Neurology Asia 2005; 10 : 35 – 38

Herpes simplex encephalitis in Hong Kong: A retrospective review

AC Hui *FRCP DTM&H*, *KF Cheung *MRCP*, *C Lui *MRCP*, KY Mok *MRCP*, SH Li *MRCP*, KC Ng *FRCPath*, KS Wong *MD FRCP*, for the CNS Infections Study Group

*Department of Medicine & Microbiology, Prince of Wales Hospital, The Chinese University of Hong Kong; *Department of Medicine, Queen Elizabeth Hospital, Hong Kong*

Abstract

We performed a retrospective study on the causes of acute viral encephalitis in Hong Kong and in particular we focused on the clinical, laboratory findings, imaging characteristics and outcome of Chinese patients with herpes simplex encephalitis. We identified 16 patients with herpes simplex encephalitis with age ranging from 24-74 years (mean 51 years). The clinical presentation was diverse. Of these 16 patients, 2 (13%) died, 4 (25%) had a poor outcome, 10 (62%) made a full recovery. Herpes simplex encephalitis was the most commonly identified cause of acute viral encephalitis among adults in Hong Kong.

INTRODUCTION

Herpes simplex encephalitis (HSE) is a rare cause of sporadic encephalitis with an estimated annual incidence of 1-2 per million.[1-3] The availability of polymerase chain reaction (PCR) to detect herpes simplex virus (HSV) DNA has revealed a wider clinical spectrum of CNS infection due to HSV, including milder forms and atypical presentations.[4-10] Older studies have suffered from ascertainment bias as the diagnosis of HSE relied on autopsy or brain biopsy material.[11-12] We studied the clinical, laboratory features and outcome of patients with HSE, and the proportion of acute viral encephalitis caused by HSV in Hong Kong, China.

METHODS

We conducted a multi-centre retrospective survey over a 6-year period from May 1998 to May 2004. Consecutive adults over the age of 15 years with a diagnosis of acute HSV encephalitis were included. The year 1998 was chosen as by this date improved diagnostic techniques such as PCR for the detection of viral DNA were widely available and a computerized system of archiving hospital episodes with International Classification of Disease diagnosis codes had been introduced in all public hospitals. Patients with a clinical suspicion of central nervous system infection who were admitted to public hospitals with a neurological service were ascertained from the computerized admission and discharge records of the hospital system. In order to establish the diagnosis of HSE, all three criteria had to be fulfilled: a) confirmatory histology or positive PCR; b) acute onset of focal or diffuse cerebral dysfunction (such as alteration in conscious level, behavioural change, hemiparesis); c) the absence of alternative causes such as drug, toxic, metabolic, anoxic encephalopathy or acute disseminated encephalomyelitis. As part of standard management guidelines issued by the Hospital Authority, the organisation that runs government hospitals, brain CT scan, cerebrospinal fluid and viral analysis are part of the routine work-up in patients with suspected acute encephalitis.[13] In addition to PCR amplification of herpes DNA, viral serologies for cytomegalovirus, Epstein-Barr virus, Japaense B virus, measles virus, mumps virus, rubella virus, coxsackie A and B, echovirus and enterovirus are available. All patients received intravenous acyclovir as empirical therapy. The medical records were reviewed by a neurologist and the relevant clinical and laboratory details were recorded: age at onset and sex, history of co-existing medical diseases, presenting symptoms, Glasgow Coma Score, blood glucose and white cell count and neuroimaging results. Cerebrospinal fluid parameters included opening pressure, protein and glucose concentrations, total and differential white cell count and microbiological

Address correspondence to: Dr AC Hui, Department of Medicine, Prince of Wales Hospital, The Chinese University of Hong Kong Shatin, Hong Kong SAR. Telephone: (852) 26323131 / 26323133, Facsimile: (852) 26375396, E-mail: cfhui@cuhk.edu.hk

investigations (Gram and Ziehl-Nielson stains). We used the Glasgow Outcome Scale (GOS) as a measure of functional status.[14] This scoring system consists of 5 levels: 1 = death within the first month; 2 = vegetative state; 3 = severe disability – conscious but requiring constant supervision; 4 = moderate disability - neurological impairment, but independent; 5 = good recovery - leading an independent life, with or without minimal neurological impairment. The premorbid and discharge GOS was recorded; a poor outcome was defined as a score of 3 or below.

