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Update on pertussis and pertussis immunization

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Pertussis is a highly contagious respiratory tract disease caused by *Bordetella pertussis* infection. The clinical manifestation of this infection can be severe enough to cause death. Although pertussis has been supposed to be a vaccine-preventable disease ever since the widespread vaccination of children against pertussis was started, since the 1990s, cases of pertussis and related fatalities are on the rise, especially in countries with high vaccination coverage. In Korea, there have been no deaths due to pertussis since 1990, and the vaccination rate continues to be approximately 94%. However, the number of pertussis cases reported to the Korea Center for Disease Control and Prevention has tended to increase in the 2000s, and in 2009, there was an obvious increase in the number of pertussis cases reported. This review aims to present the latest information about the pathogenesis, diagnosis, treatment, and prevention of pertussis.

Key words: Pertussis, Vaccination, Outbreak

Introduction

Pertussis is an acute respiratory tract infection caused by *Bordetella pertussis*; this infection is most severe in infants. Pertussis was a major cause of infant death before the introduction of vaccination. There are still 60 million cases of pertussis each year worldwide, resulting in about 300,000 deaths[1]. Most of the deaths have been of unvaccinated children from developing countries. However, pertussis cases are increasing in Western countries with high vaccination coverage since the 1990s[2]. In Korea, an average of approximately 11.5 cases of pertussis is reported to the Korea Center for Disease Control and Prevention (KCDC) each year, and there have been no fatalities since the 1990s[3]. However, in the 2000s, the pertussis cases reported tended to increase, with up to 66 cases being reported in 2009[4, 5]. Since the diagnosis of the reported cases was confirmed by PCR and culture without serology, the actual number of cases must be much more than 66 in 2009. This trend of increasing pertussis cases is now becoming obvious in Korea. This article was intended to review the latest knowledge about the pathogenesis, epidemiology, diagnosis, treatment, and prevention of pertussis.

Pathogenesis

Pertussis is a mucosal infection whose pathogenesis is induced by the local and systemic effects of toxins.

More than 95% of pertussis cases occur during epidemics and in endemic areas and are caused by *B. pertussis* infection; the remaining 5% of cases are caused by infection with *Bordetella parapertussis*[6]. *B. pertussis* is the only gram-negative coccobacillus,

and *Bordetella* spp. possess the pertussis toxin (PT), which is the bacteria's major virulence protein that infects only humans. B. pertussis organisms are acquired through aerosols and have strict tropism for the ciliated epithelium of the respiratory tract. Attachment to target cells is mediated by filamentous hemagglutinin (FHA), some agglutinogens (especially FIM2 and FIM3), a 69-kd nonfimbrial surface protein called pertactin (PRN), and PT. Bacterial survival is aided by ciliostasis related to the tracheal cytotoxin (TCT) and impaired leukocyte function due to PT and the adenylate cyclase (AC) toxin. Local epithelial damage and respiratory tract symptomatology are mediated by the TCT and AC toxins. PT plays a major role in the severity of pertussis cough, encephalopathy, and lymphocytosis by preventing migration of the organism from the circulating blood[7].

Epidemiology

Pertussis is highly contagious, with attack rates as high as 100% in susceptible individuals who have been exposed to contaminated aerosol droplets at close range. Natural disease and vaccination elicit broad antibody and cell-mediated immune responses. However, neither the disease nor vaccination confer complete or lifelong immunity against the disease or protect against reinfection. Protection against the typical disease begins to wane 3 to 5 years after vaccination and is not measurable by 12 years. When exposed to pertussis infection, over 50% of vaccinated people develop asymptomatic, mild desease[8] and become a source of infection for infants in whom pertussis may result in hospitalization and death.

Pertussis is a significant cause of mortality in early infancy worldwide, despite widespread vaccination. It remains endemic in many industrialized countries, which have reported increases in incidence during the past several decades. This increase has been mainly among adults and adolescents, and chronic cough that persisted for over 2 weeks was the main cause (20-37.2%), although death and hospitalization from pertussis continue to occur predominantly in unvaccinated infants aged less than 6 months[9, 10].

