LETTERS TO THE EDITOR

Detection of Epstein-Barr virus genome in peripheral leucocytes and CSF by the polymerase chain reaction in two patients with Epstein-Barr virus related to aseptic meningitis

Epstein-Barr virus, a lymphotropic herpes virus that causes infectious mononucleosis, also causes neurological disorders such as encephalitis, cerebellitis, meningitis, and the Guillain-Barré syndrome. The detection of the Epstein-Barr virus genome has been described.^{1,2} We report two patients with aseptic meningitis having symptoms similar to those of infectious mononucleosis, in whom the Epstein-Barr virus genome was detected in peripheral leucocytes and CSF by the polymerase chain reaction (PCR).

Patient 1, a 34 year old Japanese man presented with fever and headache in May 1993. He had no underlying disease. Eight days after the onset of symptoms, he was admitted to our hospital. No rash, lymphadenopathy, or hepatosplenomegaly was noted. He was alert and showed mild signs of meningeal irritation. No other neurological abnormalities were found. Laboratory data showed leucocytosis (11 200), 3% atypical lymphocytes, and a slight increase in aspartate aminotransferase and γ -glutamyl-pyruvic transaminase. The Paul-Bunnell test was negative. His CSF showed lymphocytic pleocytosis (65/mm³), including 3% atypical lymphocytes and a mild increase in protein, but the CSF concentration of glucose was normal. Serum testing showed Epstein-Barr viral capsid antigen (VCA)-IgG and VCA-IgM. VCA-IgG decreased 160 times to 40 times between the acute stage and recovery (three months) and VCA-IgM also decreased (10 times to <10 times) whereas Epstein-Barr nuclear antigen increased from <10 times to 80 times. There were no significant antibody titres for herpes simplex, varicella zoster, or cytomegalovirus. Findings on chest radiographs, ECG, brain CT, and EEG were normal.

Patient 2, a 20 year old Japanese woman presented with fever and headache in June 1993. She had tonsillitis and swelling of the lymph nodes in the postauricular region. Neurological examination on admission showed only mild meningeal signs. Three per cent atypical lymphocytes were found in the peripheral blood and CSF. The Paul-Bunnell test was negative. Her CSF showed mild pleocytosis (102/mm³), a mild increase in protein, and a normal glucose concentration. Serum and CSF EBV VCA-IgG decreased more than four times between the acute to recovery stage (serum 320 times to 40 times, CSF 4 times to <1 times). No other significant changes in viral antibody titres were found. Normal results were obtained on brain CT and EEG.

We made a presumptive diagnosis of Epstein-Barr virus meningitis in both patients on about the 10th day after onset of illness, based on symptoms resembling those of infectious mononucleosis and the presence of raised Epstein-Barr virus anti-

body titres. Both responded well to conservative treatment. Meningeal signs disappeared and CSF findings became normal within one month of onset of symptoms.

Peripheral leucocytes and CSF were subjected to capillary PCR.³ The PCR analysis was performed with 1 μ l of extracted DNA from about 500 μ l leucocytes with buffer, and with a 50 μ l sample of CSF. The primers for the EBNA1 gene have been described by Telenti *et al*⁴ using the sequences: 5'-GTCATCATCATC-CGGGTCTC for the plus strand and 5'-TTCGGGTGGGAACCTCCTTG for the minus strand. Amplification of DNA by rapid and high sensitivity capillary PCR was carried out for 40 cycles at 94°C for five seconds (denaturation), 42°C for five seconds (annealing), and 72°C for three seconds (extension). Products of the PCR were visualised with UV light by staining with ethidium bromide after gel electrophoresis, and Epstein-Barr virus DNA was detected as a specific 220 bp band. DNA extracted from Daudi cells was used as the Epstein-Barr virus positive control. Epstein-Barr virus DNA was detected in the CSF obtained 10 days after onset in patient 1, and eight days after onset in patient 2, and continued to be detected for three weeks after onset in both patients, whereas DNA was positive in the leucocytes four weeks after onset. Analysis by PCR was also performed for leucocytes and CSF samples from five control subjects with aseptic meningitis caused by Behçet's disease, but no Epstein-Barr virus DNA was found in these cases.

