Clinical Medicine 2009, Vol 9, No 3: 231–5

Management of suspected herpes simplex virus encephalitis in adults in a UK teaching hospital

David J Bell, Ruth Suckling, Michael M Rothburn, Tom Blanchard, David Stoeter, Benedict Michael, Richard PD Cooke, Rachel Kneen and Tom Solomon

ABSTRACT – The outcome of herpes simplex virus (HSV) encephalitis is improved with prompt initiation of aciclovir treatment. Delays are common, but there is little understanding of why they occur. The case notes of 21 adults admitted with suspected HSV encephalitis over one year were reviewed. The median (range) duration of illness was 2.5 (1–99) days. Seventeen (81%) patients had a lumbar puncture (LP) performed, at a median (range) time of 24 (2–114) hours after encephalitis was suspected. Lumbar puncture was delayed for a computed tomography (CT) scan in 15 patients, but only one of these had contraindications to an immediate LP. The median (range) time from presentation to starting aciclovir was 48 (2–432) hours. HSV-PCR (polymerase chain reaction) was requested on cerebrospinal fluid from 12 patients, one of whom was positive. Five (24%) patients were given the wrong dose of aciclovir. Overall the management of suspected HSV encephalitis was often sub-optimal, with delays in LP occurring due to unnecessary CT scans, and the wrong aciclovir dose administered. Guidelines for the management of suspected encephalitis are needed.

KEY WORDS: aciclovir, central nervous system infection, encephalitis, herpes simplex virus, lumbar puncture

[1]**David J Bell,** Specialist Registrar; [2,6]**Ruth Suckling,** Specialist Registrar; [3]**Michael M Rothburn,** Consultant Medical Microbiologist and Infection Control Doctor; [4]**Tom Blanchard,** Consultant in Infectious Diseases and Tropical Medicine; [6]**David Stoeter,** Specialist Trainee; [2,6]**Benedict Michael,** Academic Clinical Fellow; [3]**Richard PD Cooke,** Consultant Medical Microbiologist; [5,6]**Rachel Kneen,** Consultant Paediatric Neurologist; [2,6]**Tom Solomon,** Professor of Neurology and Medical Research Council Senior Clinical Fellow

[1]Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, Liverpool; [2]Division of Neurology, Walton Centre for Neurology and Neurosurgery, Liverpool; [3]Department of Clinical Microbiology, University Hospital Aintree NHS Trust, Liverpool; [4]Department for Infectious Diseases, North Manchester General Hospital, Manchester; [5]The Roald Dahl EEG Unit, Royal Liverpool Children's NHS Trust, Liverpool; [6]Brain Infections Group, Divisions of Neurological Science and Medical Microbiology and School of Tropical Medicine, University of Liverpool

Introduction

Herpes simplex virus (HSV) encephalitis is a rare but serious neurological infection with an estimated annual incidence of 1 in 250,000 to 500,000.[1] The classic presentation of HSV encephalitis is of a fever, headache, altered consciousness, focal neurological signs and seizures.[2,3] Intravenous aciclovir is an effective treatment, reducing mortality and morbidity.[4,5] Several publications have shown that delays in initiating treatment are associated with a worse prognosis,[2,6] however, there has been little work to understand why the delays occur. To better understand the processes involved in managing such patients the case notes of adults with suspected HSV encephalitis admitted to a teaching hospital in the UK over a 12-month period were retrospectively reviewed.

Methods

The study was conducted at University Hospital Aintree, a large teaching hospital in Liverpool serving a population of approximately 330,000 with around 88,000 attendances to the accident and emergency (A&E) department each year. Two methods were used to identify patients with suspected encephalitis admitted between June 2003 and May 2004. The electronic hospital pharmacy records were searched for prescriptions of intravenous (iv) aciclovir, and patients who received aciclovir for oral or genital herpetic lesions or for treatment of varicella zoster virus skin infections were subsequently excluded. In addition, the microbiology electronic records were searched for requests for HSV-PCR (polymerase chain reaction) on cerebrospinal fluid (CSF), or for 'encephalitis' in the clinical information. Data were collected from the hospital notes on the presenting history and clinical features, the dates and times of medical review and relevant investigations, the treatments given and the final diagnosis made. The study was registered with the hospital audit department and all data were handled according to national guidance.