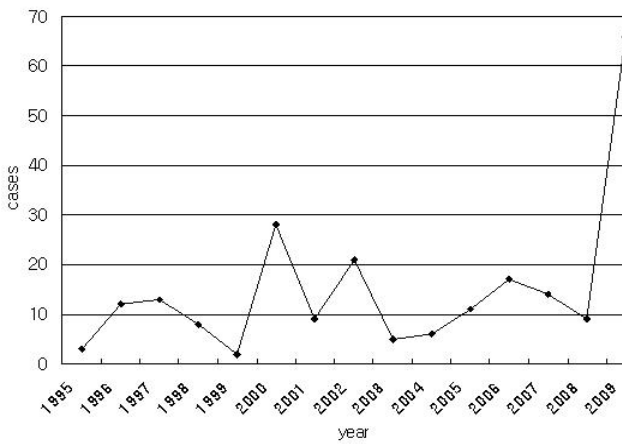

Fig. 1. Number of cases of pertussis reported in Korea (1995-2009).

In Korea, the incidence of pertussis has dramatically decreased since DTwP vaccination started in 1958 and DTwP was changed to DTaP in 1982. The number of pertussis cases reported to the KCDC was approximately 11.5 cases each year until 1991, but the incidence of pertussis seems to be on the rise since 2000, although the vaccination rate continues to be over 94%. In 2009, 66 cases of pertussis were reported. The KCDC confirmed that these cases were pertussis by culture or PCR of pertussis from nasal specimens and a positive rate of culture and PCR is very low compared to serologic study. On the basis of the sensitivity of the test and reporting rate in 2009, it can be assumed that more than 2,000 pertussis occurred in 2009 (Fig. 1).

Clinical manifestations and complications

Classical pertussis has 3 stages of clinical symptoms: catarrhal, paroxysmal, and convalescent. These stages are only seen in unimmunized toddlers and children. The 3 classical stages commence after 3-12 days of bacteria incubation. Nonspecific symptoms such as rhinorrhea, sneezing, mild fever, and eye infection without significant conjunctivitis occur after about 2 weeks in the catarrhal stage, and these symptoms are followed by characteristic paroxysmal stage symptoms such as a dry, intermittent, irritative hack which evolves into paroxysms. In the paroxysmal stage, a healthy-looking, playful toddler suddenly begins to express an anxious aura and experiences bouts of uninterrupted coughing while drawing a single breath. The coughs are followed by a loud whoop as inspired air passes through the still partially closed glottis (Fig. 2).

In infants younger than 3 months, the catarrhal phase usually lasts for a few days or is not recognized at all; the paroxysmal and convalescent stages are protracted, with periods of spasmodic coughing throughout the first year of life. In the paroxysmal stage, young infants frequently present with gagging, gasping, choking, cyanosis, apnea, or an "apparent life-threatening event" instead of paroxysmal coughing; whooping is absent.

In immunized children and adults, all stages of pertussis are shortened, and it is not uncommon for the disease to not have distinct stages and show chronic cough paroxysms that continue for more than 2 weeks.

