The Reemergence of Pertussis in Immunized Populations: A Case Study

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OBJECTIVE: To present a case of classical pertussis occurring in previously vaccinated male siblings, 11 and 13 years of age, living in El Paso TX; also to present an overview and update of the changing epidemiology of pertussis including pathophysiology, diagnosis, and treatment.

DESIGN: Nasopharyngeal swabs and blood samples were collected from two male siblings, 11 and 13 years of age, presenting with cold-like symptoms and persistent cough during the second week of infection. Nasopharyngeal swabs were plated onto Bordet-Gengou agar plates and incubated for 48 hours. Blood samples were analyzed for the presence of antibodies (IgM and IgA) against *Bordetella pertussis* antigens using indirect enzyme linked immunosorbent assay (ELISA).

SETTING: Cultures and serological analysis was conducted at the University of Texas at El Paso, Clinical Laboratory Science Program Research facility.

RESULTS: Bacterial cultures of both children were positive for *Bordetella pertussis* and the sera revealed positive IgM and IgA antibodies (>11 PANBIO UNITS) against a mixture of antigens including: pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae.

CONCLUSIONS: Pertussis immunity wanes overtime, leaving most adolescents and adults susceptible to infection. Physicians must be prepared to diagnose and treat pertussis in any age group regardless of vaccination status.

ABBREVIATIONS: AC = adenylate cyclase; DaTP = acellular DTP; DFA = direct fluorescent antibody; FHA = filamentous hemaglutinin; PCR = polymerase chain reaction; PRN = pertactin; UTEP = University of Texas at El Paso.

INDEX TERMS: *Bordetella pertussis*; pertussis epidemiology; pertussis.

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Bordetella pertussis, the etiologic agent of whooping cough, continues to be an important cause of morbidity in the United States.[1-3] Despite vaccination coverage for over 50 years, pertussis has not been eradicated.[3-6] Primary vaccination is effective in 80% of the cases.[7] However, this protection is transient making the vaccinated host vulnerable to infection.[7-9] Recently, major outbreaks of the disease have been documented in highly immunized populations worldwide and throughout the U.S.[6,10-17] Data from these outbreaks reveal a remarkable epidemiological shift. Historically, the occurrence of pertussis was primarily in infants or under-immunized pre-schoolers. These recent studies now demonstrate an epidemiological shift of increasing disease in older children, adolescents, and adults.[5,6,18,19] The cause of the increased incidence has not been definitively determined. However, factors such as waning vaccine-induced immunity, vaccine quality, antigenic variation of *Bordetella* strains, and undetected mild illness in adults and adolescents have been proposed.[18,20] Outbreak investigations have documented that *B. pertussis* infections occurring in adults have subsequently been transmitted to other adults and children.[8,9] Therefore, previously immunized adults and adolescents are an important reservoir for *B. pertussis*.[16,19,21] Pertussis can be difficult to diagnose and is often unrecognized or misdiagnosed in adolescents and adults, since the classic presentation of whooping cough may not be present. In addition, laboratory results may be non-diagnostic if the specimen is not appropriately collected.[7,22,23] The following

is a case of classical pertussis occurring in El Paso TX in male siblings despite vaccination coverage.

CASE PRESENTATION

Two Caucasian male siblings, ages 11 and 13 years, each with a history of asthma, presented with cold-like symptoms and a light persistent cough of 10-day duration. Their pediatrician diagnosed a viral infection with no apparent signs of a serious illness. The patients were treated with cough syrup and decongestants. A couple of weeks later, the boys developed progressive coughing spells with inspiratory whoop and post-tussive vomiting. The boys re-visited their pediatrician's office, going home without a specific diagnosis or treatment plan, though it was apparent that their condition had worsened considerably. When the mother inquired about the possibility of a pertussis infection, the answer was that the boys were fully vaccinated and such infection was very unlikely. The anguished mother heard about the UTEP *Bordetella pertussis* research and contacted the investigator. Nasopharyngeal swabs were collected at this time (during the second week of infection) and blood samples were collected for serology. The cultures of both children were positive for *Bordetella pertussis* and the sera revealed positive IgM and IgA antibodies (>11 PANBIO UNITS) against a mixture of antigens including: pertussis toxin, filamentous hemaglutinin, pertactin, and fimbriae assayed by indirect enzyme linked immunosorbent assay (ELISA) (IgM, IgA ELISA kits, Panbio, Australia).

The mother took the children to a pediatric infectious disease specialist, who made the diagnosis of pertussis. The 13-year-old child had received the complete DPT series (five DPT doses) while the 11-year-old boy received only three DPT doses due to a prior reaction. The two boys and other family members were placed on a course of azithromycin. Both boys showed clinical improvement thereafter, but persisted with a cough for several weeks.

