Distinguishing Features and Treatment Implications of Herpes Simplex Virus CNS Infections in Canadian Infants <90 Days Old: A Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) Study

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BACKGROUND

- In the pre-acyclovir era, HSV CNS infection was associated with very high morbidity and mortality
- Since antiviral drugs improve outcomes, clinicians need to be able to clinically detect young infants most likely to have HSV to facilitate early initiation of therapy
- Limited data exist on outcomes of infants who require prolonged therapy and those completing prophylaxis

OBJECTIVES

- Identify clinical and laboratory features associated with HSV CNS disease in infants <90 days old, and describe outcomes following antiviral therapy and prophylaxis

MATERIALS & METHODS

- Retrospective chart review across 7 Canadian Paediatric academic centers
- Infants <90 days old admitted January 1, 2013 - December 31, 2014 who had microbiologically-confirmed viral CNS infection were selected from PICNIC's database on CNS infections
- **Case**: Infant with HSV identified by PCR testing of CSF during life or at autopsy.
- Comparators: All cases of non-HSV CNS infections
- **Unfavorable Outcome**: Neurodevelopmental morbidity (deafness, visual impairment, hypotonia, hypertonia, developmental delay) OR death
- **Analysis:** χ^2 or Fisher's exact test for categorical data, Mann-Whitney U test for continuous data

RESULTS

Table 1: Demographics

Characteristics	HSV N=8	Non-HSV N=104	P value
Gender (M), N (%)	3 (38)	54 (52)	0.489
Age (d), median (range)	**16 (4-20)**	**25 (3-84)**	**0.020**
Gestational age (wks), median (range)	37 (37-38)	37 (29-38)	0.277
Maternal infection, N (%)	3 (38)	3 (3)	**0.004**
ICU admission, N (%)	4 (50)	12/99 (12)	**0.016**
Length of hospital stay (d), median (rang	25 (21-63)	3 (1-73)	**<0.001**

Table 2: Clinical features

Characteristics	HSV N=8	Non-HSV N=104	P value
Seizures at any time, N (%)	5 (63)	5 (5)	**0.001**
Seizures during admission, N (%)	4 (50)	5 (5)	**0.001**
Post-discharge seizures, N (%)	1/7 (14)	0	0.064
Long-term seizures requiring treatment, N (%)	4/7 (57)	1/103 (1)	**<0.001**
Extra-CNS disease, N (%)	6 (75)	8 (8)	**<0.001**
Coinfection, N (%)	1 (13)	4 (4)	NS

Fig.1 Seasonality

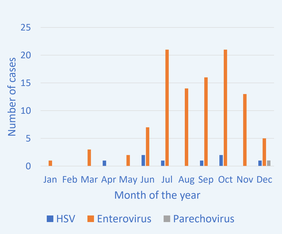


Fig. 2 Timing of presentation

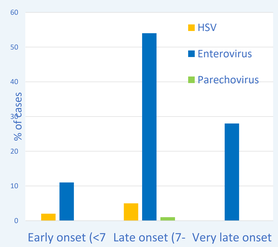
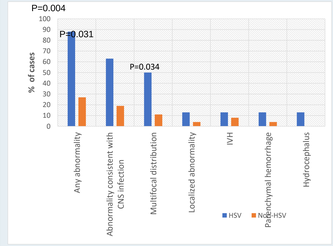


Table 3: CSF findings

CSF parameter	HSV N=8	Non-HSV N=104	P value
CSF WBC (x10^6/L), median (range)	82 (1-218)	153 (0-6400)	0.090
CSF WBC <30 x10^6/L, N (%)	4 (50)	33/100 (33)	0.265
CSF glucose (mmol/L), median (range)	2.3 (2.0-2.8)	2.4 (1.4-3.7)	0.580
CSF protein (g/L), median (range)	0.745 (0.125 -28.5)	0.79 (0.261-3.86)	0.603
≥1 CSF parameter suggesting bacterial meningitis, N (%)	1 (13)	65/101 (64)	0.006

Fig 3: Head imaging abnormalities



Treatment and Recurrence

All HSV cases received ACV for a median of 21d

- Two (25%) remained persistently PCR-positive
- One died 42d into treatment without clearing HSV
  - ACV-resistance confirmed post-mortem
- One required 51d of treatment to clear HSV
- Four (57%) surviving infants received ACV prophylaxis for ≥6 months
  - Two weeks after stopping suppressive antiviral therapy, one infant developed infantile spasms with virologically-proven CNS recurrence

Fig. 4: Complications

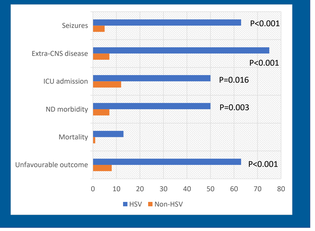


Table 4: Factors associated with HSV diagnosis

Factors	Univariate analysis P value
Age <1 year	0.056
Gender	0.489
Seasonality	0.098
ICU admission	**0.016**
Seizures at presentation*	**<0.001**
Extra-CNS involvement*	**<0.001**
Abnormal imaging	0.098
Unfavorable outcome	**<0.001**

- Of the 112 cases of viral CNS infections, HSV accounted for 8 (7%)
- 8 (100%) of HSV cases and 45 (43%) of non-HSV cases presented at <21 days old; among these cases, seizures were more likely in HSV than non-HSV cases (4 (50%) vs. 4 (8%); p=0.013)
- 4 (50%) of HSV cases had no pleocytosis
- HSV cases were more likely to require ICU admission (p=0.016), present with seizures (p<0.001) and have extra-CNS disease (p<0.001)

OUTCOME

Table 5: Outcome

Outcome	HSV	Non-HSV	P value
Mortality, N (%)	1 (13)	1 (1)	0.136
ND Morbidity, N (%)	4/7 (57)	7 (7)	**0.003**
Unfavourable Outcome, N (%)	5 (63)	8 (8)	**<0.001**

SUMMARY

- HSV is a less common cause of viral CNS infection, but is the main driver of long-term morbidity or mortality
- HSV is associated with: seizures, extra-CNS disease, abnormal imaging, ICU admission, and longer duration of hospitalization
- HSV2 has a greater association with disseminated disease and unfavourable outcome
- There is a potential for acyclovir resistance with treatment duration longer than the standard course

CONCLUSIONS

- High levels of suspicion must be maintained for young infants presenting with seizures in the first 3 weeks of life, with or without extra-CNS disease
- Infants with HSV CNS infection often have no CSF pleocytosis
- High rates of positive HSV PCR at 21 days; critical to ensure CSF clearance
- Resistance testing should be considered if PCR remains positive beyond 21 days
- Follow-up post-prophylaxis is necessary, as CNS recurrences may still occur; consider and investigate for HSV reactivation if these infants present with infantile spasms/worsening neurodevelopmental status

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