Title: High prevalence of developmental concern amongst infants 12-months following hospitalized parechovirus infection

Authors: Philip N Britton^{*1,2}, Gulam Khandaker^{*1}, Ameneh Khatami², Suzy Teutsch¹, Stephanie Francis³, Brendan McMullan³, Cheryl A Jones^{1,2}

*These authors contributed equally to the manuscript.

Affiliations:

1. Marie Bashir Institute of Infectious Diseases and Biosecurity, University of Sydney;
2. The Children's Hospital at Westmead;
3. Sydney Children's Hospital, Randwick, New South Wales, Australia.

Address for correspondence:

Dr Philip Britton
C/o Discipline of Paediatrics and Child Health
The Children's Hospital at Westmead
Locked Bag 4001, Westmead
NSW Australia 2145 Email: philip.britton@health.nsw.gov.au

Short title: 12-month outcome following parechovirus infection

Word count: 2535

Key Words: central nervous system, infant, newborn, outcome, development.

Funding Source:

NHMRC post-graduate scholarship (1074547), the Royal Australasian College of Physicians (RACP) NHMRC Award for Excellence, and Norah Therese Hayes-Ratcliffe/Sydney Medical School Dean's paediatric infectious diseases fellowship to PB;
NHMRC Health Early Career Fellowship (1054414) to GK;
NHMRC Centre for Research Excellence Grant (1001021) to CJ.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/jpc.13728](https://doi.org/10.1111/jpc.13728)

Figure 1 - ASQ3 bar graph low res.tif

Figure 2 - LOS pie chart low res.tif

Title: High prevalence of developmental concern amongst infants 12-months following hospitalized parechovirus infection

Abstract:

Aim:

Human parechovirus (HPeV) is an increasingly recognised cause of sepsis and central nervous system (CNS) infection in young infants for which there are limited long-term outcome data. We aimed to assess neuro-developmental outcome and quality of life in infants following hospitalized HPeV infection.

Methods:

Cohort study: 12-month follow-up of infants who were hospitalized with confirmed HPeV infection to the Sydney Children's Hospitals Network during an outbreak in Sydney in 2013. Telephone interviews with parents/guardians. We administered standardised questionnaires including: Ages and Stages questionnaire (ASQ), Liverpool Outcome Score-follow-up (LOS-f/up), Pediatric Quality of Life Inventory Infant scales (PEDS-QL), and Short-Form health survey (SF-12).

Results:

We followed up 46 of 79 infants (58%) aged between 12 and 16 months who had been hospitalized with HPeV infection; 19% showed significant concern in developmental attainment (ASQ3 scored <2 SD below population mean); 50% showed some concern (<1 SD below mean). ASQ3 developmental outcome was associated with presence of neuro-developmental sequelae (lower total LOS score), and poorer health-related quality of life (HRQOL) in physical functioning (Peds QL physical component score), but not overall HRQOL (total Peds QL score), or parental HRQOL (SF-12 scores). No significant associations were identified between clinical or laboratory features during acute hospitalisation and adverse outcome on ASQ3.

Conclusions:

A high proportion of infants show developmental concern at 12-month follow-up post-hospitalization with HPeV infection. Clinical features during hospitalisation did not associate with adverse outcomes at 12 months. These results suggest that careful follow-up is required for young infants hospitalized with HPeV disease may be warranted..

Key Words: Parechovirus, central nervous system, infant, newborn, outcome, development.

Abbreviations:

ASQ=Ages and Stages questionnaire; CNS=central nervous system; CSF=cerebro-spinal fluid; cUS=cranial ultrasound; EEG=electro-encephalogram; HPeV=human parechovirus; HRQOL=health-related quality of life; MRI=magnetic resonance imaging; SD=standard deviation

39 **'What is already known on this topic'**

- 40 • Human parechovirus (HPeV) is an increasingly recognised cause of sepsis and central nervous
41 system (CNS) infection in young children.
42 • HPeV encephalitis, the most severe form of HPeV CNS disease, can result in significant
43 neurological morbidity including cerebral palsy and epilepsy.

