Horan Seamus (Orcid ID: 0000-0002-9112-8178)

Running Head: **HERPES IN THE HINDBRAIN**

Title: **A CASE OF HERPES SIMPLEX VIRUS (HSV) RHOMBENCEPHALITIS IN A CHILD**

Article type: Instructive Case

Abbreviations:

HSV – herpes simplex virus

GCS – Glasgow coma scale

IV - intravenous

MRI – magnetic resonance image

ADEM - acute disseminated encephalomyelitis

CSF – cerebrospinal fluid

PCR - polymerase chain reaction

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.15690

HERPES IN THE HINDBRAIN:

A CASE OF HERPES SIMPLEX VIRUS (HSV) RHOMBENCEPHALITIS IN A CHILD

A 2-year-old previously well male, initially presented to the emergency department with one day of fever, listlessness and vomiting, and three days of coryzal symptoms. He had no other symptoms. Examination was unremarkable and full blood examination including white blood cell count and differential was normal. The child was discharged home, diagnosed with a presumed viral gastro-enteritis for outpatient review the next day.

The following day, he became irritable with ongoing fevers and had a brief episode of floppiness with a glazed expression and eye deviation. On re-presentation to the emergency department, he was febrile ($39^{O}C$) and tachycardic (heart rate of 135-150 bpm) with a Glasgow Coma Scale (GCS) score fluctuating between 11 and 15.

On examination, eye movements were convergent towards the midline with intermittent left eye abduction and elevation. Several non-responsive episodes associated with hypotonia were observed. The remaining cranial nerve and peripheral nervous system examinations were normal. Anticonvulsant therapy was commenced with intravenous (IV) phenytoin and midazolam. The patient was commenced on empiric intravenous cefotaxime and acyclovir for possible meningoencephalitis and admitted to the paediatric ward.

Further deterioration was observed overnight with persistent drowsiness, central hypotonia, dysphagia, dysphasia, decreased limb tone and reflexes (more pronounced in the upper limbs) and GCS of 9 to 11. An urgent magnetic resonance image (MRI) of his brain under general anaesthetic showed T2 signal abnormality, oedema and expansion of the lower brainstem and cervical spinal cord from the cervicomedullary junction to the T1-T2 disc level (Figure 1). The brainstem and cervical cord appearance was consistent with demyelination and acute disseminated encephalomyelitis (ADEM). He was intubated and transferred to the paediatric intensive care unit and a lumbar puncture performed.

Cerebrospinal fluid (CSF) examination demonstrated leukocytes 130 cells/mm^3, polymorphs 12 cells/mm^3, lymphocytes 118 cells/mm^3, erythrocytes 12 cells/mm^3, protein 0.4 mmol/L and glucose 3.0 mmol/L. On day three of admission, polymerase chain reaction (PCR) of CSF was positive for herpes simplex virus (HSV) type 1 and negative for enterovirus. The patient was commenced on high-dose methylprednisolone for five days, his antivirals were continued and antibiotics ceased.

He was extubated on day seven of admission and transferred to the ward. His ophthalmoplegia resolved but he had persistent central hypotonia, and decreased power and reflexes in the upper limbs. Intravenous acyclovir was ceased after 21 days and he commenced oral suppressive valacyclovir for a minimum duration of 12 months. A repeat MRI performed on day 23 of admission showed gliosis and volume loss involving the anterior aspect of spinal cord from C5-6 to the cervicomedullary junction, with changes more prominent on the left compared to the right. The patient was discharged home after 33 days.

The patient was referred to outpatient rehabilitation for management of residual issues of poor oral intake and tolerance of feeds, poor sleep pattern, hypotonia and upper limb weakness. His weakness and hypotonia improved over several weeks and at his 2-month review he was well, with a normal neurological examination and normal motor and language development.

DISCUSSION

The term "rhombencephalitis" refers to inflammatory disease of the rhombencephalon or hindbrain, with the term "brainstem encephalitis" often used interchangeably. In Australia, HSV is responsible for 5% of paediatric encephalitis and it is the third most common cause of infectious encephalitis, but rhombencephalitis is rare. (1) There have been only six other cases of paediatric HSV rhombencephalitis described in the literature, summarised in table 1.

