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ORIGINAL ARTICLE

Epidemiology and long-term neurological sequelae of childhood herpes simplex CNS infection

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Aim: Herpes simplex CNS infection is a rare but important cause of neurological disability. Long term outcomes after HSV CNS infection in Australia have not yet been fully described. We sought to provide a comprehensive review of HSV CNS infection in children using a retrospective 13-year evaluation of statewide laboratory and clinical records and a parent survey conducted at least one year after the initial infection.

Methods: All positive PCR HSV 1 and 2 results from cerebrospinal fluid (CSF) or brain tissue were obtained from Queensland pathology providers for children aged 0–16 years between 1 January 2005 and 31 December 2017. Clinical data were obtained from patient records and longer-term outcomes via parent survey at least 1 year after initial infection.

Results: Forty-three children were identified over the 13-year period, 17 (39.5%) neonates and 26 (60.4%) non-neonates. The annual incidence for HSV CNS infection in Queensland children aged ≤16 years was 0.3/100 000 (95% confidence intervals (CIs): 0.2–0.4) with neonates at highest risk (incidence 2.5/100 000 live births, 95% CI: 1.5–3.9). HSV 1 was the predominant serotype in both neonates and non-neonates (9/17, 52.9% neonates and 19/26, 73.1% non-neonates). Seven (16.3%) children died, five (5/17, 29.4% neonates), directly attributable to HSV CNS infection (all neonates). Twenty-five (58.1%) had neurological morbidity at discharge (9/17 neonates (52.9%) vs. 16/26 (61.5%) non-neonates) and 20/27 (74.1%) reported long-term neurological morbidity at follow-up (5/9 neonates (55.6%) vs. 15/18 non-neonates (83.3%)). Seven children (two neonates and four non-neonates) with long-term neurological sequelae had no neurological morbidity identified at discharge.

Conclusion: Significant long-term neurologic sequelae were seen in children with HSV CNS infection even in children with no neurological disability identified at discharge from hospital. Careful neurodevelopmental follow-up of all children is recommended.

Key words: brain; CNS; encephalitis; herpes simplex virus; paediatric.

What is already known on this topic

1 Herpes simplex virus (HSV) Central Nervous System (CNS) infection, although uncommon, can be associated with significant neurological morbidity, particularly encephalitis.
2 Neurological outcomes for children with HSV CNS infection remain difficult to predict and prognosis guarded, even after early diagnosis and management.
3 Mortality from HSV CNS infection is rare in children but more frequent in neonates most often as part of disseminated infection.

What this paper adds

1 Young children less than 12 months, particularly neonates are most at risk of HSV CNS infection.
2 CNS infection is associated with long-term neurologic sequelae even in children with no neurological disability identified at discharge from hospital. Careful neurodevelopmental follow up of all children is recommended.

Herpes simplex virus (HSV) CNS infection, although uncommon, can be associated with significant neurological morbidity, particularly encephalitis. The Australian Childhood Encephalitis (ACE) study is the most comprehensive prospective cohort of all-cause childhood encephalitis in Australia and has demonstrated that HSV was independently associated with adverse outcomes at discharge, including death or neurological morbidity (adjusted odds ratio (OR): 20.3), although long-term outcomes were not described.[1] Furthermore, a recent systematic review demonstrated that of all childhood infective encephalitis, HSV encephalitis had the highest rate of long-term sequelae (64%).[2]

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Using International Classification of Diseases discharge coding data, the contemporary annual incidence of meningoencephalitis in Australian children is between 3.8 and 5 per 100 000, comparable with international estimates; HSV represents 6%.[3] This differs from adult populations, where HSV is the most common infectious cause of encephalitis (13%).[4]

Since the advent of HSV polymerase chain reaction (PCR) testing, the clinical manifestations of HSV CNS infection in children are better understood.[5] Non-specific features such as lethargy and fever are most common in children with features described in adults such as encephalopathy, focal neurological deficits and seizures less frequent, making early diagnosis in children challenging.[6] Clinical outcomes for children with HSV CNS infection remain difficult to predict and prognosis guarded, even after early diagnosis and management.[1–3,7,8]

Within Queensland, there is a unique opportunity to comprehensively identify cases of HSV CNS infection given the state-wide single public laboratory service with three minor private providers. We provide a comprehensive review of HSV CNS infection in children using a retrospective 13-year evaluation of state-wide laboratory and clinical records and a parent survey conducted at least 1 year after the initial infection.

