RESEARCH ARTICLE

Surveillance of neonatal herpes in the British Isles 2004-2006 [version 1; peer review: awaiting peer review]

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v1 **First published:** 04 Mar 2020, **9**:163
https://doi.org/10.12688/f1000research.21538.1
Latest published: 04 Mar 2020, **9**:163
https://doi.org/10.12688/f1000research.21538.1

Abstract

Background: Neonatal herpes simplex virus (HSV) infection is rare but potentially devastating and can result in neonatal death or serious disability. National incidence was estimated at 1.65/100,000 live births in an earlier British Paediatric Surveillance Unit (BPSU) study of births 1986-1991.

Methods: A second surveillance study of neonatal HSV was undertaken through the BPSU 2004-2006, with follow-up information collected on surviving children in early childhood.

Results: Over the three-year period, 85 infants were reported with confirmed neonatal HSV, an estimated incidence of 3.58/100,000 live births (95% CI 2.86-4.42), about double that reported almost two decades earlier. Over 40% of infants were pre-term compared with 25% in the earlier period. Just over 70% had central nervous system (CNS) or disseminated infection, and among these 54% had no skin, eye or mouth lesions noted. Almost all received antivirals, but 22 (26%) neonates died, all with disseminated or CNS infection. All but six infections were typed, of which 57% involved HSV-2; the increased risk of adverse outcomes associated with HSV-2 in the earlier study was confirmed and strengthened, with twice as many deaths or long term disability in infants with HSV-2 than HSV-1. As before, a reported history or diagnosis of maternal HSV infection was rare prior to infant diagnosis. Likely timing of infant exposure to HSV could only be assigned in 43% of cases, of which just over half were probable postnatal transmissions.

Conclusions: Neonatal HSV infection remains rare although incidence doubled in the British Isles between the late 1990s and the mid-2000s. These findings suggest that future research should explore the relationship between pre-term delivery and infant susceptibility, and also the role of postnatal acquisition of infection. Healthcare professionals and new parents must continue to be aware of this rare condition in order to enable prompt investigation and instigation of treatment.

Keywords

Neonatal Herpes, HSV, surveillance, neonates

Open Peer Review

Reviewer Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the UCL Child Health gateway.

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Author roles: Tookey PA: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Mahdavi S**: Formal Analysis, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Peckham CS**: Conceptualization, Funding Acquisition, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The National Screening Committee provided financial support by paying the BPSU fee for inclusion. The work was undertaken at the UCL Institute of Child Health, University College London, and incidental costs were met by the Centre for Paediatric Epidemiology and Biostatistics.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Tookey PA, Mahdavi S and Peckham CS. **Surveillance of neonatal herpes in the British Isles 2004-2006 [version 1; peer review: awaiting peer review]** F1000Research 2020, **9**:163 https://doi.org/10.12688/f1000research.21538.1

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Introduction

Neonatal herpes simplex virus (HSV) infection is a rare but potentially devastating condition which can follow primary or recurrent maternal infection in pregnancy or be acquired postnatally through direct contact with infected secretions. Transplacental transmission is unusual, and perinatal infection is usually acquired through an infected birth canal[1,2].

The incidence of neonatal HSV infection ranges from about 10 per 100,000 live births in the USA[3] to 2–6 per 100,000 in the UK[4], Australia[5] and Canada[6]. Maternal infection close to term increases the risk of neonatal infection, and infants whose mothers have primary infection close to delivery are more likely to acquire infection than those whose mothers have recurrent infection[7].

Although oral infection is predominantly associated with HSV-1, and genital infection with HSV-2, there is considerable crossover[8]. Reactivation appears to be more frequent following HSV-2 than HSV-1. Prior HSV-1 infection is partially protective against the acquisition of HSV-2 and may prevent the severe clinical manifestations associated with primary infection. Many women who have had genital HSV would not be aware of it, as both primary infection and reactivation can be asymptomatic[9].

Surveillance of neonatal HSV was first undertaken through the British Paediatric Surveillance Unit (BPSU) in 1986–1991; estimated incidence of infection was then 1.65/100,000. Neonatal infection was attributed to HSV-1 and HSV-2 in equal proportion, but the virus could not be typed in one third of cases; more than half of the 76 infants reported died, or had substantial disability at follow up[4].