Results

In total, 29 patients were identified who had been prescribed iv aciclovir. Examination of the microbiology requests did not identify any additional patients. Of the 29, eight were excluded from subsequent analysis because the aciclovir had been prescribed to treat shingles or mucosal herpes lesions. In the remaining 21 patients,

aciclovir had been prescribed at some time during their admission for suspected HSV encephalitis. The patients were all initially seen in the acute medical admissions unit or A&E department. The clinical features of the patients are shown in Table 1.

The median (range) time from presentation to the first medical assessment was 1.5 (0–7) hours (data available for 17 patients). The median time from admission until encephalitis was first suspected was 11 (0–384) hours (data available for 18 patients). For nine patients, encephalitis was considered in the differential diagnosis during their initial assessment. For the other 12, the diagnosis was considered (documented in the notes) later; for one patient this was 16 days after admission. Possible diagnoses included in the initial differential diagnosis for the 21 patients are shown in Table 2 together with the final diagnoses reached. One patient had HSV encephalitis proven by PCR of the CSF.

Table 1. Presenting clinical features for 21 patients with suspected herpes simplex virus encephalitis.

		Number of patients with data available
Age in years, mean (range)	53.2 (23–87)	21
Male (%)	15 (71.4)	21
Glasgow Coma Score, median (range)	14 (3–15)	19
Duration of illness in days, median (range)	2.5 (1–99)	21
Headache (%)	7 (35)	20
Vomiting (%)	4 (20)	20
Confusion or behavioural change (%)	14 (70)	20
Seizures – history or witnessed in hospital (%)	5 (23.8)	21
Temperature >37.5°C (%)	8 (38.1)	21
Rash (%)	1 (4.8)	21
Neck stiffness (%)	1 (4.8)	21
Photophobia (%)	1 (4.8)	21

Table 2. Initial differential diagnoses and final diagnosis for 21 patients in whom herpes simplex virus (HSV) encephalitis was suspected.

	Diagnoses included in the initial differential*	Final diagnosis (n=21)
Encephalitis, including HSV	9	1
Cerebrovascular accident	5	3
Urinary tract infection/ pneumonia	7	9
Meningitis (bacterial or viral)	3	2**
Subarachnoid haemorrhage	2	1
Hyponatraemia	2	1
Post ictal	3	1
Drug reaction	1	0
Sagittal sinus thrombosis	1	0
Central nervous system tumour	0	2
Subdural haemorrhage	0	1

*The total is >21 because many patients had more than one diagnosis in the initial differential; **Both were viral

Lumbar punctures and computer tomography scans

Seventeen (81%) of the 21 patients had a lumbar puncture (LP) performed. The median (range) time from presentation to LP was 30 (7–408) hours (n=15). The median time from encephalitis first being suspected to the LP being performed was 24 (2–114) hours (n=11). A computer tomography (CT) scan was performed prior to LP in 15 of these 17 (88%) patients and the median time from presentation to CT scan was 6 (1.5–403) hours. Only one of these 15 patients needed a CT scan before a LP, according to existing guidelines[7,8]; this patient presented in deep coma. None of the other patients had any contraindications to an immediate LP. Four patients did not have a LP. In one of these, the procedure was thought unsafe due to a possible cervical spine injury and in two cases, a diagnosis of cerebrovascular accident was made on CT scanning so LP was no longer thought necessary. In the fourth case, there was no documentation to indicate why LP was not done. Four patients had a second LP during their admission.

Nineteen of the 21 patients had CT scans, 10 were reported as normal and nine abnormal; three showed infarcts, three showed cerebral atrophy and three were reported as being 'in keeping with' or 'suggestive of' HSV encephalitis. One of these patients had the diagnosis confirmed by PCR. The final diagnoses for the other two patients were a brain tumour (anaplastic astrocytoma) and a subarachnoid haemorrhage.