What is already known on this topic: - Herpes simplex virus (HSV) Central Nervous System (CNS) infection, although uncommon, can be associated with significant neurological morbidity, particularly encephalitis. - Neurological outcomes for children with HSV CNS infection remain difficult to predict and prognosis guarded, even after early diagnosis and management. - Mortality from HSV CNS infection is rare in children but more frequent in neonates most often as part of disseminated infection. What this paper adds: - Young children less than 12 months, particularly neonates are most at risk of HSV CNS infection. - CNS infection is associated with long-term neurologic sequelae even in children with no neurological disability identified at discharge from hospital. Careful neurodevelopmental follow up of all children is recommended.

Methods

Inclusion criteria

Children in Queensland aged ≤16 years (including autopsy cases) with HSV 1 or 2 PCR detection in cerebrospinal fluid (CSF) or brain tissue from 1 January 2005 to 31 December 2017.

Case definitions

HSV CNS infection was defined as detection of HSV 1 or 2 DNA by PCR in CSF or brain tissue. Encephalopathy was defined as altered levels of consciousness or lethargy in young infants, with exclusion of encephalopathy from other causes. Encephalitis diagnosis required two minor additional criteria for possible encephalitis and three or more minor criteria for confirmed encephalitis. Minor criteria included: fever more than 38°, generalised or partial seizures not attributable to a pre-existing seizure disorder, new onset of focal neurologic findings, elevated CSF white cell count (WCC) or abnormalities on neuroimaging or electroencephalography suggestive of encephalitis.[9,10] Elevated CSF WCC count (or CSF pleocytosis) was defined as ≥5/mm^3 (for older children aged >2 months age), ≥15/mm^3 (for young infants aged 4–8 weeks age) or ≥ 20/mm^3 in neonates (≤28 days of life).[11] CSF WCC was adjusted for blood contamination. Abnormal CSF protein concentrations were defined as >1 g/L in neonates and ≥0.35 g/L in children (>1 month age).[11] A normal CSF glucose level was defined as >3.6 mmol/L in neonates or >4.5 mmol/L in older infants and children.[12]

Children were also evaluated for the presence of one or more of the following: herpetic lesions of the skin, eye and mouth (SEM) or evidence of disseminated disease (bleeding, bruising or coagulopathy, jaundice in the presence of hepatic dysfunction, pneumonitis or hepatosplenomegaly).[13]

Cases were analysed as neonates (≤28 days of age) and non-neonates (29 days to 16 years).

Case ascertainment and data extraction

All positive PCR HSV 1 and 2 results from CSF and brain tissue (including autopsy cases) were obtained from all accredited pathology (including private) providers in Queensland for children aged 0–16 years, between 1 January 2005 and 31 December 2017.

Patient records were examined for details of age, sex, birthweight, gestational age, Aboriginal or Torres Strait Islander status, potential risk factor/source of infection (exposure to maternal genital disease in neonates, past history of HSV infection or exposure to an orolabial lesion in all children), clinical features at presentation, medical history, laboratory findings, hospital course, treatment and short-term outcome.

Death records for all confirmed cases were reviewed with the assistance of the Queensland Health Statistical Service.

Outcome

Qualitative outcomes at discharge were extracted from the medical records. For a subset of the study group, longer-term outcomes were sought using a parental survey (see Supporting Information) sent at least 1 year after initial infection to assess for: developmental delay, persisting neurological deficit or seizure disorders. If children had died, primary caregivers were not contacted.

Data analysis

Incidence rates were calculated per 100 000 live births for each year (2005–2017).14 Means, standard deviations and medians with interquartile ranges were used depending on whether the data were normally distributed or not. Logistic regression was performed to determine statistically significant risk factors for adverse outcomes and long-term sequelae. Exact logistic regression was used for those outcomes where one of the cell values in the contingency table was 0 and therefore conventional logistic regression would not be applicable. Upper limit of the 95% confidence intervals (CIs) was not estimable in these instances.

Ethics

Ethics approval for this study was obtained from the Children's Health Queensland Hospital and Health Service (Queensland Children's Hospital) Human Research Ethics Committee.