44 **'What this paper adds'**

- 45 • This is the first study to systematically study the outcome of hospitalised HPeV infection in
46 infants using standardised outcome measures.
47 • A high proportion infants aged 12-16 months 12 months following hospitalized HPeV infection
48 had concerns identified in development; one fifth with significant concern (developmental
49 attainment $\leq$ 2SD below the population mean). Significant concern was most frequently
50 identified in gross-motor and problem-solving domains.
51 • No specific clinical or diagnostic features during acute hospitalisation were associated with
52 developmental outcome, although the majority of children did not have adequate neurological
53 testing to categorise the nature of their central nervous system infection.

Introduction:

Human parechovirus genotype 3 (HPeV 3) is an increasingly recognised cause of sepsis and central nervous system (CNS) infection in young children (1-4). Despite a number of publications describing the frequency and clinical features of HPeV 3 infection (1-7), there are limited outcome data reported. A number of authors suggest a good outcome (2, 6, 8, 9); however this is based primarily on clinician reports at discharge without the use of standardised measures. We and others have reported a high prevalence of neurological morbidity in survivors of infant HPeV encephalitis (10, 11), which represents the most severe form of HPeV CNS disease. However the outcome of all forms of HPeV 3 infection causing hospitalisation in infants is poorly defined. Although HPeV can be detected in the cerebro-spinal fluid (CSF) in many hospitalised infants, the nature of the CNS infection is difficult to characterize due to challenges in to applying encephalitis case definitions in this age group (7, 12, 13), in particular because of the non-specific features of encephalopathy, the low frequency of comprehensive testing (neuroimaging, electro-encephalograms-EEG) and the characteristic lack of CSF pleocytosis (11, 14). Studying the long term outcome of the all forms of hospitalized HPeV infection (severe HPeV disease) is therefore important.

An outbreak of HPeV3 infection occurred in the southern hemisphere Spring/Summer of 2013-14 in New South Wales, Australia, causing a large number of infants to be hospitalized (15). The majority of infants in this series were admitted to one of the two hospitals in the Sydney Children's Hospitals Network (SCHN), the Children's Hospital at Westmead (CHW) or Sydney Children's Hospital (SCH), Randwick. Here we sought to assess the developmental progress, quality of life, and neurological function of these infants at 12 months following their admission to hospital with HPeV disease.

Methods:

Participants:

Between December 2014 and February 2015, we contacted the parents/guardians of the 79 infants from the series reported by Khatami *et al.*(12) who were admitted to the SCHN between October

2013 and January 2014 with laboratory proven HPeV infection (HPeV RNA detected by reverse transcription polymerase chain reaction (RT-PCR) from any acute specimen). Questionnaires were sent to parents/guardians and then completed with one of the study investigators in a telephone interview. Telephone interviews were undertaken to maximise participant response rate. Interviewers ensured questionnaire completion. Where parents sought question clarification, interviewers were instructed to not provide their own interpretation, repeat questions verbatim, and encourage parents to give “their response”. Clinical data from the acute hospital admission were collected by retrospective chart review of included infants, and have been previously reported (12). A sub-set of these acute variables was selected for this outcome analysis, decided upon by the study investigators (Table 2). To facilitate analysis continuous variables (e.g. fever, liver function tests) were categorised as dichotomous.

Outcome measures:

The primary outcome measure was developmental outcome at 12 months post-discharge using the age-appropriate Ages and Stages questionnaire Version 3 (ASQ3; <http://agesandstages.com/>). ASQ3 is a series of 21 developmental screening questionnaires completed by parents/guardians of children aged between 1 to 66 months (each questionnaire covers between one and six months) to determine the level of developmental attainment. The questions are stratified into five domains including: communication, gross motor, fine motor, problem-solving, and adaptive skills. An additional section assesses the overall health and development of the child. Questionnaire results were scored by two study investigators (PB and GK) using the ASQ3 age-specific scoring sheet. We categorised the ASQ3 responses as ‘Significant’, ‘Some’ or ‘No’ developmental concern according to questionnaire defined sub-scale cut-off scores (quantitative results: ‘Significant’ concern corresponds to the ASQ cut-off set at >2 standard deviations (SD) below the population mean of developmental attainment; ‘Some’ concern corresponds to the cut-off set at >1 SD and ≤ 2 SD). Where concern regarding developmental attainment was identified in the overall responses section

of the ASQ (qualitative results), the response was categorised as 'Some concern'. Where the parents only expressed concerns about health issues not directly relevant to developmental attainment (e.g. recurrent infections) these were not categorised as 'Some' concern.

