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Acyclovir treatment of herpes simplex encephalitis: experience in a district hospital

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Summary: Herpes simplex encephalitis may be underdiagnosed in Britain. We report eight patients treated at one hospital over three years. Fever, impaired consciousness or focal neurological signs were seen in all patients at presentation but herpes simplex encephalitis was rarely considered as the initial diagnosis. The electroencephalogram was the only initial investigation that was abnormal in each case and was the most useful test in establishing a clinical diagnosis. The diagnosis was confirmed by laboratory methods in each case. Following acyclovir treatment five patients were able to resume normal activities, one patient has moderate disability and two patients died. Three patients showed clinical evidence of relapse but two improved after further treatment with acyclovir.

Herpes simplex encephalitis is a treatable condition and should be considered in all patients presenting with fever and neurological signs. The electroencephalogram is usually abnormal and the changes may be characteristic of the condition.

Introduction

Herpes simplex encephalitis (HSE) is recognized to be the most common form of severe viral encephalitis seen in this country. Without specific treatment it carries a mortality of up to 70% and survivors often show serious neurological disability.[1] Two recent trials have shown that treatment with acyclovir results in a significant improvement in the natural history of this condition.[2,3] The mortality rate has been reduced to 20–30% and the incidence of disability in survivors has also been reduced. Despite this therapeutic advance, HSE remains a difficult management problem. It is agreed that early diagnosis and treatment are necessary to obtain the best outcome[3] but there is still debate about the appropriate methods to be used in establishing a diagnosis.[4,5] We have found that HSE is seen more frequently than reported incidence figures for this country would predict, but HSE is rarely considered in the initial differential diagnosis when such patients are admitted to hospital. We therefore report our experience with eight patients seen over the last three years.

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Patients and methods

Between July 1983 and June 1986 eight patients with proven HSE were treated at this hospital. The diagnosis was confirmed by laboratory methods in each case. In surviving patients there was a significant rise in the titre of complement fixing antibodies to herpes simplex virus (HSV) in blood and cerebrospinal fluid (CSF). The plasma:CSF albumin ratio was used to calculate the antibody index which confirmed the occurrence of intrathecal antibody synthesis.[7] In one patient who died HSV type 1 was isolated from the brain at post mortem, in the other the presence of HSV antigens in the brain was shown by immuno-gold silver staining.[8]

A computed tomographic (CT) scan and serial electroencephalograms (EEGs) were done in all of the patients. All of the patients were treated with intravenous acyclovir 10 mg/kg eight hourly for 10 days and with dexamethasone 4 mg six hourly in reducing dosage. In addition, all of the patients received anticonvulsants, usually intravenous phenytoin. Outcome was assessed at routine clinical follow-up and by psychometric testing at an interval after the end of treatment. The degree of residual disability was classified as described by Whitley *et al.*[3,9]

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Table I Radiological and electroencephalographic findings on admission

Patient	*CT scan*	*EEG*
1	Right temporal lesion.	Repetitive complexes right temporal region.
2	Small ventricles.	Repetitive complexes left temporal region.
3	Small ventricles.	Repetitive complexes left temporal region.
4	Left temporal lesion.	Repetitive complexes left temporal region.
5	Left temporal lesion.	Slow wave abnormality left temporal region, later appearance of repetitive complexes.
6	Left temporal lesion.	Slow wave abnormality left temporal region, no repetitive complexes.
7	Cortical atrophy.	Repetitive complexes right temporal region.
8	Normal.	Repetitive complexes, right temporal region.

Results

Five patients were initially admitted to this hospital centre and three were referred from other local hospitals. In all of the patients there had been a prodromal illness lasting from 1 to 7 days in which the common features were fever, headache and increasing mental confusion. On admission all of the patients were pyrexial with a temperature of 38.5°C or more. Seven of the patients showed impairment of consciousness which varied from drowsiness to coma; only one patient was alert at the time of admission and he was dysphasic. Three other patients were also dysphasic and one patient had a mild hemiparesis. An homonymous upper quadrantic visual field defect was present in one patient. Two patients had seizures near the time of admission. Only two patients showed signs of meningism.

A CT head scan was performed on admission to this hospital (Table I). In four patients a focal low attenuation lesion was present affecting the temporal lobe unilaterally (Figure 1). These four patients all had focal neurological signs and had had a longer duration of symptoms by the time of the scan. Two other patients with focal neurological signs developed similar CT scan abnormalities later in the illness. In the other patients the initial scan was normal or showed decreased ventricular size.

The initial CSF was abnormal in six patients and became abnormal on the day following admission in one other patient. In one patient the CSF remained normal throughout the illness. The principal abnormality was an elevation of the CSF lymphocyte count (31 to 246 cells/mm^3), five patients showed an increase in the CSF red cell count (6 to 255 cells/mm^3), and one patient showed an increased CSF protein concentration but none showed xanthochromia or reduced CSF glucose.

