Chapter

A Creeping Matter of Urgency: Herpes Simplex Encephalitis

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Herpes Simplex Virus Encephalitis [HSVE] is a rare but clinically important viral infection that has a bleak prognosis if not treated early. Encephalitis is inflammation of the brain with associated neurological dysfunction. HSVE is one of the most commonly identifiable pathogens in developed countries [1]. In Australia, just over half of the cases of acute encephalitis identified over the period of 1976 – 2008 are from unknown pathogens. The most common pathogen for encephalitis representing just over 25% is herpes simplex virus [2]. This article will focus on the diagnosis, investigation and management of HSVE.

A Case Creeping In

JW, a 53 year old gentleman, presented to the emergency department with concerns of a headache lasting one week and difficulty expressing words. Despite regular paracetamol, the headaches became more frequent and persisted with no associated aura. He denied any flu like symptoms, vomiting, fever or prodromal illness. His medical history included hypertension and type two diabetes mellitus and took telmisartan, sitagliptin and metformin. He is a non-smoker who does not drink alcohol or take recreational drugs. He denies any significant family history, recent travel, animal exposure or any contact with sick persons. Clinically, he was haemodynamically stable within normal limits and afebrile. He was orientated with intermittent expressive dysphasia. His pupils were equal in size, symmetric and reactive to light and accommodation. There was no facial asymmetry or focal neurological deficit. Other systems in examination were normal. Routine blood investigations, including full blood count, electrolytes urea and creatinine, liver function tests were within normal limits.

He was commenced on aspirin and a statin. Further investigations, including blood tests [lipid profile, HbA1c (glycosylated haemoglobin A1c), thyroid function tests and Vitamin B12], a carotid doppler screen, CT brain [Computed tomographic], MRI [Magnetic resonance imaging] and MRA [Magnetic resonance angiography] were requested. The CT brain identified no intracranial pathology. The carotid study showed less than 50% stenosis of both right and

left carotid arteries. The HbA1c was 13.2% and total cholesterol 6.5 mmol/L. The MRI brain study identified small vessel disease with no other abnormalities.

Context and Clinical Features

The epidemiology of HSVE in western countries supports a bimodal distribution seen in infants and the elderly. The annual incidence is 2 – 4 per million [3]. The aetiology however is heavily influenced by epidemiological risk factors for encephalitis such as age, geographic location, animal contact, immunocompromised, occupation, season and travel [Table 1].

Classically, the syndrome of encephalitis is characterised by fever, headache, altered conscious state and focal motor signs. Invariably, HSVE presents with the above signs plus aphasia and personality changes.

Pathology

History has known of the virus since the Greeks defined herpes, 'to creep in'. This very derivation emphasises how the virus can creep under the complacency of the clinician if one is not aware. HSV is part of the alphaherpesvirus subfamily of herpes viruses with two types: HSV1 and HSV 2. HSV1 is more common in the elderly and HSV 2 in neonates. It infects the nervous system causing neurological disease with a predilection for establishing latency and replicating during primary infection and reactivation [4]. HSVE has a predilection for the inferior and anteromedial temporal lobes, insular cortices, and cingulate gyri. The pathological involvement of the temporal and frontal lobe structures illustrates how memory impairment is one of the most disabling features [5,6].

Investigations

Individuals with suspected encephalitis should have a lumbar puncture, unless there is a contraindication, with appropriate imaging afterwards [CT or MRI]. The cerebrospinal fluid [CSF] should be screened for HSV 1, HSV 2, Varicella Zoster Virus [VZV] and entero-

viruses. One must account for the pre-test probability of the disease based on the clinical presentation to aid interpretation of results and guide management. Routine blood investigations can be non-specific at first, but may point to a source of infection. An electroencephalogram [EEG] has more of an adjunct role in HSVE, nonetheless it may assist in excluding non-convulsive seizure activity. MRI is the most sensitive imaging modality for assessing encephalitis, but if not accessible, a CT study may be used.

The Case Continued to Creep In

On Day 4, J.W. had a second generalised tonic clonic seizure with a temperature of 39°C. A lumbar puncture and blood culture were performed [Table 2] and investigations were sent for HSV and VZV polymerase chain reaction [PCR], meningococcal PCR and cryptococcal, as well as urine cultures. Intravenous benzylpenicillin and acyclovir were administered. An EEG study identified generalised cerebral dysfunction with no epileptiform discharges. A transthoracic echocardiogram showed no structural or valvular abnormality. His clinical picture changed later with both expressive and receptive dysphasia, by which time a positive HSV PCR was reported. The vasculitis and thrombolytic screen, HIV serology, neuronal specific antibodies and syphilis serology were negative. A repeat MRI brain study showed changes in the left temporal lobe extending to the posterior frontal lobe, left insular cortex and medial left occipital lobe [Figure 1]. His global nonafluent aphasia and seizures continued to worsen. Acyclovir was completed for 21 days. A month later, the gentleman returned home with ongoing supportive services for his dysphasia, memory and right hemiparesis.