In the light of the increasing prevalence of sexually transmitted diseases and demographic and social changes within the British population, a second BPSU study was carried out 2004–2006, with preliminary results presented in BPSU Annual Reports[10] but not elsewhere. To enable comparison over time, and with a third study being instigated through the BPSU, we want to make the final data from the second study more widely available, and highlight the changes occurring in the 20 years between the two completed national studies.

Methods

Ethical statement

Ethics approval for this study was granted by London MREC (reference MREC/03/2/80; PIAG/BPSU 2-10(g)/2005). Cases were notified through the normal BPSU protocols to this study between 2004 and 2006; paediatricians were not required to request patient consent for reporting, cases were pseudonomysed, and the study team had no contact with reported cases.

Data collection

This study was carried out through the BPSU's active national surveillance scheme, established in 1986, whereby consultant paediatricians (mainly members of the Royal College of Paediatrics and Child Health) report specified rare paediatric conditions on a monthly basis. On receipt of a report the BPSU notifies the appropriate study investigator who contacts the reporting clinician for further details. Respondents make a nil return if they have no cases to report; the BPSU monitors response rates, which at the time of this study were 94%. Full details of the BPSU methodology have been described elsewhere[11]. For this study, paediatricians were asked to report any infant under one month of age with a laboratory-confirmed diagnosis of HSV infection, or any such infant treated with antiviral drugs for suspected HSV infection, or any stillborn infant in whom HSV was suspected, born between 1 January 2004 and 31 December 2006. Respondents were then asked to complete a standard questionnaire providing demographic, clinical and laboratory details including maternal and perinatal information, presentation and treatment. Subsequently, the notifying paediatrician was asked to provide brief follow-up information on the health outcome of the surviving children, including any further treatment required, in their second or third year of life. All clinical and laboratory investigations were undertaken locally as part of the normal care of the infant.

Case definition

Infants with neonatal HSV confirmed by virus culture, polymerase chain reaction (PCR) or immunofluorescence (IF) on a sample taken within 28 days of birth, were classified as confirmed cases. HSV type was reported by the notifying paediatrician on the basis of laboratory results.

Paediatricians were asked to classify infant presentation as disease localised to the skin, eye and/or mouth (SEM), disseminated infection, with or without central nervous system (CNS) and/or SEM involvement, or CNS infection with or without SEM involvement, as described by Whitley[1], and in accord with other similar studies[4–6].

Adverse health outcomes among survivors were classified as mild, moderate or severe, based on the latest clinical findings reported to the study.

Data analysis

Data were managed in a study-specific Microsoft Access 2002 database (Microsoft Corp., Redmond, Washington, USA) and were analysed using Access and Excel.

Results

Overall, 194 reports of neonatal herpes were received, and 85 infants were classified as confirmed cases of neonatal HSV.

Of these, 99 reports were excluded: 53 were duplicates and 46 did not meet the case definition; the latter category included 25 infants treated with acyclovir and reported as suspected cases, but subsequently determined, on the basis of laboratory findings, not to have neonatal HSV. The remaining 10 reports could not be classified as confirmed or excluded as no clinical or laboratory information was provided after the initial case report. This paper focuses on the 85 confirmed cases of neonatal HSV.

Confirmed neonatal cases

A total of 45 boys and 40 girls, including two twin pairs, were reported with confirmed neonatal HSV over the three years. Seventy-one infants were born in England, nine in Scotland, and the remaining five in Wales, Northern Ireland or Ireland, giving a minimum estimated incidence of 3.58/100,000 live births (95% CI 2.86-4.42) in the British Isles. In almost all cases (79, 93%), the virus was typed: 34 (43%) HSV-1, and 42 (53%) HSV-2, with another three infants (4%) reported with dual infection (grouped with those with HSV-2 in this report).

Maternal and birth factors

Table 1 shows maternal and infant characteristics. Median maternal age at delivery was 25 years (range 15–45), and only 5% of mothers were reported to be of black or minority ethnic origin. Two sets of twins were delivered vaginally, at 32 and 34 weeks gestation. Just over a third of singletons (35%) were delivered by caesarean section, but in no case was this because of concerns about herpes infection in pregnancy. Median gestational age was 38.5 weeks (range 26–42); 42% of singletons were pre-term (<37 weeks). Median singleton birthweight was 2755 grams (range 948–4700) and all term infants weighed at least 2500 grams at delivery, apart from one born at 37 weeks gestation.