During the telephone interview, we also administered the: the Liverpool Outcome Score-follow-up (LOS-f/up 2013), the Pediatric Quality of Life Inventory Infant scales (PEDS-QL infant; <http://www.pedsql.org/>), and the Short-Form health survey (SF-12). Results from these scores were our secondary outcome measures. The LOS-f/up is a 15 item questionnaire that assesses neurological function in children following encephalitis (<http://www.path.org/vaccineresources/details.php?i=677>) (16, 17). For each item the child is assigned a score out of 5. The LOS can be reported as a total score out of 75, or alternatively a summary score assigned as the lowest score for any single item. We categorised the LOS f/up summary scores as: 1-2 = severe neurological sequelae; 3-4 = mild-moderate sequelae; 5 = nil sequelae. The PEDS-QL infant is an age-specific generic questionnaire (<http://www.pedsql.org/>) designed to measure health-related quality of life (HRQOL) in children aged between 13 and 24 months. It assesses the presence/frequency of stated "problems" in five dimensions (physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning) on a five-point Likert scale. The PEDS-QL responses are assigned three scores out of 100: a total health score, a psycho-social health score and a physical health score. A higher score indicates better HRQOL. The SF-12 is a 12-item questionnaire that assesses HRQOL amongst adults; here the parents/guardians of the infants followed up for this study. It is scored online (at: <http://www.sf-36.org/demos/SF-12.html>) giving a quantitative measure of HRQOL in two dimensions: the physical-component score (PCS) and the mental component score (MCS). Scores range from 0 to 100 with a higher score indicating a higher HRQOL.

Analysis:

We analysed the results of the outcome questionnaires descriptively, and stratified the results of the LOS-f/up, PEDS-QL, and SF-12 questionnaires by the ASQ3 results. We performed a univariate comparison of the acute clinical features of the infants according to their 12 month outcome determined using the ASQ3. Data were analyzed using Microsoft™ Excel™, 2010 and SPSS™ v22, 2014 (SPSS Inc, Chicago, Illinois).

Approval for this study was obtained from the SCHN Human Research Ethics Committee (approval number 13/SCHN/191).

Results:

Seventy nine infants were admitted to hospitals in the SCHN with confirmed HPeV infection during the 2013/2014 outbreak. Follow up was complete on 42 infants, including 26 from CHW and 16 from SCH. Partially completed ASQ3 questionnaire responses were received from an additional four.

There were no deaths reported between discharge from hospital and follow-up. The primary reason for loss to follow-up was inability to contact the parent/guardian of potential participants.

To determine if the infants in the follow up cohort were representative of the complete study cohort, we compared the acute clinical features of those children with follow-up data available to those we were unable to follow-up. We found no statistically significant differences between the two groups in the frequency of key demographic and clinical features (Supplementary table). There were trends to a higher proportion of females in the follow-up cohort (57% vs. 36% not f/up; p-value=0.08) and a higher proportion of children in whom neuro-imaging was performed (cranial ultrasound 23% vs. 9% not f/up (p=0.09); MRI brain 15% vs. 3% (p=0.08). This cohort includes four infants with confirmed HPeV encephalitis that have been recruited into a prospective, cohort study for childhood encephalitis study (the Australian Childhood Encephalitis study). Their 12 month outcomes (ASQ and clinical) have been already reported (11). To our knowledge, none of the infants had received formal developmental assessment at the time of our follow-up telephone interviews.

152 Amongst the infants with complete ASQ3 questionnaires, all 42 children were diagnosed during their
153 acute admission with a 'sepsis-like' illness. On retrospective review, five children would meet the
154 case definition (18) for a diagnosis of encephalitis (two of: seizures, abnormal EEG or abnormal MRI).
155 Of the remaining 37 children, none had an EEG performed and in five an MRI was performed that
156 was reported to be normal or with minor non-specific findings.

