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Research Article

Epidemiological Characteristics and Clinical Manifestations of Whooping Cough in Bulgaria: A Report on 33 Patients

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Abstract

Introduction: Pertussis (whooping cough) is a highly contagious vaccine-preventable airborne bacterial infection which affected patients of all ages. Among babies the incidence of hospitalization exceeded compare to all other age groups. Pertussis is manifested with distinctive coughing paroxysms. The aim of this study is to show the epidemiological characteristics and clinical manifestations of whooping cough during an epidemic outbreak in Stara Zagora region, Bulgaria and to clear up its origin.

Materials & Methods: During the period of 20th August 2016 to 28th September 2016, thirty-three children with whooping cough were passed through the Department of Infectious Diseases, Stara Zagora University Hospital, Bulgaria. They were aged between 2 months and 19 years. An even distribution by sex was demonstrated. The diagnosis was confirmed by clinical, laboratory, serological and molecular-genetic investigations. A careful epidemiologic study was done at the epidemic outbreak.

Results: A typical clinical manifestation was demonstrated in all patients. We observed a mild clinical form in 15, moderate - in 12 and severe in 6. A typical "*visiting card*" of the disease - leukocytosis plus lymphocytosis - was established in 27 patients. Seven patients had pulmonary complications. More of our patients were partially immunized or not immunized. All of them belonged to Roma society and lived in poor housing conditions.

Conclusion: Whooping cough is a disease which usually has a benign course and favorable outcome. Recently we have seen a strange, but widespread course against immunizations. The lack of adequate specific prevention could lead not only to whooping cough, but could result in many serious and life-threatening diseases and epidemic outbreaks.

Keywords: Whooping cough, Clinical features, Vaccine

Introduction

Pertussis (whooping cough) is a highly contagious vaccine-preventable airborne bacterial infection which affected patients of all ages [1]. The disease is characterized by paroxysmal cough, also known as a "*100-days cough*". The illness is caused by Gram-negative bacteria, named *Bordetella pertussis* (*B. pertussis*). Outbreaks occur periodically every three to five years [2]. Pertussis is endemic worldwide, particularly in young children regardless of ethnicity, climate or geographic location [3].

The permanent sources of the infection are adults; consequently the etiologic agent is widespread in society [4]. Unvaccinated or incompletely vaccinated babies are in a great risk of complications and even lethal outcome [5].

In spite of pertussis vaccination program in many countries around the world the disease continued to be a global problem of the present day [6].

The aim of this study is to show the epidemiological characteristics and clinical manifestations of whooping cough during an epidemic outbreak in Stara Zagora region, Bulgaria and to clear up its origin.

Materials and Methods

During the period of 20th August 2016 to 28th September 2016 thirty-three patients with whooping cough were hospitalized at the Department of Infectious Diseases, Stara Zagora University Hospital, Bulgaria. They were in age between 2 months and 19 years. The distribution by age and sex was showed in Figure 1. Clinical,

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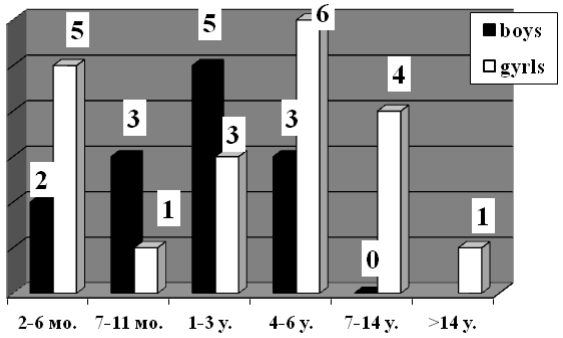
laboratory, epidemiological, serological and molecular-genetic investigations were completed in all. Instrumental methods as X-ray and abdominal ultrasound were applied in some patients.

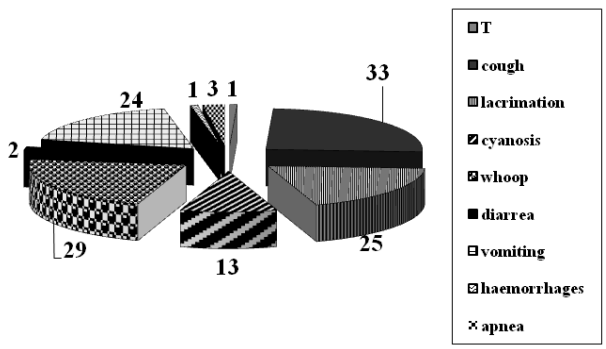
The medical procedures of this study were approved by the Local Ethics Committee of Stara Zagora University Hospital, Bulgaria (2 Stoletov Str., 6000 Stara Zagora).