Cerebrospinal fluid analysis

CSF opening pressure was recorded in 11 out of the 17 LPs performed (65%). The white blood cell (WBC) and red blood cell (RBC) counts were recorded in all cases. Seven of the 17 patients had CSF WBC

counts greater than 4 per mm^3 (Table 3). The WBC differential was documented in five of these seven cases. For four (24%) LPs, the CSF protein and glucose were not recorded and in 10 (59%) cases the plasma glucose was not measured at the same time as the CSF glucose. HSV-PCR was requested on the CSF from 12 (70.6%) of the 17 LPs. This was positive in one case though a negative result was documented in only eight patients' notes.

Other investigations

Eleven patients had magnetic resonance imaging (MRI) scans, including two of the three patients who did not have CT scans. One of these had typical features of HSV encephalitis with high signal in the right temporal lobe (the patient who was PCR positive). The other scans were reported as showing infarcts (3), brain tumours (1 pituitary tumour and 1 astrocytoma), subdural haemorrhage (1) and subarachnoid haemorrhage (1). The remaining three scans were unremarkable. Two patients had electroencephalograms (EEG) preformed; one was normal but the patient with proven HSV encephalitis had a characteristic EEG.

Treatment

Sixteen of the 21 patients were started on the correct dose of aciclovir (10 mg per kg three times daily), but for five (24%) a lower dose was given and no explanation for this was documented in the notes. The median (range) time from hospital presentation to administration of the first aciclovir dose was 48 (2–432) hours (data available for 15 patients). Seventeen (81%) of the 21 patients who received iv aciclovir also had an LP; in eight cases aciclovir was started after the LP was performed, and in seven cases it was started before the LP. In two cases the times were not documented. The median (range) duration of iv aciclovir treatment was three (1–14) days. The patient with PCR-confirmed herpes simplex encephalitis (HSE) received 14 days of iv aciclovir. Two patients received 10 days of iv aciclovir. One of these with a CSF pleocytosis of 42 WBC/mm^3, 75% lymphocytes, and a negative HSV-PCR, had a final diagnosis of viral meningitis. The other patient was admitted collapsed, did not have an LP, and was treated blindly with antibiotics and aciclovir for a suspected central nervous system infection. The final diagnosis was a cerebrovascular accident. Aciclovir treatment was stopped after seven days or less in the remaining 18 patients. In 10 cases the stated reason was that an alternative diagnosis had been made and in one case because of the normal CSF result. In seven cases, no reason was documented in the notes for discontinuing treatment.

Discussion

HSV encephalitis is a serious and life-threatening condition with a high mortality and significant long-term disability in survivors.[1,9] The introduction of aciclovir treatment has reduced the mortality from about 70% to less than 20%.[4,5] However several studies have shown that if treatment is not started within about 48 hours of admission, there is an increased incidence of neurological sequelae.[2,6]

This study at a large university teaching hospital has shown that the management of patients with suspected encephalitis is often sub-optimal. Although encephalitis was considered in the initial diagnosis for nearly half the patients, the median time between suspecting encephalitis and performing a LP was 24 hours. In nearly all patients a CT scan contributed to this delay, even though most patients could have had an LP without waiting for the CT, because there were no contraindications to an immediate LP. The median delay for a CT scan was six hours, suggesting that even once it had been done there was still a lack of urgency about performing a LP afterwards. In two patients the CT scan suggested an alternative diagnosis, so that LP was no longer necessary, but this is not a rationale for delaying an LP until after a CT scan. Contraindications to immediate LP include focal neurological signs, new onset seizures, papilloedema, deep coma and known immunocompromise,[7,8,10,11] because patients with these features may have raised intracranial pressure with brain shift, and thus be at risk of herniation syndromes.[8]

Table 3. Cerebrospinal fluid (CSF) results and final diagnoses for the six patients with CSF white blood cell (WBC) counts raised above 4 cells/mm^3.