A few reports have described the detection of the Epstein-Barr virus gene by PCR in the blood and CSF of patients with neurological disorders caused by the Epstein-Barr virus. Imai *et al*¹ analysed CSF by PCR and Southern blotting, and found Epstein-Barr virus DNA in the CSF of five children with meningoencephalitis associated with infectious mononucleosis during the acute stage. Landgren *et al*² reported the detection of Epstein-Barr virus DNA by nested PCR in the serum and CSF of two patients with encephalitis and myelitis. In both of our cases, Epstein-Barr virus DNA was found in peripheral leucocytes and CSF during the acute stage of aseptic meningitis associated with a syndrome resembling infectious mononucleosis. Detection of Epstein-Barr virus DNA was possible for three to four weeks after onset. Due to the difficulty in isolating Epstein-Barr virus, few studies have isolated it from the CSF of patients with neurological disorders.⁵ Our experience indicates that the detection of Epstein-Barr virus DNA by PCR is useful in diagnosing Epstein-Barr virus related to aseptic meningitis and in evaluating its pathophysiology.

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"Silent diabetes": non-ketotic hyperglycaemia presenting as aphasic status epilepticus

A 74 year old, right handed, retired messenger had been well until two weeks before admission. On that day he had telephoned his daughter, who found his speech difficult to understand. Over the subsequent days, his speech became more incoherent but he expressed his wishes by pointing, and other basic mental functions were preserved; he washed and dressed himself and found his way around the house. Immediately before admission, his walking became unsteady and relatives noticed some other errors—for example, holding his knife and fork in the wrong hands. A key feature of this history was its progressive course. There was a history of occasional drop attacks of uncertain cause before the age of 30.

On examination, appropriate verbal and motor responses were sporadic and formal assessment showed a pronounced deficit of receptive and expressive function. He could only just write his name but could find his way around the ward without guidance. General and neurological examination were otherwise normal. Routine investigations showed a blood glucose concentration of 38.7 mmol/l with serum osmolality of 303 mmol/l but no ketonuria or systemic acidosis. Electrolytes and full blood count were normal. Glycosylated haemoglobin was 16%. Brain CT showed generalised atrophy but no focal lesion. His CSF was acellular with protein concentration raised at 1.18 g/l; there were no oligoclonal bands. Glucose concentration in CSF was 14.6 mmol/l (blood 28.7 mmol/l). Electroencephalography showed low to medium amplitude delta activity over the left hemisphere. There were scattered theta waves bilaterally and occasional sharp components in both temporal regions but no features of an encephalitis. There was a clear seizure discharge, initially at 12 Hz, slowing to 10 Hz, maximal over the left mid to posterior temporal area, lasting two minutes (figure). During this discharge, he was asked how he felt and was able to nod. There was no evidence of ictal motor activity. Intravenous diazepam resulted in drowsiness with no other change in his clinical state. Cerebral blood flow was assessed by SPECT with ^{99m}Tc-HMPAO interictally, and showed reduced uptake in the left superior temporal and inferior frontal gyri.

He was treated with insulin and phenytoin and over the next five to seven days his condition deteriorated, despite gradual normalisation of blood glucose and appropriate phenytoin treatment. He became increasingly drowsy, with motor accompaniments to his seizures appearing for the first time.

EEG showing seizure discharge evolving over a wide distribution over the left hemisphere with rhythmic activity at 12 Hz and up to 70 μV. The right hemisphere shows alpha rhythm with superimposed slower rhythms and no seizure activity.

Initially these were subtle; nystagmus to the right and twitching of his right index finger but more gross movements of his arm supervened. At no stage was there a generalised convulsion. Addition of other anti-convulsants caused increasing drowsiness without clear benefit and these were subsequently withdrawn. Five weeks after the onset, his speech started to return and within seven days he was coherent with good short and long term memory. Epilepsy and diabetes were well controlled six months later with phenytoin and oral hypoglycaemic agents and repeat SPECT showed resolution of the blood flow abnormalities.