Treatment

A great concern for HSE is the high morbidity and associated long term sequealae with neuropsychological dysfunction and impaired quality of life [7]. It has been recognised that age and level of consciousness are prognostic factors, additionally, the time of ini-

tiation of antivirals affects outcome [8]. The clinical presentation of HSVE can be non-specific in immunocomprised individuals and children, it is therefore important to consider the diagnosis early on and to commence anti virals [9].

Conclusions

The two large randomised trials in the 1980s established the effectiveness of Acyclovir as the drug of choice that reduced morbidity and mortality [10,11]. The advent of Acyclovir has revolutionised the approach to treatment particularly with its good safety profile; however, before the introduction of acyclovir, the mortality rate if untreated was 70%. Treatment has since reduced this to 25 – 30%, but, the associated morbidity is grave with most survivors having short term memory impairment, dysphasia, behavioural changes and epilepsy. The UK national guidelines for the treatment of viral encephalitis highlight the importance of commencing intravenous acyclovir within six hours of admission whilst further investigations are pending if there is a strong clinical suspicion with normal imaging or first CSF [12]. The treatment is for 14 to 21 days with a repeat lumbar puncture CSF PCR to confirm eradication of HSV. In the immunocompromised, it is well recognised that HSV and VZV may have atypical and subtle features as common pathogens for acute encephalitis [13]. An MRI alongside appropriate microbiological investigations should be sought with a higher threshold to commence Acyclovir for at least 21 days and repeat CSF PCR [14].

There are two recognised trends from the Australian data: an ageing population with increased comorbidities and risk of immunosuppression and an increase in the 'unknown' aetiological group of arboviral or zoonotic pathogens [15]. There is an overall decrease in the number of findings attributed to sound preventative public health measures, clinical awareness and medical care. Vacillating with alternative diagnoses, especially when current treatment is not progressing, suggests a clinician ought to consider empirical treatment early, particularly in immunocompromised patients given significant benefits to mitigate mortality and morbidity.

Table 1: Common cause of acute encephalitis in Australia. (Table adapted from US guidelines and aetiology of encephalitis Australia [16,17]).

Epidemiological clues	Pathogen
Geography	Northern Australia - arbovirus infection (Murray Valley, Kunjin), scrub typhus; leptospirosis, melioidosis, Japanese B encephalitis, Hendra virus and Australian bat lyssavirus infection
Age	Neonates - HSV 2, CMV, rubella, listeria monocytogenes, T. gondii. Infants - Japanese encephalitis, murray valley encephalitis, influenza. Elderly – Sproadic CJD, HSV 1, L. monocytogenes.
Immunocompromised	VZV, CMV, HIV, C. neoformans, T. gondii, humans herpes virus 6.
Occupation	Animals – rabies, C. burnetii, bartonella species Horses – Hendra Health care workers – HIV, VZV, measles, M. Tuberculosis.
Season	Summer – Agents transmitted by mosquitoes Winter – Influenza
Travel	Africa – Rabies, West nile, P. falciparum. Central America – Rabies, Eastern equine encephalitis virus, R. rickettsia, P. falciparum. Europe – West nile nirus, tickborne encephalitis virus. South east asia – Japanese encephalitis, tickborne encephalitis
Animal contacts	*Bats* - Australian bat lyssavirus *Horses* - Hendra virus *Cats - Bartonella henselae, coxiella burnetii, T. gondii* *Dogs - Rabies* *Rodents* - murine typhus, hantavirus *Arthropods* - arbovirus infection (Murray Valley, Kunjin virus),scrub typhus, Q fever. Birds – Cryptococcus neoformans
Immunisation	VZV, Japanese encephalitis, polio, measles, mumbs, rubella.

Table 2: Patient's test results. All other tests were within normal limits for electrolytes, urea and creatinine, liver function tests, thyroid function tests and Vitamin B12. A vasculitis and thrombolytic screen, HIV serology, neuronal specific antibodies and syphilis serology were negative.

Test	Level	Comment
Glucose Random	19.3 mmol/L	High
Haemoglobin	146 g/L	Normal
WCC	17.2 x10^9/L	High
Platelets	190 x10^9/L	Normal
Abs Neutrophils	15.2 x10^9/L	High
Abs Lymphocytes	1.7 x10^9/L	Normal
Abs Monocytes	0.2 x10^9/L	Normal
Abs Eosinophils	0.0 x10^9/L	Normal
Hba1c	13.2%	High
Cholesterol	6.5mmol/L	High
PT	15 s	Normal
APTT	28 s	Normal
INR	1.1	Normal
CSF Glucose	8.5mmol/L	High
CSF Protein	0.73 g/L	High

