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María Ramírez Hidalgo [a,*], Alfredo Jover-Sáenz [a], Mercè García-González [b], Fernando Barcenilla-Gaite [a]

[a] *Unidad Funcional de Infecciones Nosocomiales, Hospital Universitari Arnau de Vilanova, Lleida, Spain*
[b] *Departamento de Microbiología, Hospital Universitari Arnau de Vilanova, Lleida, Spain*

* Corresponding author.
E-mail address: ferchita@gmail.com (M. Ramírez Hidalgo).

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Human parechovirus sepsis induced coagulopathy in an infant☆

Sepsis por parechovirus humano que indujo coagulopatía en un lactante

The human parechovirsus (HpeV) is a member of the Picornaviridae viral family and has a fecal–oral route of transmission; it can cause nonspecific fever in adults. Cases of encephalitis/sepsis due to HpeV have been reported in infants.[1,2] One possible consequence of the viral infection is acute coagulopathy.[3] We hereby present the case of an infant with sepsis and coagulopathy who underwent the routine tests available at local level that could not confirm the source of infection. A larger virological study conducted at the national virology lab revealed infection due to HpeV. We recommend routine studies to rule out HpeV in infants with no obvious etiology of sepsis.[4]

One eight-week old infant without a significant personal history is assessed due to clinical manifestations of fever, irritability and diarrhea of one (1) day duration. The clinical examination shows one single blue macular exanthema on the infant's right thigh. The heart and respiratory rates are 220 beats and 50 breaths per minute, respectively. Temperature is 101.3 °F and the capillary refill time is over four (4) seconds – suggestive of poor peripheral perfusion and a situation of clinical sepsis. The additional tests conducted showed leukocyte counts of 4×10^9/l and CRP values of 23 mg/l, and lactate levels of 2.7 mmol/l. The INR was 1.5. Prothrombin time (PT) was 16.1 s (normal = 8.7–2.7), and the activated partial thromboplastin time (aPTT) was 67 s (normal = 8.7–2.7). The liver function tests showed ALT levels of 22 U/l; bilirubin levels of 7.1 μmol/l; ALP levels of 196 U/l; and GGT levels of 16 U/l, all within normal ranges. A complete screening for sepsis including lumbar puncture; blood cultures; urine cultures; and coprocultures was conducted followed by the administration of a triple empirical antibiotic therapy (amoxicilin, gentamicin, and cefotaxime) and due to an inadequate peripheral perfusion, boluses of crystalloid solutions are administered too. On day two, the diarrhea gets worse with presence of swelling in the infant's lower limbs and scrotum areas. The controls reveal that the APPT extends over 100 s. The preliminary results from the blood, fecal and urine samples tested negative and the lumbar puncture confirmed glycorrhachia levels of 2.9 mmol/l and proteinorrhachia levels of 0.29 g/l.

We conducted X-rays of the chest and the abdomen and pelvic and cranial ultrasound scans and they all looked normal. We added teicoplanin to the antibiotic therapy to treat possible MRSA due to the local epidemiological situation of a higher incidence rate of infections due to MRSA. The fact that there was no improvement following the multiple antibiotic therapy and that the active source of infection could not be identified was suggestive that the etiology of sepsis could be viral. For a more in-depth study, the samples collected were sent to the national virology lab where unlike the procedures conducted at hospital standard labs, the CRP testing to rule out the presence of HpeV is routine. On day three, the fever stops. The CRP tested positive for HpeV RNA in fecal, pharyngeal, blood, and CSF samples. On day four, the patient's vital signs went back to normal and the antibiotic therapy was withdrawn. The patient was discharged from the hospital on day eight.

The clinical presentation of HpeV goes from a self-limited fever disease to sepsis with high mortality rate.[5] The pathogenesis that leads to coagulopathy in infections due to HpeV is different from that of disseminated intravascular coagulation (DIC). In the DIC, the tissue factor is released after vascular damage, or after the cytokine release. The DIC PT and aPTT are extended; the fibrinogen level is high, normal, or even reduced, and there is a rapidly decreasing plateletcrit. According to the diagnostic algorithm for the DIC created by the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation that takes all the aforementioned parameters into consideration, scores ≥5 have 97 per cent specificity and 91 per cent sensitivity in the diagnosis of DIC. Our patient scored 1 only, with normal platelet and fibrinogen levels during the course of the sepsis.[6] This made us consider the possibility of a viral etiology as the cause of the clinical manifestations. The takeaway message here is that one situation of sepsis that does not improve with multiple antibiotic therapy or extended aPTT without use of fibrinogen concentrate should make the physician think of a viral infection. There are many viruses that can cause this activation of endothelial cells, which may activate the blood coagulation cascade, inducing the expression of the tissue factor. This is a multifactor process also mediated by the molecule-leukocyte adhesion. Similarly, the edema secondary to the inflammation leads to the activation of the intrinsic blood coagulation cascade. This has been the case of our patient's pattern of coagulation with PT and INR peaks on day 2, and aPTT peaks on day 4.