157 We identified concerns with developmental attainment in 50% (21/42); 19% (8/42) of whom showed
158 significant concern and a further 31% (13/42) showed some concern (Figure 1). Where significant
159 concern was identified, it was most frequent in the gross-motor (5/42; 12%) and problem-solving
160 (3/42; 7%) domains. In the eight infants showing significant concern, only one had required further
161 hospitalisation (this was due to a subsequent enterovirus meningitis); five showed significant or
162 some concern in two or more domains; and seven qualitative concern in one or more areas (gross-
163 motor, hearing, behaviour, staring episodes). Of importance, seven of these eight infants with
164 significant concern had been assessed as being without neurological sequelae at discharge or at
165 short-term follow-up. For the remaining infant, there was no information available regarding short-
166 term outcome. Of the five children who would meet a case definition for encephalitis, three showed
167 developmental concern at 12 months; one with significant concern, two with some concern. Four
168 infants showed qualitative concern in the overall response section of the ASQ3, but did not show any
169 developmental concern in the quantitative results (developmental domain sub-scales).

170 Using the LOS-f/up questionnaire, 39% (17/44) of infants followed up showed some neurological
171 sequelae; two infants with severe neurological sequelae identified in individual LOS questions (gross-
172 motor function) and fifteen with mild-moderate sequelae (communication, motor function and
173 behaviour)(Figure 2). None of the infants had ongoing seizures.

174 In Table 1 we show the LOS-f/up, PEDS-QL infant and SF-12 scores stratified by the results of the
175 ASQ3. Infants with developmental concern identified on ASQ3 had significantly lower mean LOS f/up
176 total score, and mean PEDS-QL physical component score compared to those without any

developmental concern. We observed no association between ASQ3 scores and mean SF-12 results or mean PEDS-QL psycho-social component and total scores.

Table 2 shows the univariate comparison of the available acute clinical and diagnostic features of infants hospitalized with HPeV infection according to their 12 month outcome determined using the ASQ3. We did not identify any acute clinical variable that was associated with adverse developmental outcome. A trend to increased length of hospital stay was noted in infants with significant concerns identified by ASQ3.

Discussion:

This is the first study to systematically report the long-term outcome of severe HPeV infection causing hospitalization. We have measured neuro-developmental outcomes and health-related quality of life using validated, standardised tools and identified that a high proportion of infants showed developmental concern at 1 year follow-up post-hospitalization when aged between 12 and 16 months; half of the infants show some concern, and one fifth significant concern. We have shown that the concern regarding developmental attainment is most prominent in the gross-motor and problem-solving domains. We have also demonstrated that these findings correspond to the presence of neuro-developmental sequelae as measured using the Liverpool outcome score, and a poorer health-related quality of life (HRQOL) in terms of physical functioning/symptoms measured using the PEDS-QL infant scales. However, we were unable to identify any acute clinical or diagnostic features from these children's original hospitalization that was associated with these outcomes, although we did note a trend towards longer total length of stay in hospital amongst infants with significant developmental concern. A probable explanation for this is that acute clinical data were collected retrospectively and we were unable to collect all potentially relevant clinical and diagnostic information, and some important investigations (e.g. MRI) were not performed on most infants. We were surprised not to identify neuroimaging markers in the acute admission that would predict adverse outcome because previous studies - including from our own study of childhood encephalitis

(ACE study) – have suggested that neuro-imaging (MRI) changes correspond with neurological morbidity (10, 11, 19). Amongst our cohort, MRI was performed infrequently (7/42), although HPeV was identified from the cerebro-spinal fluid in the majority (91%; 31/34 tested). Cranial US was performed more often (11/42), however we have shown that this modality can be normal even in children with significant brain MRI abnormalities (11). Cases of HPeV infection have been described where full recovery has been described despite acute MRI abnormalities, however these cases have not been assessed using standardised outcome measures (2). A further concern is that many infants in our cohort with significant concern in neuro-development had been previously described as having ‘recovered fully’. Given the possible importance of MRI findings in identifying infants with HPeV CNS infection at risk of adverse neuro-developmental outcome (10, 11, 19), we suggest that a low threshold be adopted for the performance of MRI in infants with severe hospitalized HPeV disease (19). Given the absence of any acute clinical features associated with outcome in this study, we cannot give a definitive threshold to guide clinicians further. However, additional clinical factors of potential concern from the literature include: very young children (aged <4 weeks), ex-prematurity, seizures, other end-organ disease (10, 11, 19).