Table 1 Demographics and clinical features of HSV CNS infection in children in Queensland ($n = 43$)

		Neonates ≤ 28 days ($n = 17$)	Non-neonates (29 days to 16 years) ($n = 26$)
Demographics	Male	9/17 (52.9%)	13/26 (50%)
	Female	8/17 (47.1%)	13/26 (50%)
	Median age at presentation (IQR)	9 days (17)	1 year (4.5)
Comorbidities	Immunocompromised†	0/17 (0%)	1/26 (3.8%)
	Pre-existing neurological disease	0/17 (0%)	2/26 (7.7%)
	Other	4/17 (23.5%)	3/26 (11.5%)
Source of infection	Past history HSV SEM disease	–	6/26 (23.1%)
	Exposure to orolabial lesion	2/17 (11.8%)	1/26 (3.8%)
	Maternal genital disease	4/17 (23.5%)	1/26 (3.8%)
	Source unknown	11/17 (64.7%)	19/26 (73.1%)
Concurrent HSV disease	HSV SEM	4/17 (23.5%)	4/26 (15.4%)
	Disseminated HSV	6/17 (35.3%)	0/26 (0%)
HSV serotype	HSV 1	9/17 (52.9%)	19/26 (73.1%)
	HSV 2	8/17 (47.1%)	7/26 (26.9%)
Clinical features	Encephalopathy	17/17 (100.0%)	19/26 (73.1%)
	Fever	12/17 (70.6%)	23/26 (88.5%)
	Seizures	10/17 (58.8%)	19/26 (73.1%)
	Focal neurological deficits	3/17 (17.6%)	9/26 (34.6%)

† child with inflammatory bowel disease on adalimumab and methotrexate. IQR, interquartile range.

Results

Forty-three children aged 0–16 years (17 neonates vs. 26 non-neonates) with HSV CNS infection were identified, the majority were 12 months or younger (33/43, 76.7%).

Four cases of HSV PCR detection from autopsy brain tissue samples were not included in the analysis because the Queensland coroner did not confirm death attributable to HSV disease deeming them to be contaminants and not of clinical significance.

The annual incidence of HSV CNS infection in children aged 16 years or younger was 0.3 per 100 000 (95% CI: 0.2–0.4); 0.2 per 100 000 (95% CI: 0.1–0.24) for non-neonates, with neonates showing a significantly higher incidence of 2.5 per 100 000 live births (95% CI: 1.5–3.9).

Baseline characteristics

There was no difference in sex distribution for both neonates and non-neonates. Median age at presentation was 9 days of age (interquartile range (IQR): 17) for neonates and 1 year of age (IQR: 4.5) for non-neonates. Aboriginal or Torres Strait Islander children were not overrepresented relative to the population in the study cohort (Table 1).[15]

Clinical characteristics at presentation

Of the 17 neonates, four (23.5%) had SEM disease and six (35.3%) had disseminated disease. Encephalopathy (17/17, 100%), fever (12/17, 70.6%) and seizures (10/17, 58.8%) were most common. Of the ten neonates with seizures at presentation, nine had status epilepticus (Table 1).

Of the 26 non-neonates, four (15.4%) had associated SEM disease, two less than 3 months of age and two aged 5 and 6 years. Fever (23/26, 88.5%), encephalopathy (19/26, 73.1%) and seizures (19/26, 73.1%) were most common. Of the 19 non-neonates with seizures at presentation, 16 presented with status epilepticus. There were seven non-neonates who did not fulfil the criteria for confirmed encephalitis (see Supporting Information).

Source of infection

Two neonates (2/17, 11.8%) and one non-neonate (1/26, 3.8%) had exposure to an orolabial lesion in a household member/relative and maternal genital disease was reported in four neonates (Table 1).

Six non-neonates (6/26, 23.1%) had a history of HSV SEM disease. Four of these children had completed treatment of HSV SEM disease two weeks prior to their HSV CNS infection, details of their previous treatment were unknown.

Laboratory investigations and imaging

HSV 1 predominated for both neonates (9/17, 52.9% HSV1) and non-neonates (19/26, 73.1% HSV 1). Of the seven non-neonates with HSV 2, four (57.1%) were aged between 1 and 12 months and the remaining were aged 10, 13 and 15 years (Table 1).

