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SHORT REPORT

One year period of invasive pneumococcal disease in children from a tertiary care hospital in Turkey in the post-vaccine era

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ABSTRACT

The incidence of invasive pneumococcal disease (IPD) has decreased after pneumococcal conjugate vaccine used; however, a breakthrough infection may still be seen after vaccination. In this study, eight pediatric inpatients and nine episodes with IPD in our center were included. Their age and gender, diagnoses, facilitating factors, the status of immunization and the antibiotic resistance of Pneumococci, serotypes of Pneumococci were noted. The isolates were subjected to disc susceptibility tests for penicillin, macrolides, and fluoroquinolones, according to the guidelines of the Clinical and Laboratory Standards Institute. Of the vaccinated seven cases, four of them (57.1%) developed IPD which their serogroups were in vaccine content. It was observed that all four cases in question had an underlying facilitating factor. Pneumococcal antibiotic susceptibility is also crucial. Three of nine isolates (33.4%) were resistant, and one isolate (11.2%) was intermediate susceptible to penicillin. Six of the nine isolates (66.7%) had macrolide resistance in our investigation. Invasive pneumococcal infections with serogroups that exist in pneumococcal conjugate vaccine content may occur in vaccinated individuals.

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Introduction

Pneumococcus is a gram-positive bacterium primarily responsible for invasive infections in childhood, such as pneumonia, meningitis and sepsis. The most important virulence of Pneumococci is capsular polysaccharide inhibiting the immune response by escaping from phagocyte in immunocompromised individuals. Over 90 serotypes have been defined for the classification of the bacteria so far. However, none of serotypes pathogenicity is equal and less of them is responsible for invasive infections.[1] Invasive pneumococcal disease (IPD) defined as the isolation of S. pneumoniae from a normally sterile fluid (blood, cerebrospinal fluid, pleural fluid, mastoid abscess, joint fluid).[2]

Pneumococcal conjugate vaccine (PCV) 7 includes capsular polysaccharide of serotypes 4, 6B, 9 V, 14, 18 C, 19 F, 23 F, included in the Childhood National Immunization Program in Turkey in November 2008. Afterward, 13-valent conjugated polysaccharide vaccine has been generated which includes 1, 3, 5, 6A, 7 F, 19A in addition to serotypes of 7-valent's and added to the schedule in April 2011.[3] The routine use of PCV13 has changed the epidemiology of IPD that arises from vaccine-serotypes, contrasting with an increase in non-vaccine types.[4] In this hospital-based retrospective series of hospitalized children with laboratory-confirmed IPD, we aimed to investigate whether the inclusion of PCV13 in the Turkish vaccination schedule was associated with reduced IPD episodes, type of invasive infection, length of hospitalization and treatment, choice of antibiotics and antibiotic susceptibility. Moreover, we will evaluate the distribution of serotypes included in PCV7 and PCV13, as well as the indirect effects of the immunization in pneumococcal disease and serotypes in children.

Material & methods

Health Sciences University, Izmir Tepecik Training and Research Hospital is a comprehensive tertiary referral hospital with a large number of inpatient and outpatient services of each internal medicine and surgical department where locate in the city center of Izmir. Pediatric inpatients with IPD in our hospital, in 2019 were included. Demographic data, such as age and gender, diagnoses, laboratory findings, facilitating factors, the sterile body fluid where pneumococcus was present, were obtained. A chosen antibiotic for treatment, length of the treatment and hospitalization day, the antibiotic resistance of Pneumococci, the status of immunization and serotypes of Pneumococci were noted. Newborn and adults were excluded from this study. This study was approved by the Ethical Committee in January 2020. The isolates were subjected to disc susceptibility tests for penicillin, macrolides, and fluoroquinolones, according to the guidelines of the Clinical and Laboratory Standards Institute.[5] Minimum inhibitory concentration was established using an Epsilometer test (E-test, Biomerieux, S.A.S.). Serotyping was performed by the

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Quellung reaction using serotype-specific antisera according to the manufacturer's instructions (Statens Serum Institut, Copenhagen, Denmark) at Hacettepe University.

Results

Streptococcus pneumoniae was isolated in nine samples throughout the year of 2019; meningitis occurred in one patient twice in a year with an interval of four months who was accepted as two separate cases, as shown in Table 1 bottom of the text (Table. 1). Seven of the eight patients were male (87.5%). The mean age of the patients was 3.9 ± 3.6 years (min-max 9 months-9 years). Four (44.5%) of the patients were diagnosed with meningitis, two with acute mastoiditis (22.3%), one with sepsis (11.2%), one with septic arthritis (11.2%), and one with pneumonia (11.2%). The average hospitalization day was 20,5 ± 12.4 days.

