Short report

Mild forms of herpes encephalitis

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SUMMARY Three cases of herpes encephalitis are described. A definite diagnosis was established and all patients made a good recovery without specific antiviral chemotherapy. These reports are representative of those forms of herpes encephalitis with a good prognosis. It is suggested that the introduction of rapid non-invasive procedures will indicate a higher incidence of herpes encephalitis than is presently accepted. The relevance of repeated episodes of herpes encephalitis with respect to the aetiology of some psychiatric disorders and in the evaluation of antiviral agents is also discussed.

The classic presentations of herpes encephalitis are those of severe diffuse meningoencephalitis or severe focal encephalitis.^{1,2} These conditions are exceptionally severe, cause a high mortality (ranging from 50 to 70%) and a considerable degree of residual brain damage in survivors.^{4,5} It has been suggested^{6,7} that milder forms of herpes encephalitis should be recognised and in this paper we report three case histories which provide supportive evidence. In patients 1 and 3 the encephalitis was focal whilst in patient 2 it was more diffuse. All the patients made a good recovery without specific antiviral therapy. These forms of encephalitis are of particular interest in the design of clinical trials of antiviral drugs for the treatment of herpes encephalitis.⁸

Patients and methods

Case 1 A 56-year-old, previously healthy lady was unconscious on admission. Relatives reported a 4 day history of drowsiness, morbid thought and irrational fear with 3 days of vomiting, nausea and anorexia. On the morning of admission she had awoken early, exhibited abnormal behaviour and then aphasia before lapsing abruptly into unconsciousness. There was no relevant past medical, family or psychiatric history. Examination was unremarkable, blood pressure was 160/90 mm Hg, pulse 100 per minute and temperature 38.2°C. The right pupil was larger than the left but there was no papilloedema; there was increased tone on the left side. During the examination she had a fit with clonic movements down the left side. The fit was controlled with intramuscular diazepam (10 mg). Two hours

after admission she regained consciousness but remained drowsy and disorientated. Blood values for urea, electrolytes and plasma glucose were within normal limits. Chest and skull radiographs were normal. One week after admission she developed stiffness of the neck and her level of consciousness decreased. Cerebrospinal fluid (CSF) taken at the time contained 70 lymphocytes per mm³, no erythrocytes, and protein of 1.78 g/l. Lumbar puncture was repeated on the following day, 255 lymphocytes were found and protein had risen to 2.02 g/l. The CSF lactate (2.9 mmol/l) was sufficiently elevated relative to blood lactate (0.9 mmol/l) to suggest a serous meningitis.⁹ An electroencephalogram (EEG) at this time suggested a right sided focus, a finding which was supported by an isotopic (99Tc) brain scan. The brain scan showed diffuse increased uptake of isotope centred on the right temporal lobe. No bacteria or viruses were isolated from CSF. Prednisolone therapy was commenced on the 10th hospital day, 50 mg/day was given for 7 days and then reduced; steroids were withdrawn completely over the next 6 weeks. On day 13 of hospitalisation she lapsed into unconsciousness and remained unconscious for 48 hours with no response to pain or loud noise, she did however respond to bright light. During this time her temperature returned to normal. On day 15, a right temporal lobe biopsy was taken. The brain was under moderate tension and found to be soft in consistency. The biopsy showed signs of early necrosis with some lymphocytic and plasma cell cuffing. No inclusions or acid fast bacilli were observed and the specimen was bacteriologically sterile. *Herpesvirus simplex* was isolated in cell culture (human embryo lung fibroblasts) within 24 hours. Retrospective CSF antibody assay indicated intrathecal synthesis of *H simplex* antibody (table 1).

The day following brain biopsy her level of consciousness improved dramatically and thereafter continued to improve. Within 2 days she was oriented in time and place and her speech was coherent. Power, tone and reflexes returned gradually to normal. Eight days after biopsy she was sitting up and listening to the radio. A rapid almost complete recovery followed. Two months later her mental state was found to be virtually normal, but her powers of

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Table 1 Case 1: Laboratory results

Hospital day	Sample	H simplex CFT	RIA	Antibody index	IgG index
12	CSF	1/16	8000	12.4	2.19
19	Serum	1/160	63000		
20	CSF	1/32	10000		
34	CSF	1/16	1300		
65	Serum	1/160	100000		
100	CSF	1/2	1000		

All CSF specimens were culture negative. *Herpesvirus simplex* type 1 was isolated in human embryo lung fibroblasts from a temporal lobe biopsy on day 15 of hospitalisation.

