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Severe enterovirus disease in febrile neonates

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ABSTRACT

Introduction: Fever in newborn infants may be due to an invasive infection with potential morbidity and mortality. Our aim was to describe the characteristics and outcome of group of febrile neonates with severe enterovirus infection compared to a group of neonates with severe bacterial infection.

Patients and methods: Prospective study including all neonates (<29 days old) admitted to a teaching hospital for fever (>38 °C), with positive bacterial cultures or enterovirus detection in sterile samples, from September 2003 to December 2004. Clinical information, analytical data at admission (complete leukocyte count and C-reactive protein concentrations), blood, urine, and cerebrospinal fluid culture results, molecular detection of enterovirus by polymerase chain reaction (PCR), and outcome were recorded.

Results: Invasive bacterial infections were observed in 62 patients: urinary tract infection (n = 57, including 8 cases of bacteremia), sepsis (n = 3), and meningitis (n = 2). Molecular tests for enterovirus were positive in 10 patients. C-reactive protein values were significantly higher in neonates with bacterial infection than in those with enterovirus infection (62.3 versus 9 mg/L, $P = 0.008$). Two patients with *Streptococcus agalactiae* meningitis, 1 with *Staphylococcus aureus* sepsis and 3 with enterovirus infection (manifested as myocarditis, hepatitis, and meningoencephalitis) required admission to the pediatric intensive care unit. Among these, 1 newborn with *S. agalactiae* and 2 of the 3 with enterovirus infection died.

Conclusions: In our series, enterovirus infection was an important cause of severe invasive disease. Specific viral diagnosis can contribute to the management of febrile neonates.

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Enfermedad grave por enterovirus en el neonato con síndrome febril

RESUMEN

Palabras clave:

Enterovirus

Recién nacido

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Introducción: En el recién nacido, el síndrome febril puede obedecer a una infección invasiva, que puede conllevar una elevada morbi-mortalidad. Nuestro objetivo fue describir las características y evolución clínica de un grupo de neonatos con fiebre sin foco debida a infección grave por enterovirus, en comparación con otro grupo de neonatos con infección bacteriana grave.

Pacientes y métodos: Estudio prospectivo de todos los recién nacidos (edad < de 29 días de vida) admitidos en un Hospital universitario por fiebre (>38 °C) y cultivo bacteriano positivo o detección de enterovirus en muestras estériles, desde septiembre de 2003 a diciembre 2004. Se recogieron datos clínicos y analíticos (recuento leucocitario y proteína C reactiva) en el momento del ingreso, hemocultivo, urinocultivo y cultivo de líquido cefalorraquídeo, detección molecular de enterovirus mediante reacción en cadena de la polimerasa (PCR) y evolución final.

Resultados: Se recogieron 62 pacientes con infección bacteriana grave: infección del tracto urinario (n = 57, incluyendo 8 casos con bacteriemia), sepsis (n = 3), meningitis (n = 2). La PCR para enterovirus fue positiva en 10 pacientes. La proteína C reactiva fue significativamente más elevada en los niños con infección bacteriana que en los casos de infección por enterovirus (62,3 versus 9 mg/L, $p = 0,008$). Dos pacientes, uno con meningitis por *Streptococcus agalactiae* y otro con sepsis por *S. aureus*, y tres pacientes con infección por enterovirus (manifestadas como miocarditis, hepatitis y meningoencefalitis) requirieron ingreso en la unidad de cuidados intensivos pediátrica. De estos, el recién nacido con infección por *S. agalactiae* y dos de los 3 pacientes con infección por enterovirus fueron exitos.

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Conclusiones: En nuestra serie, la infección por enterovirus fue una causa importante de enfermedad grave. El diagnóstico viral específico podría contribuir al manejo del neonato febril.

