Short report

Periodic EEG complexes in infectious mononucleosis encephalitis

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SUMMARY  The presence of periodic EEG complexes in patients with an acute viral encephalitis is generally held to suggest that infection is due to herpes simplex. We now report a patient with clinical and laboratory findings of infectious mononucleosis, and neurologic involvement manifested by lymphocyte meningitis, coma, seizures, aphasia, hemiparesis and hemianopsia. Serial EEGs showed periodic, predominantly left-sided slow wave complexes occurring every 4 to 5 seconds, which disappeared with clinical resolution of the illness. In view of our findings and the similar findings reported previously by others in another case of infectious mononucleosis encephalitis, an EEG showing periodic complexes in the clinical setting of acute viral encephalitis should not be considered pathognomonic of herpes encephalitis, and infectious mononucleosis should be included in the differential diagnosis.

Involvement of the nervous system in infectious mononucleosis has been recognised for 50 years, and occurs in 0·7 to 26·5% of patients in different series. The most common patterns of involvement include lymphocytic meningitis, polyneuritis, encephalomyelitis and mononeuritis, although a cerebellar syndrome, transverse myelitis, autonomic neuropathy, and chorea, have also been described. Encephalomyelitis may be focal in character. In a small number of patients, neurologic involvement may be the initial or predominant manifestation of infectious mononucleosis.

The importance of differentiating various types of viral encephalitis has been enhanced by the development of specific antiviral therapy for herpes encephalitis. The decision to perform routine brain biopsy, or to treat without biopsy in suspected cases, depends in part upon the reliability with which clinical and non-invasive laboratory features can distinguish herpes encephalitis. Among the features that have been considered helpful in this regard are focal neurologic findings, CT abnormalities and a characteristic EEG pattern. However focal encephalitis due to infectious mononucleosis may mimic herpes encephalitis, and CT scans early in the course of herpes encephalitis are often normal.

The value of the EEG in the diagnosis of herpes encephalitis is based upon the frequent—but not invariable—occurrence of repetitive slow wave complexes occurring at regular intervals of 1 to 4 seconds. These complexes may be bilateral, unilateral or focal, and often arise from one or both temporal lobes. Periodic complexes are nonspecific, as they may be seen in a variety of viral, metabolic and degenerative disorders. However the clinical features, temporal profile and cerebrospinal fluid formula in such disorders are generally distinct from those of herpes encephalitis, and the EEG findings rarely cause diagnostic confusion since the periodic complexes differ in their morphology, repetition rate and distribution in these different disorders.

The EEG in the encephalitis of infectious mononucleosis is most often characterised by diffuse or focal slow activity. Other patterns may be seen, however, and a single case has been reported in which infectious mononucleosis encephalitis was associated with periodic slow wave EEG complexes that could be confused with those occurring in patients with herpes encephalitis. We report a second such case, and discuss its implications in the

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early management of patients with viral encephalitis.

Case report
A 17-year-old boy previously in good health had complained of headaches for three days when his family observed a generalised tonic-clonic seizure, and took him to the local hospital. On arrival he was obtunded, and exhibited intermittent activity interpreted as seizures. Temperature was 38.2°C (100-7°F). Examination showed a supple neck and cervical adenopathy. WBC count was 17,900/mm³, with 74% lymphocytes and 5% monocytes. Blood count and serum chemistry were otherwise normal. Lumbar puncture showed an opening pressure of 160 mm water,with CSF containing 1 WBC/mm³, 172 RBC/mm³, protein 1.25 g/l and glucose 0.87 g/l. Brain CT scan showed an equivocal left temporal lucency. Because of concern about the possibility of herpes encephalitis, the patient was transferred to the University of California Medical Center, San Francisco. On admission, his temperature was 39°C. The neck was rigid and Kernig's sign was present. Skin and mucous membranes were normal except for pharyngeal erythema and exudate. There was symmetrical anterior and posterior cervical, axillary and inguinal adenopathy. The liver and spleen were not enlarged. On neurological examination he was alternately agitated and stuporous, but consistently responsive to mild noxious stimulation with symmetrical purposeful movements of the face and limbs. Optic fundi were normal, the pupils reacted to light, and extra-ocular movements were full. The deep tendon reflexes were absent, and both plantar responses were flexor.

