A pediatric case of acute meningitis due to *Streptococcus pneumoniae* serotype 33D

Ayşe Kaman, Türkan Aydın-Teke, Fatma Nur Öz, Gülsüm İclal Bayhan, Özge Metin, Zeynep Gökçe Gayretli-Aydın, Gönül Tanır

Division of Pediatric Infectious Diseases, Dr. Sami Ulus Maternity and Children's Research and Training Hospital, Ankara, Turkey. E-mail: ayse092003@yahoo.com

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Streptococcus pneumoniae is a leading cause of bacterial meningitis in children. It is also responsible for bacteremia, sepsis, pneumonia, sinusitis and acute otitis media in young children worldwide. The serotypes included in the 7-valent conjugated pneumococcal vaccine (PCV7)—1, 5, 6A, 6B, 14, 19F, 23F—are those most commonly responsible for invasive pneumococcal disease (IPD) globally. Unvaccinated children are at greater risk for meningitis. The rate of non-vaccine serotypes as causes of invasive disease has increased. Although the incidence rate of IPD is highest in children aged <2 years, the rare, non-vaccine serotypes of S. pneumoniae may be responsible for acute meningitis in older, unvaccinated children. In this report, we present a pediatric case of meningitis due to *S. pneumoniae* serotype 33D, which has not been previously identified as a cause of IPD in those countries where PCV7 is routinely administered, including Turkey.

Key words: meningitis, child, Streptococcus pneumoniae.

Invasive pneumococcal disease (IPD) is diagnosed by the isolation of *Streptococcus pneumoniae* from a normally sterile site, such as blood or cerebrospinal, joint, pleural or pericardial fluid. In 2008, the World Health Organization (WHO) estimated that worldwide, IPD caused nearly 500,000 deaths annually among children younger than 5 years of age. Over 90 pneumococcal serotypes, based on their antigenically distinct polysaccharide capsules, have been described[1]. It has been reported that greater severity of the disease, risk of invasiveness and case fatality rate are associated with some pneumococcal serotypes. Furthermore, some serotypes are more likely to exhibit antibiotic resistance[2]. Routine use of the seven-valent conjugated pneumococcal vaccine (PCV7) in infants has reduced the incidence of IPD caused by the vaccine serotypes. Vaccine serotypes have become less prevalent in serotypes isolated from cases of IPD, while non-vaccine serotypes have increased as causes of invasive disease as a result of serotype replacement[3]. Serogroup 33 has emerged among the non-vaccine serotypes causing invasive disease[4]. Here, a pediatric case without predisposing conditions for IPD and having acute meningitis due to penicillin-resistant *S. pneumoniae* serotype 33D is presented.

Case Report

A 12-year-old female patient was admitted to our hospital with a one-day history of high fever, headache and vomiting. She had not had a pneumococcal vaccine. Her vital signs on admission were as follows: blood pressure 100/70 mmHg, body temperature 38.8 ^{o}C, heart rate 90/bpm. Physical examination revealed oropharyngeal hyperemia, nuchal rigidity, and positive Kernig and Brudzinski signs. The rest of the physical examination findings were unremarkable. Routine laboratory investigation results were as follows: white blood count (WBC) 21,700/mm^3, erythrocyte sedimentation rate (ESR) 36 mm/h (0-10 mm/h) and C-reactive protein (CRP) 76 mg/dl (0-8 mg/dl). Cerebrospinal fluid (CSF)

