Unexpected outcome (positive or negative) including adverse drug reactions

Neonatal sepsis: A, B, C—don't ever forget herpes

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A 5-day-old male presents to the emergency department septic and jaundiced, is resuscitated and started on broad spectrum intravenous antibiotics. However tragically in this case despite showing initial signs of stabilisation, he deteriorated with refractory metabolic acidosis and disseminated intravascular coagulation, and later passed away. At postmortem, disseminated herpes simplex virus-1 (HSV-1) was found. Paediatricians are well aware of the risk factors for bacterial neonatal sepsis and actively seek information from parents to identify those children at risk. When however should a viral aetiology be considered? Should all neonates receive empirical therapy until proven otherwise? The authors review the literature surrounding neonatal HSV infection and discuss the potential pitfalls of empirical treatment.

BACKGROUND

This case calls to our attention the need for increased awareness of herpes simplex virus (HSV) as a possible diagnosis in a septic neonate particularly in patients under 21 days of age, in whom progressively abnormal liver function is noted, or in whom no bacterial cause is found. In particular, it highlights how quickly deterioration can occur without treatment as well as its disastrous consequences. The septic neonate is an all-too familiar scenario seen in emergency departments and paediatric units alike, and so this case report will hopefully serve to raise awareness of a devastating differential diagnosis.

CASE PRESENTATION

A 5-day-old male infant presented to the local emergency department with a 24 h history of poor feeding, lethargy, fever and jaundice. He had been born at term by normal vaginal delivery, with no history of prolonged rupture of membranes, maternal group-B streptococcus, or fever during labour. There was no antenatal history of note. He had received intramuscular vitamin K at birth, and had since been formula fed.

He was fluid resuscitated and commenced on intravenous flucloxacillin and gentamicin as per the local neonatal protocol. An axillary temperature taken within the emergency department was 37.4°C. Initial bloods on admission revealed a C-reactive protein (CRP) of 39, serum bilirubin of 276, γ -glutamyl transpeptidase of 146 and aspartate transaminase (AST) of 263. There was a neutrophilia of 9.7, although overall white cell count was normal (15.2). A venous gas was normal. A full septic screen was performed. In view of hyperbilirubinaemia, he received 6 h of phototherapy.

By day 5, there seemed to be a slow improvement in the patient's condition. Antibiotics were subsequently stopped in view of negative blood, urine and cerebrospinal fluid (CSF) cultures. Blood tests on completion of antibiotics revealed an improved CRP (13.3) but liver function tests, in particular the glucose tolerance test had progressively increased (382). AST was not repeatedly performed in this period.

Later that day, there was a sudden deterioration in the patient's condition. Examination revealed pallor, signs of shock and new-onset hepatomegaly. A pale, blood-stained stool was passed, and investigations revealed a marked metabolic acidosis had developed despite fluid resuscitation. The patient was re-cultured and antibiotics restarted. An urgent abdominal ultrasound was performed to exclude ischaemic bowel, which revealed free fluid in the upper abdomen, as well as a hydropic gallbladder with wall thickening. No intussusception was identified. The patient continued to deteriorate and was intubated and ventilated, with plans made for immediate transfer to a tertiary paediatric intensive care unit. Signs of disseminated intravascular coagulation developed, with profuse bleeding from cannulation sites, lungs, rectum and umbilicus, which was confirmed on coagulation studies. Despite continued resuscitation and ionotropic support, he suffered several brief cardiac arrests before the decision was made to withdraw care.

In view of the uncertain cause of his sudden deterioration and death, a postmortem examination was conducted. The cause of death was established as disseminated HSV infection, with complications including massive liver necrosis (figure 1), and bilateral adrenal haemorrhage (figure 2). Herpes PCR was subsequently positive for HSV-1 strain.

DIFFERENTIAL DIAGNOSIS

In this case, the initial diagnosis was suspected bacterial sepsis. Blood, urine and CSF cultures however were subsequently negative. There was no evidence of group-B streptococcus infection in the mother, and no perinatal risk factors for bacterial sepsis were noted. At post mortem, disseminated HSV-1 was found to be the underlying diagnosis.

