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Bell's Palsy
Virology
Written: 12 February 2010

CLINICAL SYNDROMES, LABORATORY DIAGNOSIS AND TREATMENT OF ORTHOMYXOVIRUSES

Clinical Syndromes

Depending on the degree of immunity to the infecting strain of virus and other factors, infection may range from asymptomatic to severe. Patients with underlying cardiorespiratory disease, people with immune deficiency (even that associated with pregnancy), the elderly, and smokers are more prone to have a severe case.

After an incubation period of 1 to 4 days, the "flu syndrome" begins with a brief prodrome of malaise and headache lasting a few hours. The prodrome is followed by the abrupt onset of fever, chills, severe myalgias, loss of appetite, weakness and fatigue, sore throat, and usually a nonproductive cough. The fever persists for 3 to 8 days, and unless a complication occurs, recovery is complete within 7 to 10 days. Influenza in young children (under 3 years) resembles other severe respiratory tract infections, causing bronchiolitis, croup, otitis media, vomiting, and abdominal pain, accompanied rarely by febrile convulsions (Table 1). Complications of influenza include bacterial pneumonia, myositis, and Reye syndrome. The central nervous system can also be involved. Influenza B disease is similar to influenza A disease.

Disorder	Symptoms
Acute influenza infection in adults	Rapid onset of fever, malaise, myalgia, sore throat, and nonproductive cough
Acute influenza infection in children	Acute disease similar to that in adults but with higher fever, gastrointestinal tract symptoms (abdominal pain, vomiting), otitis media, myositis, and more frequent croup
Complications of influenza virus infection	Primary viral pneumonia Secondary bacterial pneumonia Myositis and cardiac involvement Neurologic syndromes: Guillain-Barré syndrome Encephalopathy Encephalitis Reye syndrome

Table 1

Influenza may directly cause pneumonia, but it more commonly promotes a secondary bacterial superinfection that leads to bronchitis or pneumonia. The tissue damage caused by progressive influenza virus infection of alveoli can be extensive, leading to hypoxia and bilateral pneumonia. Secondary bacterial infection usually involves Streptococcus pneumoniae, Haemophilus influenzae, or Staphylococcus aureus. In these infections, sputum usually is produced and becomes purulent.

Although the infection generally is limited to the lung, some strains of influenza can spread to other sites in certain people. For example, myositis (inflammation of muscle) may occur in children. Encephalopathy, although rare, may accompany an acute influenza illness and can be fatal. Postinfluenza encephalitis occurs 2 to 3 weeks after recovery from influenza. It is associated with evidence of inflammation but is rarely fatal.

Reye syndrome is an acute encephalitis that affects children and occurs after a variety of acute febrile viral infections, including varicella and influenza B and A diseases. Children given salicylates (aspirin) are at increased risk for this syndrome. In addition to encephalopathy, hepatic dysfunction is present. The mortality rate may be as high as 40%.

Laboratory Diagnosis

The diagnosis of influenza is usually based on the characteristic symptoms, the season, and the presence of the virus in the community. Laboratory methods that distinguish influenza from other respiratory viruses and identify its type and strain confirm the diagnosis (Table 2).

Test	Detects
Cell culture in primary monkey kidney or Madin-Darby canine kidney cells	Presence of virus; limited cytopathologic effects
Hemadsorption to infected cells	Presence of HA protein on cell surface
Hemagglutination	Presence of virus in secretions
Hemagglutination inhibition	Type and strain of influenza virus or specificity of antibody
Antibody inhibition of hemadsorption	Identification of influenza type and strain
Immunofluorescence, ELISA	Influenza virus antigens in respiratory secretions or tissue culture
Serology: hemagglutination inhibition, hemadsorption inhibition, ELISA, immunofluorescence, complement fixation	Seroepidemiology
Genomics: RT-PCR	Identification of influenza type and strain

Table 2

Influenza viruses are obtained from respiratory secretions. The virus is generally isolated in primary monkey kidney cell cultures or the Madin-Darby canine kidney cell line. Nonspecific cytopathologic effects are often difficult to distinguish but may be noted within as few as 2 days (average, 4 days). Before the cytopathologic effects develop, the addition of guinea pig erythrocytes may reveal hemadsorption (the adherence of these erythrocytes to HA-expressing infected cells). The addition of influenza virus-containing media to erythrocytes promotes the formation of a gel-like aggregate due to hemagglutination. Hemagglutination and hemadsorption are not specific to influenza viruses, however; parainfluenza and other viruses also exhibit these properties.

More rapid techniques detect and identify the influenza genome or antigens of the virus. Rapid antigen assays (less than 30 min) can detect and distinguish influenza A and B. Reverse transcriptase polymerase chain reaction (RT-PCR) using generic influenza primers can be used to detect and distinguish influenza A and B, and more specific primers can be used to distinguish the different strains, such as H5N1. Enzyme immunoassay or immunofluorescence can be used to detect viral antigen in exfoliated cells, respiratory secretions, or cell culture and are more sensitive assays. Immunofluorescence or inhibition of hemadsorption or hemagglutination (hemagglutination inhibition [HI]) with specific antibody can also detect and distinguish different influenza strains. Laboratory studies are primarily used for epidemiologic purposes.

Treatment, Prevention, and Control

Hundreds of millions of dollars are spent on acetaminophen, antihistamines, and similar drugs to relieve the symptoms of influenza. The antiviral drug amantadine and its analogue rimantadine inhibit an uncoating step of the influenza A virus but do not affect the influenza B and C viruses. The target for their action is the M2 protein. Zanamivir and oseltamivir inhibit both influenza A and B as enzyme inhibitors of neuraminidase. Without neuraminidase, the hemagglutinin of the virus binds to sialic acid on other viral particles to form clumps, thereby

preventing virus release. Zanamivir is inhaled, whereas oseltamivir is taken orally as a pill. These drugs are effective for prophylaxis and for treatment during the first 24 to 48 hours after the onset of influenza A illness. Treatment cannot prevent the later host-induced immunopathogenic stages of the disease.

The airborne spread of influenza is almost impossible to limit. However, the best way to control the virus is through immunization. Natural immunization, which results from prior exposure, is protective for long periods. A killed-virus vaccine representing the "strains of the year" and antiviral drug prophylaxis can also prevent infection.

The influenza vaccine is a mixture of extracts or purified HA and NA proteins from three different strains of virus. The vaccines are prepared from virus grown in embryonated eggs and then chemically inactivated. Killed (formalin-inactivated) virion preparations have also been used. Ideally the vaccine incorporates antigens of the A and B influenza strains that will be prevalent in the community during the upcoming winter. For instance, the trivalent influenza vaccine used for the 2006-2007 season included A/New Caledonia/20/1999 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like antigens. Vaccination is routinely recommended for persons older than 50, healthcare workers, pregnant women who will be in their second or third trimester during flu season, people living in a nursing home, people with chronic pulmonary heart disease, and others at high risk. As of 2008, all children aged 5-18 years should also be vaccinated. Persons with allergies to eggs should not get the vaccine.

A live vaccine is also available for administration as a nasal spray instead of a "flu shot." The trivalent vaccine consists of reassortants for the HA and NA gene segments of different influenza strains, with a master donor virus that is cold adapted to optimum growth at 25° C. This vaccine will elicit a more natural protection, including cell-mediated, antibody and mucosal-secretory immunoglobulin (Ig)A antibody. Currently the vaccine is recommended for people ages 5 to 50.

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