The incidence and presentation of neonatal herpes in a single UK tertiary centre, 2006–2013

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ABSTRACT

Background Neonatal herpes infection can have devastating outcomes for otherwise healthy babies. In the UK, the stated incidence is low at 1.65 per 100 000 live births, which is in contrast with an incidence of 33 per 100 000 in the USA. We aimed to discover the current incidence of neonatal herpes infection in our tertiary service, determine the timing of presentations, and to consider which presenting features could be used for early recognition and prognostication.

Methods All cases of neonatal herpes infection occurring in the last 8 years were reviewed, and those cases from an agreed population were used to calculate an incidence. The statistical associations between clinical features and death were examined.

Findings There were 57 291 live births between 2006 and 2012. Nineteen cases were identified including 10 from the study population (17.5/100 000 live births). There were nine deaths, all presenting later than 6 days of age. Independent predictors of death were haemodynamic instability, coagulopathy, bleeding and central nervous system features at presentation. All presentations occurred within 2 weeks of birth and were varied and often non-specific.

Interpretation Our incidence rate of 17.5 per 100 000 live births represents a significant increase and is much more in line with the higher incidence rates seen in the USA. The range of presentations shows the non-specific nature of this disease. We advocate a heightened awareness of this treatable disease in the UK, and encourage adoption of modern rapid diagnostic techniques and the wider inclusion of Aciclovir in treatment regimens for neonatal sepsis.

What is already known on this topic

- Neonatal herpes is a treatable infection if recognised early.
- Neonatal herpes presents with muco-cutaneous, central nervous system and systemic manifestations.
- Disseminated disease is associated with high mortality.
- There is often no history of antenatal herpes in affected cases.

What this study adds

- An incidence of neonatal herpes of 17.5 per 100 000 live births, within the UK.
- Clinical manifestations of neonatal herpes are often non-specific and present in the first few weeks of life.
- Alanine transaminase (ALT) is a useful marker for herpetic hepatitis in those presenting with non-specific signs of sepsis.
- Recognition of the need for a wider awareness of neonatal herpes infection and its management within the UK.

INTRODUCTION

The stated incidence of neonatal herpes infection per 100 000 live births varies widely from eight to 60 in the USA, up to 4.6 in mainland Europe, and only 1.65 in the UK.[1–7] Therefore, a UK tertiary service with 10 000 deliveries per annum would expect to see one case every 6 years, and many UK paediatricians will not have managed a case. This relatively low incidence, calculated from a cohort between 1986 and 1991, could be expected to increase in the wake of a recent significant increase in sexually transmitted diseases[8] in the UK.

Importantly, neonatal herpes infection usually follows no identifiable maternal risk and can produce an array of non-specific symptoms in the first few weeks of life, leading to delays in effective antiviral treatment. Five per cent of cases have acquired the infection in utero. The extent of disease, for peripartum (85%) and postnatal (10%) transmission cases, is classified into three categories; skin, eye and or mouth (SEM) disease (45%), central nervous system (CNS) disease (30%), and disseminated disease (25%).[9] This distribution represents experience in the postantiviral era. Before this, more than half of cases presented as disseminated disease.[9] We present all cases of neonatal herpes disease managed by our service within the past 8 years, to determine incidence and examine the presentation characteristics and outcomes.

METHOD

Cases were identified by admission (Badger and PICANET) and laboratory databases. Inclusion criteria were all patients up to 28 days of life, with a positive test (PCR on vesicle swab, secretions, blood or cerebrospinal fluid, CSF) for herpes simplex, who had been looked after by our neonatal or paediatric services, and were born between January 2006 and December 2013. Once identified, case summaries were taken from the medical notes.