DISCUSSION

In this era of antibiotics and high vaccination coverage, pertussis has been relegated from a prime childhood killer to a half-forgotten threat. However, during the past few years, evidence shows that pertussis continues to be a threat for North American children and the adult population.[1,2,24] Pertussis vaccines have been effective in controlling infant disease, but the transmission of *Bordetella pertussis* has not been eliminated.[21,26] Vaccine- induced immunity wanes after five to ten years, allowing vaccinated hosts to become susceptible to infection.[8,26] This susceptibility is reflected in recent outbreaks in highly vaccinated populations worldwide.[9-14]

For the past few years, pertussis has been a health concern in Texas.[17] Since March 26, 2000, 14 deaths have been reported, and several outbreaks occurred throughout the state, and more than 200 hospitalizations have been reported in 2002.[27,28]

The present case report highlights the need for awareness and education of pertussis infections to our communities and for clinicians to consider the diagnosis of pertussis in older children and adults, despite either an atypical clinical presentation or lack of laboratory confirmation. More important, clinicians should not exclude the diagnosis of pertussis based on vaccination status.

PATHOGENESIS AND PATHOPHYSIOLOGY

Pertussis is a highly contagious respiratory disease that is caused by the gram-negative, coccobacillus *Bordetella pertussis*. Humans are the only reservoir. No animal or vector is known to exist. Transmission occurs through contact with airborne droplets of respiratory secretions. The contagious period is seven days following exposure to the organism and during the catarrhal stage. This period is usually two to three weeks after the onset of symptoms. Pertussis lacks a seasonal pattern, however, most cases occur during the summer and fall.[3,29] *B. pertussis* produces several virulence factors that are involved in the pathogenesis of the disease. The following pathophysiological sequence of events has been proposed by Weiss and Hewlett: 1) attachment, 2) evasion of host defenses, 3) local damage, and 4) systemic effects.[30] Two major non-fimbrial adhesions play an important role in attachment: filamentous hemaglutinin (FHA) and pertactin (PRN). Mutants lacking either one are unable to attach ciliated epithelial cells and cause ciliostasis and cell damage.[31-33] Pertactin stimulates leukocytes to express integrins, which function as receptors for FHA, leading to macrophage phagocytosis via CR3 avoiding oxidative burst and triggering intracellular survival.[32,34] Following attachment and onset of infection, adenylate cyclase (AC) toxin plays an important role in cell damage and impaired leukocyte function. The cytotoxic activity of the AC results when the enzyme is activated by the host calmodulin leading to uncontrolled production of cAMP altering the metabolism of the invaded cell.[35] Tracheal cytotoxin and possibly dermonecrotic toxin are involved in local damage to ciliated cells. It is believed that systemic disease is mediated by pertussis toxin. Despite the identification and purification of a number of antigens and active components of *B. pertussis* the pathogenesis of infection is poorly understood and the immunity of infection is incompletely defined.

CLINICAL CHARACTERISTICS

Pertussis signs and symptoms manifest after an incubation period of one to two weeks. Typical pertussis has been divided into three clinical phases: catarrhal, paroxysmal, and convalescent. During the catarrhal phase, mild upper respiratory symptoms with progressive cough occur. This phase lasts one to two weeks. Due to the minimal symptoms during this phase, the diagnosis of pertussis is rarely considered. However, the recovery of the organism is the highest at this time.[29,32] The paroxysmal phase of pertussis is characterized by severe cough classically followed by an inspiratory whoop. Post-tussive vomiting is common and cough paroxysms are worst at night. However, only 6% of the patients exhibit the classic inspiratory whoop.[3] Most complications of pertussis occur during this phase, including secondary infections (otitis media and pneumonia), trauma associated with paroxysmal cough, and central nervous system abnormalities.[36] This paroxysmal phase lasts four to six weeks and is the period in which pertussis is easily recognized. During the convalescent or recovery phase there is a gradual decrease of cough until it disappears completely. This phase lasts several weeks. In older persons, adults and adolescents, or those partially protected by the vaccine the manifestation of the disease is atypical. Pertussis may present as persistent cough (>six days) and may be indistinguishable from other upper respiratory infections. Some studies have reported isolation of *B. pertussis* from 25% or more of adults with cough illness lasting >seven days.[33,36,37]

DIAGNOSIS

Confirmation of *B. pertussis* infection can be one of the most difficult challenges the clinician can face. The gold standard and preferred laboratory test is isolation of the organism by culture.[38] Isolation of *B. pertussis* is readily achieved during the catarrhal phase, however it is during this phase that the diagnosis of pertussis is often not suspected, especially in older children and adults.[33] Specimens from the nasopharynx, not the throat, should be obtained using a calcium alginate or Dacron™ swab. Cotton swabs should not be used because these contain fatty acids, which inhibit bacterial growth.