TREATMENT

The patient was initially managed for suspected bacterial sepsis with intravenous flucloxacillin and gentamicin as per the local protocol. Unfortunately, despite this the patient deteriorated and required aggressive resuscitation and

Figure 1 The image shows the liver at postmortem with typical surface spots (main image) with similar foci of necrosis on cut surface (inset).

ionotropic support. After several cardiac arrests and development of a profound coagulopathy, care was withdrawn.

OUTCOME AND FOLLOW-UP

A post mortem was conducted and revealed the patient had died due to disseminated HSV-1 infection.

DISCUSSION

Disseminated neonatal herpes simplex infection (NHSV) is a devastating condition with mortality of up to 85%. Despite the era of effective antiviral therapy, NHSV disease identification and management remains challenging. Genital HSV infection is a significant risk factor for acquiring NHSV disease and with numbers increasing in the UK, this raises the possibility for antenatal screening of the virus.¹ Genital herpes is typically caused by the HSV-2 strain, although cases caused by HSV-1 are on the rise.²

While a high proportion (85%) of NHSV infection is acquired during delivery, transmission may also occur in the antenatal (5%) and postnatal (10%) periods.³ The risk of transmission to the neonate depends upon the timing and type of infection. Primary infection within the last trimester is associated with the greatest risk of transmission (33%) and disseminated disease in the neonate. It has been suggested this is in part due to the lack of type specific neutralising antibodies produced by the mother prior to delivery. In comparison, third trimester disease reactivation carries a transmission rate of approximately 3%.^{4 5} In the case of our patient, there had been no antenatal concerns regarding maternal genital infection.

Our patient, a 5-day-old male, presented to the emergency department with a short history of fever and non-specific symptoms and signs. Many studies have commented on the narrow age range on presentation of HSV disease.^{3 6 7} Fidler *et al.*³ found that all patients who

were subsequently found to have disseminated NHSV presented between 5 and 9 days old, while Caviness *et al.*⁶ reported that patients aged less than 21 days old were at greatest risk. Other reports suggest an incubation period of approximately 1 week following transmission before disseminated disease becomes apparent.⁵

In many neonates, often a history of fever is the first concern that prompts professionals to screen for sepsis. Our patient was no exception. Fever was reported by parents, although was not present on admission. In one study,⁶ fever was found in only 30% of patients subsequently diagnosed with HSV infection. Half were normothermic on presentation, with a further 20% reportedly hypothermic. In addition, most children with NHSV present with a combination of non-specific symptoms and signs,³ as was the case here. A recent case-control study by Caviness identified several features within the history and presentation that may prompt physicians to consider NHSV sooner.⁸ These included a history of maternal fever (OR 28.9) and severe respiratory distress in the neonate (OR 2.7). There was no sign of a vesicular rash during our patient's admission. A Canadian study found that of the 58 cases of NHSV identified during a 3 year-period, 34 cases were localised to the skin, mouth and eyes. Of the 10 cases diagnosed with disseminated disease, only two were found to show signs of skin or mucosal involvement.⁹

Many factors may be attributable to the difficulty in diagnosing NHSV. First, it is perceived that relatively few neonates develop NHSV. Caviness *et al.* however demonstrated that its prevalence was not dissimilar to that of bacterial meningitis (0.2% vs 0.4% with no statistically significant difference).⁶ Long⁷ therefore argues that as paediatricians will go to great lengths to diagnose and treat bacterial meningitis, why not adopt the same management for HSV?

Figure 2 Adrenal gland at postmortem. There is focal patchy necrosis with cells containing viral inclusions in adjacent tissue (inset; arrows point to inclusions).