Table 1. Characteristics of 83 women and their 85 infants.

Maternal age at delivery (71/83 women)	N (%)
<20 years	14 (20)
20–24 years	18 (25)
25–29 years	13 (18)
30–34 years	14 (20)
35 years +	12 (17)
Ethnicity (80/83 women)	
White	76 (95)
Black and minority ethnic	4 (5)
Previous live births (72/83 women)	
None	40 (56)
One	18 (25)
More than one	14 (19)
Mode of delivery (singletons 80/81)	
Vaginal delivery	52 (65)
Elective caesarean section	2 (3)
Emergency caesarean section	26 (32)
Gestational age, weeks (singletons 80/81)	
>36 weeks	46 (58)
32–36 weeks	22 (27)
<32 weeks	12 (15)
Birthweight (singletons 73/81)	
2500 grams and more	42 (58)
1500–2499 grams	22 (30)
<1500 grams	9 (12)
Likely exposure (83 pregnancies)	
Insufficient information	47 (57)
Probably maternal genital HSV	17 (20)
Probable postnatal exposure	19 (23)

Clinical presentation

As shown in Table 2, 61% (52/85) of infants presented with SEM lesions, and for 24, this was the sole manifestation. Of the 61 infants with disseminated or CNS infection, 54% (33) had no SEM lesions reported. Infants with HSV-1 were more likely to have SEM lesions than those with HSV-2 infection (25/34, 74%; 23/45, 51%); CNS and disseminated infection were more common in infants with HSV-2 infection (36/45, 80%; 19/34, 56%).

Treatment

Most infants (82/85, 96%) were treated with acyclovir. Two of the three untreated infants died in the second week of life, and were only diagnosed at post-mortem with disseminated infection; the third, with localised infection only, was reported well at age 30 months. Two infants started treatment prior to presentation with clinical symptoms because their mothers were known to have had genital herpes infection in pregnancy (one diagnosed before delivery, one just after); another 23 were treated on the day of presentation with symptoms. The remaining 57 infants started treatment a median two days after presenting with clinical symptoms, 95% within six days. Two infants started treatment more than two weeks after the onset of reported clinical symptoms despite having SEM involvement, but neither had any problems reported at the last follow up. Among the 63 infants who survived the neonatal period, median duration of the initial course of treatment was 14 days, and 45% received subsequent courses of treatment.

Outcome

It is known that 23 children (27%) have died, all but one in the neonatal period (Table 3 and Figure 1); all of those who died had disseminated or CNS infection, only five also had SEM lesions, and 45% were pre-term. Of neonates with HSV-2,

Table 2. Clinical manifestation and virus type.

	HSV-1	HSV-2	Virus type NK	Total
SEM only (localised)	15	9	0	**24**
Disseminated with SEM	7	6	3	**16**
Disseminated no SEM	6	14	1	**21**
CNS with SEM	3	8	1	**12**
CNS no SEM	3	8	1	**12**
Total	**34**	**45**	**6**	**85**

HSV, herpes simplex virus; NK, not known; SEM, skin, eye and/or mouth; CNS, central nervous system.

Table 3. Virus type, clinical manifestation and outcome.

	Neonatal death	Sequelae	No sequelae	Lost to follow-up at <12 months	Total
Virus type					
HSV-1	6	4	17	7^	**34**
HSV-2	14	13*	12	6^	**45**
Type NK	2	2	2	0	**6**
Clinical manifestation					
Localised	0	4	13	7^	**24**
Disseminated	20	4	10	3^	**37**
CNS	2	11*	8	3	**24**
Total	**22**	**19**	**31**	**13**	**85**

* Includes one postneonatal death.

^ Cell includes infant with developmental delay (see Figure 1).

HSV, herpes simplex virus; NK, not known; CNS, central nervous system.