In order to estimate the incidence of herpes simplex in a geographically defined population, a study area was defined based on the mothers'

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postcode of residence, and identified a geographical area where almost all births occur in our maternity service. Data from the Office for National Statistics (ONS) for registered births in 2006 and 2007 were used to identify postcode sectors where the percentage of live births delivering at our maternity service was greater than 85%. The percentage of all births in this area delivering at our maternity service was actually much higher than this cut-off (96.7%), since nearly all women living in close proximity to the units deliver there. The total number of live births to mothers resident in this area for the years 2006–2012 was then obtained from ONS; data for 2013 was not available. The incidence of herpes simplex to children from this area over this time period was calculated as the rate per 100 000 live births to mothers resident in the study area, with 95% CI.

The statistical associations between clinical features and death were examined using two-tailed Fisher's exact tests. The chair of the local ethics committee confirmed that full ethical approval was not needed, and that anonymisation was sufficient. Developmental progress of the survivors was taken from their most recent outpatient review.

RESULTS

There were 80 986 live births between 2006 and 2013 in our maternity service. Fifteen cases were identified which were in-born and four further patients were transferred in from local hospitals for tertiary care.

Ten cases were born to mothers resident in our defined geographical area from 2006 to 2012 from 57 291 live births, giving a rate of 17.5 per 100 000 live births (95% CI 8.4 to 32.1 per 100 000 live births).

All nineteen cases were part of the clinical review of cases. Nine (47%) babies died, all of whom presented between seven and 12 days of age. There were eight premature babies of which five died. Serotype information was available in 17 cases; nine cases were caused by herpes simplex virus (HSV1) (four died), and eight by HSV2 (four died). Eighteen cases received Aciclovir and one was diagnosed at postmortem. Twelve received Aciclovir within 24 h of hospital presentation. On follow-up (range 0–48 months, median 11.5 months), eight of 10 surviving babies (80%) were developmentally normal, one had a hemiplegia and one had mild developmental delay (figure 1). Two babies had recurrent cutaneous herpes. The demographic data, antenatal risk factors, clinical presentation data and outcomes are summarised in table 1. Table 2 shows the associations between clinical features and mortality. Haemodynamic instability, bleeding, CNS symptoms and coagulopathy were significantly associated with death at the 1% significance level. Raised alanine transaminase (ALT) showed evidence of an increased risk of death at the 5% significance level, which may indicate the pattern of deterioration, particularly in disseminated disease.

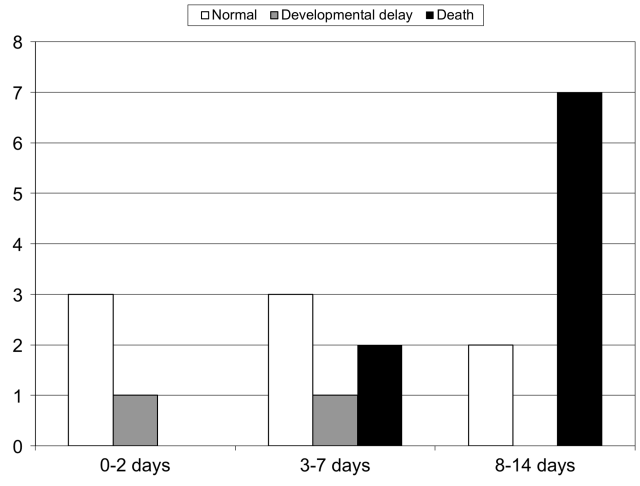

Figure 1 Patient outcomes by presentation age.

Case summaries

Summarised briefly below are the key historical features of all nineteen cases, demonstrating the range and timing of presentation seen (table 1). Some cases are described in more detail to highlight the variance seen within the three classification groups (SEM, CNS and disseminated disease).

Presentation at 0–2 days

Four cases presented within 48 h of birth, and represent either in utero or early perinatal infection. Baby A was born at 28 weeks with extensive left-sided vesicular lesions and contractures. The other three cases differed significantly in their presentation. Baby D required resuscitation at birth and received therapeutic hypothermia for moderate encephalopathy. CSF revealed neutrophilic pleocytosis and HSV2. Baby B was well apart from three clear vesicles on the forearms. Baby C developed worsening respiratory distress (pneumonitis), requiring tertiary care on day 5. A single clear vesicle on the face and a seizure prompted prescription of Aciclovir. MRI of brain was normal at discharge.