RESULTS

HSE was diagnosed in 16 immunocompetent patients over this 6 year interval: 8 men and 8 women, mean age 51 years (range 24-74 years). Cases were sporadic and no seasonal variation was detected. The clinical features at presentation are listed in Table 1. Five cases developed generalized tonic-clonic and one simple partial motor seizures. The mean Glasgow Coma Score was 13.5 (range 3-15) on admission. The cerebral spinal fluid findings are listed on Table 2. One patient had a normal cerebrospinal fluid protein level and another did not exhibit pleocytosis but no patient had normal values for both of these parameters. The mean peripheral white cell count was 10.0 x 10^9/dL. Cranial CT scans were done in all 16 and demonstrated unilateral temporal lobe edema in 7, fronto-temporal oedema in 2 and temporal lobe infarct in one. CT scans were normal in 6 and 4 of these proceeded to MRI imaging which showed temporal lobe oedema. EEG was abnormal in the 13 cases which were done in the acute stage. The most common abnormality was diffuse slowing in 4, focal slowing in 3, periodic lateralized epileptiform discharge (PLED) in 4 (one bilateral), and focal sharp waves in 2 others. Mean duration of hospitalisation was 23.5 days, range 15 to 45 days. Two patients (13%) died, 4 (25%) had a poor Glasgow Outcome Scale score and the remaining 10 (62%) recovered fully.

During this same period our survey also registered 28 cases of acute encephalitis. The other identifiable causes being: varicella-zoster (5 cases), Japanese encephalitis (4 cases), Coxsackie (2 cases) and enterovirus (one case).

DISCUSSION

The epidemiology of acute viral encephalitis differs from region to region.[15-17] In Asia, Japanese encephalitis is a common form of viral encephalitis. Newer pathogens such as the Nipah and enteroviruses have emerged as causes of epidemic encephalitis in Malaysia, Singapore and Taiwan.[18-19] The increased prevalence of mosquito

Table 1: Presenting features of patients with herpes simplex encephalitis

Feature	n	percentage
Fever	15	94
Headache	7	44
Confusion	7	44
Convulsion	6	38
Neck stiffness	5	31
Dysphasia	2	13
Hemiparesis	2	13
Coma	1	6
Memory loss	1	6

Table 2: Cerebrospinal fluid findings in patients with herpes simplex encephalitis

Parameter	Mean	Median	Range
Pressure in cmH_2O	18	17	6 - 28
Protein level in g/dl	1.6	0.9	0.3 - 6
White blood cell count per mm^3	170	119	0 - 684
Glucose concentration in mmol/l	3.8	3.8	0.2 - 7.9

vectors has led to more cases of Japanese encephalitis in Hong Kong, a disease which had not previously been endemic.[20] Despite the presence of these viruses we found that in our locality, the most common aetiology of acute viral encephalitis where the cause is identified is HSV (16 out of 28 cases, 57%). Similar to previously reported series, we found that the clinical presentation was diverse. The majority of cases had abnormalities on imaging and in the CSF, but a small percentage did not have pleocytosis or elevated protein. Based on the current finding that HSV contributes to a major proportion of viral encephalitis in our setting, a search for HSV PCR and empirical treatment with acyclovir are justified whenever a clinical diagnosis of viral encephalitis is made.

This study has several limitations. The retrospective nature of this study may have led to underascertainment and patients were not systematically investigated. Follow up was restricted to discharge from hospital so that complications which developed after this period, such as seizures, were not included. Although this survey was restricted to public hospitals, in Hong Kong 90% of patients with acute neurological disorders are managed in the public sector.[21] A prospective survey with uniform clinical and laboratory work-up would give a more accurate picture.