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Introduction

Fever is the main symptom of infection and sometimes the only clinical manifestation of a serious infectious disease, particularly in newborns. Approximately 10% of fevers in children under the age of 90 days are due to potentially harmful bacterial infections.¹ Differentiating patients with serious febrile illnesses from those who suffer more benign infectious processes has always been a challenge for pediatricians, and has resulted in aggressive approaches to fever management at these early ages. The usual diagnostic and therapeutic approach to a neonate with fever includes hospitalization, collection of blood urine, and cerebrospinal fluid (CSF) for bacterial culture, and empirical parenteral antibiotic treatment.² Additional microbiological analyses are performed depending on the clinical suspicion at admission and later evolution. The combination of anamnestic data, clinical examination, and laboratory findings can sometimes help to identify infants at a high risk for a life-threatening bacterial infection. Medical advances in the prevention and control of neonatal bacterial infections have been extensively reported, whereas less is known about the medical management of viral infections.³

Enterovirus infection is a significant cause of fever in young infants^{4–7} and shows a mild and self-limited clinical course in most cases. Nonetheless, serious enterovirus infections leading to hepatitis, myocarditis or septicemia have been reported.^{8–10} Molecular detection of enterovirus by polymerase chain reaction (PCR) techniques may provide an early etiologic diagnosis in febrile infants and facilitate the initial management of these patients.

In this study, we describe the characteristics and outcome of enterovirus infections and compare them to those of classical bacterial infections in a series of febrile neonates attended at a pediatric emergency department.

Patients and methods

A prospective observational study was performed in a series of neonates (<29 days of age) admitted for fever of unknown source to Sant Joan de Déu University Hospital from September 2003 to December 2004. Sant Joan de Déu, located in the metropolitan area of Barcelona (Spain), is a 345-bed public health community hospital for children and is a referral centre for the geographic area of Barcelona.

Our hospital guidelines contain a diagnosis and treatment protocol to evaluate neonates with fever (rectal temperature above 38 °C) of unknown source. It includes complete blood analysis, and culture of urine, blood and CSF. Parenteral antibiotic treatment is then initiated in all these patients at admission. Enterovirus is not a routine determination and is only analyzed when cultures are negative or there is no response at 24–48 hours after starting antibiotics.

Newborns who met the following criteria were enrolled in the study: younger than 29 days, fever of unknown source, admitted to the emergency department, and confirmed diagnosis of bacterial or enterovirus infection. The exclusion criterion was nosocomial bacterial infection. The study was approved by the hospital Ethics Committee.

Medical data from eligible newborns included the following information: age and sex, results of the clinical examination at

admission, vital signs, past medical history, clinical evolution, and final outcome. Results of total white blood cell count (WBC), with differential cell count, C-reactive protein (CRP) levels (CRP; Architect Analyzer, Abbott Diagnostics, Abbott Park, Illinois, USA), bacterial culture in urine, CSF and blood, and enterovirus detection by specific pan-enterovirus PCR (Light Diagnostics Pan-Enterovirus Oligodetect[®] Chemicon, California USA) were also included. For total WBC, cell count, and CRP levels, the analysis was performed with the results from the first sample, taken at the emergency department.

Statistical analysis

Patients with bacterial infection or a positive enterovirus PCR were included in the statistical analyses (performed with SPSS[®], version 12.1). Differences for discrete variables were estimated with the Fisher exact test. Quantitative variables were compared using the Student *t* test. *P* values <0.05 were considered statistically significant.

Results

During the study period, 328 febrile neonates enrolled in the study presented fever without an apparent source. The age range was 3 to 28 days, 185 were male (56.4%), and 143 (43.6%) were female. Bacterial cultures were positive in 62 patients (18.9%), yielding the following diagnoses: urinary tract infection in 49 infants (79%), with accompanying bacteremia in 8 cases (13%); sepsis in 3 patients (5%); and meningitis with bacteremia in 2 patients (3%). The most prevalent bacterial pathogen was *Escherichia coli* (43 cases, 69%), which accounted for most of the urinary tract infections, with or without bacteremia, whereas *Streptococcus agalactiae* was responsible for 4 cases of sepsis or meningitis. Two patients had cutaneous cellulitis and 2 had impetigo with negative blood culture, but positive local testing for *Staphylococcus aureus*. No patients were excluded because of a nosocomial bacterial infection.