Presentation at 3–7 days

Five of the six cases had received early antibiotics for symptoms or risk factors for sepsis and four were still in hospital. Baby E deteriorated on day 5 with pyrexia, lethargy and a mottled appearance. A raised ALT prompted Aciclovir treatment. Baby F presented to the emergency department on day 5 with new respiratory distress and poor feeding. Blood results showed deranged liver function and mild coagulopathy. Baby G was born at 35 weeks and was conservatively managed for necrotising enterocolitis (NEC) from day 2. Pyrexia and irritability developed on day 7. There was no improvement until a small crusted area was seen on the right nostril and Aciclovir was started. The NEC presentation may have been herpetic enterocolitis. Baby H developed pyrexia and lethargy on day 6, and vesicles on the face, trunk and limbs on day 9. By 3 months, there had been one episode of recurrence involving the face.

Baby I presented on day 6 with a history of pyrexia, irritability and respiratory distress. Investigations revealed a mildly raised C reactive protein (CRP) and ALT (71 IU/L), deranged clotting and CSF pleocytosis. Aciclovir was added, but deterioration continued with hepatic and cardiac failure. Baby J was born at 32 weeks and transferred for management of moderate respiratory distress complicated by pneumothorax. On day 7, Baby J deteriorated with new respiratory distress, lethargy, hypotension, metabolic acidosis and coagulopathy. The ALT was very high (742 IU/L) having been normal on day 5. Aciclovir was started, but Baby J died on day 9.

Presentation at 8–14 days

Baby K presented with pyrexia, poor feeding and a papulovesicular rash. There were three episodes of cutaneous recurrence in the first year. Babies L, O, P, Q and S all presented in fulminant hepatic failure. Baby P died within 12 h of admission, and was extensively investigated for a metabolic disease. Baby L's mother had chorioamnionitis and gonococcus infection. All

Table 1 Demographic data, clinical features, laboratory features and outcomes

				Presentation					Clinical Presentation							Investigations								
Case	Gestation	Age at first symptoms	Age at hospital presentation	NICU	Postnatal ward	Emergency department	Antenatal risk factors	Preceding illness	Herpetic muco-cutaneous lesions	RDS	Poor feeding	CNS	Fever	Bleeding	HD instability	Coagulopathy	Raised CSF cell count	Max CRP (mg/L)	Max ALT (IU/L)	HSV Serotype	HSV PCR	Type of presentation	Time to Aciclovir (Days)	Outcome
A	28	1	1	+			Premature labour		+	+						+	ND	64	7	1	Blood, swab, ETS	CI	0	Hemiparesis
B	T	1	1	+					+								–	<5	24	?	Swab	SEM	0	Normal
C	T	1	1	+				RDS, Seizure	+	+		+					–	28	43	1	Swab, ETS	DIS	5	Normal
D	T	1	1	+			Previous genital herpes			+		+					+	<5	41	2	CSF	CNS	3	Normal
E	T	5	5	+				RDS, Sepsis		+	+		+		+		–	49	320	2	Blood	DIS	1	Normal
F	T	4	5			+		RDS		+	+					+	ND	33	745	2	Blood	DIS	2	Normal
G	35	6	6	+			GBSc	NEC	+	+			+				–	48	23	1	Swab, blood	SEM	1	Mild delay
H	34	6	6	+			Premature labour, GBSc		+		+		+				–	<5	15	1	Swab, blood	SEM	4	Normal, skin recurrence
I	T	6	6			+				+	+	+	+		+	+	+	36	1995	1	CSF, Eye swab	DIS	2	Died day 3
J	32	7	7	+			PPROM, chorioamnionitis	RDS		+		+		+	+	+	–	23	742	2	CSF, blood	DIS	1	Died day 2
K	T	8	8			+			+		+	+	+				–	54	29	1	Swab	SEM	0	Normal, skin recurrence
L	34	8	8		+		PPROM, chorioamnionitis			+	+	+		+	+	+	ND	11	884	2	Blood, CSF, Swab	DIS	1	Died day 2
M	25	8	8	+			APH, chorioamnionitis	Sepsis	+	+		+			+	+	–	122	8	1	Swab	SEM	0	Died day 1
N	T	8	12			+	Previous genital herpes				+	+	+				+	<5	20	2	CSF	CNS	0	Died day 1
O	T	8	11			+				+	+	+		+	+	+	ND	<5	1931	?	Blood	DIS	1	Died day 5
P	36	10	11			+	PPROM, stomatitis			+	+	+		+	+	+	+	<5	1119	1	Liver, CSF	DIS	ND	Died day 1
Q	T	10	11			+			+	+	+	+		+	+	+	ND	12	4020	1	Blood, swab	DIS	0	Died day 5
R	T	10	10		+		PROM, pyrexia		+		+	+	+				+	<5	ND	2	Blood, swab, CSF	CNS	1	Normal
S	35	11	11			+	PPROM			+	+	+		+	+	+	ND	<5	784	2	Blood	DIS	0	Died day 2