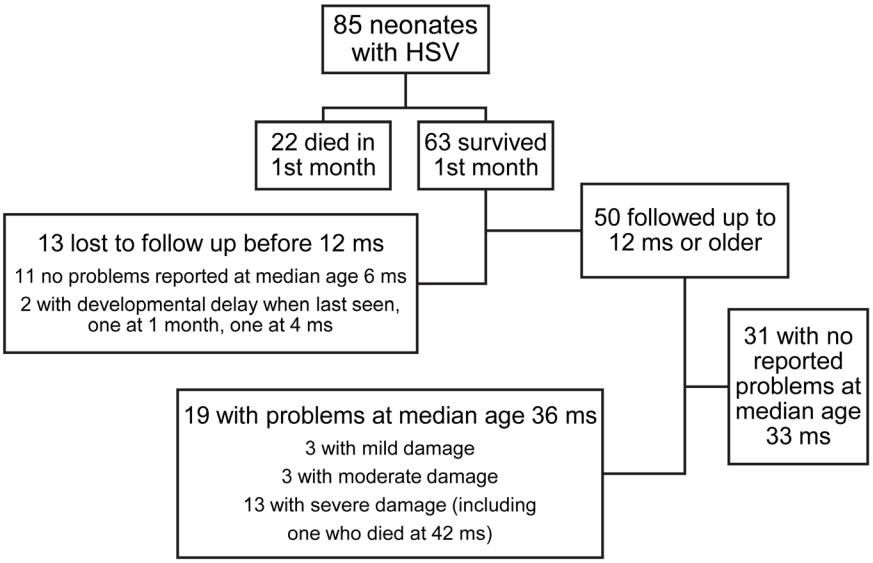

Figure 1. Flow chart. HSV, herpes simplex virus; ms, months.

15 (33%) of 45 died and six (18%) of 34 with HSV-1 (HSV type unknown for two). Two previously asymptomatic infants who died unexpectedly in their second week of life were diagnosed with disseminated HSV-1 infection at post-mortem; the other 20 neonates who died started treatment a median of one day after presentation with symptoms, 95% within five days; all but one died within 15 days of birth.

Of the 63 survivors, 13 (21%) were lost to follow up before their first birthday at a median age of five months: two showed signs of developmental delay when last seen at the ages of one and four months; the remaining 11 had no problems reported at last follow up (Figure 1).

Follow-up information was provided for the remaining 50 children at a median age of 34 months (range 12–65 months). Long-term sequelae were reported in 2/4 surviving children whose virus was not typed, 4/21 (19%) children with HSV-1 infection, and 13/25 (52%) of those with HSV-2. Severe developmental delay and major health problems including recurrent seizures, visual impairment, and quadriplegia or hemiplegia (median age at follow up 37 months, range 24–65) were reported in 13 children, including one child who died aged three years. Another six children had less severe problems reported, including speech and language delay, mild developmental delay and/or visual or hearing impairment (at median age 33 months, range 28–57). The remaining 31 children were

reported well or with only minor health issues (at median 33 months, range 12–62).

Likely source of infection

For 48 infants (including a pair of twins), it was not possible to determine timing of exposure to HSV, that is, whether they had been exposed prenatally or around the time of delivery to maternal genital infection, or postnatally to an oral cold sore or whitlow. For the other 37 infants, 18 (including a pair of twins) were probably exposed to pre/perinatal maternal genital infection, and 19 to a probable postnatal source (Table 1).

Among the infants with probable pre/perinatal exposure, the risk was only identified prior to delivery in two cases: one woman, diagnosed with genital HSV during pregnancy, was treated with acyclovir for seven weeks between diagnosis and delivery by emergency caesarean section when she went into early pre-term labour. Another pregnant woman had reported a past history of genital HSV; following a pre-term vaginal delivery her baby was diagnosed with neonatal HSV and subsequently the mother was found to be shedding virus in the genital tract. Two more mothers reported a history of genital herpes prior to pregnancy after their babies were diagnosed. Another thirteen women were retrospectively found to have had symptoms compatible with current or recent genital HSV, including two with partners who were also diagnosed with genital infection.

In 19 cases, a parent or relative was reported to have a 'cold sore' or similar lesion around the time of delivery or infant diagnosis, or to have frequent oral cold sores; this comprised six mothers or fathers with non-genital HSV lesions, five parents who reported that they frequently had oral cold sores, and eight symptomatic visiting relatives.

Among the 35 infants with type of HSV known and a likely source of infection identified, it was more likely to be postnatal exposure (11/18, 61%) for infants with HSV-1 than for infants with HSV-2 (7/17, 41%). Median gestation was 39 weeks (range 27–42) for infants probably exposed to postnatal infection; 38 weeks (26–42) for infants whose likely exposure was unknown, and 34.5 weeks (27–41) for those with likely pre/perinatal exposure.