Statistical analysis was performed by Excel 2007 (Microsoft, Redmond, Washington, USA) and SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA).



	boys	gyrls
2-6 мо.	2	5
7-11 мо.	3	1
1-3 у.	5	3
4-6 у.	3	6
7-14 у.	0	4
>14 у.		1

Figure 1. Distribution of patients with Whooping cough by age and sex.



T	1
cough	33
lacrimation	25
cyanosis	13
whoop	29
diarrea	2
vomiting	24
haemorrhages	1
apnea	3

Figure 2. Clinical manifestations of Whooping cough.

Results

Medical history and clinical manifestation

The beginning of the disease in our patients was gradual with symptoms similar to a common cold such as runny nose, mild dry cough and low-grade temperature. Two of investigated patients had an acute start according to data of their parents. Temperature up to 38°C had only one patient. It is difficult to determine accurately the duration of the catarrhal period. It was between 8 and 14 days (Mean ± SD: 10.8 ± 3.4). The cough tended to come in short bursts - paroxysms - followed by racking gasps for air - whooping noise. A typical inspiratory whoop was marked in 88% of patients. Attacks could occur spontaneously, but usually they were provoked by yawning, eating or crying. They were more common at night. 21% of children (younger than 6 months) had a short catarrhal stage. In them the paroxysms were multiple and severe although they were not as clearly manifested as in older ones.

Gaggling and gasping appeared as early symptoms in all children. An apnoea was demonstrated in 9% of them. The number of coughing paroxysms varied from 5 to 25 (Mean ± SD: 16.25 ± 5.7). Paroxysms associated with vomiting at the end of coughing were seen in 73% of patients. Eyes' haemorrhages as a result of cough exertions were fixed in one child. During the hospital stay the patients were restless and irritable with poor appetite. Different signs of respiratory deficiency were registered in 18% of patients. All of them had tachydyspnea and cyanosis which was exacerbated by paroxysms. Clinical manifestations were presented in Figure 2. Physical signs of pneumonia which were radiologically proven had 18% of children, data for bronchitis were found in 3% of all patients.

The typical laboratory data - leukocytosis with lymphocytosis were observed in 82% of patients (Table 1). The leukocytes count varied from 18.6 to 46x10^9/L (mean 21,3 ± 6,4). The mean value of lymphocytosis was 69.08 ± 3.8% (range: 62.2-72.2%).

The diagnosis was first suspected based on the typical clinical manifestation and data from the epidemiological study. Laboratorial findings supported the diagnosis. A polymerase chain reaction (PCR) was applied. All, except three patients had PCR positive results. Enzyme-linked immunosorbent assay (ELISA) test showed positive results for Anti-*B. pertussis* IgM in 70% of patients. Those up to 3 months old had a negative result.

The mean hospital stay was 9.12 ± 2.1 days (range: 6-15). All patients were followed up for one month. Approximately half of them had residual mild cough that was provoked by physical efforts.

Epidemiological characteristics

The epidemiological study showed that 4 municipalities were affected in Stara Zagora region. The first 5 cases were hospitalized at the Department of Pediatrics of one Municipal Hospital by presumption of acute respiratory disease for 2 days. After that they were transferred to the Department of Infectious Diseases (Stara Zagora University Hospital) with suspicion of whooping

Index	Typical Clinical picture	Epidemiological contact	Leukocytosis + Lymphocytosis	+ ELISA	+ PCR
Number	33	31	27	27	30

Table 1. Grounds of the diagnosis Whooping cough.

Immunization status	Complete immunization	Partly immunized	Non immunized	Undervaccinated age
Number	4	18	11	3

Table 2. Immunization status of the patients.

cough. The verification of immunization status indicated that only 12% of patients had completed a vaccination regiment (Table 2). Three of them without immunization were 2 months old.

Almost all patients with their parents and relatives were attended to Roma wedding on 20th August 2016. The contact group consisted of 111 persons. Fifty-five of them were children. Extreme prophylaxis with macrolides was administered. The main source of infection was children or adults with an atypical course of the disease. Seventy children were epidemiologically studied. They were contact persons of the first 5 children with whooping cough who had been first hospitalized at the Department of Pediatrics (Municipal Hospital). It was found that they had a regular age-related immunization status. A meeting of Regional Health Inspection (Stara Zagora, Bulgaria) was held with all general practitioners (GPs) from the affected municipalities to learn about the epidemic situation in the region. They were instructed to take immediate extraordinary immunization in children with incomplete regiments. A letter has been prepared and sent to all GPs in the region about the emerging epidemic outbreak of whooping cough. The information on the site of the Regional Health Inspection (Stara Zagora) under heading "*Whooping cough*" and "*Vaccines – a guarantor of your child's health*" was published.