CFT = Complement fixation test performed by standard technique¹⁰ in microtitre plates using reagents kindly provided by the Division of Microbiological Reagents and Quality Control, Public Health Laboratory Service, Colindale, London.

RIA = *H simplex* IgG antibody measured by radio-immunoassay¹¹ results are expressed in arbitrary units.

Antibody Index = normal (that is non-disease) Antibody Index = 0 to 1.9¹¹.

IgG Index = a valuable indication of intrathecal IgG synthesis.¹² Normal range in our laboratory is 0.28 to 0.6.

abstraction were slightly impaired. Her family also reported that she had become mildly disinhibited. After discharge she has suffered from grand mal epilepsy. The first attack occurred 2 months after discharge. No other sequelae have been noted and her epilepsy is now completely controlled on daily phenytoin (100 mg) and phenobarbitone (30 mg).

Case 2 A 42-year-old lady was admitted with a 5 day history of frontal headache, photophobia, vomiting and anorexia. There was no relevant past medical, psychiatric or family history. Physical examination was unremarkable. Her temperature was 38.2°C and there was no lymphadenopathy. Her pulse was 100 per minute and regular, blood pressure was 130/90 mm Hg. There was no neck stiffness and no neurological abnormalities were found. After admission her temperature settled promptly and spontaneously. Lumbar puncture was not performed initially as there were no specific signs and only conservative treatment with analgesics was given. There was some initial improvement but this was followed by drowsiness and slight confusion. A lumbar puncture was performed on the 8th hospital day. The CSF was slightly turbid and contained 1020 erythrocytes per mm³ and 330 lymphocytes per mm³, protein was raised at 1.75 g/l. No bacterial or viral growth was obtained on culture. Plain radiographs of chest and skull were normal. Electroencephalography showed asymmetric slow wave activity more marked on the left side. Further CSF taken 2 days later contained 750 erythrocytes and 250 lymphocytes per mm³. After a further 4 days CSF contained 89 erythrocytes per mm³ and no leucocytes, protein was still elevated at 1.75 g/l. The patient was now feeling extremely well and was discharged to home 3 days later. A brain scan (99Tc) at this time was

normal. One month after discharge she was readmitted for a further lumbar puncture and discharged the next day. This CSF contained 2 erythrocytes and 8 lymphocytes per mm³ and protein of 0.72 g/l. Apart from a partial loss of memory of events prior to her illness the patient has suffered no sequelae. Relevant laboratory investigations are summarised in table 2.

Case 3 A 37-year-old man was well until 5 hours before admission. He complained of a severe left sided headache of increasing intensity. He experienced difficulty in seeing and weakness of the left arm. He became drowsy but was excited and noisy when transferred to hospital. At age 10 years he had been involved in a road traffic accident and suffered a subdural haematoma. A right lateral flap had been opened and a clot aspirated. He had made a good recovery although at age 25 years he developed epilepsy. He suffered migrainous headaches at intervals but was well between attacks, he was reported to have a poor memory. Physical examination was unremarkable, his temperature was elevated at 39.5°C, pulse was 64 per minute, blood pressure 140/70 mm Hg. Neurological examination was virtually impossible (the patient was extremely restless), however there was no papilloedema and the plantars appeared to be flexor. A full blood count was normal and CSF was clear and colourless containing 28 white cells per mm³ (50% polymorphs, 50% lymphocytes); protein was 0.15 g/l. An electroencephalogram revealed marked bitemporal slow waves more pronounced on the right than on the left. A right carotid angiogram revealed no abnormality. On the third hospital day, a right temporal lobe brain biopsy was performed and ventricular CSF was collected at the same time. The brain was neither haemorrhagic nor oedematous. Examination of the biopsy mater-

Table 2 Case 2: Laboratory results

Hospital day	Sample	H simplex CFT*	H simplex antibody serum: CSF ratio	Poliovirus type 2† neutralising antibody	Poliovirus antibody serum: CSF ratio
2	Serum	1/10	20:1	—	320:1
10	CSF	1/8		1/1	
12	Serum	1/160		1/160	
48	CSF	1/16			

All CSF specimens were culture negative. Insufficient CSF remained for albumin, immunoglobulin G and H simplex RIA antibody assays.