The principal complications of pertussis are apnea; secondary

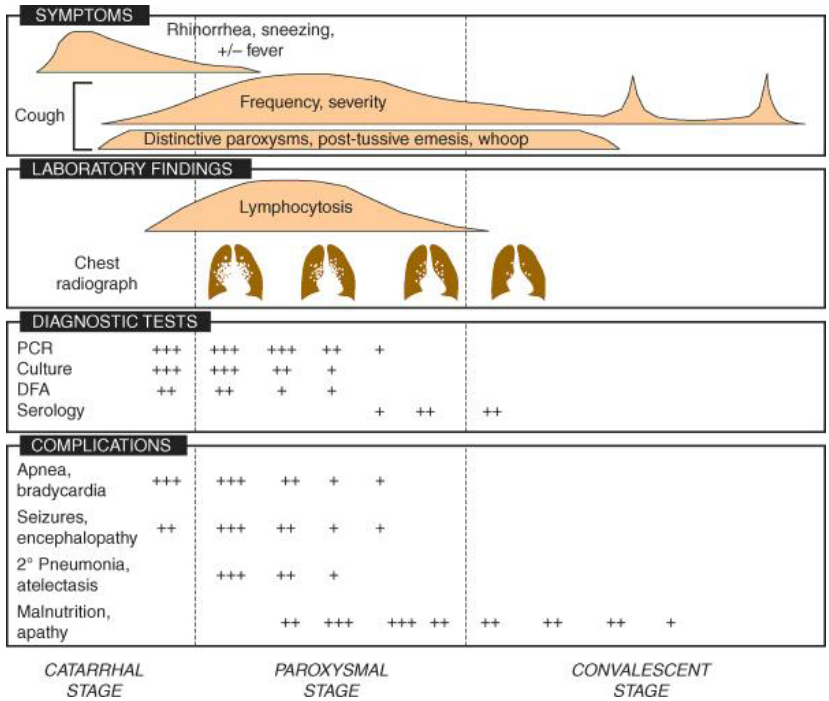

Fig. 2. Manifestations and complications of pertussis. Abbreviations : DFA, direct fluorescent antibody; PCR, polymerase chain reaction. Adapted from Cherry JD, Brunell PA, Golden GS, et al. Report of the task force on pertussis and pertussis immunization-1988. Pediatrics 1988;81[Suppl]:939-84.)

infections such as pneumonia and otitis media; respiratory failure because of apnea, pneumonia, or pulmonary hypertension; and physical sequelae because of forceful coughing. Pertussis-related complications and mortality are reported, especially in patients younger than 2 months, who have the highest reported rates of pertussis-associated hospitalization (>90%), pneumonia (15-25%), seizures (2-4%), encephalopathy (0.5-1%), and death (0.5-1%)[11-13]. There are several reports on pertussis as a significant cause of sudden infant death syndrom[14-16].

Diagnosis

Pertussis should be considered as a diagnosis in very young infants who have not completed 3 doses of vaccination and have classical symptoms or in children who display major symptoms such as chronic paroxysmal cough without significant fever, general weakness, and sore throat and do not have physical signs such as wheezing and rales. Chlamydia trachomatis infection in very young infants and adenovirus, Mycoplasma pneumoniae, and Chlamydia pneumoniae infections should be the differential diagnosis for children because despite the abovementioned differences, it is not easy to diagnose pertussis on the basis of only clinical symptoms and signs, especially if secondary infections such as pneumonia are present.

The laboratory finding characteristic for pertussis is leukocytosis (leukocyte counts of 15,000-100,000 cells/mm^3) due to absolute lymphocytosis in the late catarrhal and paroxysmal stages. The degree of leukocytosis parallels the severity of illness and is mainly observed in unvaccinated children; leukocytosis is not common in adolescents, adults, and partially immunized children with pertussis[17, 18]. Chest x-ray findings are normal in most cases, although chest x-ray images of hospitalized young infants may show hilar infiltration, interstitial edema, atelectasis, and, rarely, pneumothrax.

There are several ways to confirm *B. pertussis* infection such as serology, culture, direct fluorescent antibody (DFA) testing, and PCR. All these methods have limitations in terms of sensitivity, specificity, or practicality.

The traditional gold standard for confirming pertussis is culture, but many factors that can influence the results, such as the stage of illness, use of antibiotics, cautious posterior nasopharyngeal sampling, adequate transport media (Regan-Lowe) and culture media (Regan-Lowe charcoal media with 10% horse blood or 5-40 μg/mL cephalexin), and vaccination status of the patient. In adolescents and adults with pertussis, culture or PCR test results are positive in <10% of cases that have been confirmed as pertussis by serology. However, PCR is more rapid and sensitive than culture for confirming pertussis[19].