Therapy

A specific etiological treatment was applied in all patients. The therapy was *Ampicillin* 100mg/kg four times a day for five days or *Sulbactam-Ampicillin* in a dose of 150mg/kg twice a day for 5 days. After the dehospitalization oral macrolides were prescribed for another 5 days. All patients had a favorable outcome.

Discussion

All of our patients met the clinical, laboratory and epidemiological criteria for whooping cough according to the definition of Centers for Disease Control and Prevention, Atlanta, USA (CDC) [1].

They had paroxysms of coughing most of them with inspiratory whoop. Most of them had post-tussive emesis, some had cyanosis and 3 had apnea. Whooping cough in the infants younger than 6 months of age had atypical clinical course [2].

Infants younger than one year old, and especially under six months may present with severe cough of any duration, poor feeding, apnea, or bradycardia without coughing paroxysms [3].

In our study children in this age group had similar clinical manifestations. They often lacked the typical whooping noise.

Data from the literature search showed that the mean hospitalisation stay was 7.9 days (SD: 10.2) for all cases from 1998 to 2012 [4].

The duration of hospital stay of our patients was longer (P-value <0.001) in infants younger than 6 months (Mean ± SD: 13.82 ± 3.6) compare to those older than 1 year of age (Mean ± SD: 6.2 ± 3.1).

A PCR assay can confirm pertussis infection quickly (with in one or two days) and is not affected by antimicrobial therapy [5].

PCR data for pertussis were positive in almost all of our patients. Three children (< 3 months old) had negative results. It was assumed the influence of immature immune status.

Patients who get the whole scheme of whooping cough vaccine and some of those with incomplete vaccination had a comparative mild clinical form. It was the most common - in 15 children. Six children without any vaccination (all of them were 11) had severe clinical form. According to the Bulgarian specialized medical materials the clinical forms of pertussis are determined by the number of cough paroxysms, the presence of cyanosis and apnea, as well as the degree of general malaise [5].

Mild form occurs in vaccinated and older individuals with paroxysmal counts up to 10 times per day often without a typical whoop. Moderate form is characterized with 10–20, while severe one has up to 50 paroxysms with tachydyspnea, cyanosis and apnea. Complications such as pneumonia, bronchiolitis, encephalitis, seizures are most common in the severe form of the disease [5].

We observed severe forms more often in children <1 year especially younger than 6 months old. Moderate clinical form had 12 patients.

In Bulgaria, the first registration of whooping cough was in 1897. For the first time whooping cough vaccine was introduced in 1957 [6].

It was replaced with an acellular vaccine in 2010. The National Immunization Calendar of Bulgaria consists of 5 obligatory acellular pertussis vaccine intakes. They are administered at 2,3,4,16 months and 6 years of age. Most of our patients are unvaccinated or incompletely vaccinated. They belonged to the Roma community. It is difficult to cover the immunizations among them because of their unwillingness and frequent migration. Most of our patients were aged up to 3 years.

Although pertussis can affect any age, most serious cases and fatalities are observed in early infancy [7]. The observed complications in our study are in children under 6 months of age who are not immunized. The secondary complications vary depending on patient's age [8].

Young infants are at the greatest risk of secondary bacterial pneumonia, the most common cause of pertussis-related deaths [9].

All our patients were fully recovered.

Our observation confirms that children who are completely vaccinated have shorter courses of illness than those with incomplete vaccination schedule [10].

Fatal cases had significantly higher peak White Blood Cell (WBC) and lymphocyte counts [10].

Culture assumed to be the gold standard for diagnosis because of its 100% specifity for identification. After the first 2 weeks, sensitivity decreases and the risk of false-negative result increases **[11].**

Almost all of our patients were hospitalized after this period. Serological and molecular-genetic methods for *B. Pertussis* detection were investigated in our study. A Polymerase Chain

Reaction assay (PCR) is the most sensitive method. It is not influenced by antimicrobial therapy [12].

Macrolides are the first line treatment. Although antibiotics are effective in eliminating *B. pertussis* after the 5th day of application, they do not alter the subsequent clinical course of the illness [13-15].

Although *Ampicillin* has not been shown to reduce pertussis transmission or symptoms, we used it as parenteral treatment in cases with severe clinical course. Antibacterial duration of 3–5 days has the same therapeutic effect as the one with duration of 10-14 days [16].

The vaccine is sufficiently effective (71-85%), to prevent the disease [17]. Despite the extensive scale of its conduct whooping cough persists. Nowadays it is one of the most common vaccine-preventable diseases. The revival of pertussis in the 21st century is a result of reduced immunogenicity of the vaccinated as well as the occurrence of mutations of *B. pertussis* [18].