Three neonates did not have a lumbar puncture performed during their hospital admission. Detection of HSV DNA from brain tissue at autopsy, with one neonate also having HSV DNA detected from liver tissue, was diagnostic in these cases.

Of the 40 children who underwent a lumbar puncture, 27 (67.5%) had pleocytosis with mean CSF WCC 184.4×10^6/L (SD ± 460.4) in neonates and 368.7×10^6/L (SD ± 916.2) in

non-neonates. Mean CSF protein was 1.4 g/L (SD ± 1.4) in neonates and 0.9 g/L (SD ± 0.6) in non-neonates. Mean CSF glucose was 2.8 mmol/L (SD ± 0.3) in neonates and 3.1 mmol/L (SD ± 0.7) in non-neonates. One non-neonate had an initial negative CSF HSV PCR, which was subsequently detected on repeat CSF at day 4 of admission. Seventeen (39.5%) children underwent end of treatment CSF sampling, 7 were neonates and 10 were non-neonates. Of these, only two neonates (2/7, 28.6%) had ongoing HSV PCR positivity, one child died and the other had antiviral treatment extended for a further 2 weeks (5 weeks total).

Thirteen neonates (13/17, 76.5%) underwent neuroimaging, 9 (69.2%) were abnormal. Cortical hypo/hyperdensity was present, with two or more regions involved in six cases. Of the 20 non-neonates (20/26, 76.9%) who had neuroimaging performed, 17 (85%) were abnormal. Cortical hypo/hyperdensity was most common (11/17, 64.7%) with two or more regions affected in 14 (14/17, 82.4%) and isolated temporal changes seen in the remaining three (3/17, 17.6%).

Ten neonates (10/17, 58.8%) underwent an electroencephalography (EEG), of which seven (7/10, 70%) were abnormal. Generalised delta or slow waves were seen in four with temporal or temporal-occipital delta or slow waves seen in three. Epileptiform activity was also seen in four neonates. Eleven non-neonates (11/26, 42.3%) underwent an EEG, 10 (10/11, 90.9%) were abnormal. Generalised delta or slow waves (6/10, 60%) were the most common finding, followed by temporal or temporal-occipital delta or slow waves (4/10, 40%). Epileptiform activity was also seen in three non-neonates.

Antiviral therapy

Fifteen (15/17, 88.2%) neonates and 24 (24/26, 92.3%) non-neonates received antiviral therapy. Median treatment duration was 21 days for both groups (IQR: 0.5, 1–28 days for neonates vs. IQR: 0, 10–35 days for non-neonates). The mean daily dosing regimen for intravenous aciclovir was 61.0 mg/kg/day (SD ± 6.0) for neonates and 58.6 mg/kg/day (SD ± 14.6) for non-neonates. Nine neonates (9/17, 52.9%) and 16 non-neonates (16/26, 61.5%) also received anticonvulsant therapy.

Four children with HSV CNS infection did not receive antiviral therapy. Two neonates had presumed bacterial sepsis but were diagnosed with disseminated HSV at autopsy. Both presented with encephalopathy and status epilepticus. Two non-neonates with HSV 2 DNA detected in CSF, aged 10 and 14 years, did not receive antiviral therapy, with one managed as presumed bacterial sepsis and the other receiving no treatment (see Supporting Information). Both children fulfilled the criteria for possible encephalitis and the reasons for not treating with antivirals were unclear. No long-term follow-up is available for these two children due to the primary caregivers being unable to be contacted, although they are alive when cross-referenced with the state death register.

Seven neonates (7/17, 41.2%) and six non-neonates (6/26, 23.1%) were prescribed 6 months of oral aciclovir suppression therapy following parenteral aciclovir. All were less than 2 years of age, range 0 days to 18 months.

Outcomes: mortality and neurological disability

Seven children died (16.3%), five directly attributable to HSV disease (11.6%; all neonates). The remaining two children (one neonate and one non-neonate) died after hospital discharge, within 12 months of their HSV diagnosis. One non-neonate's course was complicated by NMDA encephalitis with death as a complication of subsequent influenza infection and the other neonate had bilateral encephalomalacia with hydrocephalus with death caused by an episode of bronchopneumonia (Table 2 and 3).