Patient ID	WBC count (/mm^3)	Lymph (/mm^3)	Neutrophils (/mm^3)	RBC count (/mm^3)	Opening pressure (cm)	CSF protein (g/dL)	CSF Gluc (mmol/l)	Serum Gluc (mmol/l)	CSF HSV-PCR	Final diagnosis
2	42	31	11	4,480	31	1.2	3.8	6.4	Negative	Viral meningitis
8	23	23	0	2,240	N/A	0.3	3.2	5.4	Negative	Died of septicaemia
9	228	182	46	132	32	0.8	3.2	5.7	Negative	Viral meningitis
51	20	N/A	N/A	1,184	11	2	2.1	4.8	Negative	Subdural haematoma
60	5	N/A	N/A	3	0	0.6	4.6	N/A	Negative	Chest infection
61	188	186	2	11	21	0.7	3.6	N/A	Positive	HSV encephalitis
63	16	11	5	59	16	0.6	2.3	4.7	Not requested	Pituitary tumour

Gluc = glucose; HSV-PCR = herpes simplex virus-polymerase chain reaction; N/A = not available; RBC = red blood cell

For one quarter of the LPs performed the protein and glucose levels were not recorded, and for nearly 60% no plasma glucose was recorded, making the CSF results potentially uninterpretable. The inability to test a blood sugar as part of the LP procedure seems to be a constant theme throughout both adult and paediatric practice.[11]

Aciclovir treatment was started before a LP for approximately half of the patients, but nearly a quarter received too low a dose. For the patient with confirmed HSV encephalitis the correct dose was given for two weeks. Most authorities now consider that aciclovir should be given for 14 to 21 days because of the risk of relapse.[12] In most other patients in this study aciclovir was stopped early, usually because an alternative diagnosis had been made, though in many cases no reason for stopping was recorded.

Most studies of encephalitis have included only patients with proven HSV disease, but at the time of hospital admission it is not known which of those with suspected disease will have it confirmed. All patients with suspected encephalitis were therefore studied so that a clearer picture of actual hospital practice could be obtained. Although HSV encephalitis is rare, patients with suspected encephalitis are not. Only by getting the management right for all suspected cases will it be right for those patients that turn out to have HSV encephalitis. Failure to get the management right has enormous consequences for the patients themselves and also because of the large health economic burden.[13] Although accurate data are not available for the UK, studies in the USA have estimated that the hospitalisation cost per case of encephalitis was $28,000 in 1997.[13] A more recent study from Sweden emphasises the long-term neuropsychiatric sequelae.[9] Interestingly a recent study in the USA showed similar delays in aciclovir administration.[14]

One limitation of this study was that it only included patients in whom encephalitis was considered, and it is possible that the diagnosis was missed altogether in some patients. The retrospective nature of the study and the dependence on what was recorded in the notes also limited the results.

This study has shown that 21 patients were treated with aciclovir for the one proven case of HSV encephalitis. Although aciclovir is relatively safe there are important side effects, particularly renal impairment secondary to crystalluria and obstructive nephropathy.[15] This reversible nephropathy usually manifests after four days of iv therapy and can affect up to 20% of patients.[16] The risks of nephropathy can be reduced by maintaining adequate hydration, monitoring renal function, and stopping iv aciclovir promptly when it is subsequently shown not to be indicated. Empirical treatment of all patients as soon as the diagnosis is considered is therefore not advocated. Rather as soon as encephalitis is suspected, LP should be performed as a matter of urgency, with or without prior CT (if indicated). Aciclovir should then be given to those whose CSF is compatible with viral infection. Unlike bacterial disease, where the presentation is often very acute and a delay of a few hours can be critical, the rarity of viral encephalitis and its more gradual progression means that a delay of a few hours to obtain a CSF result is probably justified.