Through them the etiological agent is able to avoid preventive role of the vaccine. Investigation of the intensity of post-vaccination immunity indicates that the duration of protection lasts 4-12 years. It is a period of childhood when the contacts are the most common and most dense and the risk of spreading the infection is highest. Immunity after infection is also incomplete and perpetual. It provides protection within 7 to 20 years [19].

Conclusion

In the described epidemic outbreak of whooping cough the clinical presentations are typical for the disease. The main reason of the occurrence of the outbreak is the serious omissions in the vaccination schedule among children. All patients had a favorable outcome. The modern trend among parents to refuse vaccines for their children is the high risk for emergence of epidemic outbreaks of various vaccine-preventable diseases. Performing strict and proper immune prophylaxis according to the requirements of the immunization calendar of the Republic Bulgaria as well as recommending vaccines for adults expecting a child is of great importance to prevent the risk of spreading the infection.

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Declaration Of Authorship

L.P. designed the study; L.P., P.P., V.T. and T.P. collected data; L.P. interpreted data; L.P. prepared the article; L.P., P.P., V.T. and T.P. performed the literature search; L.P. conducted statistical analysis. All authors approved the final version of the article.

Competing Interests

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

1. Centers for Disease Control and Prevention (CDC)
2. Waters V, Halperin SA. *Bordetella pertussis*. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed., Philadelphia (USA), *Elsevier Saunders*. 2015;28(5):2619-2628.
3. Heymann DL. Pertussis. In: Control of Communicable Diseases Manual. 18th ed., American Public Health Association, Washington (USA), 2004,399-404.
4. Deen JL, Mink CA, Cherry JD, Christenson PD, et al. Household contact study of *Bordetella pertussis* infections. *Clin Infect Dis.* 1995;21(5):1211-1219.
5. Benamrouche N, Tali Maamar H, Lazri M, Hasnaoui S, et al. Pertussis in north-central and Northwestern regions of Algeria. *J Infect Dev Ctries.* 2016;10(11):1191-1199.
6. Gregory DS. Pertussis: a disease affecting all ages. *Am Fam Physician.* 2006;74(3): 420–426.
7. Sizaire V, Garrido-Estepa M, Masa-Calles J, Martinez de Aragon MV. Increase of pertussis incidence in 2010 to 2012 after 12 years of low circulation in Spain. *Euro Surveill.* 2014;19(32):20875.
8. Geneva M. (2009) Pertussis. In Genev G. et al. A textbook on infectious diseases for medical students from the higher medical schools (163-166). Sofia, Medicina and fizkultura. [in Bulgarian].
9. Andonova L. Pertussis (Whooping Cough) - all age disease and problem for health community in many countries [in Bulgarian]. *Top Medica.* 2012;3(1):5-7.
10. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other *Bordetella* subspecies. *Clin Microbiol Rev*. 2005;18(2):326-382.
11. Plott K, Pascual FB, Bisgard KM, Vitek C, et al. Pertussis deaths - United States, 2000. MMWR *Morb Mortal Wkly Rep*. 2002;51(28):616-618.
12. Tozzi AE, Rava L, Ciofi degli Atti ML, Salmaso S, Progetto Pertosse Working Group. Clinical presentation of pertussis in unvaccinated and vaccinated children in the first six years of life. *Pediatrics.* 2003;112(5):1069-1075.
13. Winter K, Zipprich J, Harriman K, et al. Risk factors associated with infant deaths from Pertussis: a Case-Control Study. *Clin Infect Dis.* 2015;61(7):1099-1106.
14. Halperin SA, Bortolussi R, Wort AJ. Evaluation of culture, immunofluorescence, and serology for the diagnosis of pertussis. *J Clin Microbiol.* 1989;27(4):752-757.
15. Edelman K, Nikkari S, Ruuskanen O, He Q, et al. Detection of *Bordetella pertussis* by polymerase chain reaction and culture in the nasopharynx of erythromycin-treated infants with pertussis. *Pediatr Infect Dis J.* 1996;15(1):54-57.
16. Altunaiji S, Kukuruzovic R, Curtis N, Massie J. Antibiotics for whooping cough (pertussis). *Cochrane Database Syst Rev.* 2007;18(3).
17. Olin P, Rasmussen F, Gustafsson L, Hallander HO, et al. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Lancet.* 1997;350(9091):1569-1577.
18. Mooi FR, Van Der Maas NA, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - two sides of the same coin. *Epidemiol Infect*. 2014;142(4):685-694.
19. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. *Pediatr Infect Dis J.* 2005;24(5Suppl):S58-561.