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Original article

Clinical, biochemical and microbiological factors associated with the prognosis of pneumococcal meningitis in children

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ABSTRACT

Background: Pneumococcal meningitis (PM) has a high morbidity and mortality. The aim of the study was to evaluate what factors are related to a poor PM prognosis.
Methods: Prospective observational study conducted on patients admitted to the Pediatric Intensive Care Unit in a tertiary hospital with a diagnosis of PM (January 2000 to December 2013). Clinical, biochemical and microbiological data were recorded. Variable outcome was classified into good or poor (neurological handicap or death). A multivariate logistic regression was performed based on the univariate analysis of significant data.
Results: A total of 88 patients were included. Clinical variables statistically significant for a poor outcome were younger age ($p = .008$), lengthy fever ($p = .016$), sepsis ($p = .010$), lower Glasgow Score ($p < .001$), higher score on Pediatric Risk Mortality Score ($p = 0.010$) and Sequential Organ Failure Assessment (SOFA) ($p < .001$), longer mechanical ventilation ($p = .004$), and inotropic support ($p = .008$) requirements. Statistically significant biochemical variables were higher level of C-reactive protein ($p < .001$) and procalcitonin ($p = .014$) at admission, low cerebrospinal (CSF) pleocytosis ($p = .003$), higher level of protein in CSF ($p = .031$), and severe hypoglycorrhachia ($p = .002$). In multivariate analysis, independent indicators of poor outcome were age less than 2 years ($p = .011$), high score on SOFA ($p = .030$), low Glasgow Score ($p = .042$), and severe hypoglycorrhachia ($p = .009$).
Conclusions: Patients younger than 2 years of age, with depressed consciousness at admission, especially when longer mechanical ventilation is required, are at high risk of a poor outcome.

Factores clínicos, bioquímicos y microbiológicos relacionados con el pronóstico de la meningitis neumocócica en niños

Palabras clave:
Pronóstico
Meningitis neumocócicas
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RESUMEN

Introducción: Las meningitis neumocócicas (MN) se relacionan con una elevada morbimortalidad. El objetivo del estudio es evaluar qué factores se relacionan con un peor pronóstico.
Métodos: Estudio prospectivo observacional con pacientes diagnosticados de MN ingresados en la Unidad de Cuidados Intensivos Pediátricos de un hospital de tercer nivel (enero 2000-diciembre 2013). El pronóstico fue clasificado en buena o mala evolución (secuelas neurológicas o muerte). Se realizó un análisis multivariante de los resultados significativos obtenidos en el análisis univariante.

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Resultados: Se reclutaron 88 pacientes. Las variables clínicas relacionadas de forma estadísticamente significativa con una peor evolución fueron: menor edad (p = 0,008), mayor duración de la fiebre (p = 0,016), sepsis (p = 0,010), menor puntuación en la Escala de Glasgow (p < 0,001), mayor puntuación en *Pediatric Risk Mortality Score* (p = 0,010) y *Sequential Organ Failure Assessment* (SOFA) (p < 0,001), ventilación mecánica (p = 0,004) y soporte inotrópico (p = 0,008) prolongados. Las bioquímicas fueron: mayor elevación de proteína C reactiva (p < 0,001) y de procalcitonina (p = 0,014) al ingreso, menor pleocitosis en líquido cefalorraquídeo (p = 0,003), intensas proteinorraquia (p = 0,013) e hipoglucorraquia (p = 0,002). En el análisis multivariante, los factores independientes relacionados con una peor evolución fueron: edad inferior a 2 años (p = 0,011), elevada puntuación en SOFA (p = 0,030), menor puntuación en la Escala de Glasgow (p = 0,042) e hipoglucorraquia intensa (p = 0,009).
Conclusiones: Los menores de 2 años con mayor depresión del sensorio al ingreso, especialmente cuando requieren soporte ventilatorio prolongado, tienen un mayor riesgo de mala evolución.

Introduction

Implementation of universal vaccination against *Haemophilus influenzae* type *b* (Hib) has changed the epidemiology and decreased the incidence of bacterial meningitis (BM) in developed countries. Nowadays, *Streptococcus (S.) pneumoniae* and *Neisseria meningitidis* are the most prevalent causes of BM beyond neonatal period.[1,2]

Pneumococcal meningitis (PM) has been related with great morbidity and mortality. In spite of diagnosis and therapeutic progress, the mortality rate persists at around 8% with an incidence of neurological handicaps of 20–30%.[3–8] Furthermore, cognitive and behavioral sequelae that affect quality of life (academic limitations, language delay, low verbal fluency, psychomotor retardation) have been reported in up to 7–10% of patients with pneumococcal meningitis.[9,10]