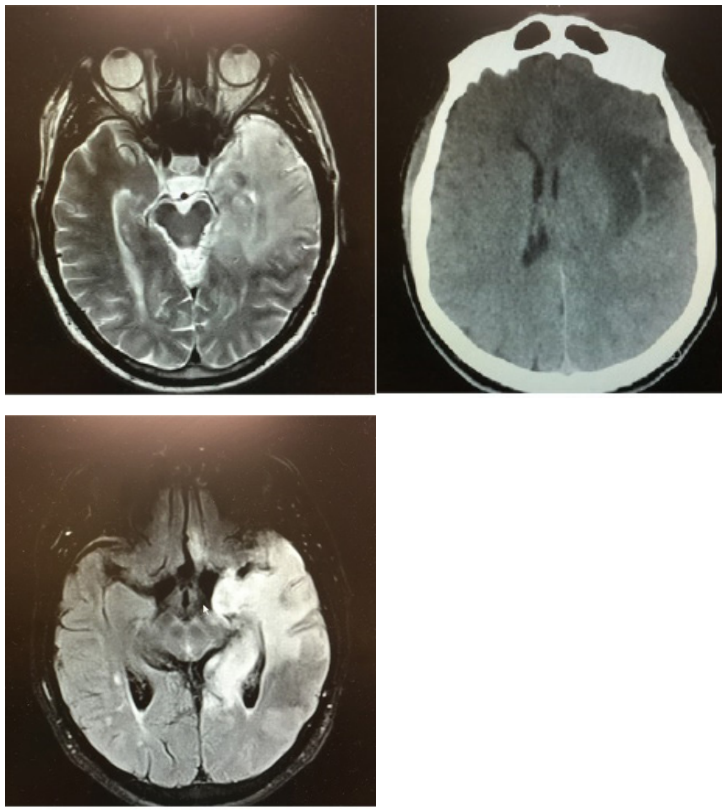

Figure 1: T2 weighted MRI scans of the brain. There is an area of increased T2/FLAIR signal involving the left temporal lobe, extending to involve the insular cortex superiorly, the medial left occipital lobe and posterior thalamus posteriorly and the posterior right frontal lobe anteriorly. There is associated mass effect with diffuse effacement of the sulci in the affected regions, midline shift to the right of up to 4 mm and partial compression of the left lateral ventricle.

References

1. Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet. 2002; 359: 507– 513.
2. Huppatz C, Durrheim D, Levi C, Dalton C, Williams D, et al. Etiology of encephalitis in Australia, 1990–2007. Emerg Infect Dis. 2009; 15: 1359–1365.
3. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, et al. Management of suspected viral encephalitis in adults—Association of British Neurologisys and British Infection Association National Guidelines. J Infect. 2012; 64:347–73.
4. Heldwein EE, Krummenacher C. Entry of herpesviruses into mammalian cells. Cell Mol Life Sci. 2008; 65: 1653-1668.
5. Hierons R, Janota I, Corsellis JAN. The late effects of necrotizing encephalitis of the temporal lobes and limbic areas: a clinico-pathological study of 10 cases. Psychol Med. 1978; 8: 21–42.
6. Rose FC, Symonds CP. Persistent memory defect following encephalitis. Brain. 1960; 83: 195–212.
7. Gordon B, Selnes OA, Hart J Jr, Hanley DF, Whitley RJ. Long-term cognitive sequelae of acyclovir-treated herpes simplex encephalitis. Arch Neurol. 1990; 47: 646-647.
8. 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: 321–326.
9. Lahat E, Barr J, Barkai G, Paret G, Brand N, et al. Long term neurological outcome of herpes encephalitis. Archives of Disease in Childhood. 1999; 80: 69–71.

10. Sköldenberg B, Forsgren M, Alestig K, Bergström T, Burman L, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet. 1984; 2:707–711.

11. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986; 314: 144–149.

12. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, et al. Management of suspected viral encephalitis in adults—Association of British Neurologisys and British Infection Association National Guidelines. J Infect. 2012; 64: 347–373.

13. Kolski H, Ford-Jones EL, Richardson S, Petric M, Nelson S, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994–1995. Clin Infect Dis. 1998; 26: 398–409.

14. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, et al. The Management of Encephalitis: Clinical practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008; 47: 303–327.

15. Britton PN, Eastwood K, Paterson B, Durrheim DN, Dale RC, et al; Australasian Society of Infectious Diseases; Australasian College of Emergency Medicine; Australian and New Zealand Association of Neurologists; Public Health Association of Australia. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J. 2015; 45: 563-576.

16. Paterson DL, Murray PK, McCormack JG. Zoonotic disease in Australia caused by a novel member of the paramyxoviridae. Clin Infect Dis. 1998; 27: 112-118.

17. Russell RC, Dwyer DE. Arboviruses associated with human disease in Australia. Microbes Infect. 2000; 2: 1693-1704.