Neurological deficit was identified at discharge in 25 of the 43 (58.1%) children (9/17 neonates (52.9%) and 16/26 non-neonates (61.5%)). Follow-up parent survey was not completed for 16 (37.2%) (8 neonates and 8 non-neonates). Of these 16 (37.2%), 11 were unable to be contacted and five neonates had died. Two non-neonates' (2/27, 7.4%) clinical course was complicated by autoimmune encephalitis. In one child, anti-N-methyl-D-aspartate (NMDA) receptor antibodies were detected in CSF (1 month following initial infection). In the other child, a diagnosis of autoimmune encephalitis was made in the setting of developmental regression and increasing seizures at 18 months of age (17 months following initial infection) with clinical response to steroids and intravenous immunoglobulin (IVIG). NMDA receptor antibodies were not detected in CSF for this child. Relapse of HSV CNS infection was also reported in a separate non-neonate. The time between the relapse of HSV CNS infection and the initial HSV CNS infection diagnosis was not available.

Of the 27 children with follow-up parent survey completed, 20 (74.1%) reported long-term neurological impairment (5/9 neonates (55.6%) vs. 15/18 (83.3%) non-neonates). Speech delay (4/9 neonates (44.4%) vs. 10/18 non-neonates (55.6%)) and global developmental delay (3/9 neonates (33.3%) vs. 8/18 non-neonates (44.4%)) were the most common. Three neonates (3/9 33.3%) and five non-neonates (5/18, 27.8%) had a seizure disorder with one neonate and three non-neonates experiencing daily seizures and seven of these children (three neonates and four non-neonates) requiring anticonvulsant treatment. Neurological morbidity was also potentially contributed to by an underlying diagnosis in four children: extreme prematurity in two (one neonate and one non-neonate), septo-optic dysplasia with associated seizure disorder in one non-neonate and Klinefelter's syndrome in the remaining neonate.

Seven of the 20 children with long-term neurological sequelae had no neurological morbidity identified at discharge. Two were neonates, four were young infants aged ≤2 months of age and one child aged 6 years. Long-term neurological sequelae in these seven children included developmental delay (4/7), seizure disorder (1/7) and focal neurological deficits and behavioural disturbance (2/7).

ICU admission was 17 times more likely (OR: 17.2) to be associated with mortality and nine times more likely to result in neurological morbidity (OR: 8.9, 95% CI: 2–39.2). HSV-2 CNS infection was 13 times more likely to result in death in neonates (OR: 13.3, 95% CI: 1.1–166.4). Further associations between acute clinical characteristics and neurological morbidity and mortality are shown in Table 3.

Discussion

Epidemiology, risk factors, management and outcome of children with HSV CNS infection in Queensland, Australia are described.

Table 2 Short- and long-term outcomes of HSV CNS infection in children in Queensland ($n = 43$)

			Neonates ≤28 days with HSV 1 ($n = 9$)	Neonates ≤28 days with HSV 2 ($n = 8$)	Non-neonates (29 days to 16 years) with HSV 1	Non-neonates (29 days to 16 years) with HSV 2
Severity and outcome at discharge	ICU		4/9 (44.4%)	8/8 (100%)	6/19 (31.6%)	1/7 (14.3%)
	Acute death		1/9 (11.1%)	4/8 (50%)	0/19 (0%)	0/7 (0%)
	Median days in hospital (IQR) (range)		23 (12) (3–31)	32.5 (33.3) (6–78)	21 (8) (8–39)	21 (23) (2–36)
	Neurological morbidity	Focal neurological symptoms	2/9 (22.2%)	7/8 (87.5%)	14/19 (73.7%)	2/7 (28.6%)
		Visual disturbance	0/9 (0%)	1/8 (12.5%)	3/19 (15.8%)	0/7 (0%)
		Hearing disturbance	0/9 (0%)	1/8 (12.5%)	1/19 (15.8%)	0/7 (0%)
		Seizures	2/9 (22.2%)	6/8 (75%)	13/19 (68.4%)	2/7 (28.6%)
Outcome at follow up	Total death		1/9 (11.1%)	5/8 (62.5%)	1/19 (5.3%)	0/7 (0%)
	Neurological morbidity ($n = 27$)	Neurological deficit, total	2/6 (33.3%)	3/3 (100%)	11/13 (84.6%)	4/5 (80%)
		Developmental delay	1/6 (16.7%)	3/3 (100%)	7/13 (53.8%)	3/5 (60%)
		GDD	0	3	6	2
		Speech and language delay	1	3	7	3
		Gross motor delay	0	3	6	1
		Fine motor delay	0	3	6	2
		Behavioural disturbance	1/6 (16.7%)	1/3 (33.3%)	4/13 (30.8%)	1/5 (20%)
		ADHD	0	0	1	0
		Autism	0	1	1	1
		Cerebral palsy	0/6 (0%)	1/3 (33.3%)	1/13 (7.7%)	1/5 (20%)
		Seizure	0/6 (0%)	3/3 (100%)	4/13 (30.8%)	1/5 (20%)
		Anticonvulsant treatment	–	3	3	1
		Visual impairment	0/6 (0%)	1/3 (33.3%)	4/13 (30.8%)	1/5 (20%)
		Hearing impairment	0/6 (0%)	1/3 (33.3%)	1/13 (7.7%)	0/5 (0%)
		Autoimmune encephalitis	0/6 (0%)	0/3 (0%)	1/13 (7.7%)	1/5 (20%)
		Relapse of HSV encephalitis	0/6 (0%)	0/3 (0%)	0/13 (0%)	1/5 (20%)