Since it is not studied on a routine basis, the true incidence of HpeV is unknown. One retrospective study of 5396 infants showed that 1 per cent of the infants hospitalized in the neonatal intensive care unit suffered from an infection, 39 per cent of whom tested positive for enterovirus or parechovirus.[7] Although there are not many clinical guidelines on the management of HpeV, the detailed monitoring of the patients' vital signs and organic functions is necessary to plan adequate support therapies, since cases of rapid progression of encephalitis or sepsis may be fatal. The rapid systematic study of the HpeV RNA through CRP testing could mean achieving the diagnosis within six (6) hours after hospital admission and thus limiting the use of unnecessary antibiotics.[8]

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Jean-Francois Bonnet[a,*], Tara M. Connelly[a], Guillermo H. Vega[b], Alfonso Rodriguez Herrera[c]

[a] *Departament of Surgery, St. Luke's Hospital, Kilkenny, Ireland*
[b] *Department of Surgery, University Hospital Waterford, Waterford, Ireland*
[c] *Departmento de Biología Molecular e Ingeniería Bioquímica, Universidad Pablo Olavide, Sevilla, Spain*

* Corresponding author.
E-mail address: jfbonnet@live.com (J.-F. Bonnet).

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Aetiology and frequency of risk factors for late onset neonatal sepsis in a level IIIBb NICU☆

Etiología y frecuencia de factores de riesgo de sepsis tardía en una unidad de cuidados intensivos neonatales de nivel IIIb

Neonatal sepsis can be classified as early onset or vertical transmission and late onset (LOS), depending on the timing of the appearance of symptoms. LOS is generally nosocomial.[1] In the latest Spanish study on LOS,[2] 730 cases of sepsis were diagnosed in 662 newborns out of a total of 30,993 hospitalised newborns. This gives an incidence of 2.4%, and an incidence density rate of 0.89 per 1000 days of admission. At present, nosocomial infections are the leading cause of morbidity and mortality in neonatal units (10–15%).[1]

We present a retrospective, descriptive study conducted in a level IIIB neonatal intensive care unit (NICU) that included all patients admitted between January 1, 2010 and December 31, 2014 with a positive blood culture and a diagnosis of LOS according to the Centre for Disease Control and Prevention (CDC) criteria.[3] In patients with suspected LOS, at least 1 ml of blood was collected and introduced into a paediatric BD BACTEC Peds Plus/F blood culture bottle (Becton Dickinson, USA) and incubated in the Bactec FX automated system for up to 5 days. Positive samples were then reseeded in standard media and analysed using mass spectrometry (MALDI-tof, Bruker Diagnostics, Germany). Isolates were confirmed against the antibiogram using the Microscan system (Beckman Coulter, USA). The study was approved by our hospital's Ethics Committee.

We observed an incidence of LOS of 6.8%, with an incidence density of 4 cases per 1000 days of admission. The median weight at birth was 1420 g (interquartile range [IQR]: 990–2310 g) and mean gestational age was 31 weeks (95% confidence interval [95% CI] 23–40.5). The median days of life at onset was 10 (IQR: 6–22). In total, 99 patients (67%) received parenteral nutrition (median duration of 8 days, IQR: 5–14) for other reasons at the time of onset of the infectious disease; 35 patients (24%) were intubated (median duration of 7 days, IQR: 5–26) before onset of LOS and 135 patients (92%) had a central venous catheter (median duration of 10 days, IQR: 6–23) at the time of onset of sepsis symptoms. The median length of hospital stay was 39 days (IQR: 19–63).

The most frequently isolated microorganisms were: *Staphylococcus epidermidis* 30% (44/147), *Klebsiella pneumoniae* (*K. pneumoniae*) 14% (21/147), *Escherichia coli* 8% (12/147), *Enterobacter cloacae* (*E. cloacae*) 7.5% (11/147), *Staphylococcus haemolyticus* 5% (7/147), *Klebsiella oxytoca* 5% (7/147), *Staphylococcus hominis* 4% (6/147), *Candida albicans* 4% (6/147), *Candida parapsilosis* 4% (6/147), *Pseudomonas aeruginosa* (*P. aeruginosa*) 4% (6/147), *Staphylococcus capitis* 3% (4/147) and *Enterococcus faecalis* 2% (3/147). The antibiotic sensitivities of these bacteria are shown in Table 1. Eight cases of extended-spectrum beta-lactamase (ESBL) producing *E. cloacae* (73%) and 5 of ESBL-producing *K. pneumoniae* (24%) were found among the isolates.

The prevalence of LOS varied greatly (up to 4.9% or up to 3.8 cases per thousand days of admission).[1,2] Although our figures are slightly higher, they were influenced by the ESBL *E. cloacae* outbreak in 2011 involving a total of 8 patients and 2 fatalities. Had the average of 2.5 cases occurred in any other year, our incidence density would be 3.2 cases per 1000 days of admission.

The most important factor in the development of LOS was venous catheters, which were used in the vast majority of our patients for a duration similar to that reported in the literature.[4] Symptoms, however, appear earlier in our centre.[5] This could be related to catheter management. In half of all cases, parenteral nutrition was scheduled to be withdrawn over the following days, which could also be a point of improvement, despite the fact that duration of parenteral nutrition in our hospital is similar to or even better than that of other centres.[6] Use of endotracheal intubation in our centre does not differ from earlier studies.[4]

Due to the aforementioned outbreak, the relative frequency of *E. cloacae* in our hospital is slightly higher than other centres,[7] but no significant differences were observed in the frequency of other microorganisms.[4]

The sensitivity profile of our gram-positive bacteria was largely similar to that observed in other non-Anglo-Saxon countries.[8] Gram-negative bacteria, even with a good profile for *P. aeruginosa*, show greater sensitivity to aminoglycosides (75%) than that described in developing countries,[9] but far less than susceptibility data from developed countries.[10] The sensitivity to carbapenems was higher (93%) than that reported in the literature,[10] even though we observed several cases of drug-resistant *E. cloacae* and *P. aeruginosa*. With regard to cephalosporins, bacteria showed high

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