of a panel of respiratory viruses. An increase in antibody titer was assessed for 4 coronavirus strains.

RESULTS: Virus-associated illnesses (29 [39.1%] of 74 illnesses in group 1 and 59 [48.7%] of 121 illnesses in group 2) occurred in all calendar quarters, most commonly in the first and fourth quarters. Coronaviruses (group 1: 14 [18.9%] illnesses; group 2: 26 [21.5%] illnesses) and enteroviruses/rhinoviruses (group 1: 14 [18.9%] illnesses; group 2: 37 [30.6%] illnesses) were most common. Virus co-infections occurred in 10 illnesses. Illnesses with 9 to 11 symptoms were more common in group 1 (17 [23.0%]) than in group 2 (15 [12.4%]) ($P < .05$). Compared with group 2, more group 1 subjects reported dyspnea, more severe disease of longer duration, and treatment for acute illness with prednisone and antibiotics. Coronavirus-associated illnesses (percent of illnesses, group 1 vs group 2) were characterized by myalgias (21% vs 68%, $P < .01$), chills (50% vs 52%), dyspnea (71% vs 24%, $P < .01$), headache (64% vs 72%), malaise (64% vs 84%), cough (86% vs 68%), sputum production (86% vs 60%), sore throat (64% vs 80%), and nasal congestion (93% vs 96%).

CONCLUSIONS: Respiratory illnesses were commonly associated with coronaviruses and enteroviruses/rhinoviruses affecting chronically ill, older patients more than healthy, young adults.

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Coronaviruses are enveloped, single-stranded, positive-sense RNA viruses and undergo RNA recombination and mutations facilitating adaptation from animals to humans.[1-5] The identification of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus as causes of human disease[2,3,6,7] has increased the clinical significance of coronaviruses. Human coronaviruses (HCoVs) cause the common cold and influenza-like illnesses. Coronaviruses and other respiratory viruses also are associated with a number of more serious acute respiratory illnesses, such as pneumonia,

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exacerbations of asthma and chronic obstructive pulmonary disease, croup, and bronchiolitis.[8-13]

Two other coronaviruses, HCoV-NL63 and HCoV-HKU1, have a worldwide distribution and cause respiratory illness along with prototype strains, HCoV-229E and HCoV-OC43.[14-29] In patients with chronic obstructive pulmonary disease studied during the 1998 to 1999 influenza season, 13.5% of illnesses were associated with HCoV-229E and HCoV-OC43 infection, with HCoV-OC43 being more common.[30-32] Coronavirus-associated illness was less severe than influenza but was associated with multiple respiratory and systemic symptoms, and hospitalization.[30] Walsh et al[33] reported HCoV-229E and HCoV-OC43 infection rates of 2.8% to 26% in healthy young and elderly adults, high-risk adults, and hospitalized patients during the winters of 1999 to 2003 and as contributions to medical disease burden.[33]

CLINICAL SIGNIFICANCE

- Coronavirus and enterovirus/rhinovirus-related acute respiratory illness were common.
- Older, chronically ill adults had more severe illnesses than young, healthy adults.
- Dyspnea was more common in older, chronically ill than in young, healthy adults.
- Respiratory illness symptom duration was longer in older, chronically ill adults.
- Older, chronically ill adults were more likely to receive antibiotics and steroids.

In this multi-year, prospective study, our goal was to underscore the manifestations and importance of HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, and other respiratory infections throughout the calendar year in at-risk older patients with underlying chronic cardiopulmonary and other diseases compared with young healthy adults.

MATERIALS AND METHODS

Study Design and Subjects

This was a prospective, observational study conducted from November 2009 to July 2013 to assess acute respiratory illness in patients aged ≥60 years with chronic lung or heart disease or both (group 1) and in healthy young adults aged 18 to 40 years (group 2). Group 1 patients were capable of attending outpatient clinics and complying with study procedures, but they were excluded if they had a life expectancy <3 years in the clinical judgment of the investigator, a febrile or respiratory illness within 15 days before enrollment, a significant bleeding disorder, asplenia, or a psychiatric condition that precluded compliance. Group 2 subjects were in good health shown by medical history and physical examination. Volunteers were excluded from group 2 if they had received immunosuppressive medications within 168 days, blood products within 120 days, or immunoglobulins within 60 days; were immunosuppressed; had a febrile or respiratory illness within 15 days before enrollment; or had a clinically significant medical condition. All patients gave written informed consent. Eligibility was confirmed by a study physician. The study received approvals by responsible institutional review boards and was conducted in accordance with the amended Declaration of Helsinki.

From November 2009 to July 2013, enrolled patients each participated for up to 2 years, received phone calls every 8 weeks to remind them to contact study personnel at the time of acute respiratory illness, were evaluated by a study physician and nurse in clinic when they had 3 symptoms or fever (body temperature ≥37.8°C) accompanied by 2 symptoms of acute respiratory illness, and kept a daily temperature and symptom diary during the illness. Nasal and oropharyngeal swab and serum specimens were obtained at the acute illness visit. Illness symptoms were reassessed, and a serum specimen was obtained 3 to 4 weeks after the onset of the illness. Clinical assessments were completed without knowledge of assay results on swab and serum specimens. Assays were performed near the end of the study.

Coronavirus-associated illness was the sudden onset of respiratory illness plus (1) a nasal and oropharyngeal swab specimen positive by reverse transcriptase polymerase chain reaction (RT-PCR) or (2) a >3-fold increase in the calculated titer of serum antibody to coronavirus (serologic change) by enzyme-linked immunosorbent assay comparing paired acute and convalescent sera assayed at the same time. Other virus-associated illness was the sudden onset of respiratory illness plus swab specimen positive for respiratory virus nucleic acid.

Virus Nucleic Acid Detection Performed in Research Laboratory

RNA was purified from swab specimens using the QIAmp kit (Qiagen, Valencia, Calif) according to the manufacturer's procedures. Testing for HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, and other respiratory viruses (respiratory syncytial virus types A and B, influenza A and B viruses, parainfluenza viruses types 1 to 4, metapneumovirus, enterovirus/rhinovirus, adenovirus, and bocavirus) was done by multiplex RT-PCR using the xTAG Respiratory Viral Panel Fast and the manufacturer's procedures (Luminex Molecular Diagnostics, Inc, Toronto, Ontario, Canada).[34,35]

Coronavirus Antibody Enzyme-Linked Immunosorbent Assay

The 4 coronavirus antigens for the antibody assay were produced as described.[30,36,37] Viral and mock antigens were used to coat flat-bottom 96-well Maxisorp Immuno-plates