Our findings suggest that severe HPeV infection that requires hospitalization may result in an adverse motor development. We have reported that children with confirmed HPeV encephalitis in early life may go on to develop cerebral palsy (CP) (11). Furthermore, the characteristic MRI imaging in this condition is of symmetrical white matter diffusion restriction (2, 4, 10, 11, 20, 21) + vergnano. We, and others, have noted the overlap of these features with those associated with hypoxic-ischaemic injury in neonates who are at high risk of cerebral palsy (11, 22). A further important contribution is the recently published autopsy findings from two cases of fatal parechovirus encephalitis (23). These show localisation of HPeV3 to meningeal cells and blood vessels in the meninges and lung, but not to brain parenchyma using *in situ* hybridisation (23). The authors have suggested that CNS tissue damage may result from dysfunction of infected blood vasculature resulting in impaired blood flow, and hypothesised that other organ dysfunction in severe

parechovirus infection might similarly be a result of a systemic vasculopathy (23). The pathogenesis of HPeV CNS infection requires further elucidation, however we suggest that the possible outcome phenotype identified in this study would concur with a vasculopathic process causing localised hypoxic-ischaemic injury.

We acknowledge some inherent limitations in this study. Firstly, the ASQ is designed as a developmental screening tool. The ASQ's own validation data shows a sensitivity and specificity of 86.1% and 85.6% respectively compared to more definitive developmental assessment. It is possible some of these children have been misclassified as a result of using the ASQ. Secondly, the LOS at follow-up questionnaire has been used in this cohort at the lower end of the age range in which it has been previously used and validated. Furthermore, the age at which developmental attainment has been assessed in this cohort is still young (12-16 months). Definitive developmental outcome in these children cannot be inferred from this assessment because of their young age. In addition, our study had a 42% loss to follow-up. This poses a possible "selection bias" to our findings, although we would again note that we found no significant differences in collected data between those followed up and not followed-up. These limitations should result in some caution when interpreting the results of this study, in particular with regard to the absolute proportions of infants with developmental concern and adverse neurological outcomes. We would, however, emphasise that the findings presented here are sufficient to conclude that it cannot be assumed that hospitalised HPeV infection in infants is associated with a benign neurodevelopmental outcome. Clearly there is a need for ongoing follow-up of this cohort to address the remaining knowledge gaps and to facilitate early intervention where required. Ideally, we would advocate that assessment occur between the ages of three and five years, using a comprehensive developmental assessment tool (e.g. Bayley Scales of Infant and Toddler Development or Griffith Mental Development Scales) and inclusion of a control group.

In conclusion, we have presented the 12-month outcome of infants hospitalized with hospitalized parechovirus infection from Sydney, Australia. We have identified a high prevalence of adverse developmental outcome amongst these infants. These results remain preliminary; however pending future research, they support a precautionary approach to the follow-up of infants admitted to hospital with severe parechovirus disease. We recommend careful follow-up with a clinician experienced in child development until, at least, school entry. Where concern is identified or expressed, a low threshold should be adopted for referral for paediatric assessment.

Acknowledgements:

The authors would like to thank Associate Professor Karen Walker for her review of this manuscript and helpful comments.

References:

1. Benschop KS, Schinkel J, Minnaar RP, Pajkrt D, Spanjerberg L, Kraakman HC, et al. Human parechovirus infections in Dutch children and the association between serotype and disease severity. *Clin Infect Dis*. 2006;42(2):204-10.
2. Skram MK, Skanke LH, Krokstad S, Nordbo SA, Nietsch L, Dollner H. Severe parechovirus infection in Norwegian infants. *Pediatr Infect Dis J*. 2014;33(12):1222-5.
3. Kolehmainen P, Jaaskelainen A, Blomqvist S, Kallio-Kokko H, Nuolivirta K, Helminen M, et al. Human parechovirus type 3 and 4 associated with severe infections in young children. *Pediatr Infect Dis J*. 2014;33(11):1109-13.
4. Felsenstein S, Yang S, Eubanks N, Sobrera E, Grimm JP, Aldrovandi G. Human parechovirus central nervous system infections in southern California children. *Pediatr Infect Dis J*. 2014;33(4):e87-91.
5. Piralla A, Mariani B, Stronati M, Marone P, Baldanti F. Human enterovirus and parechovirus infections in newborns with sepsis-like illness and neurological disorders. *Early human development*. 2014;90 Suppl 1:S75-7.
6. Levorson RE, Jantausch BA, Wiedermann BL, Spiegel HM, Campos JM. Human parechovirus-3 infection: emerging pathogen in neonatal sepsis. *Pediatr Infect Dis J*. 2009;28(6):545-7.
7. Harvala H, Robertson I, Chieochansin T, McWilliam Leitch EC, Templeton K, Simmonds P. Specific association of human parechovirus type 3 with sepsis and fever in young infants, as identified by direct typing of cerebrospinal fluid samples. *J Infect Dis*. 2009;199(12):1753-60.
8. Walters B, Penaranda S, Nix WA, Oberste MS, Todd KM, Katz BZ, et al. Detection of human parechovirus (HPEV)-3 in spinal fluid specimens from pediatric patients in the Chicago area. *J Clin Virol*. 2011;52(3):187-91.
9. Sharp J, Harrison CJ, Puckett K, Selvaraju SB, Penaranda S, Nix WA, et al. Characteristics of young infants in whom human parechovirus, enterovirus or neither were detected in cerebrospinal fluid during sepsis evaluations. *Pediatr Infect Dis J*. 2013;32(3):213-6.
10. Verboon-Macielek MA, Groenendaal F, Hahn CD, Hellmann J, van Loon AM, Boivin G, et al. Human parechovirus causes encephalitis with white matter injury in neonates. *Ann Neurol*. 2008;64(3):266-73.
11. Britton PN, Dale RC, Nissen MD, Crawford N, Elliot E, Macartney K, et al. Parechovirus Encephalitis and Neurodevelopmental Outcomes. *Pediatrics*. 2016.
12. Khatami A, McMullan BJ, Webber M, Stewart P, Francis S, Timmers KJ, et al. Sepsis-like Disease in Infants Due to Human Parechovirus Type 3 During an Outbreak in Australia. *Clin Infect Dis*. 2015;60(2):228-36.
13. Harvala H, Griffiths M, Solomon T, Simmonds P. Distinct systemic and central nervous system disease patterns in enterovirus and parechovirus infected children. *J Infect*. 2014;69(1):69-74.
14. Britton PN, Dale RC, Elliott E, Festa M, Macartney K, Booy R, et al. Pilot surveillance for childhood encephalitis in Australia using the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. *Epidemiol Infect*. 2016:1-11.
15. Cumming G KA, McMullan BJ, Musto J, Leung K, Nguyen O, Ferson MJ, Papadakis G, and Sheppeard V. Parechovirus genotype 3 outbreak among infants, New South Wales, Australia, 2013–2014. *Emerg Infect Dis*. 2015.
16. Lewthwaite P, Begum A, Ooi MH, Faragher B, Lai BF, Sandaradura I, et al. Disability after encephalitis: development and validation of a new outcome score. *Bull World Health Organ*. 2010;88(8):584-92.
17. Pillai SC, Hachon Y, Tantsis E, Prelog K, Merheb V, Kesson A, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics*. 2015;135(4):e974-84.

18. Venkatesan A, Tunkel AR, Bloch KC, Luring AS, Sejvar J, Bitnun A, et al. Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium. *Clin Infect Dis*. 2013.
19. Vergnano S, Kadambari S, Whalley K, Menson EN, Martinez-Alier N, Cooper M, et al. Characteristics and outcomes of human parechovirus infection in infants (2008-2012). *European journal of pediatrics*. 2015;174(7):919-24.
20. Gupta S, Fernandez D, Siddiqui A, Tong WC, Pohl K, Jungbluth H. Extensive white matter abnormalities associated with neonatal Parechovirus (HPeV) infection. *Europ J Paediatr Neurol*. 2010;14(6):531-4.
21. Belcastro V, Bini P, Barachetti R, Barbarini M. Teaching neuroimages: neonatal parechovirus encephalitis: typical MRI findings. *Neurology*. 2014;82(3):e23.
22. Volpe JJ. Neonatal encephalitis and white matter injury: more than just inflammation? *Ann Neurol*. 2008;64(3):232-6.
23. Bissel SJ, Auer RN, Chiang CH, Kofler J, Murdoch GH, Nix WA, et al. Human Parechovirus 3 Meningitis and Fatal Leukoencephalopathy. *Journal of neuropathology and experimental neurology*. 2015;74(8):767-77.

