Original Article

Clinical and Laboratory Features of Pertussis in Hospitalized Infants with Confirmed Versus Probable Pertussis Cases

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Abstract

Background: The clinical presentations of pertussis infection have considerable variation. Many infections and illnesses can cause prolonged repetitive paroxysmal cough that could be confused with *Bordetella pertussis* infection. **Aim:** This retrospective study was designed to compare the clinico-laboratory findings between two groups of hospitalized infants with confirmed, and those who have clinical pertussis disease; to identify the possible additional diagnostic clues "for the diagnosis of confirmed pertussis disease". **Subjects and Methods:** The study population consisted of infants ≤12 months of age with clinical diagnosis of pertussis that fulfilled the World Health Organization definition for pertussis or those diagnosed by physicians. Clinico-laboratory findings were compared between two groups of patients (confirmed vs. clinical cases). **Results:** From a total of 118 infants admitted with a clinical diagnosis of pertussis, 16% (19/118) were confirmed by laboratory to have confirmed pertussis. Twelve of 19 (63%) and 71.99% of confirmed and clinical cases were younger than 6 months of age, respectively. For most patients, the duration of symptoms before hospitalization was <14 days. There were no significant differences between two groups of patients for paroxysmal cough and facial discoloration. However, whoop and apnea were more common among confirmed pertussis cases: $P=0.01$, and $P=0.02$, respectively. Leukocytosis (≥16,000/ml) ($P=0.01$) and lymphocytosis (≥11,000) ($P=0.02$) were reported significantly more frequently in confirmed pertussis cases. **Conclusion:** Given the unavailability of a highly sensitive diagnostic test, in every afebrile patient with paroxysmal cough lasting for ≥7 days associated with whoop and/or apnea, particularly if accompanied by leukocytosis/lymphocytosis, pertussis disease should be considered. In this situation, prompt administration of empiric treatment for cases, and providing control measures to prevent infection transmission to contacts are recommended.

Keywords: Clinical pertussis, Clinical presentation, Confirmed pertussis, Infant

Introduction

The clinical presentation of *Bordetella pertussis* infection has considerable variation[1,2] that depends on the age of patients,[3,4] previous immunization or infection,[4-8] co-infection with other respiratory microbes,[9-14] the presence of passively acquired antibodies,[15-17] and perhaps other factors related to the host and organism.[1] The classic manifestations of pertussis in unvaccinated susceptible subjects are described as the presence of repetitive paroxysmal coughing episodes, inspiratory whoop, posttussive vomiting, and cough lasting for ≥2 weeks.[1,2,18,19] Mild and atypical presentations of pertussis are common,[1,2,20] particularly in young infants,[3,4,15] and previously immune individual.[4-8] Therefore, illnesses caused by other respiratory microbes are often confused with pertussis.[9-14] An accurate diagnosis of pertussis cannot be made by clinical symptoms alone, and the laboratory confirmation of a clinical pertussis illness is required.[1,18,20] The challenge is for most countries to provide basic laboratory facilities for the diagnosis of pertussis. In this regard, the World

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Health Organization (WHO)[19] and the Centers for Diseases Control and Prevention (CDC)[20] developed a case definition for pertussis for the epidemiological purpose. If purely standard clinical criteria were used to diagnose pertussis, this would result in considerably over- or under-diagnosis of pertussis.[20]

During 2008-2011, Iran and Mazandaran province experienced a pertussis epidemic.[21] The aim of the present study was to compare the clinico-laboratory findings among two groups of patients younger than 12 months of age, who were hospitalized and treated as probable pertussis cases, and those confirmed by laboratory tests, to identify the possible additional diagnostic clues to support the clinical diagnosis of pertussis, particularly for regions with limited access to diagnostic laboratory services.

