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Case Report
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Fatal Multidrug-Resistant Serotype 19A Pneumococcal Meningitis in a Toddler: The Importance of Vaccination

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Introduction

Acute Bacterial Meningitis (ABM) is a process of inflammation of the encephalic and medullary leptomeninges. Due to its high morbimortality, its diagnosis should be established without delay and treatment should be started immediately.

Its incidence has progressively decreased in our setting, thanks to the development of vaccines against most of the pathogens involved. Even so, *Neisseria meningitidis* and *Streptococcus pneumonia* continue to be the most frequently detected bacteria in children older than 3 months [1-4].

The most effective preventive measure for ABM due to *S. pneumonia* is pneumococcal conjugate vaccination [5-7], with maximum serotype coverage. Many countries do not include serotypes associated with severe meningoencephalitis and penicillin resistance, such as serotype 19A, since they continue to administer decavalent pneumococcal conjugate vaccines [8]. It is important to know the vaccination status and the type of pneumococcal vaccine received in children upon arrival to Spain from countries with different immunization schedules.

Abbreviations

MBA: Acute Bacterial Meningitis; PCR: Polymerase Chain Reaction; CSF: Cerebrospinal Fluid; CT: Computed Axial Tomography.

Clinical Case

We present the case of a 20-month-old female infant from Iceland just arrived to Spain in June 2022. She had no relevant clinical history, with vaccination up to date according to her country, including pneumococcal conjugate decavalent vaccine.

The patient presented at the emergency room with 48 h evolution of fever and upper respiratory symptoms, being diagnosed with a probable viral infection in a local hospital in Madrid, progressing in the next few hours to vomiting and gait disturbance. Physical examination revealed poor general condition with prolonged capillary refill time, drowsiness and neck stiffness. Given the clinical deterioration and suspicion of septic shock, initial stabilization was performed, requiring volume expansion. Blood tests and blood culture were requested and intravenous cefotaxime was started. Blood analysis showed a leukocyte count of 4,900/microliter, with 40.3% neutrophils, 9.8% lymphocytes and 2% monocytes, hypertransaminasemia (ALT 894 U/L, AST 553 UI/L, alkaline phosphatase 213 UI/L, LDH 961 UI/L). An elevation of acute phase reactants (C-reactive protein 23.7 mg/dl and procalcitonin 59 ng/ml) was detected, as well as altered coagulation with INR of 1.68. Blood gas analysis showed metabolic acidosis with hyperlactatemia.

Due to the lack of improvement, the patient was transferred to the Pediatric Intensive Care Unit (PICU), suspecting meningoencephalitis with associated septic shock. On arrival at the PICU, she was unstable with a neurological examination compatible with intracranial hypertension. A decortication posture with anisocoria was observed, as well as generalized seizures refractory to anticonvulsant therapy. In following blood tests, values were consistent with multiorgan failure maintaining leukopenia (up to 3,300/microliter) with thrombocytopenia (16,000/microliter), NT-proBNP 15,021 pg/ml and D-dimer of 18,243 ng/ml.

Brain computed axial tomography (CT) was consistent with hypoxic-ischemic encephalitis. A lumbar puncture was performed in which Cerebrospinal Fluid (CSF) showed bacterial meningitis (4000 red blood cells/mL, 26 cells/microliter with 52% polymorphonuclear, 628 mg/dl protein and glucose <10 mg/dl). After obtaining microbiological samples, antimicrobial treatment was changed to vancomycin, meropenem and acyclovir. Given the persistence of intracranial hypertension

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refractory to medical treatment, surgical intervention was decided, in which an external ventricular drainage was placed.

Streptococcus pneumonia and *Enterovirus* B were detected in CSF by molecular biology technique (PCR). Despite high-dose antimicrobial treatment and optimization of supportive care, there was fulminant progression, confirming encephalic death by neurological examination, EEG and CT less than 24 h after admission.

After the patient's passing, the presence of *Streptococcus pneumonia* was confirmed in CSF culture and blood culture. Serotype determination was performed, being reported as type 19A. The antibiogram showed multi-resistance to antibiotics, specifically, high level of resistance to penicillin and cefotaxime (MIC to penicillin 4 micrograms/ml and cefotaxime: 6 micrograms/dl). Immunologic work up showed immunoglobulin values within the normal range (IgG 582 mg/dl; IgA 96 mg/dl and IgM 111 mg/dl), and a complement study indicated a discrete hypocomplementemia C4 5.1 mg/dl (normal values 11.2 mg/dl to 39.1 mg/dl), with C3 99.5 mg/dl (normal values 98.6 mg/dl to 207.9 mg/dl). A genetic panel for immunodeficiencies and necropsy could not be performed.

Discussion

Although less and less frequent, pneumococcal meningitis continues to be a major health issue in children in our environment. Both primary care and hospital pediatricians should be familiar with the clinical manifestations in order to establish an early diagnosis that allows treatment to be initiated as quickly as possible.

With respect to invasive pneumococcal disease, its incidence in children is higher in the group under 5 years of age, and the most frequent serotypes are 8, 3, 9N, 19A and 22F (3 and 19A are included in the 13-valent vaccine). Although the incidence of pneumococcal meningitis has decreased over time, it is still associated with a morbidity of around 20% to 25% with a mortality of 5% to 10% at present.

Currently, there are two types of vaccines against *S. pneumonia*; polysaccharide and conjugated vaccines with a carrier protein. There are two types of conjugated vaccines marketed: tridecavalent and decavalent. Thanks to the high vaccination coverage, and to the improvement of hygienic measures, the incidence of invasive pneumococcal disease has markedly decreased in Spain. Although in our setting most of the infant population has received the 13-valent conjugate vaccine, in migrant or transient population, other vaccination patterns can be found, as in the case of our patient.

The available polysaccharide vaccine, known as 23-valent. The polysaccharides of the pneumococcal capsule are not bound to proteins, which makes the immune less robust than with the conjugate vaccine [7,9]. It causes an immune tolerance phenomenon and does not impact on nasopharyngeal colonization. It can be administered from 2 years of age. In children, it should be reserved always after the conjugate vaccine, for patients at high risk of invasive pneumococcal disease.

The pneumococcal conjugate vaccine contains capsular polysaccharides of the 13 most prevalent pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) which, together with a carrier protein, generate an adequate and long-lasting immune response, with long-term protection. This vaccine has been included in the Spanish children's vaccination schedule since 2016, being therefore free of charge, with a 3-dose.

It has proven to be effective in the prevention of invasive pneumococcal disease (97% for meningitis and sepsis), preventing infection from 80% of the circulating serotypes. Among them, serotype 19A stands out, which is characterized by its association with mastoiditis and meningitis, as well as by its high prevalence of resistance to penicillin [10].

Likewise, it is useful to rule out primary immunodeficiencies in fulminant pneumococcal infections.

The aim of this case is to draw attention on the still present pneumococcal meningitis in a highly immunized population of children that can have a fulminant outcome, particularly with aggressive serotypes like 19A, that may be highly resistant to penicillin and cefotaxime. It is necessary to emphasize the importance of adapting and completing the vaccination schedules of patients born outside Spain and achieving optimal immunization of the infant population.

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