Key: ALT, alanine transaminase; APH, antepartum haemorrhage; CNS, central nervous system; CI, congenital infection; CSF, cerebrospinal fluid; DIS, disseminated disease; ETS, endotracheal secretions; GBSc, group B streptococcus colonisation; HD, haemodynamic; HSV, herpes simplex virus; LP, lumbar puncture; ND, not done; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PPROM, preterm prelabour rupture of membranes; PROM, prolonged rupture of membranes; RDS, respiratory distress; SEM, skin/eye/mouth disease.

Table 2 Clinical features and risk of death examined by Fisher's Exact tests (two-tailed)

Variable	Categories	Death rate	p Value
Fever	Raised	2/7	0.349
	Normal	7/12	
Rash	Present	2/9	0.069
	Absent	7/10	
Bleeding	Present	6/6	0.0031
	Absent	3/13	
Haemodynamic instability	Present	9/9	0.0011
	Absent	1/10	
Respiratory symptoms	Present	8/14	0.303
	Absent	1/5	
CNS symptoms	Present	9/12	0.003
	Absent	0/7	
Poor feeding	Present	7/12	0.349
	Absent	2/7	
ALT	Raised	7/9	0.023
	Normal	2/10	
Coagulopathy	Present	8/10	0.0055
	Absent	1/9	
CRP	Raised	5/11	1.000
	Normal (<5)	4/8	

ALT, alanine transaminase; CNS, central nervous system.

had raised ALT and were bleeding. Despite full intensive care all were too unwell to proceed to liver transplantation.

Baby Q had been seen in the emergency department 5 days prior to admission with parental concerns about breathing. Baby R was noticed to have a vesicular scalp rash on day 10, prompting Aciclovir. Over the next 24 h pyrexia, lethargy and poor feeding developed. Baby M was delivered at 25 weeks following chorioamnionitis. Upon deterioration on day 8, Aciclovir was added when extensive oral vesiculo-ulcerative lesions (HSV1) were noted on laryngoscopy. Pseudomonas was found in blood and lung tissue. Baby N was seen in primary care from day 8 with poor feeding, stiffening episodes and fever, before being admitted on day 12. His neurological condition deteriorated rapidly leading to death within 48 h.

DISCUSSION

Our tertiary service has managed 19 cases of neonatal herpes disease in the last 8 years. All cases presented within the first 2 weeks often with non-specific features. Neonatal herpes has been rare in the UK. The first British Paediatric Surveillance Unit (BPSU) Survey of neonatal herpes (June 1986 to December 1991) calculated an incidence of 1.65 per 100 000 live births.[7] The incidence of 17.5 per 100 000 live births found in this paper represents an 11-fold increase in two decades.

