Human Bocavirus: A New Viral Pathogen

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(See the article by Allander et al. on pages 904–10)

In this issue of Clinical Infectious Diseases, Allander et al. [1] report a study of the recently discovered human bocavirus (HBoV) in children hospitalized with wheezing. This study is a nice example of what is likely to be an increasingly common challenge and opportunity in infectious diseases: determining what diseases novel pathogens cause. HBoV was first described in 2005 after large-scale molecular screening for virus genome sequences led to its discovery in respiratory specimens [2]. Among the sequences identified were those from a novel parvovirus related to minute virus of canine and bovine parvovirus that was designated “human bocavirus.” Because the virus sequences were amplified from respiratory specimens, the investigators hypothesized that the virus would cause respiratory disease, and they and others have since documented the presence of HBoV in 1.5%–11.3% of respiratory specimens obtained from patients with acute respiratory illness. Another new human parvovirus, PAR4, was recently identified by large-scale molecular screening for viruses, this time in blood specimens obtained from patients with acute HIV syndrome [3]. However, PAR4 has not yet been linked to human disease. Given that there has been improvement in the tools used to detect and characterize pathogens (e.g., microarray technology, consensus PCR assays, and high-throughput sequencing, such as high-density picolitre reactors [4]), there is likely to be a growing number of new viruses to study. For example, in the past 5 years, 4 novel viruses (excluding HBoV) have been detected in respiratory specimens obtained from patients with acute respiratory illness. Human metapneumovirus and 2 coronaviruses, severe acute respiratory syndrome coronavirus (SARS CoV) and NL63, were first isolated in tissue culture and were then characterized by different methods designed to amplify and sequence novel viruses [5–10]. Another human coronavirus, HKU1, and multiple bat coronaviruses were identified with PCR assays designed to amplify any coronavirus genome [11, 12]. Large-scale molecular screening has recently been used to identify numerous novel viruses from coastal waters [13].

Once a novel virus has been detected, an important next step is to determine what disease it causes. Many novel viruses have been first detected in specimens obtained from patients with a specific illness, which, in turn, provided clues to possible disease associations. When the initial detection of a virus provides few clues to disease associations, looking for possible disease associations is, at best, challenging.

Acute respiratory illness and, now, wheezing are hypothesized to be caused by HBoV infection. Koch’s postulates have provided the standard for establishing a causal link between a pathogen and disease. Time-modified postulates that account for changes in our understanding of pathogens and disease in general include (1) consistently finding the pathogen in patients with the disease more often than in control subjects, (2) replicating the disease after challenging an appropriate animal with the pathogen, and (3) reisolating the pathogen from the challenged animal. A causal relationship is also supported by demonstration of the pathogen in affected tissue (especially histologically), demonstration of an immune response to the pathogen, and prevention of disease with a specific intervention, such as immune therapy or vaccination.

Progress in establishing a causal link between newly discovered viruses and disease has often been aided by the availability of stored specimens from patients with the disease in question. Well-characterized stored specimens with good clinical and epidemiologic data from patients with a variety of illnesses are a valuable resource for identifying and characterizing virus-disease associations. However, without appropriate controls, such specimens cannot provide evidence of an association between the pathogen and the disease.
Two recent studies of HBoV included control subjects and demonstrated an association between HBoV infection and acute respiratory illness, but whether HBoV actually causes acute respiratory illness remains uncertain, especially given the high rate at which other viruses are detected in HBoV-positive specimens [14–16]. The rate at which other viruses are detected in nasopharyngeal aspirate specimens for the case patients, 4.1 and 1.6 years, respectively) were considerable enough to possibly affect detection rates. We are not given sufficient information to know whether differences in the timing of collection of specimens from HBoV-positive subjects and control subjects may have contributed to the differences in detection rates.

We are likely to see an increasing number of novel viruses discovered, and it is worth designing studies to take advantage of this opportunity. Appropriately collected, handled, and stored specimen sets with good clinical and epidemiologic data and institutional review board approval for future testing will be great assets in efforts to identify and evaluate novel virus-disease associations. Such specimen sets that also have appropriate controls will be even more valuable; they allow investigators to determine which associations are likely important and worth pursuing.

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References