ACKNOWLEDGEMENTS

Other members of the CNS infections study group: Mandy Au-Yeung, Pamela Youde Eastern District Hospital; Eric Chan, Tuen Muen Hospital; KH Chan, Queen Mary Hospital; KF Hui, United Christian Hospital; Patrick Kwan, Prince of Wales Hospital; Anita Lam, Caritas Medical Centre; KK Lau, Princess Margaret Hospital; KL Tsang, Tseung Kwan O Hospital; Winnie Wong, Queen Elizabeth Hospital; HM Yeung, Nethersole Hospital.

REFERENCES

1. Skoldenberg B, Forsgren M, Alestig K, Bergstrom T, Burman L, Dahlqvist E et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet* 1984; 2: 707-11.
2. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, Hanley D, Nahmias AJ, Soong SJ. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med* 1986; 314: 144-9.
3. Whitley RJ. Viral encephalitis. *N Engl J Med* 1990; 323: 242-50.
4. Aurelius E, Johansson B, Skoldenberg B, Staland A, Forsgren M. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet* 1991; 337: 189-92.
5. Rozenberg F, Lebon P. Amplification and characterization of herpesvirus DNA in cerebrospinal fluid from patients with acute encephalitis. *J Clin Microbiol* 1991; 29: 2412-7.
6. Klapper PE, Cleator GM, Longson M. Mild forms of herpes encephalitis. *J Neurol Neurosurg Psychiatry* 1984; 47: 1247-50.
7. Fodor PA, Levin MJ, Weinberg A, Sandberg E, Sylman J, Tyler KL. Atypical herpes simplex virus encephalitis diagnosed by PCR amplification of viral DNA from CSF. *Neurology*1998; 51: 554-9.
8. Domingues RB, Tsanaclis AM, Pannuti CS, Mayo MS, Lakeman FD. Evaluation of the range of clinical presentations of herpes simplex encephalitis by using polymerase chain reaction assay of cerebrospinal fluid samples. *Clin Infect Dis* 997; 25: 86-91.
9. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, Lebon P, Canton P, Rozenberg F. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenterstudy. *Clin Infect Dis* 2002; 35: 254-60.
10. Lakeman FD. Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis* 1995; 171: 857-63.
11. Kennedy PG. A retrospective analysis of forty-six cases of herpes simplex encephalitis seen in Glasgow between 1962 and 1985.*Q J Med* 1988; 68: 533-40.
12. Roman-Campos G. Toro G. Herpetic brainstem encephalitis. *Neurology* 1980; 30: 981-5.
13. Jennett B, Bond M. Assessment of outcome after severe brain damage. A practical scale. *Lancet* 1975; I: 480-4.
14. Hong Kong Hospital Authority. Management Guidelines, Internal Medicine, 3rd edition, 2002.
15. Koskiniemi M, Manninen V, Vaheri A, Sainio K, Eistola P, Karli P. Acute encephalitis. A survey of epidemiological, clinical and microbiological features covering a twelve-year period. *Acta Med Scand* 1981; 209: 115-20.
16. Davison KL, Crowcroft NS, Ramsay ME, Brown DW, Andrews NJ. Viral encephalitis in England, 1989-1998: what did we miss? *Emerg Infect Dis* 2003; 9: 234-40.
17. Lee TC, Tsai CP, Yuan CL, Wei CY, Tsao WL, Lee RJ *et al.* Encephalitis in Taiwan: a prospective hospital-based study. *Jpn J Infect Dis* 2003; 56: 193-9.
18. Huang CC, Liu CC, Chang YC, Chen CY, Wang ST, Yeh TF. Neurologic complications in children with enterovirus 71 infection. *N Engl J Med* 1999; 341: 936-42.
19. Goh KJ, Tan CT, Chew NK, Tan PS, Kamarulzaman A, Sarji SA, Wong KT, Abdullah BJ, Chua KB, Lam SK. Clinical features of Nipah virus encephalitis

among pig farmers in Malaysia. *N Engl J Med* 2000; 342: 1229-35.
20. Chung PH, Lam R. Epidemiology of Japanese encephalitis in Hong Kong, 1967-2003. *Pub Health Epid Bulletin* 2004; 13: 17-21.
21. Hong Kong Department of Health. Annual Departmental Reports: 1996-2001.