

Survey of pertussis in patients with prolonged cough

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Background and Purpose: Pertussis is an acute respiratory tract illness resulting from *Bordetella pertussis*. Widespread use of pertussis vaccine over the past 50 years has decreased the incidence of pertussis. The incidence of pertussis in adolescents and adults has increased in many areas of the world. This study aimed to evaluate the etiologic role of *B. pertussis* in patients with prolonged cough in Taiwan.

Methods: Patients with cough lasting for more than 1 week were recruited. Nasopharyngeal swabs were taken for culture of *B. pertussis* and detection of nucleic acid of *B. pertussis* by polymerase chain reaction. Serum samples were collected in a subset of patients for assay of immunoglobulin G and immunoglobulin A antibodies against pertussis toxin.

Results: In total, 111 patients were recruited. Thirty-three patients agreed to have their serum samples taken and tested. Eight patients had evidence of acute infection with *B. pertussis*; among them, 1 was diagnosed by polymerase chain reaction and 7 by serology. Older subjects were more likely to suffer from pertussis than younger subjects. The incidence of pertussis in patients with prolonged cough was 7.2%. However, the rate could have been as high as 21% in those with serum samples tested.

Conclusions: We conclude that pertussis is a prevalent disease in Taiwan, especially in adolescents and adults.

Key words: *Bordetella pertussis*, child, cough, pertussis vaccine, polymerase chain reaction

Introduction

Pertussis is a highly contagious respiratory disease caused by *Bordetella pertussis*. It has affected children younger than 5 years and caused the greatest morbidity and mortality in infants aged under 6 months [1,2]. The incubation period of pertussis cough varies between 7 and 13 days. Three distinct phases of pertussis have been delineated. During the catarrhal phase, clinical findings — such as rhinorrhea, lacrimation, mild conjunctival injection, malaise, and low-grade fever — are indistinguishable from those of many other upper respiratory tract or systemic infectious diseases. The paroxysmal phase follows the catarrhal phase and consists of a series of short expiratory bursts, followed by an inspiratory gasp, which can result in the typical

whoop. The paroxysmal coughing stage lasts about 4-5 weeks. The final convalescent phase is characterized by a marked decrease in the intensity of coughing and the frequency of paroxysms.

The principal complications of pertussis are secondary infections, such as otitis media and pneumonia. Pneumonia is a leading cause of death; it can result from aspiration during whooping and vomiting. Cerebral complications occur infrequently. At the peak of the paroxysmal phase, frequent vomiting can lead to dehydration and nutritional compromise, especially in infants and young children.

The incidence of pertussis has been decreasing in Taiwan over the past 50 years due to the wide use of pertussis vaccine. However, an increase in the incidence in pertussis has been noted recently [3,4]. Adults with atypical, undiagnosed pertussis represent a major source of transmission. Infants who are not yet fully immunized are at the greatest risk for morbidity and mortality from pertussis.

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It is difficult to make a firm diagnosis of pertussis. Isolation of *B. pertussis* in the setting of clinical illness is considered the gold standard, although it is clearly limited in sensitivity. Polymerase chain reaction (PCR) has been applied to pertussis diagnosis in both investigational and routine clinical care settings and has been demonstrated to be both sensitive and specific [5].

The purpose of this study was to evaluate the incidence of pertussis in patients with prolonged cough via bacterial culture, serology and PCR.

Methods

From May 2002 through April 2003, a group of patients who presented with cough for more than 1 week from a clinic of National Taiwan University Hospital were enrolled in this study after written consent was obtained. At enrollment, nasal swabs for culture and PCR assay were obtained from all subjects, and serum samples were taken if the subjects agreed.

Microbiology

Specimens for culture and PCR assay were collected using rayon-tipped swabs on aluminum shafts. Two nasal swabs were obtained from the patient, one from each nostril. The swab was bent to conform to the nasal passage and held against the posterior aspect of the nasopharynx. The swab was left in place for 30 sec to 1 min, removed and immediately inoculated onto half strength Regan-Lowe agar as transport and enrichment medium. It was transported in room temperature within 12 h to the laboratory. Swabs were incubated on B-G agar plates and incubated in a moist atmosphere at 35°C without elevated carbon dioxide for up to 12 days. Most isolates could be detected in 3 to 5 days. Young colonies of *B. pertussis* and *B. parapertussis* are small and shiny, resembling mercury drops, and colonies become whitish-gray with age. Species identification was done with standard procedures.