Magnetic Resonance Imaging (MRI) findings of HSV encephalitis in children generally show a predisposition to the temporal lobes. (2) The mechanism of HSV entry into the brain is thought to be due to reactivation of the viral genome in the trigeminal ganglion resulting in spread via the trigeminal nerve. (3) This could explain the characteristic lesions seen on neuroimaging. Computer tomography imaging findings are of contrast enhancement, oedema, mass effect, and haemorrhagic necrosis, mainly in the temporal lobes. (2)

Almost one third of HSV encephalitis cases affect those below the age of 20. (2) A 2015 review of 33 cases of adult HSV-1 encephalitis found temporal involvement in almost all (96.8%) cases. (4) In contrast, a study by De Tiège et al found that of 31 *paediatric* patients with HSV-1 encephalitis who had brain imaging, characteristic temporal lobe lesions were observed in only 60% of cases, with the parietal lobe the next most commonly affected region (22%). (5) None of the 31 cases in this study demonstrated hindbrain involvement.

In regard to rhombencephalitis, the majority of available literature relates to adults. A 2010 review by Livorsi et al of published cases of HSV rhombencephalitis in adults identified the most common manifestations as neuro-ophthalmologic findings (81%), cranial nerve deficits (69%) and fever (69%). (6) Of the seven reported cases of paediatric HSV rhombencephalitis (including this case), six had cranial nerve deficits (86%), five were febrile (71%) and three had neuro-ophthalmological findings (43%). Peripheral weakness was notably common in the paediatric cases of HSV rhombencephalitis, with this present in five of the seven cases (71%).

Although outcomes for HSV encephalitis have dramatically improved since the introduction of acyclovir therapy, it is still a cause of significant morbidity and mortality. Of 26 cases of paediatric HSV encephalitis in the study by Lahat et al (all of whom were treated with acyclovir), 10 had long-term neurological sequelae (36%) and 2 patients died (7%). (7) However, there is no available literature on outcomes for paediatric HSV *rhombencephalitis*, with the only available data relating to adults. A study of 24 adults with HSV rhombencephalitis demonstrated a mortality rate of 22% in patients treated with acyclovir. (6) Of the four reported cases of paediatric HSV rhombencephalitis who were treated with acyclovir, including our case, all made remarkable recoveries, as indicated in Table 1. Our case also received five days of intravenous

methylprednisolone. While steroid therapy was shown to be beneficial prior to the advent of acyclovir, the role of adjunctive steroids in HSV encephalitis is unclear, with an absence of randomised clinical trial evidence but recent experimental models and clinical observations suggesting benefit. (8)

Paediatric HSV rhombencephalitis is rare and there is limited information in the literature at present. Much of our current understanding relies on data from adult populations or from paediatric HSV encephalitis affecting other regions of the brain. However, our analysis suggests paediatric HSV rhombencephalitis is a unique subset with distinctive clinical presentations, imaging findings and outcomes. Further research in this area would be beneficial.

LEARNING POINTS

- HSV is responsible for 5% of paediatric encephalitis, but rhombencephalitis is rare. The majority of literature available on rhombencephalitis relates to adult populations and there are only six reported cases of paediatric HSV rhombencephalitis.
- The most common presenting features of rhombencephalitis in adult populations were neuro-ophthalmologic findings, whereas in paediatric populations cranial nerve deficits were more common.
- While outcomes of HSV encephalitis have improved significantly since the introduction of acyclovir therapy, it is still a cause of significant morbidity and mortality. However, of the four known cases of paediatric HSV rhombencephalitis who received acyclovir therapy, all made remarkable recoveries.