ADHD, attention-deficit/hyperactivity disorder; GDD, global developmental delay; HSV, herpes simplex virus; ICU, intensive care unit; IQR, interquartile range.

Most children (76.7%) presented in the first 12 months of age (neonates 12 times more at risk than older children) with only ten children older than one year. Clinician awareness of at-risk age groups may facilitate prompt and targeted empiric aciclovir use.

Whilst the investigation and management of children in this study were generally consistent with nationwide guidelines, there were some discrepancies suggesting the need for further clinician education.[10,16] One quarter of children did not undergo neuroimaging and 40% of neonates and 58% of non-neonates did not have an EEG. Distinguishing encephalitis from meningitis in children can be difficult; neuroimaging and EEG are useful adjunct tools. Four children (two neonates with unrecognised disseminated disease) with HSV CNS infection did not receive antiviral treatment; interestingly, the two non-neonates who were not treated had no adverse neurological outcome reported at discharge, possibly suggesting a more benign meningitic process akin to that described in adults.[6]

Almost 40% of children (7 neonates and 10 non-neonates) underwent an end of treatment CSF HSV PCR test. This is

Table 3 Factors associated with adverse outcome (death or neurological morbidity)

Predictors	OR for death (95% CI)	OR for neurological morbidity at discharge (95% CI)	OR for neurological morbidity at follow-up (95% CI)
Age			
<3 months	6.7 (0.7, 61.5), $P = 0.09$	0.4 (0.1, 1.4), $P = 0.15$	0.8 (0.1, 4.3), $P = 0.75$
≥3 months	0.2 (0.0, 1.4), $P = 0.09$	2.6 (0.7, 9.0), $P = 0.15$	1.3 (0.2, 7.6), $P = 0.75$
ICU admission	17.2 (2.3, –), $P = 0.03$	8.9 (2.0, 39.2), $P = 0.04$	4.9 (0.5, 48.6), $P = 0.17$
Clinical features			
Focal neurological deficits	0.8 (0.1, 4.7), $P = 0.81$	18.4 (2.1, 160.3), $P = 0.01$	1.7 (0.3, 10.8), $P = 0.59$
Status epilepticus at admission	5.4 (0.6, 49.2), $P = 0.14$	36.7 (6.5, 206.8), $P = 0.01$	24.0 (2.2, 260.3), $P = 0.01$
Encephalopathy	3.4 (0.37, 31.3), $P = 0.28$	23.0 (4.0, 131.8), $P = 0.01$	0.9 (0.1, 6.2), $P = 0.94$
Abnormal neuroimaging	2.0 (0.2, –), $P = 0.55$	39.9 (5.0, –), $P = 0.01$	11.3 (1.1, 114.4), $P = 0.04$
Abnormal EEG	1.4 (0.1, –), $P = 0.80$	30.2 (2.6, –), $P = 0.01$	1.3 (0.1, 20.7), $P = 0.84$
HSV serotype			
HSV 1	0.2 (0.0, 0.9), $P = 0.04$	0.9 (0.3, 3.2), $P = 0.86$	0.3 (0.0, 3.1), $P = 0.32$
HSV 2	6.5 (1.1, 39.1), $P = 0.04$	1.1 (0.3, 4.0), $P = 0.86$	3.2 (0.3, 32.5), $P = 0.32$