In order to overcome the potential referral bias that can arise with single centre studies, the incidence rate in this paper was estimated using a geographically defined population based on the mothers' residence at the time of delivery. Potentially, some eligible cases from this study area may have been delivered at neighbouring maternity services: however, the number would be small (>96% delivered in our service) with little impact on the estimation of the incidence of neonatal herpes.

Since all the babies included in the estimation of the incidence of neonatal herpes were born at our maternity service, and the study population used were from a single predominantly urban area, it is possible that the incidence of herpes seen here is not representative of that found across the whole of the UK. This might be due to local demographic characteristics or obstetric practice. However, even if this were the case, it is very unlikely to account for the large increase in incidence when compared to earlier estimates.

Further, it is unlikely that other cases of CNS disease or disseminated disease from our study population were managed elsewhere, but it is possible that some cases of SEM disease were managed without investigations in primary care.

This incidence approaches those seen in the USA where genital herpes has become endemic and there is a higher expectation of seeing neonatal herpes disease. There has been a general increase in sexually transmitted diseases[8] since the first BPSU survey, and genital herpes may go unrecognised as it is often asymptomatic. Of a large cohort of women in labour (39 949) without clinical evidence of HSV infection, 128 (0.3%) were found to have subclinical shedding and were at risk of passing infection onto their babies.[10] This risk of vertical transmission was estimated as 57% for first-episode primary infection, 25% for first-episode non-primary infection, and 2% with recurrent genital infection.[10] The risk of transmission also varies with serotype, duration of rupture of membranes, maternal antibody status and extent of viral shedding.

In England, first-episode genital herpes has increased by 89% between 2003 and 2012.[8] Of note, our region is not atypical for genital herpes infection rates, with 57.9 cases per 100 000 population in 2012, compared to the national mean of 60.3. It is likely that a significant rise in herpes infections in people of reproductive age is the explanation for our higher incidence of neonatal herpes, and that this increase will be seen elsewhere in the UK. However, even at this higher incidence, services with up to 5000 deliveries per annum, will only see one case per year. These cases may be seen and reassured in the early stages of the disease before presenting in extremis. Where the anticipation of this illness is low, some of these cases may be mislabelled as culture-negative sepsis, with a resultant poor outcome and no change in assessment or treatment practices.

Our 8-year experience identified one congenital case and 18 perinatally acquired cases. Of our 15 in-born cases, five (33%) were classified as SEM disease, three (20%) as CNS disease and seven (47%) as disseminated disease. Additionally, three of the four out-born cases had disseminated disease. This high proportion of cases with disseminated disease is different from other published data[7 9 11] and may reflect small numbers, management of SEM disease elsewhere, or differences in the extent of diagnostic testing. Ten babies (53%), including six premature babies, were still in hospital when they became symptomatic, and this, along with a relatively low proportion of CNS cases, may explain their earlier age at presentation compared to other studies.[11] Despite this relatively early presentation, the mortality rate was very high (86% in the disseminated disease group and 53% for the in-born population as a whole) and is similar to the poor outcomes of the preantiviral era.[12]

Our high mortality rate may reflect our case mix (eg, number of premature babies, number exposed to prolonged rupture of membranes or number presenting with hepatitis), but may also highlight delays in diagnosis or different approaches to managing the risk of perinatal herpes, that are a reflection of previously understood transmission rates and very low incidence rates. For those going home and presenting to the emergency department, two had been seen for non-specific symptoms before admission.

Aciclovir was started on admission in seven cases. One of the earlier cases died within 12 h of hospital presentation and did not receive Aciclovir. Of the other eight cases of disseminated

disease with a raised ALT, two received Aciclovir on admission, four within 24 h and two within the second 24 h period. The case with evolving pneumonitis made a full recovery after receiving Aciclovir 5 days into the illness, whereas six cases with hepatitis succumbed within 48 h despite intensive care and treatment. No patients in the series received long-term suppressive therapy.