REFERENCES:

1. Pillai SC, Hacohen 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.
2. Tyler KL. Update on herpes simplex encephalitis. Rev Neurol Dis. 2004;1(4):169-78.
3. Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: herpes simplex and varicella-zoster. Lancet Neurol. 2007;6(11):1015-28.
4. Singh TD, Fugate JE, Hocker S, Wijdicks EFM, Aksamit AJ, Jr., Rabinstein AA. Predictors of outcome in HSV encephalitis. J Neurol. 2016;263(2):277-89.
5. De Tiege X, Heron B, Lebon P, Ponsot G, Rozenberg F. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. Clin Infect Dis. 2003;36(10):1335-9.
6. Livorsi D, Anderson E, Qureshi S, Howard M, Wang YF, Franco-Paredes C. Brainstem encephalitis: an unusual presentation of herpes simplex virus infection. J Neurol. 2010;257(9):1432-7.
7. Lahat E, Barr J, Barkai G, Paret G, Brand N, Barzilai A. Long term neurological outcome of herpes encephalitis. Arch Dis Child. 1999;80(1):69-71.
8. Meyding-Lamade U, Jacobi C, Martinez-Torres F, Lenhard T, Kress B, Kieser M, et al. The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE): a multicenter, randomized, double-blind, placebo-controlled trial. Neurol Res Pract. 2019;1:26.

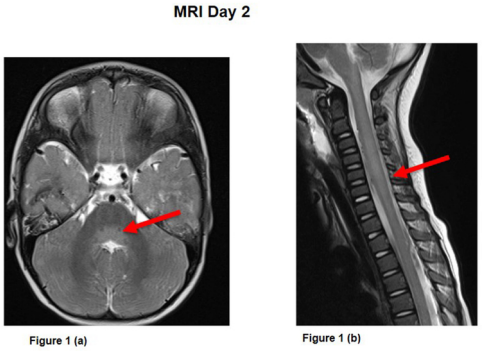

Figure 1. Axial T2 weighted images of the posterior fossa (a) and a sagittal T2 weighted sequence of the cervical spine and brain stem (b) demonstrating increased T2 signal and swelling (arrows) of the lower brainstem and cervical cord from cervicomedullary junction to T1-T2.

JPC_15690_Figures - Herpes in the Hindbrain.jpg

TITLE PAGE

TITLE: A Case of Herpes Simplex Virus (HSV) Rhombencephalitis in a Child

RUNNING HEAD: HERPES IN THE HINDBRAIN

Article type: Instructive Case

Author listing and affiliations:
Dr Allya V Makhijani MBBS DCH [1,2,4]
Dr Seamus Horan MD [2]
Dr Martin Tuszynski MBBS FRACP [1]
Prof. Michael Ditchfield MBBS MD FRANZCR [1,2]
A/Prof Jim P Buttery MBBS MD MSc FRACP [1,2,3,4]

Affiliations:
[1] Monash Children's Hospital, Monash Health, Victoria, Australia
[2] Department of Paediatrics, Monash University, Victoria, Australia
[3] SAEFVIC, Murdoch Children's Research Institute, Victoria, Australia
[4] Department of Paediatrics, University of Melbourne, Victoria, Australia

Corresponding Author:
Dr Allya Makhijani
Department of Infection and Immunity
Monash Children's Hospital, 246 Clayton Rd, Clayton, Victoria, 3168 Australia.
Phone: +61 3 9594 4564
Fax: +61 3 9594 4533
Email: allya.makhijani@gmail.com

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

Potential Conflicts of Interest:
The authors have no conflicts of interest relevant to this article to disclose.

Funding
There are no conflicts of interest to declare for any of the authors.

Contributors' Statement:

Dr Makhijani had a substantial contribution to concept and design, conducted a literature review, drafted the initial manuscript and approved the final manuscript as submitted.

Dr Horan conducted the current literature search and revised the manuscript for submission.

Dr Tuszynski identified the case for publication, assisted in case analysis, revision of the manuscript and approved the final manuscript as submitted.

Dr Ditchfield found adequate radiological information from the case, added important intellectual content and approved the final manuscript as submitted.

Dr Buttery contributed significantly to design and analysis, added important intellectual content, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors agree to be accountable for all aspects of the work including investigating and resolving any concerns with accuracy or integrity of the work.