The EEG was the only initial investigation that was abnormal in every case (Table I). In all of the patients the EEG showed a diffuse excess of slow activity more marked on the clinically affected side. In addition repetitive complexes were present in the initial record in six patients (Figure 2, Table I). The complexes did not have a stereotyped form in all patients nor were all of them regularly periodic but this pattern sometimes evolved later. In one other patient repetitive complexes developed on the EEG within 48 hours of admission but in one patient such complexes were not present at any stage of the illness.

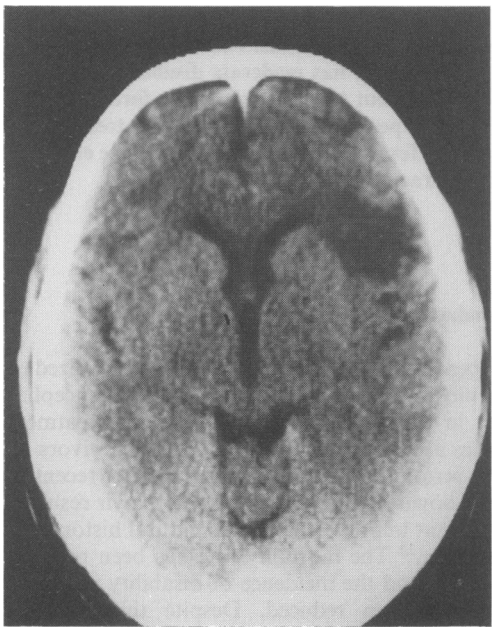

Figure 1 CT head scan for case 1 on admission showing right temporal low attenuation lesion.

Treatment was initiated on the basis of clinical

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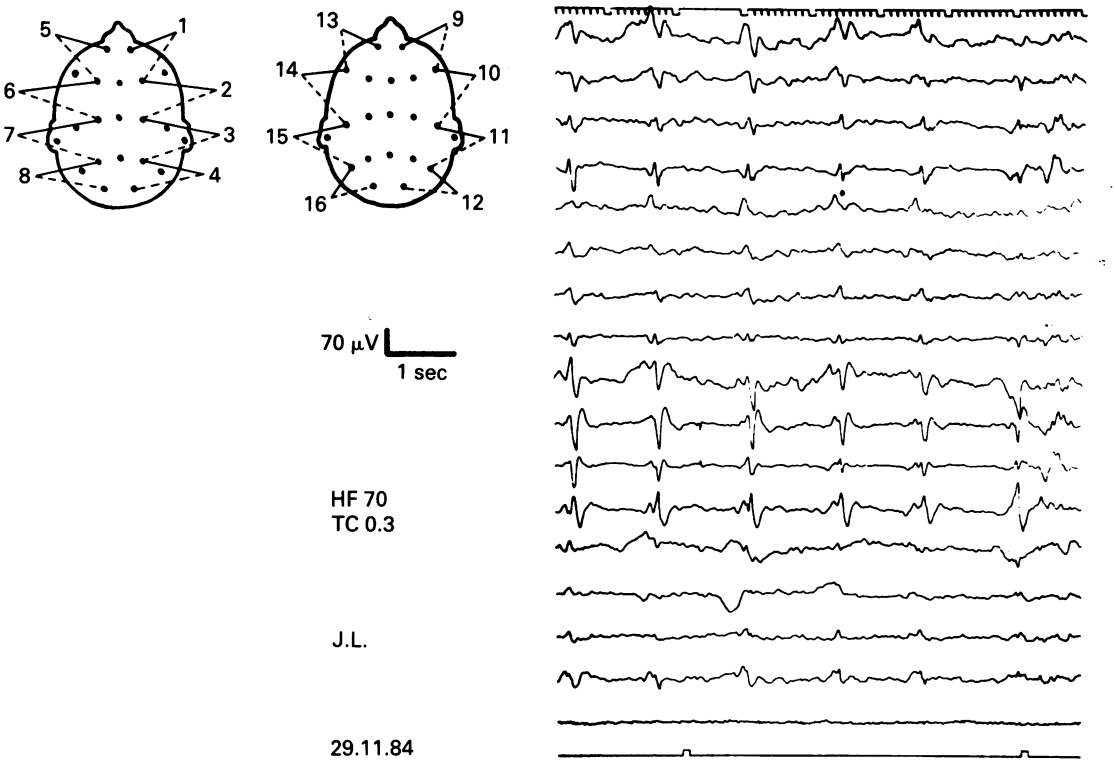

Figure 2 Electroencephalogram for case 1 two days after admission showing stereotyped complexes with regular recurrence rate. (Channels numbered from the top).

Table II Treatment and outcome.