If the clinical suspicion is strong, and the first CSF is normal, the drug should be started anyway and LP repeated after 24–48 hours, because an initial LP can be normal.[17] However if there are to be long delays before an LP is performed aciclovir should be started presumptively,[17] and a LP performed as soon as possible afterwards. Presumptive treatment does not remove the need for a LP and will not affect the result of the HSV-PCR test, if LP is performed soon after. Once treatment has started, if another diagnosis becomes apparent then it is reasonable to stop the aciclovir. Similarly if the CSF HSV-PCR is negative, aciclovir can be stopped, though an early CSF can be falsely negative, in which case the CSF should be re-checked.[18,19]

In summary this study suggests that the management of some patients with suspected encephalitis is suboptimal. As a consequence local guidelines have been developed.[17] National guidelines for the management of suspected encephalitis in the UK were suggested nearly 15 years ago and it is clear that they are now needed.[20]

Acknowledgements

We thank our colleagues Lisa Grimes and Annmarie Byrne in the audit department for assistance in obtaining the notes; Ava Easton and Elaine Dowell of the Encephalitis Society, Julia Granerod, David Brown and Natasha Crowcroft of the Health Protection Agency for helpful discussions; and Dr Nick Beeching for helpful comments.

Funding

TS is a Medical Research Council Senior Clinical Fellow.

References

1 Whitley RJ. Herpes simplex encephalitis: adolescents and adults. *Antiviral Res* 2006;71:141–8.
2 Raschilas F, Wolff M, Delatour F *et al.* Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis* 2002;35:254–60.
3 Fodor PA, Levin MJ, Weinberg A *et al.* Atypical herpes simplex virus encephalitis diagnosed by PCR amplification of viral DNA from CSF. *Neurology* 1998;51:554–9.
4 Skoldenberg B, Forsgren M, Alestig K *et al.* Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet* 1984;2:707–11.
5 Whitley RJ, Alford CA, Hirsch MS *et al.* Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med* 1986;314:144–9.
6 McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* 1997;63:321–6.
7 Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001;345:1727–33.
8 van Crevel H, Hijdra A, de Gans J. Lumbar puncture and the risk of herniation: when should we first perform CT? *J Neurol* 2002;249:129–37.

9 Hjalmarsson A, Blomqvist P, Skoldenberg B. Herpes simplex encephalitis in Sweden, 1990–2001: incidence, morbidity, and mortality. *Clin Infect Dis* 2007;45:875–80.
10 van de Beek D, de Gans J, Spanjaard L *et al.* Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004;351:1849–59.
11 Kneen R, Solomon T, Appleton R. The role of lumbar puncture in suspected CNS infection – a disappearing skill? *Arch Dis Child* 2002;87:181–3.
12 Yamada S, Kameyama T, Nagaya S, Hashizume Y, Yoshida M. Relapsing herpes simplex encephalitis: pathological confirmation of viral reactivation. *J Neurol Neurosurg Psychiatry* 2003;74:262–4.
13 Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988–1997. *Clin Infect Dis* 2002;35:175–82.
14 Benson PC, Swadron SP. Empiric acyclovir is infrequently initiated in the emergency department to patients ultimately diagnosed with encephalitis. *Ann Emerg Med* 2006;47:100–5.
15 Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. *Am J Med* 1988;84:1067–71.
16 Pacheco LR, Tavares HM, Moyses Neto M *et al.* Acute renal failure related to intravenous acyclovir. *Rev Assoc Med Bras* 2005;51:275–8.
17 Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: a clinician's guide. *Pract Neurol* 2007;7:288–305.
18 Cinque P, Cleator GM, Weber T *et al.* The role of laboratory investigation in the diagnosis and management of patients with suspected herpes simplex encephalitis: a consensus report. The EU Concerted Action on Virus Meningitis and Encephalitis. *J Neurol Neurosurg Psychiatry* 1996;61:339–45.
19 Steiner I, Budka H, Chaudhuri A *et al.* Viral encephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol* 2005;12:331–43.
20 Gleadle J, Dixon C, Brown MM, Schon F. The use of acyclovir in suspected encephalitis. *J R Soc Med* 1994;87:7–8.

Address for correspondence: Professor T Solomon, University of Liverpool Divisions of Neurological Science and Medical Microbiology, 8th Floor Duncan Building, Daulby Street, Liverpool L69 3GA.
Email: tsolomon@liv.ac.uk