Enterovirus was detected in 10 patients with a mean age of 14.8 days (range 4–27 days). Six patients (40%) were male. There were no other bacterial or viral infectious etiologies in these cases. Two patients were moderate ex-premature neonates (gestational age, 34 and 35 months).

Other viral etiologies in the overall series included influenza A virus in 6 patients, respiratory syncytial virus in 25 patients, and rotavirus infection in 3 cases. Two patients had lymphocytic meningitis, without an etiological viral diagnosis.

Serious Bacterial Infection versus Enterovirus Infection

The clinical data in the 2 patient groups (bacterial or enterovirus infection) are shown in Table 1. Although there were no significant differences in age between the groups, 50% of patients with an enterovirus infection were newborns younger than 10 days. These younger patients presented the poorest evolution and most were admitted to the pediatric intensive care unit (PICU). C-reactive protein values were significantly higher in newborns with microbiologically confirmed bacterial infections (range 2.5–266.4 mg/L, mean 62.3 mg/L) than in those with enterovirus infection (range 0.4–19.2 mg/L, mean 9 mg/L)

Table 1
Characteristics and Clinical Outcome Data in Patients with Bacterial Infection or Enterovirus Infection

	BI group (N = 62)	EI group (N = 10)	P
Age, days			
Mean $\pm$ SD	16.36 $\pm$ 4.9	14.8 $\pm$ 8.9	NS
Sex			
Male	27 (43.5%)	6 (40%)	NS
WBC			
Leukocytes $\times 10^3$	14.4 $\pm$ 7.1	12.5 $\pm$ 5.2	NS
Band count (%)	2.75%	1.03%	NS
CRP mg/L (range) mean	(2.5–266.4) 62.3	(0.4–19.2) 9	0.008
PICU admittance	3 (4.8%)	3 (30%)	
Evolution			
Good	59 (95.1%)	7 (70%)	
Death	1 (1.6%)	2 (20%)	
With sequelae	2 (3.2%)	1 (10%)	

BI, Bacterial infection group; CRP, C-reactive protein; EI, Enterovirus infection group; N, Number of observed cases; NS, Non-significant; PICU, pediatric intensive care unit; WBC, white blood cell.

$P = 0.008$. No statistically significant differences were found between the 2 groups for WBC count and band count.

With regard to the clinical outcome, the PICU received 3 infants with enterovirus and 3 infants with sepsis/meningitis from the bacterial group. A poor evolution leading to death occurred in 2 infants with enterovirus infection. The first case was an infant born of a healthy, 29-year-old mother who had a mild febrile illness in the antepartum, with no other relevant clinical data. Antibiotic treatment was started from the first day of the neonate's life due to the high risk of infection. The illness had a biphasic pattern: 6 days after birth, the newborn showed mild febrile signs. Some 48 hours later, the condition had progressed to severe systemic involvement with meningitis and cardiomyopathy. The results of bacterial cultures, serological analysis, and metabolic studies were negative. PCR testing for enterovirus in CSF and blood samples was positive. The newborn died on day 20 after birth.

The second case showed similar preliminary data: first pregnancy of a healthy mother with a febrile illness in the antepartum, and no other relevant data. The newborn showed symptoms of a febrile illness at 4 days after birth. Twenty-four hours later, the symptoms were consistent with a metabolic syndrome (fever, lethargy, hypotonia, and hepatitis), but metabolic studies and bacterial culture were negative. The progression was fulminant, and the patient died 8 days after birth. Liver biopsy with molecular diagnostic methods was positive for enterovirus. As to the 13 neonates with confirmed hematogenous bacterial spread, 11 (84.6%) had a good evolution, 2 (15.3%) were left with moderate disability, and there was 1 death (7.7%) in a patient with fulminant *S. agalactiae* sepsis.