Figure Legends:

Figure 1: Developmental outcome assessed using the Ages and Stages questionnaire (ASQ3) in infants 12 months following hospitalization with severe human parechovirus (HPeV) infection. Shown is a bar graph of the total score and sub-scale scores of ASQ3 indicating no concern, some concern (1-2 SD) or significant concern (<2SD) (n=42).

Figure 2: Neurological sequelae assessed using the Liverpool Outcome Score (LOS) in infants 12 months following hospitalization with severe human parechovirus (HPeV) infection. Pie Chart shows proportion of infants with severe (LOS=2), moderate (LOS=3), mild (LOS=4) or nil/minor (LOS=5) sequelae (n=44).

Table 1: Univariate comparison of total Liverpool Outcome Scores (LOS), infant and parent/guardian health-related quality of life (Peds QL; SF12) with developmental attainment as determined using Ages and Stages questionnaire (ASQ3) in infants 12 months hospitalization following severe HPeV infection.

	ASQ Nil concern N=21	ASQ Some concern N=13	ASQ Sig. concern N=8	P value (ASQ concern vs. no concern)	P value (ASQ Sig. concern vs. no concern)
LOS total Mean score (SD)	74.5 (0.98))	73.9 (1.75)	72.8 (2.12)	0.033	0.004
PedsQL Mean score (SD)					
Total score	90.5 (9.61)	89.2 (7.46)	87.4 (8.21)	0.46	0.43
Physical component score	94.8 (5.33)	91.3 (7.20)	90.8 (4.78)	0.042	0.071
Psychological component score	87.8 (12.95)	87.7 (8.67)	84.9 (12.15)	0.74	0.59
SF12 Mean score (SD)					
PCS	56.2 (2.64)	54.4 (5.46)	56.3 (4.69)	0.42	0.93
MCS	54.4 (5.61)	55.5 (8.07)	52.5 (9.77)	1.00	0.52

*Student t-test.

Abbreviations: ASQ=Ages and Stages Questionnaire, LOS=Liverpool Outcome score, MCS=Mental Health Composite Scale, PCS=Physical Health Composite Scale, PedsQL=Pediatric Quality of Life Inventory-Infant scales, Sig.=significant, SD=standard deviation. vs.=versus.

Table 2: Univariate comparison of the clinical and diagnostic features during acute admission with parechovirus infection with developmental attainment determined using the Ages and Stages Questionnaire (ASQ3) 12 months following admission.

	ASQ Nil concern (N=21)	ASQ Some concern (N=13)	ASQ Significant concern (N=8)	p-value (ASQ concern vs. no concern)	p-value (ASQ Sig concern vs. no concern)
Demographics*					
Mean age in days (SD)^	41.5(30.86)	44.9 (28.79)	42.0 (17.26)	0.79	0.96
Age <14 days	4 (19)	3 (23)	1 (13)	1.0	1.00
Age 14-28 days	5 (24)	1 (8)	2 (25)	0.70	1.00
Age >28 days	12 (57)	9 (69)	5 (63)	0.75	1.00
Female sex	12 (57)	7 (54)	5 (63)	1.00	0.79
Clinical features					
Fever (>39.5°C)	9 (43)	4 (33)	4 (57)	0.96	0.51
Rash	13 (62)	9 (69)	6 (86)	0.37	0.24
Irritability	21 (100)	12 (92)	7 (88)	0.15	0.10
Lethargy	7 (33)	7 (54)	3 (38)	0.24	0.83
Poor perfusion	13 (62)	11 (85)	4 (50)	0.51	0.56
Oedema	2 (10)	1 (8)	1 (13)	1.00	0.81
Seizures	2 (10)	1 (8)	1 (13)	1.00	0.81
Myoclonic jerks	2 (10)	1 (8)	0 (0)	0.55	0.37
Diagnostic features					
CSF pleocytosis	3 (15)	3 (23)	0 (0)	0.95	0.26
CSF parechovirus PCR positive [#]	14 (67)	9 (69)	5 (63)	1.00	0.55
Coagulopathy	5 (56)	2 (40)	1 (50)	0.61	0.89
Hepatitis [¶]	7 (44)	6 (50)	3 (60)	0.60	0.53
Low albumin	5 (31)	3 (25)	2 (33)	0.82	0.93
Head ultrasound scan abnormal/scan done	0/6 (0)	2/4 (50)	0/1 (0)	-	-
MRI scan abnormal/scan done	1/2 (50)	1/4 (25)	1/1 (100)	-	-
EEG abnormal/EEG done	1/2 (50)	1/1 (100)	1/1 (100)	-	-
Treatment and Severity					
Intravenous analgesia	6 (29)	3 (25)	1 (13)	0.52	0.37
Significant respiratory support [†]	2 (10)	3 (23)	1 (14)	0.38	0.76
Mean total length of stay in days (SD)	4.8 (2.14)	5.8 (1.95)	6.5 (2.78)	0.06	0.083
ICU admission	7 (35)	4 (31)	3 (43)	1.00	0.71

