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Antigen-specific H1N1 influenza antibody responses in acute respiratory tract infections and their relation to influenza infection and disease course☆,☆☆

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ABSTRACT

Background: Early antibody responses to influenza infection are important in both clearance of virus and fighting the disease. Acute influenza antibody titers directed toward H1-antigens and their relation to infection type and patient outcomes have not been well investigated.
Objective: Using hemagglutination inhibition (HI) assays, we aimed to characterize the H1-specific antibody titers in patients with influenza infection or another respiratory infection before and after the H1N1-pandemic influenza outbreak. Among patients with acute influenza infection we related duration of illness, severity of symptoms, and need for hospitalization to antibody titers.
Methods: There were 134 adult patients (average age 34.7) who presented to an urban academic emergency department (ED) from October through March during the 2008–2011 influenza seasons with symptoms of fever and a cough. Nasal aspirates were tested by viral culture, and peripheral blood serum was run in seven H1-subtype HI assays.
Results: Acutely infected influenza patients had markedly lower antibody titers for six of the seven pseudotype viruses. For the average over the seven titers (log units, base 2) their mean was 7.24 (95% CI 6.88, 7.61) compared with 8.60 (95% CI 8.27, 8.92) among patients who had a non-influenza respiratory illness, $p < 0.0001$. Among patients with seasonal influenza infection, titers of some antibodies correlated with severity of symptoms and with total duration of illness ($p < 0.02$).
Conclusion: In patients with acute respiratory infections, lower concentrations of H1-influenza-specific antibodies were associated with influenza infection. Among influenza-infected patients, higher antibody titers were present in patients with a longer duration of illness and with higher severity-of-symptom scores.

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1. Background

Factors that increase the risk of severe influenza infection include host factors such as extremes of age, comorbid illnesses, pregnancy, and obesity [1–3]. Most patients infected with influenza virus either are asymptomatic or develop mild, non-life-threatening respiratory tract infections. However, with the emergence of the pandemic 2009 H1N1 strain, the majority of serious illnesses and 90% of deaths occurred among young healthy adults who lacked any of these risk factors [4]. Unidentified factors must affect the host's innate immune response and thus lead to severe disease progression.

During the early stages of infection, neutralizing antibody titers are low, but crucial to fighting off infection [5]. Neutralizing antibody responses are induced strongly in healthy individuals and contribute to virus clearance [6]. Hospitalized influenza-infected individuals demonstrate lower total and neutralizing anti-influenza antibody titers than do respiratory syncytial virus-infected control subjects. This difference suggests a protective effect of higher influenza antibody titers [7]. An overall reduction in antibody titers produced during severe acute influenza infection occurs in both human and mouse models [8–10]. Clinically, little is known of how such variations in antibody responses may influence susceptibility to infection by new circulating H1 influenza viruses.

In 2009 a novel pandemic H1N1 influenza A virus (H1N1/09) spared the elderly but caused severe disease in middle-aged individuals, even though this younger population had more-robust preexisting immunity against seasonal H1 strains. One theory for this pattern was that cross-reactive antibodies to the pre-1957 circulating H1N1 virus protected the older population [11,12]. Elevated antibody titers against the H1N1/09 virus were associated with previous seasonal 2007 H1N1 infection, which may have contributed to the lower burden of the 2009 influenza pandemic [13].

Not all prior influenza vaccinations or infections leading to preexisting influenza antibodies may be beneficial. The presence of cross-reactive antibodies to one influenza virus strain can reduce production of B cell antibodies to a second encountered strain [14,15]. Low-affinity influenza antibodies have been detected in individuals with severe concurrent bacterial pneumonia [16]. Preexisting serum antibodies that cross-react with, but do not protect against, the H1N1/09 influenza virus in middle-aged adults may have led to higher disease severity and worse outcomes [16]. Such conflicting data and an overall lack of information on early antibody response to natural infection and patient outcomes indicate a need for further investigation of H1-specific antibody response to various H1 pseudotype viruses in patients with pre- and post-H1N1-pandemic influenza infection.

2. Objectives

We aimed to characterize H1-specific antibody titers before and after the H1N1-pandemic influenza outbreak among patients with influenza infection and patients with other respiratory tract infections. The resulting data allowed us to compare those two groups' antibody responses on individual H1-pseudotype viruses, to compare responses among those viruses, and to compare H1N1/09 patients versus seasonal influenza patients. Among influenza-infected patients, we also explored the relation between H1-specific antibody titers and severity of patient-reported symptoms, total duration of symptoms, and need for hospitalization.

3. Methods

3.1. Study design and setting

This prospective observational study involved patients presenting to the ED with symptoms of influenza-like illness (ILI), which included a cough and a fever [17]. The study setting was an urban academic Level 1 trauma center with an annual census greater than 100,000 patients. The study involved three influenza seasons. The first season spanned the months of January through March of 2009 and included subjects with seasonal influenza infection. The second and third influenza seasons spanned the months of October through March 2009–2010 and 2010–2011. The pandemic H1N1 influenza virus emerged during this time period, and subjects with H1N1 influenza infection were enrolled.

3.2. Selection of participants

Patients presenting to the adult ED, 18 years of age or older, whose chief complaints were fever and cough were approached for enrollment. Patients with symptoms lasting more than 3 days, a history of immunosuppressant medications, a recent diagnosis of pneumonia, or current antibiotics were excluded. The exclusion of patients with symptoms lasting longer than 3 days draws on our previous work on cytokine markers in this group [18] and captures subjects with an acute infection [19]. The primary analysis excluded subjects with a diagnosis of concurrent influenza and bacterial pneumonia infection. Secondary analysis compared those patients with patients who had influenza infection alone.

3.3. Clinical data

Patients completed a survey about their past medical history, current illness, and symptom severity. During this initial ED visit, both nasal washing and blood samples were collected from each patient and vital signs recorded. After enrollment patients were followed by chart review (if admitted to the hospital) or with a telephone survey at four weeks. The follow-up aimed to determine duration of symptoms and the presence of any potential complications. A score for severity of symptoms (SOS) was calculated for each patient as they presented to the ED. The previously validated instrument asked patients to rate, on a scale from 0 (none) to 3 (severe), the severity of seven symptoms: cough, nasal obstruction, sore throat, fatigue, headache, myalgia, and feverishness [20,21].

3.4. Laboratory assays

During January through March of 2009, we used the rapid point-of-care Enzyme-Linked Immunosorbent Assay (ELISA) to screen patients presenting to the ED who were suspected of having an acute infection with influenza. We enrolled only subjects who had a positive test confirming influenza A antigen which included both H3N2 and H1N1 subtypes.

With the emergence of the pandemic 2009 H1N1 virus, the rapid ELISA assay was discontinued because it lacked sensitivity in detecting the novel H1N1 influenza strain [22]. Without a reliable rapid test to identify influenza-infected individuals, we altered the study design to enroll all patients (ages 18–65) who presented with symptoms of ILI. To test for the presence of influenza virus, we used a viral culture technique. In brief, after centrifugation specimens were processed for culture in rhesus monkey kidney cells for two days. Then, using monoclonal antibodies, they were assessed for the presence of viral particles. The Rhode Island State Laboratory confirmed pandemic-H1N1/09-positive cultures by virus particle detection through polymerase chain reaction, used nationally at that time [23].

3.4.1. Pseudotype lentiviral vectors

Recombinant lentiviral vectors expressing a luciferase reporter gene were produced as previously described [24,25]. We used 7 pseudotype viruses expressing H1 antigen, representing over 30 years of H1 influenza virus in circulation in

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