Subjects and Methods

Until the year 2007, the annual incidence rate of pertussis reported to the Iranian CDC (Ir-CDC) was very low (<0.2/100,000 population).[8,22] From that, the number of clinical pertussis cases reported to Ir-CDC increased sharply, and continued for >3 years. This pattern was more prominent in Mazandaran, North of Iran and resulted in more hospitalization rate among children in the region.[23] To identify the possible additional diagnostics clues, this study was designed to compare the clinical features, laboratory and radiologic findings, and hospitals courses of pertussis disease between two groups of patients with confirmed versus probable pertussis cases. We reviewed the medical records of the infants younger than 12 months of age who were hospitalized, treated, and discharged with: Probable pertussis disease, whooping cough, pertussis syndrome, pertussis-link cough illness in Bouali Sina Hospital affiliated to the Mazandaran University of Medical Sciences during the period March 2008 to April 2012 in Sari, North of Iran. The clinical (probable) pertussis case definition was based on the Ir-CDC[22] and the WHO[19] criteria. The clinical case definition for pertussis to report a case consisted of an acute cough illness lasting ≥14-days with at least one pertussis associated symptom; paroxysmal cough, inspiratory whoop, and posttussive vomiting without any obvious cause. Furthermore, for this study, any afebrile coughing illness lasting ≥7-days and associated with paroxysm, whoop, facial discoloration during coughing episodes, or apnea as a presenting symptom or as a postparoxysmal event (irrespective of its duration) in infants <6 months of age was considered as a probable pertussis case. A confirmed case was defined as a probable case that was culture or polymerase chain reaction (PCR) positive. The laboratory diagnosis was made by nasopharyngeal sample culture or PCR for *B. pertussis*. The samples were obtained from all the hospitalized patients within 24 h of admission by trained nurses and were inoculated within transport media, and for further processing within 48-72 h, the samples were transferred to Pasteur Institute, Tehran. The cases involved all hospitalized probable pertussis, and surveillance was limited to infants younger than 12 months of age. This study was approved by the Research Committee of the Hospital and the Mazandaran University of Medical Sciences. Information obtained included age, sex, fever, paroxysm, whoop, facial discoloration, laboratory data, including the results of culture/PCR for pertussis, white blood cell counts (WBC), absolute lymphocyte counts (ALC) (leukocytosis and lymphocytosis were defined as 16,000 and 11,000 cells/ml of blood, respectively), chest X-ray (CXR) findings, antibacterial treatment, bronchodilator and corticosteroid therapy, management in pediatric intensive care unit (PICU), and outcome. Immunization status of the patients according to their medical records was determined (vaccination status was defined as under the age of vaccination (<2 month of age), partially immunized (receipt of <3-dose of vaccine; ages 2-6 months), and fully immunized (received of ≥3-doses of pertussis vaccine). Based on the patient's age and nasopharyngeal samples results, the infants were designated into two different groups: Confirmed pertussis cases and clinical pertussis cases as the control group. The differences between the data collected (clinical signs/symptoms, WBC, and ALC) for confirmed pertussis and those with probable pertussis were compared with paired *t*-test and Fisher's exact test. $P \leq 0.05$ was considered as statistically significant.

Results

During the 4-year study period, 174 hospitalized patients (age range: 15 days to 13 years) met the criteria and were identified. Of the 174 cases, 13.2% (23/174) were confirmed by culture and/or PCR. PCR was performed in nearly all cases. From the 174 cases identified, 118 (68%) were younger than 12 months of age and included in the analysis. Of the 118 patients, 19 (16%) cases were confirmed to have pertussis by the laboratory. Nearly, 63% (12 of 19) of the confirmed pertussis and 71.7% (71 of 99) of clinical cases were younger than 6 months of age. There were no significant differences according to the sex: Male ratio 47.3 versus 49.5% (P = not significant [NS]), the mean duration of symptoms before the day of admission was 9.8 (3.4) days versus 10.7 (2.8) days; (P = NS) and the frequency of physician visits before hospitalization (73.7% vs. 72.9%) (P = NS) between the confirmed cases and patients with clinical pertussis, respectively. However, the duration of hospital stay was significantly longer in confirmed than probable cases; $P = 0.04$, and those requiring PICU care $P < 0.001$, respectively. The clinical signs and symptoms before the day of admission were available for the entire hospitalized patients (confirmed and probable cases) [Table 1]. There were no significant differences for paroxysms, facial discoloration during coughing episodes, and posttussive vomiting between the confirmed versus the clinical pertussis cases. However, whooping and apnea (as a presenting compliant or as a postcoughing event) were significantly more frequent among the confirmed than the probable cases ($P = 0.01$ and $P = 0.02$), respectively [Table 1]. Vaccination information was available for all patients. The results indicated that 4 of 19 (21%)

Table 1: Comparison of clinical features and laboratory findings, between confirmed versus probable pertussis cases in hospitalized infants ≤12 months of age from 2008 to 2012*

Variables	Confirmed cases *n*=19	Probable cases *n*=99	*P* value
Paroxysmal cough (%)	17 (90)	89 (90)	NS
Facial discoloration (%)	14 (75)	78 (80)	NS
Posttussive vomiting (%)	3 (16)	20 (20)	NS
Whooping (%)	10 (52)	25 (24)	0.01
Apnea (%)	9 (48)	21 (21)	0.02
WBC**	13 (68)	39 (39)	0.02
Lymphocytosis (%)**	15 (79)	46 (46)	0.01

