Outcomes beyond hospital discharge in infants and children with viral meningitis: a systematic review

Jessica A. Hudson, MRCPCH¹; Jonathan Broad, MRCPCH²; Natalie G. Martin DPhil^{2, 3}; Manish Sadarangani, DPhil^{2,4}; Dominic F. Kelly, PhD²; Andrew J. Pollard, FMedSci²; Seilesh Kadambari, PhD²

Author Affiliations: ¹ Department of Public Health, John Radcliffe Hospital, Oxford. ² Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, Oxford, ³Department of Paediatrics, Christchurch School of Medicine, University of Otago, New Zealand ⁴ Vaccine Evaluation Center, BC Children’s Hospital Research Institute, University of British Columbia, Vancouver BC, Canada

BACKGROUND

Viral meningitis is common however the longterm management is inconsistent. In a recent British study only 38-46% patients received any follow-up during the 12 months after hospital discharge.

METHODS

- Medline, Embase, clinicaltrials.gov, Cochrane review were searched for studies from 1990 to December 2017.
- Search terms used were ‘viral meningitis’ OR specific viruses AND meningitis AND terms for outcomes such as ‘hearing’ AND terms for child or neonate.

Inclusion criteria	Exclusion criteria
•Human studies •Children 0-16 years •Confirmed viral meningitis •Defined outcome beyond hospital discharge .	•Encephalitis or meningoencephalitis •Case reports and conference abstracts

Viral meningitis defined by a clinical diagnosis of meningitis and either CSF positive for a specific virus on culture or PCR, or CSF lymphocytosis with virus identified from any site by PCR, culture or antibody titres.

Results: Study flowchart (PRISMA)

Results: Outcomes post hospital discharge following viral meningitis for all studies meeting inclusion criteria

Study	Virus	Age at time of infection	Follow-up timing	Hearing	Speech & language	Motor	Cognition	Behavior	Seizures	Other
Baker et al 1996	EV	Infants <90 days (n= 16 and 13 controls)	Annual evaluation for 3 years	No deficits	Subtle deficits in receptive language	No deficit in Bayley assessment		N/A	N/A	No growth deficit
Biaukula et al 2011	EV	1 month - < 5 years (n=12)	6-8 weeks and 1 year post discharge	Sensorineural deafness in 2/8 who had audiometry	N/A	Normal neurological examination in all cases	N/A	N/A	N/A	Mean PaedQL score 93.4 (95% CI 82.2–104.5)
Balasubramanian et al 2016	EV	Neonates >32 weeks gestation (n=33)	1 year of age	N/A	N/A	Cerebral palsy in 1 infant	Median GQ 98.5 (SD 7.1). Not significantly different from population mean (p = 0.27)	N/A	¹ Seizure in one infant	Growth comparable to birth centiles. Hydrocephalus and VP shunt in one infant
Chang et al 2007	EV71	0.1 - 7.7 years (n=61)	1-7.4 years post infection	N/A	No delay in language development	No delay in gross or fine motor development	Mean IQ 99±12 (WISC-III). 13% full scale IQ < 85	ADHD diagnosed in 2	No seizures	N/A
Gau et al 2007	EV71	0 days-12.6 years (n=42 and 172 controls)	3-7 years after infection	N/A	N/A	No neurological sequelae	N/A	Increased risk of ADHD compared to controls	N/A	N/A
Hu et al 2015	EV71	6 months - 11 years 8 months (n=74)	2-6 months post discharge	N/A	N/A	N/A	Wechsler intelligence test or Gesell Scale comparable to children of same age	N/A	N/A	N/A
Robin et al, 2008	Chikungunya virus	6 months - 12 years (n=3)	6 months post discharge	N/A	N/A	1 Ex 27/40 preterm had mild hypertonia lower limbs	N/A	N/A	N/A	N/A
Hristeva et al 1993	Echovirus Coxsackie Other	Neonates < 28 days old (n=6)	3 months to 3 years	Normal	Normal	N/A	N/A	N/A	No seizures	N/A
Rorabaugh et al, 1993	Coxsackie Echovirus Other	Under 2 years (n=216)	1 month after onset 18 months old 30 months old 42 months old	N/A	N/A	No significant difference in development on Bayley scale and Kaufmann assessment		N/A	N/A	N/A
Bao et al 2012	Coxsackie (n=4) Influenza EV	2 days - 11 years 8 months (n=6)	9 days - 18 months post discharge	1 child with coxsackie virus mild BAEP impairment	N/A	N/A	N/A	N/A	N/A	N/A

References

1. Biaukula VL, Tikoduadua L, Azzopardi K, et al. Meningitis in children in Fiji: etiology, epidemiology, and neurological sequelae. *International Journal of Infectious Diseases*.16:e289–e295.
2. Hristeva L, Booy R, Bowler I, et al. Prospective surveillance of neonatal meningitis. *Arch Dis Child*. 1993;69:14-18.
3. Rorabaugh ML, Berlin LE, Heldrich F, et al. Aseptic Meningitis in Infants Younger Than 2 Years of Age: Acute Illness and Neurologic Complications. *Pediatrics*. 1993;92:206-211.
4. Baker RC, Kummer AW, Schultz JR, et al. Neurodevelopmental Outcome of Infants with Viral Meningitis in the First Three Months of Life. *Clinical Pediatrics*. 1996;35:295-301.
5. Bao X, Wong V. Brainstem auditory-evoked potential evaluation in children with meningitis. *Pediatric Neurology*. 1998;19:109-112.
6. Chang L-Y, Huang L-M, Gau SS-F, et al. Neurodevelopment and Cognition in Children after Enterovirus 71 Infection. *New England Journal of Medicine*. 2007;356:1226-1234.
7. Gau SS-F, Chang L-Y, Huang L-M, et al. Attention-Deficit/Hyperactivity–Related Symptoms Among Children With Enterovirus 71 Infection of the Central Nervous System. *Pediatrics*. 2008;122:e452–e458.
8. Robin S, Ramful D, Le Seach F, et al. Neurologic manifestations of pediatric chikungunya infection. *Journal of child neurology*. 2008;23:1028-1035.
9. Hu Y, Jiang L, Peng H-I. Clinical Analysis of 134 Children with Nervous System Damage Caused by Enterovirus 71 Infection. *The Pediatric Infectious Disease Journal*. 2015;34:718-723.
10. Balasubramanian H, Wagh D, Rao S, et al. Developmental outcomes in cerebrospinal fluid proven enteroviral meningitis in neonates>32weeks of gestation. *Journal of Paediatrics and Child Health*. 2016;52:327-332.

Conclusions

- Generally favourable outcomes with limited long term sequelae
- Some effects seen on: language, hearing and behaviour
- Long-term neurodevelopment studies are warranted