Serology

Serum samples were tested for immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to pertussis toxin (PT) by use of enzyme-linked immunosorbent assay (Institut Virion Serion GmbH, Würzburg, Germany) [5-7].

PCR

B. pertussis DNA was detected in nasal swab specimens by PCR after extracting swabs in 0.15 M sodium

chloride-0.001 M disodium ethylenediamine tetraacetic acid for 1 min and boiling for 15 min. Primers were directed at repeated insertion sequence 481 of *B. pertussis*. The sequences of these 2 primers were 5'-GATTCAATAGGTTGTATGCATGGTT-3' and 5'-TTCAGGCACACAACTTGATGGGCG-3'. The amplicon was 181 bp in size.

Case definitions

A case was considered to be confirmed pertussis if: 1) culture was positive; or 2) PCR of nasopharyngeal aspirate specimens was positive for *B. pertussis*; or 3) serologic definition was met when either IgG anti-PT >100 EU/mL or IgA anti-PT >20 EU/mL [5,6,8,9].

Statistics

Analysis of variance and student *t* tests were used to compare differences among the groups. A chi-squared test and Fisher's exact test were used to compare frequencies between the groups.

Results

In this study, 111 patients with cough lasting for 1 week or longer were enrolled. All patients received bacterial culture and PCR tests. Only 33 patients agreed to have their blood samples taken for serologic tests. The male to female ratio was 55:56. The median age was 11 years (range, 1-75 years). Fifteen were aged 1-4 years, 34 were aged 5-9 years, 25 were aged 10-19 years, and 37 were age ≥20 years. The median duration of cough was 16 days (range, 1 week to 2 years). Seventy-eight patients had received pertussis vaccine, and most of them were younger than 15 years old. Eleven patients had not received any pertussis vaccine, and vaccination history was unknown in the other 25 patients.

Eight patients were confirmed to be cases of pertussis. One had nucleic acid of *B. pertussis* detected by PCR, and 7 were confirmed by serology. No positive culture of *B. pertussis* was noted (Tables 1 and 2).

The overall incidence of pertussis in prolonged cough patients was 7.2%, and the incidence of pertussis in 33 patients who undertook serological study was 21%.

One patient was younger than 10 years, 2 were between 10 and 20 years, and the other 5 were older than 20 years. The prevalence of pertussis seemed to be higher in adolescents and adults in our study.

Clinical characteristics of participants are shown in Table 3. Patients with pertussis tended to be older than

Table 1. Detection of *Bordetella pertussis* (culture and PCR) in patients with prolonged cough

Laboratory test	1-4 years (n = 15)	5-9 years (n = 34)	10-19 years (n = 25)	≥20 years (n = 37)	Total (n = 111)
Culture	0	0	0	0	0
PCR	0	0	1	0	1
≥1 Laboratory test positive	0	0	1	0	1 (0.9%)

Abbreviation: PCR = polymerase chain reaction

patients without pertussis. Gender and duration of cough were not significantly different between these 2 groups.

Discussion

Pertussis was a major cause of morbidity and mortality among infants and children in the prevaccine era [10]. With the widespread use of pertussis vaccine, pertussis is now being perceived as a rare disease. Although there are many reports showing that the incidence of pertussis has been increasing in recent years, especially in older children and adults, it is not clear whether pertussis is still prevalent in Taiwan. Our results show that pertussis is common among Taiwanese patients suffering from prolonged cough. Overall, 7.2% of patients with prolonged cough had evidence of acute pertussis infection. If we consider only those undergoing serological examination, 21% of them had pertussis.