examination revealed a turbid fluid with a WBC of 4800/μl (96% polymorphonuclear cells and 4% lymphocytes), protein, 423 mg/dl and glucose, 5 mg/dl. Simultaneous blood glucose was 178 mg/dl. Gram-positive diplococcus was seen on a Gram-stained preparation of the CSF. Acute bacterial meningitis was diagnosed, and ceftriaxone (100 mg/kg/d, iv), vancomycin (60 mg/kg/d, iv) and dexamethasone (0.8 mg/kg/d, iv for 2 days) were empirically initiated. On CSF culture and antibiogram, penicillin-resistant, ceftriaxone- and vancomycin-susceptible *S. pneumoniae* was detected. Minimal inhibitory concentration (MIC) levels of penicillin and vancomycin were not available. The MIC level of ceftriaxone was 0.06 μg/ml. Thereafter, the *S. pneumoniae* isolate was identified as serotype 33D. Serotyping was performed by means of the Quellung reaction[5] in the Department of Medical Microbiology of the Istanbul University Faculty of Medicine·. A follow-up lumbar puncture was performed on the 14th day of the treatment. CSF examination showed a turbid fluid with a WBC of 45/μl (100% polymorphnuclear cells), protein, 58 mg/dl and glucose, 43 mg/dl. CSF culture was negative. The patient was judged to have fully recovered after having received 14 days of ceftriaxone and vancomycin treatment and was discharged from the hospital. During a subsequent outpatient visit, her neurologic examination was normal. Significant elongation was observed in the right wave latencies of brainstem auditory evoked potential (BAEP) monitoring, and bilateral prolonged p1 latency was observed on visual evoked potentials (VEP) monitoring. Neurology polyclinic checkup visits were recommended, but she was lost to follow-up.

Discussion

With the *Haemophilus influenzae* type b (Hib) vaccine having come into universal use, *S. pneumoniae* has become the most common cause of bacterial meningitis in infants and young children. The overall mean annual incidence of pneumococcal meningitis in children was found to be 7.5 cases/100,000 in European countries, ranging from 0.7 in the United Kingdom to 22.0 in Spain[6]. *S. pneumoniae* was detected in 55 of 243 bacterial meningitis cases by multiplex polymerase chain reaction (PCR) assay in a multicenter pediatric study from Turkey in 2008[7].

The highest incidences of IPD are seen in children aged <2 years and in adults aged >65 years. Our patient was an unvaccinated 12-year-old. The incidence of pneumococcal meningitis in Europe was reported to be 10–37.8/100,000 for children aged <2 years and 5.8–20/100,000 for children aged <5 years. Neurological deficits prior to meningitis, recent neurosurgery, a previous episode of meningitis, head injury, presence of cerebrospinal fluid shunts, sinusitis, recurrent otitis media, perforated otitis media, extreme prematurity and congenital malformation were found to be underlying medical conditions in children with pneumococcal meningitis in European studies[6]. Our patient had none of these risk factors.

The changing epidemiology of IPD in the United States after licensure of PCV7 has been investigated extensively[3,8]. In a retrospective cohort study of pneumococcal meningitis among 68 children in Utah, PCV7 serotypes were identified in 64% of cases before and 25% of cases after licensure of PCV7. No differences were found in terms of neurologic sequelae and case fatality rate[8]. The incidence of IPD caused by PCV7 serotypes has been reduced after vaccination in many populations where the vaccine has a widespread usage. However, non-vaccine serotypes have increased as causes of IPD due to serotype replacement, and these serotypes continue to be associated with substantial mortality as well as long-term morbidity in pneumococcal meningitis[3,8]. The serotype distribution has been reported to differ according to age group. Certain serotypes, particularly 1 and 5, are seen more frequently in older children (aged >2 years or >5 years). It has been reported that PCV7 coverage for meningitis also varies by age; in the Netherlands, it was found to be 59% for children aged <5 years, but 68% for those aged <2 years. Similarly, in Spain, PCV7 coverage for meningitis was determined to be 64% for those aged <14 years, increasing to 80% for children aged <2 years[6]. The serotype distribution of 93 *S. pneumoniae* isolates from children with IPD was investigated in Turkey during 2001–2004. It was found that the rate of cases preventable by PCV7 was 63% in the 0–24 month age group. The rare, non-vaccine serotypes found in this study were 2, 10A, 12A, 12B and 17[9]. During 2008-2010, just after the introduction of routine PCV7 vaccination in

Turkey, 19F and 6B were reported to be the PCV7 serotypes most commonly responsible for IPD, and 19A, 3, 1, 6A and 8 the non-PCV7 serotypes most responsible. The rare, non-vaccine serotypes detected in this study were 7A, 8, 15, 15C, 2, 10, 6, 17, 16F and 23A[10]. Recently, the non-vaccine serotype 35F was reported in an 11-year-old child in Turkey with penicillin-susceptible *S. pneumoniae* meningitis[11]. In a nationwide population-based cohort study of IPD conducted in Denmark in 1977–2007, 77 serotypes were isolated from 18,858 IPD patients; serotype 35F was found in 0.57% of cases. No cases of serotypes 9L, 10C, 11F, 11C, 11D, 19C, 25A, 32A, 32F, 33D, 40, 47F or 47A were identified[12]. In the present case, serotype 33D was found to be the cause of meningitis. This serotype has not previously been reported as a cause of IPD in those countries where PCV7 is routinely administered, including Turkey.