*All confirmed and probable cases were treated with a macrolide and bronchodilator, **WBC: white blood cell counts ≥16,000 and lymphocytosis ≥11,000 cell/ml. NS: Not significant

of the confirmed and 22 of 99 (22%) probable cases were fully immunized. A CXR was taken for all hospitalized patients. Of 118 CXR findings, 61 (51.7%) were abnormal (hyperareation, perihilar infiltration, and one case with aspiration pneumonia in the pertussis cases). However, these abnormal findings were not significantly different between the two-groups of patients. Leukocytosis (>16,000 WBC/mm^3) and lymphocytosis (>11,000 lymphocytes/mm^3) were significantly more frequent in confirmed cases than those with clinical pertussis $P = 0.02$ and $P = 0.01$, respectively [Table 1]. During the hospitalization, one 5-week-old and 9-week-old infants with confirmed pertussis developed seizures and aspiration pneumonia, respectively. All patients in both groups were treated with a macrolide and a bronchodilator. Five of the 19 (26%) of confirmed pertussis and 27 of the 99 (27%) of clinical cases were treated by an antibacterial agents other than a macrolide antibiotic. Fortunately, no mortality was reported.

Discussion

Bordetella pertussis infection has a wide-spectrum of clinical expression. Paroxysmal cough, facial discoloration during coughing episodes, and posttussive vomiting are the primary symptoms in the clinical diagnosis of pertussis and the mainstay of the WHO[19] and the Ir-CDC[21] case definition for *B. pertussis* infection. In this study, the typical symptoms of pertussis were observed in the majority of hospitalized patients. Whoop and apnea were two symptoms which were observed significantly more frequently in patients with confirmed pertussis than clinical pertussis. Whoop, a forceful inspiration of air through a narrow glottis, usually develops after a paroxysmal cough, and is a characteristic of pertussis disease. Its presence in infant represents true pertussis particularly during an outbreak, although in some occasions, other diseases may mimic whooping cough and result in confusion.[1,2] These symptoms may be absent in neonate,[1,3,15] or older children with pertussis.[4,6,7] Otherwise, the frequency of apnea in patients with pertussis as presenting symptoms or as a sign of postparoxysm exhaustion is variable and depends on patient's age: Higher rates were reported in younger infants. A similar clinical presentation was reported in several other studies worldwide.[24-28] In a large multicenter study: Report of the active immunization monitoring program among hospitalized children <2 years of age conducted by Halperin *et al*. in the Canada;[24] a total of 1082 pertussis cases requiring hospitalization was reported. Most cases (91.9%) were infants <12 months of age, and 79.1% were <6 months of age. Virtually, all hospitalized children (93.7%) had a history of paroxysmal cough, and more than 58% who had vomiting and cyanosis were observed in 64.4% of cases.[24] Furthermore, whoop and apnea were reported in 43.9% and 26.2% of infants less than 6 months of age, 46.9% and 6.4% of infant older than 6 months, respectively. During a national active surveillance of pertussis among infants in Australia,[25] 140 hospitalized infants with pertussis disease (73% confirmed) were detected. Of those, 96% had paroxysmal cough and 67% cyanosis during coughing. Whooping and apnea were reported in 47% and 41% of cases, respectively. As part of a large vaccine efficacy trial, to describe the clinical presentations of culture-confirmed pertussis in children and their contacts with cough illness lasting ≥7 days in an outpatients setting, a study was designed and conducted by Heininger *et al*. in Germany,[26] 3629 samples were submitted, and *B. pertussis* was isolated in 601 (16.1%) cases 7.6% of cases were fully vaccinated. A total of 2079 out of 3629 (57.3%) was reported to have paroxysm during the course of their illness. Of the 601 culture positive, 68.1% had paroxysms, whereas 1670 of 3028 (55.2%) of culture-negative patients also had paroxysms. The frequency of whooping is was 90.1% in those with positive culture versus 45% in cases that were culture negative. However, the rate of apnea reported in their study was much lower than those reported by Halperin *et al*. and was 15.9% in infants less than 6 months of age and 1% in the older ones.