Discussion

Although reported incidence of neonatal HSV was double that reported in the first BPSU study (3.58 v 1.65 per 100,000, 95% CI 2.9-4.4 v 1.3-2.0) carried out almost two decades earlier[4], it remained at a very low level and similar to estimates from the Australian and Canadian Paediatric Surveillance Units[5,6]. Improvements in diagnostic techniques and clinical awareness may have had an impact on the reported incidence. Although the BPSU is an active reporting system with a high response rate, our estimate can only be a minimum: it is likely that there is an element of under-reporting to this national scheme; in addition, in the later study there were 10 reports of infants with insufficient information to confirm or exclude the diagnosis. However, since the methodology in the first and second BPSU studies was the same, changes over time are likely to be real. Our estimate is also considerably lower than that reported by Batra *et al.* for the period 2006–2012, based on an urban single centre population in England (17.5 per 100,000, 95% CI 8.4-32.1)[12]. This could reflect differences in study methodologies, the population under review, or a further increase over time.

It was encouraging that most infections could be characterised as HSV-1 or HSV-2, in contrast to the earlier BPSU study when around a third could not be typed. Most infants were diagnosed in time to receive antiviral treatment (only three were not treated at all) unlike the earlier study where 20% of infants received no antivirals. There was also only one postneonatal death reported, compared with seven (9%) previously with a similar length of follow up. The observation from the earlier study that a higher risk of adverse outcome is associated with HSV-2 was confirmed and strengthened, with death or long-term morbidity almost twice as common in those with HSV-2 infection as in those with HSV-1. Nonetheless, the overall proportion of adverse outcomes was lower than in the earlier study (overall 51% compared with 58%).

A major difference between this study and the earlier one was the increase in the proportion of pre-term births – over 40% compared with 25%. In this respect our findings concur with those of Batra *et al.*[12]. It is possible that pre-term infants are at increased risk of acquiring HSV following perinatal exposure to primary or recurrent maternal infection, due to lack of adequate transfer of maternal antibodies at this stage of gestation[13–15]. This is an issue which requires further exploration.

Although it was not possible to assign a likely source of infection in about 60% of cases, there were notable differences between the infants with probable postnatally acquired infection, who tended to be of normal gestation and more likely to have HSV-1 and SEM involvement, and those with probable pre/perinatal exposure, who tended to be born earlier and to have HSV-2. As with the previous study, a history of past infection or diagnosis prior to delivery was extremely rare, and maternal infection was generally only identified after diagnosis in the infant.

Future investigations of the national picture with respect to this rare but devastating condition should consider the role of postnatal acquisition and virus type, and the relationship between pre-term delivery and neonatal HSV following both primary and recurrent maternal genital infection. The introduction of screening for HSV susceptibility in pregnancy would not address the issue of infection in pre-term babies exposed to recurrent infection, in view of the lack of transfer of maternal antibody. The important contribution of postnatal acquisition must not be ignored or minimised in the debate around pregnancy screening. The assumption that neonatal herpes is mainly due to maternal genital infection must be challenged – in this study almost a quarter of all cases, and about half of those where a likely source was identified, were attributable to postnatal exposure to cold sores and other herpetic lesions.

These findings underline the importance of continuing awareness of this rare condition, both among healthcare staff and new parents, with prompt investigation and instigation of treatment.

Data availability

Underlying data

The data for this study was collected 2004–2006. At that time, approval to share raw individual patient data was not required or requested. Identifiers including maternal and infant dates of birth and other demographic characteristics were collected as essential study data and adequate anonymisation of data is not possible due to the rarity of the disease. Assurances were provided that all data would be kept securely and not shared outside the study team. Under these circumstances, data cannot be made publicly available, even in an anonymised form. If researchers wish to access these data for the purposes of further research, they may contact the corresponding study author, Dr Pat Tookey, by email (p.tookey@ucl.ac.uk), providing details of the information required and the intended use of the data, for example comparison with other similar case series, and we will do our best to facilitate this.

Acknowledgements

We thank the British Paediatric Surveillance Unit (BPSU), supported by the Department of Health, for facilitating the data collection, and acknowledge the invaluable contribution of the reporting clinicians. Dr David Brown (Health Protection Agency) and Richard Lynn (British Paediatric Surveillance Unit) contributed to the design of the study, and Janet Masters (d.2012) worked on data collection and data management. Any views expressed in this paper are those of the authors.

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