Second, the possibility of HSV infection is often overlooked by the clinicians that will first attend to such a patient. In a London telephone survey, conducted regarding neonatal sepsis,³ all paediatric specialist registrars interviewed reported they would perform bacterial culture of blood, urine and cerebrospinal fluid (CSF), however only 10% suggested viral culture of CSF (7% suggesting HSV PCR). Bacterial causes were easily proffered, and only the presence of a vesicular rash or neurological signs prompted registrars to suggest aciclovir as first-line therapy. These findings were in keeping with Caviness' study, that found only 28% of neonates with suspected infection underwent viral testing, compared with patients who were screened for a bacterial cause (bacterial CSF and blood cultures were sent on 45% and 53% on neonates, respectively).⁶ Third, despite advances in PCR detection of viral infections, the availability of these techniques in the UK is not yet widespread, which thereby causes delays in diagnosis.

Where there is a high index of suspicion, 'surface cultures' (nasopharynx, rectum, skin, conjunctivae, skin vesicles, blood and CSF) should be performed prior to initiation of therapy if possible.¹⁰ Viral PCR in the case of our patient was subsequently positive for HSV-1 strain, however this only became apparent after intensive care support was withdrawn. In a study by Kropp *et al*,⁹ disseminated disease was more likely to be caused by HSV-2, although this was not statistically significant.

Current obstetric management within the UK is to allow vaginal delivery unless herpetic lesions are present, in which case caesarean section is considered. In some cases, suppressive aciclovir is given in the final weeks of pregnancy, which may reduce the need for intervention.² When vaginal delivery does occur, both mother and baby

can be treated with aciclovir. It has been suggested that an effective HSV vaccine given in pregnancy may not only reduce the rate of primary infection in pregnancy, but enhance the immunity of mothers with evidence of previous infection, as well as the transplacental transfer of virus-specific antibodies.⁵

Treatment of NHSV is high dose intravenous aciclovir (60 mg/kg/day) in three divided doses. Figures suggest that with early treatment, mortality of disseminated HSV can fall from 85% to 25%.¹¹ In this case, antiviral therapy was not commenced before rapid deterioration. A study by Kimberlin *et al*.¹² showed that the time from onset of HSV-attributable symptoms to commencement of antiviral therapy has not changed in the last 20 years (median time 5.5 days) despite advances in this field. Several authors^{3 10} suggest that evaluation and empirical treatment for NHSV is warranted in the presence of any of the following: where there is a clinical suspicion of NHSV (skin vesicles, seizures); marked elevation of hepatic transaminases; a sepsis like picture is present (including hypothermia); or the infant appears more ill than would be expected for another suspect diagnosis. Long⁷ also suggests that the presence of a mononuclear cell CSF pleocytosis should prompt consideration of antiviral therapy, a finding supported by Caviness.⁸

However is this always the best and safest option? With risk versus benefit in mind, Kimberlin provides the counterargument that once started, intravenous aciclovir should be continued until 'surface cultures' are negative, which may take up to 5 days from a reference laboratory, thereby effectively doubling the duration of a hospital admission to 'rule out sepsis'.¹⁰ In addition, neutropenia is a recognised side-effect of high dose aciclovir, and may affect up to 20% of patients on this treatment regime. Should the patient

actually have a bacterial infection rather than NHSV, such empirical therapy could prove harmful.¹¹

This case calls to our attention the need for increased awareness of HSV as a possible diagnosis in a septic neonate. In particular, it highlights how quickly deterioration can occur without treatment, as well as its disastrous consequences. An important marker of herpes sepsis in this case may have been raised hepatic transaminases, a sign of impending liver necrosis. Following this report, we recommend careful consideration of empirical use of acyclovir in septic neonates: particularly those under 21 days of age, in whom progressively abnormal liver function is noted, or in whom no bacterial cause is found.

Learning points

- ▶ Disseminated HSV infection has a high mortality, although early treatment may reduce this to 25%.
- ▶ Disseminated HSV may not necessarily present with skin lesions.
- ▶ HSV should be considered in neonates less than 21 days of age in who raised hepatic transaminases are found, or when there is no evidence of positive bacterial culture.
- ▶ Surface swabs as well as blood and CSF for HSV PCR should be taken alongside a septic screen in 'at risk' neonates.

Competing interests None.

Patient consent Obtained.

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