In five (55.6%) cases, facilitating factors related to developing infection was detected which were cochlear implant in a diagnosis of mastoiditis (case 1), suspected IPEX syndrome in the diagnosis of sepsis which is a rare immune deficiency acronym, includes the initial letter of "Immunodysregulation Polyendocrinopathy Enteropathy X-linked" (case 3), suspected immune deficiency in a diagnose of meningitis (case 2 and 6, same patient) and forearm fracture in a diagnose of septic arthritis (case 9). Case 4, 5, 7 and 8 had no underlying conditions. Case 4 was referred to another center because of the intensive care unit need. Despite appropriate treatment, subdural empyema developed after meningitis. It was learned that the patient was discharged after surgical treatment and long-term antibiotic treatment. Case 5 was hospitalized due to mastoiditis after acute otitis media, and S. pneumoniae was isolated from the mastoid abscess. After drainage and medical treatment, the patient improved. Case 7, who was diagnosed with meningitis, was discharged without any complications. Case 8 with S. pneumoniae isolation in pleural fluid was followed up with the diagnosis of pneumonia.

Six of the eight patients (75%) were vaccinated according to our national vaccination schedule. Five of them had their three doses of PCV13 and a booster dose as well. Exceptionally, the patient with meningitis twice had three doses of PCV7 and a booster dose with PCV13. Two of the nine samples (22.2%) were isolated from children who were not vaccinated; case 3 with sepsis had the only single dose of PCV13 when he was two months old and then his vaccination schedule was interrupted throughout the examination of immune deficiency and the case 9 with septic arthritis and bacteremia was 15 months old boy from Syria and unvaccinated. When the serogroups of isolated Pneumococci were examined, two patients were identified as 19F, one patient as E group (not typed), 15B, 3, 23F, 35B, 14 and 6A. Six of the nine isolates (66.7%) were serogroups in the vaccine content, including the patient who had three doses of PCV7. The most striking finding was that among these vaccinated seven cases, four of them (57.1%) developed IPD, which their serogroups were in vaccine content.

The treatment of five (55.6%) patients was third-generation cephalosporin alone, while the treatment of four (44.5%) was arranged with a third-generation cephalosporin and vancomycin. The total length of treatment was 18.7 ± 12.8 days on average, and the mean hospitalization day was 20.5 ± 12.4 days. Three of nine isolates (33.3%) were found resistant against penicillin, and six of nine isolates (66.6%) were found resistant to macrolides. At the end of the treatment, eight cases recovered and one patient referred to another hospital owing to the need for an intensive care unit.

Discussion

Streptococcus pneumoniae is the primary cause of community-acquired pneumonia, although the incidence of IPD has decreased after vaccination. Although the vaccine is highly effective and cold chain process is carried out diligently by a remote automated system in our country, the breakthrough infection may still be seen after PCV vaccination. A breakthrough infection is defined as IPD in a child who has received ≥1 PCV7 or PCV13, of which the pneumococcal isolate is a vaccine serotype.[6,7] The risk of breakthrough infection is increased, especially in children with inadequate vaccinated, immunodeficiency or have a facilitating factor.[7] In our study, it is noteworthy that four of the six patients with IPD with vaccine content have an underlying facilitating factor. Vaccine failure is defined as vaccine type infection in a child who completed age-appropriate PCV vaccination series according to ACIP.[7] In our series, patients who had breakthrough infection had vaccine failure. Breakthrough infection and also vaccine failure developed in cases 2, 4, 6 and 8. This finding indicates that the breakthrough infection in our study is 57%. Park et al.[7] observed breakthrough infections among 155 of the 753 patients (20%) with pneumococcal invasive infections who had at least one dose of PCV7. Our higher vaccine breakthrough rate could be attributable to the underlying facilitating factor, which was frequently observed in our cases.