Because pertussis vaccine provides a limited duration of protection of up to 12 years, adolescents and adults are at risk of contracting pertussis. This phenomenon has been repeatedly observed. Studies concerning adults or adolescents suffering from prolonged cough show that around 12-25% of them have evidence of acute infection with *B. pertussis* [11-14]. Serological surveys of the general population report that adolescents have the highest antibody titers to both PT and FHA, suggesting recent natural infection [7,15]. During 1994-1996, the average incidence among persons aged 10-19 years increased 106% in the United States [16].

The shift of pertussis infection to adolescents and adults makes them important sources of infection for younger children [17,18]. A study from Paris documented that adults were the primary source of

pertussis for about two-thirds of infants hospitalized with pertussis [18]. Nelson reported that, in 12 of 14 reported cases of pertussis occurring in young infants from 1971 to 1977, the source of the infection was an adult [4]. Similarly, in a pertussis outbreak in Ohio in 1987, 6 of the 9 established epidemiologically linked chains of transmission involved an adult [19].

Overall, pertussis carries significant morbidity and mortality no matter what age the infection occurs. For 8927 reported cases of pertussis in the United States that occurred from 1980 to 1989, the incidence of pneumonia ranged from 24.7% for infants under 1 month of age to 2.9% for adults over age 19, with an overall incidence of 14.6% for all age groups [20]. The incidence of seizures ranged from 4.1% in infants <1 month of age to 0.5% in the 10 to 19 years age group and 0.8% in the >20 years age group. The case fatality rate was 6/1000 for infants under 1 year of age, with the highest rate (13/1000) occurring in infants aged <1 month. Seventy-nine percent of reported deaths occurred in children under 1 year of age.

Postels-Multani et al reported that among 257 patients with pertussis, 80% suffered from coughing for >21 days, whereas 53% of the patients suffered from coughing followed by vomiting and/or choking [21]. Various complications were seen in 23% of the patients and included otitis media, pneumonia and severe weight loss. The patients with laboratory evidence of pertussis had significantly longer duration of cough than did patients without laboratory evidence of pertussis (56 days vs 46 days) [22].

PCR has been demonstrated to be both sensitive and specific in detecting pertussis infection. However, the sensitivity of PCR was low in this study. This may

Table 2. Pertussis serologic results (IgG and IgA to PT) in patients with prolonged cough

Laboratory test	1-4 years (n = 6)	5-9 years (n = 5)	10-19 years (n = 9)	≥20 years (n = 13)	Total (n = 33)
IgG to PT	0	1	1	3	5
IgA to PT	0	0	1	5	6
≥1 Laboratory test positive	0	1	1	5	7 (21%)

Abbreviations: IgG = immunoglobulin G; IgA = immunoglobulin A; PT = pertussis toxin

Table 3. Clinical characteristics of study subjects with or without laboratory evidence of pertussis

	Patients with laboratory evidence of pertussis (n = 8)	Patients without laboratory evidence of pertussis (n = 103)
Median age (years)	25	11
Gender (male/female)	3/5	52/51
Vaccinated	4	73
Days with cough	21	16
Clinical diagnosis		
Upper respiratory infection	2	53
Sinusitis	0	12
Asthma	0	16
Bronchitis	1	3
Pneumonia	0	13
Possible pertussis ^a	5	6

^aSignificantly more frequent in patients with laboratory evidence of pertussis ($p=0.00011$, Fisher's exact test).

be due to the fact that specimens were collected too late in our study. The average duration of coughing at the time diagnostic intervention was undertaken in this study was 40 days.

Since the incidence of pertussis in chronic prolonged patients has increased, booster vaccination beyond childhood may be an option to decrease the prevalence of pertussis. Whole cell pertussis vaccines are regarded as unsuitable for routine use in adults because of reports of frequent moderate to severe reactogenicity at the injection site and occasional systemic reactions. The introduction of safe and effective acellular pertussis vaccines provides us with an opportunity to reconsider booster immunization of adolescents and adults [23,24].

In conclusion, pertussis is still a prevalent disease in Taiwan. The incidence of pertussis in Taiwanese patients suffering from coughing more than 1 week is likely to be in the range of 7.2% and 21%. Booster vaccinations of adolescents and adults could be considered for future control of pertussis.

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