Recognizing the prognostic factors would be very useful in indicating early and individualized treatment in these patients with PM. The contributions of clinical, microbiological and biochemical, and therapeutic approaches, as well as neuroimaging findings, have been analyzed in recent years in PM patients. The idea has been identify patients at greater major risk. The most important prognosis factors in relation to neurological handicaps seem to be hypoglycorrhachia,[11] mechanical ventilation requirement,[12] late diagnosis, ataxia, and not receiving dexamethasone treatment.[13–15] The final prognosis probably depends on a combination of different factors but few studies have undertaken an integral analysis of them. The aim of the present study was to determine what clinical, biochemical, and microbiological factors are related to the prognosis of *S. pneumoniae* meningitis patients.

Methods

This was a prospective, observational, non-interventional study of patients admitted to the Pediatric Intensive Care Unit (PICU) at Hospital Sant Joan de Déu, with a diagnosis of PM. In 1999 a database was created in order to prospectively recruit all data of patients with BN. The study period was from January 2000 to December 2013. In Catalonia, with a population of around 7 million and 1.2 million people aged 18 years or younger, this hospital with 345 beds (18 PICU beds) captured around 17% of all pediatric hospital admissions during the study period.

Patients from 7 days to 18 years of age diagnosed with PM were included. PM was defined by characteristic clinical signs and symptoms (stiff or painful neck, vomiting, headache, persistent fever, bulging fontanelles) and compatible cerebrospinal fluid (CSF) alterations (CSF cell count up to 10 cells/mm^3) along with isolation of *S. pneumoniae* and/or DNA detection of pneumococcal genes by Real-Time PCR[16] in blood or cerebrospinal fluid. We excluded patients with known primary immunodeficiency (humoral, cellular, phagocytic, complement alteration, congenital asplenia) or known secondary immunodeficiency (human immunodeficiency virus, nephrotic syndrome, cardiopulmonary chronic disease). The sepsis diagnostic criteria published in 2008[17] were used.

DNA detection of *S. pneumoniae* was carried out using published procedures that included the study of pneumolysin (*ply*) and *wzg* genes (both had to be simultaneously positive to confirm any case as a positive pneumococcal infection), and subsequent direct capsular typing of *S. pneumoniae* DNA positive samples.[16,18]

Pneumococcal strains were identified with standard microbiological methods that included the optochin sensitivity test and an antigenic test targeting the capsular polysaccharide (Slidex pneumo-kit, BioMérieux, Marcy-l'Etolie, France). In addition, strains were also sent to the National Pneumococcus Reference Center at Majadahonda, Madrid, Spain, to complete serotype study with Quellung reaction and to determine the minimum inhibitory concentrations (MICs) of penicillin and other antibiotics with Agar dilution technique. Antibiotic susceptibilities were defined according to the breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[19]

Serotypes were classified into high invasive disease potential serotypes (1, 4, 5, 7F, 9V, 14, 18C and 19A) and lower invasive disease potential serotypes (all others) according to the classification of Brueggemann[20] and Sleeman.[21]

At our hospital, all patients with a diagnosis of PM are admitted to the PICU for the first 24 h of the disease. The protocol treatment included cefotaxime (300 mg/kg/day, maximum 12 g/day, for 10 days) plus vancomicyn (40 mg/kg/day for 3 days, or longer if cefotaxime resistant *S. pneumoniae* is isolated) and dexamethasone (0.6 mg/kg/day; maximum 16 mg/day, for 3 days), in all cases.

Variables registered were *(a)* demographic: age, gender, previous pneumococcal vaccination with 7-valent conjugate pneumococcal vaccine (PCV7), 10-valent conjugate pneumococcal vaccine or 13-valent conjugate pneumococcal vaccine (PCV13); *(b)* PM risk factors: acute otitis media (AOM), recent cranial surgery, cranial trauma antecedent; *(c)* clinical: fever hours' duration previous to PM diagnosis, previous antibiotic treatment; Pediatric Risk Mortality Score (PRISM) III, Glasgow Score and Sequential Organ Failure Assessment (SOFA) score at admission, focal neurological signs (neurological deficit, seizures), mechanical ventilation (MV), and inotrope requirement; *(d)* biochemistry at admission: lactate, CSF leukocyte count and CSF levels of protein and glucose, Boyer Score punctuation, C-reactive protein (CRP) and procalcitonin (PCT) levels at diagnosis and 24–48 h after admission; *(e)* microbiological: *S. pneumoniae* serotype, and penicillin, erythromicyn, and cefotaxime susceptibility.