When invasive infections caused by serogroups in the vaccine content were evaluated, it was observed that 19F appeared more frequently. In a study conducted by Ceyhan et al.[8] among the 335 cases diagnosed with invasive pneumococcal infections between 2008 and 2014, 19F was found as the most common serogroup at 15.8%. In the study carried out by Xue et al.[9] it was found to be the highest in 19F (19.9%) serogroup in sterile body fluid among 171 patients with IPD. However, in children under five years of age, it was 14 at the highest with the ratio of 22% and the second one was 19F at 20%.[9] In our report, 19F was the most common serotype observed in 22.2% of the patients, and this rate was similar to other reports. Many studies, because 19F serogroup frequently is appeared as a cause of breakthrough infection, suggest that the vaccinated individuals may have a higher serum antibody requirement for 19F serogroups infection to protect the host compared to other serogroups; however, the vaccine response has been shown to provide a protective threshold of immune response development to all serogroups.[10]

Pneumococcal antibiotic susceptibility is of substantial issue. In our study, it was observed that three isolates (33.4%) were resistant, and one isolate (11.2%) was intermediate susceptible to penicillin. It was observed in a study conducted by Lin et al.[11] between 1999 and 2004 that 25.5% of Pneumococci was resistant,

Table 1. Demographic, clinic and laboratory characteristics of patients.

	Age (months)	Facilitating factor	Diagnose	LOH[2] (days)	LOT[3] (days)	Outcome	Antibiotic susceptibility				Pneumococcus serogroup	Immunization status
							Penicillin	Cephalosporine	Macrolide	Vancomycin		
CASE 1	16	Cochlear implantation	Mastoiditis	6	6	Alive	Susceptible	-	Resistant	-	Group E, unclassified	PCV 13/3 + 1
CASE 2*	103	Selective IgA deficiency, chronic ITP[1]	Meningitis	14	14	Alive	Susceptible	Susceptible	Resistant	-	19F	PCV 7/3 PCV 13/+1
CASE 3	9	IPEX syndrome	Sepsis	30	15	Alive	Intermediate susceptible	-	Resistant	Susceptible	19F	PCV 13/1
CASE 4	32	None	Meningitis	42	45	Referred	Resistant	-	Susceptible	Susceptible	15B	PCV 13/3 + 1
CASE 5	41	None	Mastoiditis	17	18	Alive	Susceptible	Susceptible	Susceptible	-	3	PCV 13/3 + 1
CASE 6*	107	Selective IgA deficiency, chronic ITP[1]	Meningitis	15	14	Alive	-	Susceptible	Resistant	Susceptible	23F	PCV 7/3 PCV 13/+1
CASE 7	96	None	Meningitis	19	15	Alive	Resistant	Susceptible	Susceptible	Susceptible	35B	PCV 13/3 + 1
CASE 8	21	None	Pneumonia	7	7	Alive	Resistant	Susceptible	Resistant	-	14	PCV 13/3 + 1
CASE 9	15	Operated arm fracture	Septic arthritis, sepsis	35	35	Alive	Intermediate susceptible	Susceptible	Resistant	Susceptible	6A	None

*Case 2 and Case 6 are the same patients mentioned in the article.
1. ITP: Idiopathic thrombocytopenic purpura
2. LOH: Length of hospitalization
3. LOT: Length of treatment

and 50.7% of Pneumococci was intermediate-susceptible to penicillin in 286 isolates. Macrolide resistance is also a concerning matter. Six of nine isolates (66.7%) had macrolide resistance in our investigation. Macrolides are antibiotics, which inhibit protein synthesis by binding to the 50S ribosomal subunit and have bacteriostatic effects on bacteria. An attempt to treat pneumococcal infections with macrolides may result in failure due to the resistance developed owing to its widespread use.[12] The data, obtained in our study and other studies, are guiding for limiting the use of macrolides, especially in noninvasive upper respiratory tract infections where Pneumococci are frequently seen.

As a retrospective observational study, the present study has some inherent limitations. First, this study was not population-based and was conducted only in one center. In several studies, regional and temporal variations in serotype distribution were reported after PCV usage. Our small sample size may possibly be attributed to that this one hospital-based surveillance method, and our data showed that we need nationwide study centers in Turkey where we may catch more cases through an active surveillance system. Our limited number of isolations is not sufficient to investigate the impacts of the PCV. We thought that although one center local data are important, national multicentric studies would be more useful if succeeded. Second, the difficulty of culture-confirmed diagnosis is an ongoing problem and both previous antibiotic usage and culture techniques limit to have accurate incidence rates in many centers. Despite these limitations, this study has provided valuable insights into the serotype distribution of S. pneumoniae in our hospital.

As a result, invasive pneumococcal infections are still widespread nowadays despite effective immunization practices. With the determination of serogroups, information about vaccine coverage and effectiveness can be revealed more clearly, the need for vaccines containing more serogroups can be evaluated. Continuing surveillance studies is important to evaluate vaccine failure and revealing solutions.

Abbreviation list

IPD Invasive pneumococcal disease

PCV Pneumococcal conjugate vaccine

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