Patient	*Age (years)*	*Conscious level at start of treatment*	*Duration of symptoms before treatment (days)*	*Outcome*
1	58	Comatose	4	Full recovery
2	61	Comatose	2	Full recovery
3	63	Disorientation	2	Minor disability
4	57	Drowsy	12	Minor disability
5	63	Drowsy	5	Moderate disability
6	32	Drowsy	7	Severe disability
7	76	Comatose	7	Died
8	78	Comatose	6	Died

radiological and electroencephalographic findings. Table II summarises the clinical state at the start of treatment and the outcome following treatment. Two patients who were comatose when treatment was started made a good recovery and returned to a normal life. Both show no subjective impairment of memory while psychometric testing shows mild memory deficits in each case. Two other patients also made a good recovery but have detectable minor memory impairment. One patient shows moderate

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disability because of residual dysphasia but she has also resumed normal activities. One patient is disabled because of residual dysphasia and severe memory impairment. Two patients died; both were elderly patients who had been comatose at the start of the treatment.

Although functional recovery continued for several months after the illness, improvement began during the initial course of acyclovir in all of the patients except one who died within a few hours of starting treatment. In four patients continuous recovery occurred but three patients showed a further deterioration 3, 7 and 19 days after acyclovir was stopped. One patient became drowsy and pyrexial and her CSF showed a rising lymphocyte count. The second patient became comatose and her EEG showed the reappearance of repetitive complexes. The third patient had two generalized seizures and became increasingly dysphasic over two days. She also developed a new homonymous hemianopia and her CSF remained abnormal. These three patients were all retreated with dexamethasone and acyclovir. The second patient continued to deteriorate and died but the other two showed a rapid improvement after the start of retreatment.

Discussion

The true incidence of HSE is unknown.[6] A recent study in Sweden found an incidence of 2.3 per million per year for the country as a whole.[2] In contrast only about fifty cases are reported each year in Britain.[10] Our unit has a central location in a well defined referral area with a population of one million. Over the last three years we have seen eight patients with HSE, an incidence rate at least equal to that seen in Sweden. The clinical features of HSE are not specific but certain features in combination strongly suggest the diagnosis.[6] A prodromal illness of headache and malaise is usually followed by rapid deterioration with fever and impaired consciousness, seizures or focal neurological signs. Disturbances of speech, memory and behaviour are common. In such patients the finding of a low attentuation lesion with a characteristic temporal localization on CT scan, or the presence of a CSF lymphocytosis both supports the diagnosis and helps to exclude other diagnostic possibilities. However, both of these investigations may be normal particularly at an early stage of the illness.[11,12]

We have found the EEG to be the most useful immediate investigation in supporting a clinical diagnosis of the HSE.[13] In each of our cases the initial EEG was abnormal showing bilateral slowing with hemisphere asymmetry and in six cases repetitive complexes were present. The use of short time constants during part of the EEG recording on admission may be important in revealing these complexes. Although not specific for HSE, in this clinical context such changes are very suggestive of the diagnosis. In this respect the EEG changes are more specific than those shown radiologically and they occur at an earlier stage of the illness. We based the decision to treat on clinical and electroencephalographic findings. Although these patients often showed characteristic features of HSE this had rarely been considered as an initial diagnosis; initial diagnoses had included stroke, viral meningitis, pneumonia and septicaemia. Failure to consider the correct diagnosis on admission was the main cause of a delay in starting specific treatment. Following current practice[14,15] the clinical diagnosis was confirmed in surviving patients using serological criteria.[7] Although brain biopsy can provide a more rapid confirmation of the diagnosis[16] the morbidity associated with this procedure[9] and its significant false negative rate,[9] together with the low toxicity of acyclovir[17] make it a difficult procedure to justify.[5]

The patients were treated with acyclovir according to recommended guidelines.[17] Two of our patients made a full recovery despite seriously impaired conscious level when treatment was started; the presence of coma may not carry the uniformly adverse prognosis that has been suggested.[3] Although memory loss was an important sequel to HSE before specific treatment became available[18] only one of our patients showed clinically significant memory impairment following recovery; in the other patients there was either absent or only minor memory impairment. Three of our patients showed a late deterioration which in two cases responded to further antiviral treatment. Although pathological confirmation was not obtained, the clinical features and response to treatment in these patients suggested that a recurrence of viral encephalitis had occurred. Relapse after antiviral treatment has been reported in patients treated with adenine arabinoside[19] and cytosine arabinoside[20] but has not previously been noted in acyclovir treated patients. The reasons why the infection is more resistant to treatment in some cases are not clear but our findings suggest that 10 days treatment can sometimes be insufficient; resolution of fever and CSF lymphocytosis might be used as additional guides to the duration of treatment.

This series of patients supports the view that HSE may be more common than presently recognized in this country. Diagnosis requires a high index of suspicion but the characteristic electroencephalographic changes often help to establish an early diagnosis. Treatment with acyclovir can result in a satisfactory outcome even in patients who are comatose when treatment is started but early diagnosis and treatment are essential in order to minimise both the morbidity and mortality resulting from this condition.

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