The EEG findings, absence of a structural lesion or markers of encephalitis, and ultimate recovery suggest his clinical state was due to recurrent focal seizure activity. When focal status epilepticus presents with motor symptoms, the diagnosis is straightforward. In this case, the initial lack of motor accompaniment, the focal nature of the deficit without obvious global confusion, and its progressive course without fluctuation, were all unusual. The progressive clinical picture, with intermittent scalp EEG seizure activity, may have been due to more continuous seizure activity in deeper structures, not manifest at the scalp, or else an increasingly severe Todd's phenomenon, affecting speech, from frequent seizures.

We have found only seven previous reports of aphasic status epilepticus in adults.^{1,2} Two had recognised epileptogenic focal lesions of the left hemisphere and two others were diabetic. In one of these, blood sugar was 23 mmol/l at the time of presentation,² although this association was not emphasised in the report and the patient, who was aphasic for 12 days, also had no other identifiable cause.

Focal motor seizures and epilepsy partialis continua may occur in up to 25% of patients with non-ketotic hyperglycaemia, unlike the generalised seizures associated with most metabolic derangements. In the

largest series, this was the first presentation of diabetes in nine of 21 patients; seizures occurred at glucose concentrations as low as 15 mmol/l.³ An appropriately sited lesion was seen in 13 of these cases, by contrast with the generalised atrophy without focal change seen on CT in our patient. In these cases too, the seizures lasted for one to four weeks, then remitted, without any clear relation to glycaemic control or anticonvulsants. The reason for this lag of clinical resolution behind metabolic correction is not clear; it seems to exceed the usual delay in dysequilibrium syndromes.

The hyperosmolarity of hyperglycaemia can itself cause infarction and regional reduction of cerebral blood flow in rats.⁴ The SPECT findings in this case would be consistent with this, although the confounding effect of the seizures themselves on cerebral blood flow cannot be excluded. Seizures may be triggered by hyperglycaemia in the cat's occipital cortex rendered irritable by local penicillin treatment.⁵ A potential mechanism is, therefore, the hyperosmolar irritation of neurons rendered ischaemic by an enhanced tendency to vascular disease and by an acute reduction in cerebral blood flow secondary to hyperglycaemia and dehydration.

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Alien hand sign or alien hand syndrome?

A precise definition of the alien hand syndrome does not yet exist. Classic descriptions comprise three or four hallmarks: (a) a feeling of foreignness of the limb, (b) failure to recognise ownership of it when visual clues are removed, (c) autonomous motor activities that are perceived as involuntary and are different from other identifiable movement disorders, and (d) personification of the affected body part.^{1,2}

The combination of lesions necessary to produce this phenomenon is not certain. Traditional studies showed that damage to the bifrontal cortex, lesions of the anterior corpus callosum alone, or combinations of frontal and callosal lesions were most often involved.^{3,4} Nevertheless, several cases of alien hand syndrome with different neuropathological findings are raising new hypotheses.^{1,5,6}

Our patient had an alien hand syndrome after a lesion in an unusual site. An 80 year old, right handed man complained of strange involuntary movements of his left hand. He was a retired pianist with a history of chronic obstructive pulmonary disease, hypertrophic cardiomyopathy, and acute myocardial infarction 17 years previously. He did not complain of any past neurological condition. He was well until the morning of admission when he was suddenly woken by "insistent touching of his neck and face". As he was living alone, he was frightened by the thought of "someone breaking into the house", and was puzzled when he realised that it was his own left hand that was scratching him. When attempting to wash and dress himself, he had serious difficulties due to the interference of his left hand, which could not be restrained from grasping his razor or unbuttoning his clothing.

The patient was fully alert and oriented, and general physical examination was unremarkable. There was no disturbance of language. He was unable to reach objects with his left hand under visual control. The cranial nerves were otherwise intact. Motor function was normal although there was a mild left hypaesthesia, and tactile neglect. He was unable to distinguish his limb from the examiner's or to recognise objects with his left hand when visual clues were absent. He was unaware of the location of his left arm. He displayed some non-goal directed activities such as scratching and raising his left hand, which he perceived as imposed and uncontrollable. These autonomous movements were sometimes triggered by movement of the right hand. There was also enormous difficulty in bimanual coordination tasks, such as taking off his glasses.