In March 2010, the Advisory Committee on Immunization Practices (ACIP) recommended the use of the 13-valent pneumococcal conjugate vaccine (PCV13) instead of PCV7 for routine immunization of infants and children[13]. PCV13, which was introduced in Turkey in April 2011, covers all of the serotypes in PCV7 as well as six additional serotypes: 1, 3, 5, 6A, 7F and 19A. As of yet, there have been few reports about the changing epidemiology of IPD subsequent to the introduction of PCV13. A study conducted in 2011 at eight children's hospitals in United States showed that serotype 19A isolates decreased by 58%; however, this remained the most commonly isolated serotype. The most commonly isolated non-vaccine serotypes were 33F, 22F, 12, 15B, 15C, 23A and 11[14]. There have been no reported cases of serotype 33D as a cause of IPD since the introduction of PCV13.

In our case, the responsible *S. pneumoniae* strain had penicillin resistance. The studies from Europe demonstrated that approximately 31% (range, 0% in Sweden and Finland to 52% in Spain) of the pneumococcal isolates in children were penicillin G resistant[6].

In conclusion, in the setting of routine infant PCV vaccination, the rare, non-vaccine serotypes of *S. pneumoniae* may be responsible for acute meningitis in older, unvaccinated children despite an absence of risk factors. To our knowledge, this is the first report of serotype 33D as a cause of IPD in the English-language literature.

REFERENCES

1. Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among Streptococcus pneumoniae isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. Int J Infect Dis 2010; 14: e197-e209.
2. Grabenstein JD, Musey LK. Differences in serious clinical outcomes of infection caused by specific pneumococcal serotypes among adults. Vaccine 2014; 32: 2399-2405.
3. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet 2011; 378: 1962-1973.
4. Gonzalez BE, Hulten KG, Lamberth L, Kaplan SL, Mason EO Jr. Streptococcus pneumoniae serogroups 15 and 33: an increasing cause of pneumococcal infections in children in the United States after the introduction of the pneumococcal 7-valent conjugate vaccine. Pediatr Infect Dis J 2006; 25: 301-305.
5. O'Brien KL, Nohynek H. Report from a WHO Working Group: standard method for detecting upper respiratory carriage of Streptococcus pneumoniae. Pediatr Infect Dis J 2003; 22: e1–e11.
6. Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among Streptococcus pneumoniae isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. Int J Infect Dis 2010; 14: e197-e209.
7. Ceyhan M, Yildirim I, Balmer P, et al. A prospective study of etiology of childhood acute bacterial meningitis, Turkey. Emerg Infect Dis 2008; 14: 1089-1096.
8. Stockmann C, Ampofo K, Byington CL, et al. Pneumococcal meningitis in children: epidemiology, serotypes, and outcomes from 1997–2010 in Utah. Pediatrics 2013; 132: 421-428.
9. Yalçin I, Gürler N, Alhan E, et al. Serotype distribution and antibiotic susceptibility of invasive Streptococcus pneumoniae disease isolates from children in Turkey, 2001-2004. Eur J Pediatr 2006; 165: 654-657.
10. Ceyhan M, Gurler N, Yaman A, et al. Serotypes of Streptococcus pneumoniae isolates from children with invasive pneumococcal disease in Turkey: baseline evaluation of the introduction of the pneumococcal conjugate vaccine nationwide. Clin Vaccine Immunol 2011; 18: 1028-1030.
11. Kara SS, Polat M, Tapisiz A, Nar Otgun S, Tezer H. [A pediatric case of pneumococcal meningitis due to Streptococcus pneumoniae serotype 35F]. [Article in Turkish] Mikrobiyol Bul 2014; 48: 346-350.
12. Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med 2010; 7: e1000348.

13. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6–18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2013; 62: 521-524.

14. Kaplan SL, Barson WJ, Lin PL, et al. Early trends for invasive pneumococcal infections in children after the introduction of the 13-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2013; 32: 203-207.