*All results reported as number of cases (percentage) unless otherwise specified. #Coagulopathy defined as an elevated international normalised ratio (INR).

^ There were three cases of late prematurity in this cohort: one 36 weeks gestation at birth – ‘significant concern’ at follow-up; one 35 weeks- ‘some concern’ at follow-up; one 33 weeks - ‘some concern’ at follow-up). All were assessed using age-appropriate ASQ even when corrected for premature birth.

¶Hepatitis defined as an AST or ALT ≥ two times the upper limit of normal. †Significant respiratory support defined as requirement for mechanical ventilation or non-invasive respiratory support including continuous positive airway pressure (CPAP).

HPeV was identified from cerebro-spinal fluid (CSF) in 28 (67%); 12 infants did not have CSF tested for HPeV; only two infants were tested and were negative. HPeV was identified from stool or rectal swab in 26 (62%), including 12 (29%) infants in whom CSF was not tested or was negative. HPeV RT-PCR was identified from naso-pharyngeal aspirate or throat swab in four (10%), including three infants in whom CSF was not tested or was negative. RT-PCR for HPeV was not performed on blood in any children.

Appendices:

Supplementary Table for editorial review: Univariate comparison of the clinical and diagnostic features of parechovirus infection during acute admission of the children followed-up compared with those not followed-up.

	Follow up done (n=46)	Not done (n=33)	P value*
Mean Age (median)	42.0 (38.5)	41.9 (32)	1.00
Sex (Female)	26 (57%)	12 (36%)	0.08
Sex (Male)	20 (44%)	21(64%)	
Fever (>39.5°C)	19 (43%)	14 (44%)	0.96
Seizure	4 (9%)	2 (6%)	0.66
Mean total length of stay in days (median)	5.5 (5)	5.0 (5)	0.34
ICU admission	15 (34%)	12 (36%)	0.84
Head ultrasound scan done	11(24%)	3 (9%)	0.09
Head ultrasound scan result equivocal/abnormal	2 (18%)	0 (0%)	0.43
MRI scan done	7 (15%)	1 (3%)	0.08
MRI scan result abnormal	3 (43%)	1 (100%)	0.29

*Chi square test for categorical variables, Student t test for continuous variables

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Britton, PN;Khandaker, G;Khatami, A;Teutsch, S;Francis, S;McMullan, BJ;Jones, CA

Title:

High prevalence of developmental concern amongst infants at 12 months following hospitalised parechovirus infection

Date:

2018-03-01

Citation:

Britton, P. N., Khandaker, G., Khatami, A., Teutsch, S., Francis, S., McMullan, B. J. & Jones, C. A. (2018). High prevalence of developmental concern amongst infants at 12 months following hospitalised parechovirus infection. JOURNAL OF PAEDIATRICS AND CHILD HEALTH, 54 (3), pp.289-295. <https://doi.org/10.1111/jpc.13728>.

Persistent Link:

<http://hdl.handle.net/11343/293511>