CI, confidence interval; EEG, electroencephalography; HSV, herpes simplex virus; ICU, intensive care unit; OR, odds ratio.

advocated by some clinicians to monitor response and consider longer durations of antiviral therapy if ongoing PCR positivity (particularly in neonates). Following the introduction of high dose (60 mg/kg/day) aciclovir and extension of therapy from 10 to 21 days in neonates,[17,18] it is likely that ongoing HSV PCR positivity will be unusual. In our study, two neonates (28.6%) had ongoing HSV PCR positivity despite both receiving high dose aciclovir and one having completed 21 days of therapy (the other died). Currently, there is no definitive evidence regarding the necessity of this practice.

Six (13.9%) children had a past history of HSV SEM disease, four had completed treatment for HSV SEM in the two weeks preceding HSV CNS infection. Three were less than 12 months of age and one aged 5 years. Most Australian experts will prescribe suppressive aciclovir for neonatal HSV CNS disease in keeping with Kimberlin's publication,[19] however this is not routine after other forms of neonatal HSV disease (SEM or disseminated disease without CNS disease) or outside of the neonatal period as the evidence for benefit of suppression is less clear.[19–21] None of the above-mentioned children received suppressive therapy. Almost one third of children with HSV CNS infection were prescribed follow-on aciclovir suppression therapy. Of the ten neonates who did not receive suppression therapy, 7 were diagnosed before the Kimberlin publication in 2011[19] supporting this practice. There may be a need to disseminate guidelines and educate key clinical practitioner groups to close gaps and promote best-practice management.

Despite investigators' concern that the four cases of HSV PCR detection from autopsy brain tissue samples deemed contaminants by the coroner may have represented HSV disease (particularly in the absence of an alternate diagnosis), this could not be confirmed and therefore cases were excluded. It does pose questions regarding current autopsy processes and whether there is consistency across the Australian states. Routine aseptic technique during autopsy examinations should be considered.

Clinical outcomes in HSV CNS infection are difficult to predict with recognised high rates of neurological morbidity, even with early diagnosis and prompt treatment.[6,22–24] A higher proportion of non-neonates with HSV 1 had adverse neurological sequelae compared to HSV 2. HSV 2 CNS infection has long been associated with worse outcomes in neonates despite a relatively benign meningitic process in immunocompetent adults.[25,26] The differences in neurological outcomes by serotype in neonates and non-neonates are likely a reflection of differences in pathophysiology of HSV 1 (olfactory route) versus HSV 2 infection (haematogenous route) and the fact that disseminated infection is generally confined to the neonatal period in immunocompetent children. A key finding in this study is that significant long-term neurologic sequelae can occur in children with no neurological disability identified at discharge from hospital, particularly in non-neonates. All children with HSV CNS infection should have close ongoing neuro-developmental follow-up, with recognition that defects may develop over time.[5]

A major strength of this study was the state-wide comprehensive ascertainment of cases using laboratory data from all major pathology providers in Queensland. Limitations included the retrospective, observational design of the study and retrospective application of a case definition of encephalitis. Whilst most children fulfilled the criteria for confirmed encephalitis, there were a small proportion of children who did not and could have had a more benign meningitic process. Long-term outcome data was also not available for children if their parents were uncontactable or declined participation. The parent survey used to assess long term outcomes was devised by the members of the study team with simple dichotomous answers to a set of defined qualitative outcomes. Further studies are required to confirm the findings from this study using validated tools to assess neurodevelopmental outcomes. Timing of parent questionnaire ranged from 1 to 7 years following initial infection.

Conclusion

Young children less than 12 months, particularly neonates are most at risk of HSV CNS infection. HSV 2 was associated with

worse neurological outcomes in neonates and HSV 1 in non-neonates. CNS infection is associated with long-term neurologic sequelae even in children with no neurological disability identified at discharge from hospital. Careful neurodevelopmental follow-up of all children is recommended.

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Supporting Information

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Appendix S1 Supporting Information