Bordetella pertussis is a very fastidious, slow-growing organism and the use of selective media (Bordet Gengou or Regan-Lowe agar) is required to plate the specimen. Success in isolating the organism declines with prior antibiotic therapy (erythromycin or trimethoprim-sulfamethoxazole) or delay in collecting the specimen. Culture is 80% sensitive when the specimen is collected during the first two weeks of infection. Sensitivity falls to 15% after the fourth week and 0% after five weeks of infection.[39,40] Nasopharyngeal specimens can also be valuable for the identification of pertussis by direct fluorescent antibody technique (DFA). The advantage this method offers is that the organisms do not have to be viable for detection, and therefore can be detected later in the course of infection. In addition, DFA can be used in the presence of antibiotics. However, DFA should not be used as a sole criterion for laboratory confirmation since various studies have shown low sensitivity and variable specificity.[29,32,39] Pertussis serology has been useful in clinical studies. It is available in some reference microbiology laboratories but is not yet standardized. Due the lack of reference values in healthy individuals and to the lack of association between antibody levels and immunity, results of serologic tests are difficult to interpret. Cases meeting the clinical case definition and serological positive but culture negative should be reported as probable cases.[29,41,42] The polymerase chain reaction (PCR) performed on nasopharyngeal material or aspirates has been found to be a rapid, sensitive, and specific method of diagnosis. Polymerase chain reaction tests should be validated and always should be offered in addition to culture but never as a replacement for culture since bacterial isolates are required for evaluation of antimicrobial resistance and for molecular typing.

In contrast to infants, immunized children and adults may not show the typical symptoms of pertussis. More typically, these patients may exhibit an insidious onset and symptoms of a mild, nonspecific upper respiratory tract infection. Pertussis in adults is not well characterized but usually consists of a prolonged cough that may last for weeks or months.[9,21,26,43] Physicians may not recognize pertussis in older children and adults who do not exhibit the classical illness. In turn, untreated children and adults may serve as a reservoir to susceptible infants.[8,44] In 1999, approximately 10% of pertussis cases reported in the U.S. occurred among persons 15 years of age or older, and outbreaks of pertussis among adults and adolescents have been reported worldwide.[31-34] Several reports indicate that 10% to 25% of patients with cough lasting two weeks or longer have been due to pertussis.[5,45-48] Epidemiological data is limited, but it has been estimated that the incidence of pertussis may be in the range of 170 to 500 cases per 100,000 adults.[9,45] Although pertussis in adults varies from subclinical infection to persistent cough, the morbidity related with pertussis in adults increases with age. Complications may include pneumonia, rib fracture, hernia, and otitis media.[49] At present, data from outbreaks, clinical and seroprevalence studies, and surveillance data suggest that adults and adolescents may be a reservoir for *B. pertussis* infection.[9,17,24,50-54]

In summary, pertussis diagnosis is based on clinical history with supportive laboratory data. Currently no single test offers acceptable sensitivity and specificity in the diagnosis of pertussis. Laboratory diagnosis is limited due to the incomplete understanding of pertussis immunity and poorly understood pathogenesis of infection.

TREATMENT AND PREVENTION

Erythromycin has been the drug of choice (14-day treatment), but azithromycin has been an effective replacement and is given for five to seven days. Antibiotic therapy eliminates the organism from secretions thus decreasing communicability and shortening the course of illness if administered early. Trimethoprim-sulfamethoxazole is an effective alternative in patients who cannot tolerate erythromycin. Prophylaxis with either drug should be administered for 14 days to all household contacts and other close contacts of persons with pertussis regardless of age and vaccination status. Management of pertussis during an outbreak requires early recognition and treatment of infected persons and contacts, complete immunization of all susceptible children, and case reporting to public health authorities. Currently, acellular vaccine (DTaP) is recommended for all doses of pertussis schedule. Whole-cell vaccine is no longer recommended in the U.S. The complete series of DTaP consists of four doses given at four to eight week intervals except for the fourth dose, which is given six to twelve months after the third dose in order to maintain adequate immunity for the preschool years.[29,41] A new booster vaccine for adults and adolescents has been approved recently. This new vaccine has the same components (diphtheria and tetanus toxoids and acellular pertussis antigens) but it is formulated with reduced antigen quantity. The new vaccine is indicated for active booster immunization as a single dose in individuals 10 through 18 years of age.

CONCLUSIONS

Introduction of the whole cell pertussis vaccine in 1949 led to the dramatic decline of pertussis and related complications. Nevertheless, the number of pertussis cases has increased steadily during last few years. The growth of an infected adult and adolescent population appears to be the cause of the recent reemergence of pertussis in the U.S. However, the possibility of antigenic variation in circulating strains of *B. pertussis* has not been studied. An optimal control of pertussis could be achieved through the immunization and periodic booster vaccines to adult and adolescent populations. The availability of this new booster vaccine will provide an opportunity to reduce disease incidence and circulation of *B. pertussis* in our communities.

In summary this case highlights the following points:

1. Pertussis is not a disease that occurs just among children. Studies show that children and young infants acquire the infection from parents, grandparents, or other older adults.
2. Physicians should be aware that vaccine immunity to pertussis wanes with time, and that pertussis may occur in any age group regardless of vaccination status.
3. Because of inherent difficulties in the laboratory diagnosis of pertussis, physicians must be prepared to diagnose and treat pertussis clinically in any age group.
4. A greater awareness and more aggressive approach to childhood and adult pertussis could be instrumental in decreasing the risk and ultimately the incidence of infant pertussis.

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