It has been suggested previously that many other infections and illnesses[9-13,28] can cause prolonged repetitive paroxysmal cough that can be confused with *B. pertussis* infection and would have fulfilled the WHO clinical criteria for pertussis diagnosis. In a serologic study, in children who coughed for more than 7-days and had no evidence of *B. pertussis* infection,[9] adenoviruses were the most frequent pathogen found, followed by the parainfluenza viruses, mycoplasma pneumonia, and respiratory syncytial virus (RSV).[9] The authors concluded that the differential diagnosis of pertussis-like cough illness by laboratory methods should include these infections. In a study by Korppi and Hiltunen,[14] *B. pertussis* etiology was studied in infants <6 months of age who were hospitalized for lower respiratory tract illnesses accompanied by cough during an RSV epidemic. *B. pertussis* was found as a co-infection in 8% of cases. In their retrospective study, RSV alone and mixed RSV-B. Pertussis cases could not be separated by clinical characteristics. The authors concluded that to avoid under-diagnosis, pertussis should be considered in all nonvaccinated infants with lower respiratory tract illnesses, also an RSV diagnosis does not exclude pertussis.[14] In a recent study on infants <6 months of age with lower respiratory

tract illness requiring PICU care for their illness, 20% had pertussis and 7% were mixed infection with RSV. The infants with pertussis suffered from cough, apnea, and whooping more often than infants without pertussis.[29] For this study, it was not possible to determine the relative roles of other respiratory microbes causing pertussis-like cough illness, and is a limitation of our study.

Leukocytosis due to ALC was recognized as a hallmark of pertussis infection 100 years ago, and is usually present at the beginning of paroxysmal cough and persists for 3-4 weeks. Adolescents and young adults, partial immune subjects, and occasionally young infants have less impressive lymphocytosis.[1,2] Most viral respiratory infections can cause relative lymphocytosis, however, this is not associated with leukocytosis and/or ALC. In this study, the statistically significant numbers of confirmed pertussis versus clinical cases showed leukocytosis and/or ALC. Similar to this, pattern was reported by Heinninger *et al*. in a large prospective vaccine efficacy trial in Germany.[26] Although ALC with/or without leukocytosis is not a confirmatory laboratory test, its presence in patients with clinical case definition for pertussis disease may support in diagnosing *B. pertussis* infection.

The laboratory diagnosis of pertussis is challenging, culture is highly specific, however, sensitivity can be low, require a long incubation, and result is influenced by several factors including: Time between cough beginning and sampling, patient age, earlier immunity (vaccinal/infection), receipt of a macrolide, and sampling methods. Rapid, highly sensitive, and specific PCR assays have been developed to detect *B. pertussis* infection. Factors that have negative effects on culture sensitivity have less impressive influence on PCR results.[20] In this retrospective study, pertussis infection was confirmed in 19 of 118 (16%) of cases. From a worldwide prospective, the challenge is for all countries to be able to provide basic laboratory diagnostic service**s**. New laboratory diagnostic tests for the rapid and reliable detection of *B. pertussis* are required. Furthermore, providing facilities capable to evaluate relative roles of other agents causing pertussis-like coughing are recommended. These methods can aid to identify true pertussis and nonpertussis cases more readily, and may lead to more efficient patient-contact medical management care.

In this study, more than two-thirds of cases in both groups were infants younger than 6 months; age group with the most severe disease and the higher complications.[1-3,15,18] Strategies to protect these groups of infants from pertussis disease and build immunity provided by active immunization, such as: Universal adolescents immunization "adolescents act as the main source of infection for transmitting to young infants",[30] neonatal immunization,[31] immunization of the mother before[32] or during pregnancy[33,34] are recommended.

In the most of our patients, the total duration of cough before hospitalization was <2 weeks, thus not fulfilling the clinical part of the WHO and Ir-CDC case definition for pertussis. Similar observations were reported also by others.[24] Although the WHO and Ir-CDC case definition played an important role in improving the sensitivity of pertussis diagnosis in epidemiological surveys, if these criteria are used purely clinically to select pertussis cases for confirmation, this may result in considerable under-diagnosis of pertussis. To improve pertussis case selection, a new case definition and strategy is required.[35]

We recognize some limitations of this retrospective study. Although significant differences were noted between pertussis cases and control subjects, our analysis was limited by a small sample size. Furthermore, there were no diagnostic facilities to assess the relative roles of other microbes causing pertussis-like symptoms in the patients, which are the main limitations of the study.

Conclusions

According to our study findings, in the case of afebrile infant with lower respiratory tract symptoms and paroxysmal cough for ≥7-days associated with whoop and/or apnea, particularly if it was accompanied by leukocytosis and/or absolute lymphocytosis, pertussis disease should be strongly considered. In this situation, especially in the lack of diagnostic laboratory facilities, empirical treatment of such suspected cases along with other control measures are recommended.[36] Development of age appropriate case definition for pertussis, providing diagnostic laboratory facilities in the province are also recommended.

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