In a study looking at the safety and efficacy of high-dose Aciclovir (60 mg/kg/day for 3 weeks), 1 year mortality from disseminated disease and CNS disease was 29% and 4%, respectively.[13] This suggests that the combination of early recognition and effective treatment significantly modifies outcomes.

After birth, a detailed awareness of the different modes of presentation and their timing combined with a high index of suspicion is the key to implementing treatment in the early part of the illness. An antenatal history of herpes infection is often missing or may not have been explored and should not be depended upon during assessment.[14 15] In retrospect, one mother had gingivo-stomatitis at delivery, and a further two had a history of prepregnancy genital herpes. In the BPSU survey,[7] only two of 76 cases had a known antenatal history, but a further 19 may have had herpes in the past when this was pursued. The maternal booking process should include the discovery of previous herpes infections and other sexually transmitted diseases, as herpes may coexist, unrecognised. New lesions or symptoms of recurrence should be pursued at the time of delivery, and this should be communicated to the neonatal and community teams who will care for the baby in the first few weeks of life. In 2013, the American Academy of Pediatrics published new guidance on the management of neonates born to women with active lesions, that included guidance on the up-to-date use of serological and viral tests, to determine in more detail the maternal infection status and, thereby, the risk to the neonate.[16 17] If the UK incidence of genital herpes infection continues to increase, then the number of babies requiring assessment of infection risk will rise, and UK services may need to adopt a similar approach, and this will require more services using onsite rapid testing to facilitate this. Accordingly, the current Royal College of Obstetricians and Gynaecologists (RCOG) information leaflet on genital herpes in pregnancy[18] does not state the risk to those without a known history of genital herpes, and does not explain the risk from a seropositive non-concordant partner. This leaflet is due to be updated and needs to become more widely available, particularly to those in high-risk groups, for example, low maternal age.

Skin involvement in eight cases served as a useful diagnostic marker, allowing prompt treatment in seven. However, some lesions were inconspicuous (single vesicle, small sore below an nasogastric tube or vesicles in the scalp) and in one case their relevance was realised late in a case of disseminated disease. Additionally, our cases had many non-specific clinical features. CRPs were only moderately raised, if at all, and poor feeding, respiratory signs and CNS signs were the most common features. Presence of a fever, bleeding, haemodynamic instability, ALT >50 IU/L, CRP >15 mg/L, or CSF changes were found in less than 50% of cases. A raised ALT was a marker of disseminated disease (hepatitis), and only one baby with an ALT >400 IU/L survived. Haemodynamic instability, coagulopathy, bleeding and CNS signs were significantly associated with death.

Early neonatal sepsis is very common and should always include consideration of herpes infection, but in a new presentation of late sepsis, an ALT measurement is useful and the inclusion of Aciclovir treatment may be lifesaving, as outcomes in HSV are significantly improved by early administration of antiviral medication.[11 13 19]

In 2006, our diagnostic HSV samples were sent to a reference laboratory in another region, with the expectation of a result being returned in 3 weeks. However, we have now adopted local PCR testing, and have agreed a twice weekly service with our own laboratory, producing same day results to help us manage a larger number of babies in which we have included herpes infection in the differential diagnosis.

Finally, if we were to extrapolate our data to the UK as a whole and compare it to Group B streptococcal (GBS) disease incidence[20] (0.5/1000 live births and a mortality rate of 10%), there would be 66 deaths from herpes disease and 40 from GBS disease, assuming 800 000 births per annum.

CONCLUSIONS

An incidence of neonatal herpes infection at 17.5/100 000 live births, is markedly higher than previous estimates in the UK. It is likely that a similar rise in incidence is occurring across the UK as the national incidence of first-episode genital herpes has risen and is higher than our local incidence. The presence of bleeding, coagulopathy, haemodynamic instability and CNS features at presentation, were significantly associated with death. We would encourage a heightened awareness of this illness within perinatal teams and adoption of modern diagnostic approaches to limit the impact of this treatable disease. We advise the wider inclusion of Aciclovir in treatment regimens for neonatal sepsis.

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