Serologic tests use enzyme immunoassay (EIA) to detect antibodies to components of *B. pertussis* and are the most sensitive tests for diagnosis in distantly immunized individuals and those evaluated after the second week of experiencing coughs. A 4-fold increase in anti-PT IgG with 4-6 week intervals appears to be the most reliable serologic test, and a single test showing an anti-PT IgG level of >94-110 EU/mL (over 2SD of the IgG level in the community) has been proposed as the diagnostic cutoff point[20].

Treatment

The goals of therapy are to limit the number, severity, and duration of paroxysms and prevent complications. Hospitalization is usually needed to treat infants with pertussis because they need supportive care such as hydration, nutrition, and monitoring for complications.

If the patient experienced uncontrolled severe cough along with hypoxia, seizures, and apnea, ventilator care should be provided along with muscle paralysis to prevent bradycardia and cardiopulmonary complications.

Antibiotics should be given to infants younger than 1 year old who have had the cough paroxysm for less than 6 weeks and to all the patients who began coughing within 3 weeks in order to improve symptoms, shorten their duration, and prevent further infection[21]. Erythromycin is the treatment of choice; 40-50 mg/kg erythromycin is prescribed for 10-14 days. Newer macrolides such as clarithromycin and azithromycin can be used instead of erythromycin and have the same effect[22].

Isolation and prevention

Since pertussis is extremely contagious, there have been many secondary cases and outbreaks of pertussis in hospitals and chronic-care facilities. To prevent infection from the index patient, droplet precautions are recommended for at least 5 days after the initiation of macrolide therapy and those who have had close exposure should get the same macrolide treatment as pertussis patients. In addition, children younger than 7 years who did not complete the 5 rounds of pertussis vaccination should complete the schedule of vaccination. Adolescents older than 11 years and adults should receive the Tdap (tetanus toxoid, diphtheria toxoid, acellular pertussis): booster vaccination.

The most important and effective way to control pertussis is vaccination. The current pertussis vaccination schedule in Korea comprises a primary series of 3 vaccinations: the first dose is administered at 2 months of age, the second is a booster vaccination given at 18 months of age, and the third dose is also a booster vaccination given at 4-6 years of age.

Despite longstanding and widespread vaccination programs, pertussis remains endemic in many industrialized countries, including Australia, Canada, Italy, Japan, the Netherlands, Switzerland, and the United States, all of which have reported recent increases in incidence. Factors contributing to pertussis resurgence remain unclear, but possible causes are waning immunity, improved surveillance and diagnosis, and adaptation of circulating *B. pertussis* strains[23, 24]. Although pertussis is classically a disease of infants and children, the main portions of the population showing an increased incidence of pertussis are adults and adolescents; these infected adolescents and adults become a source of infection for infants. Consequently, pertussis-related mortality increases[25].

To solve the problem of waning immunity after pertussis vaccination and disease, Tdap booster vaccination for adolescents older than 11 years and adults has been started since 2006 in the United States and was introduced in Korea in 2009.

Conclusion

Pertussis was a leading cause of death of children before pertussis vaccination was started, and the disease continues to be a leading cause of child mortality. The incidence and mortality of pertussis has been increasing since 1990 in developed countries despite these countries having vaccination rates of 95%. After widespread vaccination, the diagnosis of pertussis is difficult because of lack of classical clinical manifestations in very young infants and vaccinated children. In Korea, the prevalence of pertussis might be increasing since 2000 and there was a pertussis outbreak in 2009. No epidemiological study based on serology has been done so far in Korea, and the exact number of pertussis cases that occur and are undiagnosed remains unknown. Therefore, we do not have any weapons to fight against future outbreaks of pertussis, a significant cause of mortality of very young infants.

Therefore, I suggest that a nationwide epidemiologic study of pertussis be undertaken immediately. The study should aim to develop methods for serologic diagnosis, new devise vaccination strategies to prevent waning immunity and reduce the number of very young unvaccinated individuals, and develop diagnosis criteria for atypical pertussis.

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