ORIGINAL ARTICLE

Relapse of neonatal herpes simplex virus infection

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Background: Neonatal herpes simplex virus (HSV) infection is a severe disease with high mortality and morbidity. Recurrence of skin vesicles is common.

Objective: To determine the features of relapse and identify the factors related to relapse.

Design: Thirty two surviving patients with neonatal herpes virus infections were enrolled. All patients received acyclovir treatment. Clinical and virological data were analysed and compared between relapsed and non-relapsed cases.

Results: Thirteen (41%) had either local skin or central nervous system relapse between 4 and 63 days after completing the initial antiviral treatment. Nine patients exhibited local skin relapses, and four developed central nervous system relapses. In one skin and two central nervous system relapse cases, neurological impairment later developed. Type 2 virus infection was significantly related to relapse (odds ratio 10.4, 95% confidence interval 1.1 to 99.0). Patients with relapse had worse outcomes than those without relapse.

Conclusion: Neonates with HSV type 2 infections have a greater risk of relapse. Relapsed patients have poorer prognoses.

Neonatal herpes simplex virus (HSV) infection is a severe disease with high mortality and morbidity. The disease is caused by both type 1 (HSV-1) and type 2 (HSV-2) forms. The prognosis for neonatal HSV infection has improved since effective antiviral drugs, such as vidarabine and acyclovir, became available.¹ However, the mortality from disseminated infection and the morbidity following central nervous system (CNS) infection remain high, despite the early administration of acyclovir.² After the primary infection, HSV remains latent in neuronal cells. Latent viruses sometimes reactivate and cause localised skin or CNS relapses. Skin vesicles often relapse in neonatal HSV infection,²⁻³ whereas CNS relapses are less common.⁴⁻⁶

In this study we sought to determine the features of relapse and identify the factors related to relapse, including both skin and CNS relapse. We analysed 32 surviving cases of neonatal HSV infection. We compared clinical and laboratory data, including viral load, for relapsed and non-relapsed patients.

PATIENTS AND METHODS

Thirty two neonates (15 female and 17 male) were enrolled. All were included in a recent study of viral load and described elsewhere.⁷ Their ages were 33–41 weeks (mean 38.1 weeks), and birth weights were 1920–4030 g (mean 2930 g). The day of onset ranged from 1 to 23 days after birth (mean 6.7 days). Diagnosis was based on the isolation of HSV or detection of HSV DNA by the polymerase chain reaction.⁸⁻⁹ HSV type was determined in 31 cases using type specific monoclonal antibody or restriction fragment length polymorphism of amplified products.⁸⁻¹⁰⁻¹¹ Twenty cases were caused by HSV-1, and 11 by HSV-2. The viral type in one case was unknown. The clinical type of neonatal HSV infection was classified according to the classification of the NIAID Collaborative Antiviral Study Group¹ as: localised skin, eye, or mouth infection (12 cases); CNS infection or encephalitis (13 cases); or disseminated infection (seven cases) involving several organs, such as the lung, liver, or adrenals, with or without involvement of the CNS.¹ All the neonates were treated with 30–60 mg/kg/day acyclovir for 5–28 days. Patients who died during the acute phase were excluded. Morbidity was determined after one year of observation.

Three patients were defined as severely disabled, and three as mildly disabled. Outcomes were unknown in two cases. The other 24 patients were normal at the time of evaluation.

To evaluate viral load, a real time polymerase chain reaction assay was carried out, as previously described.⁷⁻¹² Samples of serum and cerebrospinal fluid (CSF) were obtained at diagnosis or within three days of the initiation of acyclovir treatment; 85% of sera and 72% of CSF samples were harvested before treatment was initiated. Copies of HSV DNA were expressed per ml for serum or CSF.

Statistical analysis was performed with the assistance of StatView 5.0 (SAS Institute Inc, Cary, North Carolina, USA). Fisher's exact test or χ^2 test was used to compare clinical differences within groups. Student's *t* test (two tailed) was used to compare the means of clinical data and viral load. For multivariate analysis, logistic regression analysis was used. *p* < 0.05 were considered significant.

