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Septic arthritis due to *Haemophilus influenzae* serotype a in the post-vaccination era in Brazil

Haemophilus influenzae (Hi) is an important bacterial pathogen in children, causing a variety of respiratory infections and life-threatening diseases such as meningitis, epiglottitis, pneumonia and septicaemia. Occasionally, Hi can also cause sporadic infections such as septic arthritis (SA). Before the advent of Hi type b (Hib) vaccination, paediatric invasive Hi disease was caused mostly by Hib isolates. Hib SA in children had been responsible for a significant proportion of cases in Europe and the United States (Bowerman *et al.*, 1997; Peltola *et al.*, 1998; Shoaib *et al.*, 2007).

Finland has the longest experience with Hib conjugate vaccines in Europe, since large-scale vaccination started in 1986. It has been considered that vaccination would probably change the epidemiology and hence the management of SA in children (Peltola *et al.*, 1998) because the importance of non-type b and non-encapsulated (NC) Hi strains could increase (Heath *et al.*, 2001; de Almeida *et al.*, 2005; Goergens *et al.*, 2005).

During the pre-vaccination period (1990–1999) in Brazil, the annual incidence of meningitis due to Hib in children up to 1 year old and up to 4 years old was 22.3 and 8.8 cases, respectively, per 100 000 inhabitants (FUNASA, 2003). In August 1999, the Hib conjugate vaccine was introduced. As of 2002, a new diphtheria–tetanus toxoid (DT) whole-cell pertussis combined with Hib conjugated vaccine (DTwP + Hib) was introduced in the National Immunization Program (NIP) in Brazil. Data from the Brazilian National Health Foundation (FUNASA/NIP/Ministry of Health) show that, in 2002 and 2003, 92.91 and 95.99 %, respectively, of eligible children received the vaccine. Since the introduction of the vaccine, only a few papers relating invasive infections with Hi non-b have been published (Zanella *et al.*, 2002; de Almeida *et al.*, 2005).

This study describes a rare case of septic arthritis due to Hi serotype a (Hia) in a child vaccinated with a DTwP/Hib conjugate vaccine. The patient was a 3-year-old female without previous history of infections admitted to a paediatric hospital of Rio de Janeiro with fever (38 °C), intensive leg pain, restricted hip joint motility and motor difficulties. There was no recent articular trauma. Blood culture for aerobic and anaerobic micro-organisms was carried out on admission. Plain radiography revealed no abnormalities. The first blood tests revealed leukocytosis with left shift and sonography imaging detected joint capsule effusion of the right hip. Surgical drainage of the hip was indicated. On the second day, exudate and joint biopsy were sent to the paediatric hospital laboratory for culture. The samples were cultured on brain heart infusion chocolate agar (Difco) enriched with 10 % defibrinated rabbit blood at 37 °C for 24 h, and bacterial growth was detected after 24 h. Gram staining of bacterial colonies was performed, showing abundant pleomorphic Gram-negative rods, suggesting *Haemophilus* spp. The suspected culture was send to the National Institute for Quality Control in Health (INCQS) for additional identification and typing tests such as slide agglutination for serotype determination, biotyping, antimicrobial sensitivity and PCR capsular typing as described previously (Falla *et al.*, 1994; Campos, 1999). Blood culture collected on admission was negative after 7 days. Treatment was initiated with 200 mg oxacillin kg^{-1} day^{-1}, since the initial suspected aetiological agent of the infection was *Staphylococcus aureus* (Goergens *et al.*, 2005). Antibiotic therapy was changed to oral 30 mg cefuroxime kg^{-1} day^{-1} after the suspicion of *Haemophilus* sp. as the causal agent of infection. On the second day, Hia was isolated from the surgical specimens but not from the initial blood culture taken on the day of admission to hospital. After culture confirmation, the antibiotic therapy was changed to parenteral 100 mg of the same drug kg^{-1} day^{-1} for 20 days. Slide agglutination for serotype, biotyping and PCR capsular typing confirmed Hia biotype III as the causal agent of infection. The Hia strain isolated was a β-lactamase producer and ampicillin resistant. After antibiotic therapy, the patient showed complete resolution of symptoms, return of normal joint function and normalization of blood parameters.

Since the introduction of Hib conjugate vaccine, the incidence of Hib invasive infections has decreased dramatically. Non-b Hi disease is uncommon in children; however, since the introduction of Hib vaccine, the relative importance of infections due to NC and non-type b encapsulated Hi has increased (Adderson *et al.*, 2001; Heath *et al.*, 2001; Zanella *et al.*, 2002; de Almeida *et al.*, 2005, Ribeiro *et al.*, 2007; Tsang *et al.*, 2007). Adderson *et al.* (2001) reported an unusual cluster of severe disease caused by Hia with clinical and epidemiological features resembling those of Hib disease. These authors showed that the *IS*1016–*bexA* deletion within the capsule gene cassette may identify more virulent strains of Hi. It was suggested that other non-type b strains may then emerge as a cause of invasive infection in the post-vaccination era. In Brazil, rare cases of invasive disease with Hia have been related. In 2002, as part of the Brazilian national epidemiological surveillance laboratories, the Adolfo Lutz Institute (São Paulo) reported 3204 invasive Hi isolates from 1990 to 1999 from blood, cerebrospinal fluid and pleural fluid from different regions of the country. Only 16 of these isolates were Hia. None of these invasive Hi cases were collected from SA (Zanella *et al.*, 2002). In the city of Salvador, in the north-east of Brazil, active surveillance for meningitis provided evidence of serotype replacement with Hia after the introduction of the Hib conjugate vaccine, but it was suggested that this was a transient and local phenomenon associated

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with a small increase in meningitis due to two Hia clonal groups (Ribeiro *et al.*, 2007).

It has been suggested that the decrease in Hib carriage due to universal vaccination may have allowed increased colonization with non-type b Hi strains, with the potential to become invasive (Waggoner-Fountain *et al.*, 1995). The case described here showed that the ability of an Hia strain to emerge as an important pathogen may depend not only on virulence but also on the ability to establish colonization and spread among children vaccinated with Hib conjugate vaccine. This report also shows the importance of improved diagnostic and characterization procedures in clinical laboratories of public health and of continued Hi surveillance in Brazil. To our knowledge, this is the first report of invasive Hia disease causing SA in Brazil since the introduction of the Hib conjugate vaccine.

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