

## Epstein-Barr virus encephalitis in an apparently healthy adult

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For more than 20 years now Epstein-Barr virus (EBV) has been known to cause severe neurological complications including encephalitis.<sup>1</sup> This can occur in the immunosuppressed as well as in primary infection of a healthy individual.<sup>1</sup> Epstein-Barr virus encephalitis is rare, occurring in less than 1% of cases, with a self-limiting nature and few sequelae, but it can cause fatal illness even in immunocompetent individuals.<sup>2</sup> We report a case of a patient who developed EBV infection in the fifth decade of life and died from fulminant encephalitis despite acyclovir therapy.

A 51-year-old Sudanese male, (scrap metal worker), was admitted through the accident and emergency department of Riyadh Medical Complex, Riyadh, Saudi Arabia, complaining of fever and altered mental behavior for 4 months. At the onset of the illness, he developed a fever that was more at night but not associated with rigors, shivers, or drenching sweats. He subsequently developed episodes of confusion, being held down by 4 of his relatives in bed all through the night to avoid injury from agitation, followed by complete recovery for days at a time. Even though a history of antibiotic therapy could not be elicited with certainty, it could not be ruled out. Married with 4 children he had been living in Saudi Arabia for the past 20 years. He was teetotal, a nonsmoker and denied any extra-marital contact. On physical examination, he was disoriented and irritable, but had no neurological deficit. Funduscopy was normal, and there was neither neck stiffness nor lymphadenopathy. Chest, heart, and abdominal examination were normal. Urinalysis revealed a trace of ketones. Laboratory investigations showed a complete blood count with a white blood cell count of  $12.8 \times 10^9$ , neutrophils 46.6%, hemoglobin 15.9 g/dl, platelet count  $195 \times 10^9$  and an erythrocyte sedimentation rate of 28 mm/hrs. Urea and electrolytes showed a glucose 4.8 mmol/l, urea 0.4 mmol/l, creatinine 63  $\mu$ mol/l, sodium 137 mmol/l, potassium 2.9 mmol/l. Liver function tests showed aspartate dehydrogenase 113.8 u/l and an alanine transaminase 56 u/l, and an alkaline phosphatase 74.2 u/l, bilirubin 8.7  $\mu$ mol/l, and a serum amylase of 285 u/l, which on repeat, both returned to normal levels. His coagulation profile was normal. C-reactive protein was 25.6 mg/dl. Reactive plasma reagin and venereal disease research laboratory (VDRL)

test were negative. Hepatitis B and C screens were non-reactive. Human immunodeficiency virus (HIV) screen for HIV 1 and 2 were negative. Thyroid profile showed a thyroid stimulating hormone (TSH) level of 2.34 mIU/l and free thyroxine (FT4) level of 9.31 pmol/l (n: 12-22 pmol/l). Mantoux test, malaria films thin and thick repeated 3 times, brucella abortus and melitensis and blood, sputum as well as urine cultures were negative. He was admitted with a provisional diagnosis of partially treated meningitis versus tuberculous meningitis and commenced on ceftriaxone 2 grams (g) intravenously 12 hourly, and isoniazid 300 milligrams (mg), rifampicin 600 mg, ethambutol 800 mg and pyrazinamide 1.2 g all per os once daily. A CT scan of the brain with contrast was carried out, which was normal. Lumbar puncture showed cerebrospinal fluid (CSF) of bloody color and not under tension, cell count revealed a total white cell count (WBC) of 80 cells/mm, lymphocytes 65% and neutrophils 35%. Red blood cell count (RBC) 900 cells/mm<sup>3</sup>. Gram stain and direct smear, India ink stain, and latex test were negative. The CSF glucose was 154.62 mg%, blood glucose 267 mg%, and lactate dehydrogenase (LDH) 15 u/l, with a protein level of 91.8 mg%. The CSF Brucella and VDRL titers were negative. The CSF culture for bacteria including brucella and tuberculosis were negative. Viral cultures were sent for, but returned as not available in our laboratory. He was continued on the medication and improved within 2 days, became oriented and amicable, ambulating and eating with good appetite. Suddenly, on the fourth day, disorientation and confusion set in yet again, and this time associated with generalized convulsions and myokymia of the facial musculature. An MRI scan with gadolinium enhancement was normal but an electroencephalogram revealed diffuse slow waves indicating an encephalopathy. Acyclovir 10 mg/kg body weight was commenced, and the lumbar puncture repeated on the 6th hospital day. It showed CSF color clear, a total WBC 5 cells/mm<sup>3</sup>, RBC 480 cells/mm<sup>3</sup>, CSF glucose of 105.1 mg% and blood glucose 129 mg%, CSF LDH of 26 u/l and CSF protein 97.1 mg%, Gram stain negative. He improved again to complete normalcy until the 10th day, when he became confused again, and lumbar puncture was repeated for the third time. This time it showed a CSF WBC count 0 cells/mm<sup>3</sup>, RBC count 0 cells/mm<sup>3</sup>, CSF glucose 95.4 mg% and blood glucose 90 mg%, CSF LDH 26 U/L, CSF protein 53.7 mg%. A week later, the CSF cell count remained the same, but CSF protein rose to 121 mg%. All CSF cultures were reported as negative. Eventually, it was decided to repeat the MRI scan but the patient died the next day prior to the scan. No other intercurrent illness could