RESULTS

After completing the initial acyclovir treatment, nine patients exhibited local skin relapses, and four developed CNS relapses. In all, 13 patients (41%) relapsed. Table 1 lists the characteristics of the relapsed patients. All four CNS relapses were manifested by recurrent seizures and a more abnormal cerebrospinal profile. Of the four patients with CNS relapse, two were initially skin localised infection. All skin relapse cases exhibited vesicles at the same site as the initial infection. Relapse occurred between 4 and 63 days after the end of acyclovir treatment. All relapsed patients received subsequent intravenous or oral acyclovir treatment for 14–90 days. Three patients with skin recurrence relapsed more than twice, and one of them exhibited frequent skin relapses and received suppressive treatment with oral acyclovir. Nevertheless, the outcomes of these three were normal at the time of assessment. In one of the skin relapse cases and

Abbreviations: HSV, herpes simplex virus; CNS, central nervous system; CSF, cerebrospinal fluid

Table 1 Characteristics of neonates with relapsed HSV infections

No	Sex	GA	Birth weight (g)	Onset day after birth	Initial clinical type	Viral type	Initial acyclovir treatment			Relapse		
							Start day after onset	Dose (mg)	Duration (days)	Relapse day after treatment	Clinical type	Outcome
1	F	33	2298	6	SEM	2	1	30	14	63	CNS	Normal
2	F	40	2930	8	SEM	1	2	30	8	8	CNS	Normal
3	M	40	2966	22	CNS	1	2	45	25	30	CNS	Severely disabled
4	F	37	2740	10	CNS	2	2	30	14	4	CNS	Severely disabled
5	F	40	3284	4	SEM	1	9	30	10	56	SEM	Normal
6	F	38	2808	2	SEM	2	9	30	10	7	SEM	Normal
7	F	40	2336	6	SEM	n.a.	3	30	5	25	SEM	n.a.
8	M	38	3190	8	CNS	2	1	40	21	5	SEM	Normal
9	F	n.a.	n.a.	9	CNS	2	6	30	14	40	SEM	Normal
10	F	33	2055	1	CNS	2	2	30	14	42	SEM	Severely disabled
11	M	n.a.	2425	5	CNS	2	8	30	21	5	SEM	n.a.
12	M	40	3604	4	Disseminated	1	7	45	21	8	SEM	Normal
13	M	39	4034	5	Disseminated	1	4	45	21	28	SEM	Normal

GA, Gestational age (weeks); n.a., not available; SEM, skin, eye, or mouth infections; CNS, central nervous system infection.

two of the CNS relapse cases, severe neurological impairment later developed.

Table 2 compares the clinical characteristics and viral loads of the relapsed and non-relapsed cases. There were no differences in birth weight, gestational age, day of onset, clinical type, viral load, or acyclovir treatment between the two groups, although duration of acyclovir treatment was somewhat shorter in relapsed patients. However, HSV-2 infection was more common in patients with relapse. Relapsed patients had worse outcomes than patients without relapse (table 2).

Clinical type, viral type, and acyclovir treatment (start after onset, dose, and duration) were further analysed by multivariate logistic regression analysis. We confirmed that viral type was associated with relapse (table 3). Patients with type 2 infection often relapsed. Although the difference was not significant, there was a trend toward relapse with shorter duration of initial acyclovir treatment; of the patients who

Table 3 Multivariate analysis of factors related to relapse

Factors	Odds ratio	95% CI	p Value*
Clinical types	1.0	0.1 to 11.4	0.93
Viral type (type 2)	10.4	1.1 to 99.0	0.02
Initial acyclovir treatment			
Start after onset (days)	1.16	0.83 to 1.63	0.38
Dose (mg/kg)	1.10	0.95 to 1.26	0.18
Duration (days)	1.18	0.96 to 1.46	0.09

*By logistic regression analysis. Bold letters indicate significant results.

relapsed, four received shorter courses (less than 10 days; patients 2, 5, 6, and 7 in table 1).

DISCUSSION

Recurrence of skin vesicles is common in neonatal HSV infections. Before antiviral treatments were established, all neonates with skin vesicles who survived neonatal HSV infections had recurrent skin lesions during the first year of life.¹³ Even after the introduction of antiviral treatments, recurrent skin lesions were seen in 46% of patients with localised skin, eye, or mouth infection in a controlled trial comparing vidarabine and acyclovir.⁶ In a Swedish study that included both treated and untreated cases, recurrent vesicles were seen in 79% of the surviving neonates.³ Relapse of CNS or disseminated infection is less common, but recurrence was seen in 8% of surviving patients with CNS or disseminated infections after completion of acyclovir or vidarabine treatments.⁶ In our patients, all of whom received intravenous acyclovir, 41% had either local skin or CNS relapses. Of note, two out of four CNS relapses occurred in patients with initial skin localised infections. Moreover, relapsed patients had worse outcomes than patients without relapse, although all three patients with severe neurological impairment had CNS diseases at initial infections. It has been shown that neurological sequelae are firmly associated with initial clinical types.²

We investigated factors associated with relapse, and found that HSV-2 infection was a risk factor for relapse. A previous study indicated a direct correlation between the incidence of recurrent skin lesions after HSV-2 localised skin disease and the development of adverse neurological sequelae.² Our finding that relapse was more common in HSV-2 infection is in agreement with this observation. A pronounced tendency for HSV-2 infections to recur is seen in genital herpes¹⁴ and meningitis.^{15, 16} Another rationale for frequent relapse after antiviral treatment in HSV-2 infection may be