*See table 1.

†Poliovirus micro-neutralisation tests were performed using standard technique with reagents kindly provided by the Division of Microbiological Reagents and Quality Control, PHLS, Colindale, London.

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ial showed largely normal tissue with some increase in perivascular lymphocytes, vacuolation and some neuronal shrinkage. *Herpesvirus simplex* was detected by immunofluorescence and the virus was also isolated in cell culture from brain and from ventricular CSF. The patient was given dexamethasone, 10 mg followed by 4 mg every 6 hours (8 doses) and then 2 mg every 12 hours (4 doses). By day 5 of hospitalisation he was sitting up. By day 8 he was fully orientated having made a complete clinical recovery. He was discharged to home on day 15. Apart from migrainous attacks and poor memory (both of which were present before the current episode) he appeared to have suffered no sequelae.

Discussion

Specific diagnosis of herpes encephalitis depends upon the demonstration of *H simplex* infection of the brain. This goal may be achieved either through examination of brain material obtained by burr-hole biopsy¹³ or by serum and CSF antibody assay with appropriate controls for blood-CSF barrier breakdown.^{11 14} In case 1 diagnosis was achieved by isolation of virus from the temporal lobe and detection of specific intrathecal *H simplex* IgG antibody synthesis, in case 2 by proof of specific intrathecal *H simplex* antibody synthesis using the technique established by MacCullum, Chinn and Gostling,¹⁴ in case 3 by isolation of virus from the temporal lobe and from ventricular CSF. Diagnosis of herpes encephalitis was thus unequivocal in all cases.

The patients received no specific antiviral chemotherapy. Patients 1 and 3 were treated with steroids whilst patient 2 was treated with analgesics. All recovered spontaneously and suffered relatively minor sequelae. Subsequent to discharge, patient 1 has suffered episodes of grand mal epilepsy. It is tempting to suggest that this epilepsy is a result of the neurosurgical intervention and not of the viral infection. In invasive procedures using burr-holes, epilepsy is a known post-operative risk.¹⁵

In contrast to severe focal and severe diffuse meningoencephalitis, we believe that mild disease with a good prognosis probably represents the more common presentation of herpes encephalitis. Mild forms of herpes encephalitis are apparently not accepted by some workers.¹⁶ However, the non-invasive methods by which this condition may be investigated are well established.¹⁷ It is our belief that less severe manifestations of the disease have not been acknowledged because of a failure to establish a diagnosis before the patient recovers. Brain biopsy together with immunofluorescent examination of the brain has been the method of choice for the diagnosis of herpes encephalitis. However, because of the hazards associated with this procedure biopsy is not usually undertaken in

mildly ill patients. The true diagnosis of many cases may thus have been missed. Although in this report, we have presented only three patients, a small number of other cases have been described by McKendrick.¹⁸ As non-invasive procedures for diagnosis^{14 11 19 20} are more frequently applied more cases will undoubtedly be recognised.

The pathogenesis of herpes encephalitis is of course far from clear²¹ and many models merit consideration. Accrued indirect evidence^{22 23} suggests that some form of reactivation event may initiate the disease. This being so, it is hard to reconcile the relative paucity of reported cases of herpes encephalitis with the apparent frequency of reactivation observed at peripheral sites. If as we suggest new diagnostic methods show that encephalitis is more common than has been previously thought then the paradox of low incidence may be explained and the low figure presently accepted to represent the incidence of herpes encephalitis will be shown to be incorrect.

As well as being of relevance in the context of epidemiology mild cases of herpes encephalitis are of particular interest in two further areas: in psychiatric illness and in clinical trials of antiviral drugs. Subclinical herpes encephalitis has previously been suggested, on immunological grounds^{24 25} to result in subsequent psychiatric or psychotic illness and Sequiera *et al*²⁶ have shown *H simplex* to be latent within the brains of three of four patients who died with chronic psychiatric illness. Is it possible that one or more reactivation events resulting in mild disease could play an aetiological role in such conditions? In relation to the study of the efficacy of antiviral drugs, cases of encephalitis with a good prognosis assume major importance. There is a real need for a predictive index of severity.⁸ If this were available it would then be more acceptable to decide whether or not to include patients in double blind placebo controlled trials of potentially useful antiviral drugs.

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