In patients without a microbiological diagnosis and a favorable clinical and analytical outcome, we hypothesized that the cause of fever was a viral agent or a non-invasive bacterial infection. The low positive culture rates were consistent with reported rates, and are attributed to the difficulty of obtaining a blood sample above 2 mL in newborns.

Discussion

Infants younger than 28 days have a greater risk of developing systemic infection compared to older infants. It is well recognized that hematogenous spread of bacterial infection is common in this

age group; hence, a focal infection can progress to sepsis. A similar pattern of infectious spread can be applied to enterovirus, as has been suggested for other pathogens, such as cytomegalovirus, herpes, and other viral and bacterial infections.¹¹

With regard to the etiology (confirmed by microbiological analysis) of neonatal fever, *E. coli* and *S. agalactiae* were the most common bacterial agents. These findings are also in keeping with the literature.¹² Our patients were not affected with early bacterial sepsis, likely because of the current advances in the prevention and management of perinatal bacterial infection.

The consequences of viral infection in newborns may differ because of several risk factors,^{13,14} such as a background of maternal infection, gestational age of the neonate, site of the infection, and the microorganism involved. In our study, the newborns with enterovirus infection showing the poorest evolution had developed symptoms within 10 days after birth, and in all cases, the symptoms were consistent with the maternal infection prior to delivery.

Based on its clinical features, enterovirus is considered a common cause of fever and aseptic meningitis in young infants as a self-limited infection. Generalized enterovirus infection in neonates occurs in one of two characteristic clinical syndromes: myocarditis (characteristically a manifestation of group B coxsackievirus infection) and fulminant hepatitis (typically from echovirus 11 or other serotypes).^{15–17} In our study, 2 patients developed multiorgan disease with a fatal evolution. In fact, enterovirus was the primary cause of death in our neonate series, with fever as the initial symptom. Enterovirus severity is probably associated with perinatal transmission and poor immunity in this age range. In general, because the immune system is immature in extremely premature babies, they have the highest incidence of mortality and morbidity. Some authors have reported a favorable outcome of treatment with pleconaril, a new antipicornaviral agent,^{8,18} but this drug is not currently available. High doses of intravenous immune globulin have also been reported to improve outcome.¹⁹ Because of the potentially serious evolution of enterovirus infection in neonates, new multicenter studies should be undertaken to evaluate the treatment strategies for this condition.

Several studies have demonstrated the value of C-reactive protein analysis to evaluate children with fever and no localizing signs of infection.^{20,21} In our series, CRP values were significantly ($P < 0.01$) higher in the bacterial group than in the enterovirus group. The 7-fold higher CRP values in the former were more useful than white blood cell count or band count to differentiate between bacterial and viral infection. Nevertheless, any of these blood markers are useful for detecting a severe viral infection such as enterovirus.

All cases of enterovirus infection were detected by pan-enterovirus PCR. This is a useful technique for fast, specific, sensitive diagnosis in various specimens, such as blood, CSF, and others.^{22,23} The use of PCR to identify febrile infants with enterovirus infection contributes positively in rational and specific management of the etiological cause of fever. Pan-enterovirus PCR is not a routine test in our hospital and is only performed in samples from febrile patients who progress poorly. This fact may mask the true prevalence of enterovirus infection in newborns. In any case, it is well recognized that enterovirus infection is very common in infants; several authors have reported incidence rates of 25% to 50% in febrile infants,²⁴ the majority with self-limited disease. The present study underscores the fact that enterovirus infection in newborns is a risk factor for serious invasive disease and a fatal evolution. Additional studies are needed to evaluate trends over time and the role of enterovirus in infections associated with serious invasive disease and neonatal death.

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