Table 2 Comparison of patients with and without relapse

	Relapse (n = 13)	No relapse (n = 19)
Birth weight (g)	2890 (580)	2960 (510)
Gestational age (weeks)	38.0 (2.7)	38.2 (2.4)
Day of onset	6.9 (5.2)	6.6 (5.0)
Clinical type of infection		
Disseminated (%)	15.4	26.3
Central nervous system (%)	46.2	36.8
Skin, eye, and/or mouth (%)	38.5	36.8
Viral load*		
Serum (copies/ml)	10 ^{2.3} (3.0)	10 ^{2.2} (2.4)
Cerebrospinal fluid (copies/ml)	10 ^{2.2} (1.7)	10 ^{1.8} (2.4)
Viral type		
Type 1 (%)	38.5	78.9
Type 2 (%)	53.8**	21.1**
Unknown (%)	7.7	0.0
Initial acyclovir treatment		
Start after onset (days)	4.3 (3.1)	3.9 (2.2)
Dose (mg/kg)	34.2 (6.7)	32.4 (7.5)
Duration (days)	15.2 (6.1)	16.9 (6.3)
Prognosis		
Normal (%)	61.5***	84.2***
Mildly disabled (%)	0.0***	15.8***
Severely disabled (%)	23.1***	0.0***
Unknown (%)	15.4	0.0

Unless otherwise indicated, results are means (SD).

*Samples obtained at diagnosis or within three days after initiation of acyclovir treatment were used.

p = 0.04 by Fisher's exact test. *p = 0.03 by χ^2 test. Bold letters indicate significantly different results.

that HSV-2 is less sensitive to acyclovir than HSV-1.¹⁷ It has been reported that CSF remains positive for HSV DNA in HSV-2 infection after the completion of acyclovir treatment.¹⁸ By contrast, clinical type and viral load were not associated with relapse, suggesting that the severity of the initial disease or the extent of infection is independent of relapse. Interestingly, several patients with relapse apparently received shorter courses of acyclovir treatment in our study. Although the difference was not significant, such short treatment could be one of the causes of relapse. In older children with HSV encephalitis, it is reported that short duration of acyclovir treatment is related to relapse.⁹ Larger amounts of acyclovir for a longer period are now recommended for patients with neonatal HSV infections.¹⁹ When acyclovir was introduced for the treatment of neonatal HSV infection, 30 mg/kg/day for 10 days was the standard regimen,⁶ whereas 60 mg/kg/day for 21 days is now preferred.¹⁹ Such longer, more intensive treatment may improve not only the prognosis of neonatal HSV infection, but also the relapse rate.

To compare viral load, we used serum and CSF samples. In neonatal HSV infections, HSV DNA is often detected in these samples.^{7–20} Persistence of HSV DNA in serum and CSF after the treatment is associated with a poor prognosis.²⁰ We recently showed that viral load was higher in the serum of patients who later died.⁷ Therefore, we considered that serum and CSF samples could be used to estimate viral burden. However, as replication of HSV occurs in the tissues, release into blood and CSF is secondary. Thus, the viral load in serum and CSF could be dependent on various factors and may not be correlated with viral load in tissues.

Neonatal HSV infection is caused by both HSV-1 and HSV-2. In the United States, 73% of neonatal HSV infection is caused by HSV-2.²¹ The predominance of HSV-2 is similar in Scandinavian countries.^{3–22} However, neonatal HSV infection is caused almost equally by HSV-2 and HSV-1 in the United Kingdom,²³ whereas two thirds of neonatal HSV infections in Japan are caused by HSV-1, as seen in this and previous studies.^{7–8} The reason for the predominance of HSV-1 in Japan is not fully understood, but is partly explained by the fact that 40% of primary genital herpes in Japan is due to HSV-1.²⁴ Moreover, serological studies show that the seroprevalence of HSV-2 is low among women in Japan.^{25–26}

In conclusion, neonates with HSV-2 infection are at greater risk of developing relapse. Relapsed patients have poorer prognoses. These results indicate that neonates with HSV-2 infection need sufficiently intensive antiviral treatment, and close observation after the treatment has finished. Oral suppressive acyclovir treatment has been tried in neonates with HSV-2 infection in order to prevent recurrent HSV disease or ameliorate the neurological outcome.^{27–28} Despite prolonged suppressive therapy, late recurrences of CNS disease have been reported.^{27–29} Moreover, an acyclovir resistant mutant has been isolated from patients receiving suppressive therapy.²⁸ Although further studies are necessary to determine a safe, effective regimen, suppressive therapy is a potential way to prevent relapse of neonatal HSV infection.

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