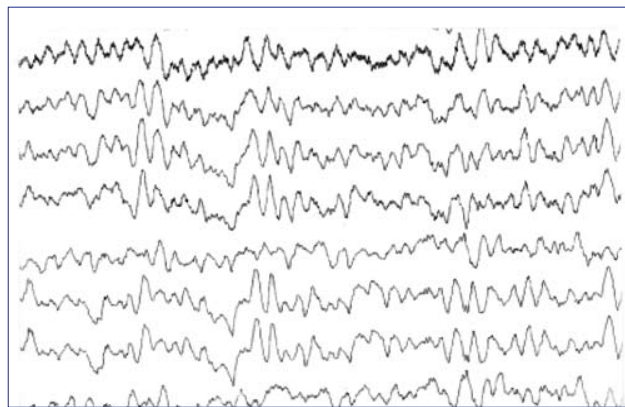
## Clinical Notes

account for it. The cerebrospinal fluid sample was sent to King Faisal Specialist hospital and Research Center microbiology department in liaison with the infectious disease service, and only Epstein Barr virus DNA was detected on viral polymerase chain reaction assays.

The neurological complication of encephalitis due to primary EBV infection has previously been reported exclusively in pediatric patients.<sup>2</sup> With 80-90% of normal adults having antibodies and therefore being immune to exogenous re-infection, endogenous reactivation seems to be the only route of infection and this occurs usually in conjunction with an immunosuppressed state.<sup>3</sup> More recently, reports of infection in adults have been noted, and 2 forms of EBV central nervous system (CNS) infections were described: 1. CNS syndromes associated with primary EBV or reactivated infection and, 2. CNS syndromes associated with chronic infection, which are either chronic or recurrent.<sup>4</sup>

Our patient was apparently immunocompetent. He had no diabetes mellitus or other chronic affliction. His HIV status for HIV 1 and 2 was negative. He was on no immunosuppressant medication. In fact, there was no record of any major illness in his past. The onset of his illness was subtle with the slow build up of episodes of confusion over a period of 4 months, becoming more regular, associated with fever culminating in utter disorientation yet interspersed with episodes of complete recovery. These episodes of normal intervals (of which there were 2 during his hospitalization) perplexed the team since they were taken at first as signs of recovery, before 24 to 48 hours later confusion would start yet again. The myokymia and generalized seizures observed are common expressions of encephalitis.<sup>1</sup> Whether our patient suffered from a chronic EBV infection or an acute infection with a protracted course is a matter of speculation since not all necessary antibody tests were performed. The complete blood count did not show the relative or absolute mononuclear lymphocytosis and thrombocytopenia usually seen in EBV infections. The blood film was not sent for atypical lymphocytes and heterophil antibodies and direct monoclonal antibody tests were not performed on serum, since the diagnosis of EBV encephalitis was not entertained initially.

As EEG is a useful tool in cases of encephalitis, so can it be in EBV encephalitis, since it not only can provide a clue to the diagnosis, it also can diagnose the complications of the latter in the form of seizure activity, which in one reported case lasted for nearly 2 months.<sup>5</sup> In our case, however, only a non-specific diffuse slowing was observed (**Figure 1**). The CSF



**Figure 1** - Electroencephalogram tracing showing diffuse slowing of brain activity.

PCR test eventually confirmed the diagnosis. The detection of EBV DNA in the cerebrospinal fluid by PCR is now the established method of diagnosis.<sup>6</sup>

In addition to EBV DNA, the presence of lytic cycle messenger ribonucleic acid indicates EBV-associated neurological disease.<sup>6</sup> Nowadays a microarray-based virus detection assay is qualitative and provides a single-format diagnostic tool for the detection of panviral CNS infections.<sup>7</sup> Both CT scan and MRI, as well as MRS (magnetic resonance spectroscopy) can be useful in the work-up and may reveal focal lesions.<sup>8</sup> These can, however, be normal as in our case (CT/MRI), in which case technetium-99m hexamethyl propylene amine oxime single-photon emission computed tomography (HMPAO-SPECT) can be used to identify areas of increased perfusion, and hence of affliction by the disease process.<sup>9</sup> Treatment is a matter of debate. With most EBV CNS infections abating spontaneously, the major part is supportive therapy including the control of seizures, and brain edema as well as hydrocephalus. Although acyclovir and its pro-drug valacyclovir are purported as a treatment in some reports, others concur with our finding that the clinical course is not influenced by it.<sup>1,2</sup> Ganciclovir, however, has been used successfully and might become the treatment of choice.<sup>10</sup> Plasmapheresis was reported to improve outcome in one case of EBV cerebellitis and points towards another treatment option once confirmed by others.<sup>11</sup> A clue to poor prognosis in our patient was the presence of sick euthyroid syndrome type 2 consisting of a normal TSH level in the presence of a low FT4.

In conclusion, we report that we dealt with an unusual case of a patient of apparently healthy immune status, who contracted EBV infection causing encephalitis with a protracted course, which did not

respond to acyclovir leading to his demise. Given the increasing amount of adult patients with this affliction in the literature, we urge to consider it in the differential diagnosis of patients with encephalitis.

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