WBC count was 15,200/mm³ with 24% lymphocytes and 1% monocytes, haemocrit 41.4%, platelet count 200,000/mm³, and sedimentation rate 8 mm/h. A test for the heterophile antibody of infectious mononucleosis (Monospot slide test) was positive. Hepatitis B surface antigen and Toxoplasma titre were negative. Lumbar puncture showed an opening pressure of 190 mm water, and CSF containing 28 WBC/mm³ (40% mono-histiocytes, 33% lymphocytes, 25% polymorphonuclear leucocytes, 2% large lymphocytes), 743 RBC/mm³, protein 0.90 g/l, glucose 0.9 g/l and glutamine 0.09 g/l (normal 0.08–0.187). CSF VDRL was non-reactive, CSF protein electrophoresis was normal, and IgG oligo-globulin bands were absent. Gram stain, India ink preparation, acid-fast stain, and bacterial, viral, fungal and acid-fast cultures were negative. A brain CT scan, performed with and without contrast, with multiple cuts through the temporal lobes, was normal. On the day following admission, WBC count was 11,000/mm³ with 15% atypical lymphocytes. Repeat lumbar puncture showed an opening pressure of 135 mm water, CSF containing 21 WBC/mm³ (59% lymphocytes, 28% mono-histiocytes, 13% polymorphonuclear leucocytes), 565 RBC/mm³, protein 0.92 g/l and glucose 1.04 g/l. Gram stain, India ink preparation, acid-fast stain and bacterial, fungal and acid-fast cultures were again negative.

On the fourth day the patient began to awaken, but remained mute. He blinked in response to threat in the left, but not the right, visual field. There was a right hemiparesis with right, and later bilateral, extensor plantar responses. WBC count was 10,800/mm³ with 24% atypical lymphocytes. An EEG showed diffuse slowing in the theta and delta frequency ranges, and over the right hemisphere low voltage generalised beta activity was also present; there was no alpha rhythm. Superimposed upon this background, periodic predominantly left-sided slow wave complexes occurred every 4 to 5 seconds (fig A), without clinical correlates. The subsequent hospital course was characterised by defervescence, full return of consciousness, and gradual but incomplete recovery of aphasia, right homonymous hemianopsia, right hemiparesis and areflexia. Repeat CT scan on day 5, and electromyogram and nerve conduction studies on day 14 were normal. Seizures recurred on day 7, but were controlled with phenytoin. EEGs performed on days 5, 9 and 11 continued to exhibit predominantly left-sided slow wave complexes with a periodicity of 4 to 5 seconds. On days 15 and 20, and at follow-up 2 months after the onset of the illness when the neurologic examination had returned to normal, EEGs showed predominantly left-sided slowing, but no periodic complexes (fig B). By day 15, a posteriorly-situated, responsive alpha rhythm was present on the right, but such activity was not seen on the left until the study performed 2 months after onset of the illness and even then it was relatively sparse and poorly formed.

Convalescent serum was obtained approximately one year after the illness for determination of IgM anti-viral antibodies by an anti-complementary fluorescent technique (Dr. Bagher Forghani, California Department of Health Services). Titres were: cytomegalovirus < 1:8, herpes simplex 1:32, Epstein-Barr anti-viral capsid antigen (VCA) ≡ 1:128, Epstein-Barr anti-nuclear antigen (EBNA) 1:2, and complete Epstein-Barr IgM immune response of 1:32.

Discussion
The diagnosis of infectious mononucleosis in this case was based upon the classical clinical syndrome of fever, pharyngitis and adenopathy, and laboratory findings of lymphocytosis with atypical lymphocytes and positive heterophile antibody (Monospot slide test). Neurologic involvement was manifested by lymphocytic meningitis, coma, seizures, and a focal syndrome consisting of aphasia, right homonymous hemianopsia and right hemiparesis. This is fully in keeping with the pattern of involvement described by others in infectious mononucleosis. While some aspects of this case caused concern about the possibility of herpes encephalitis, pharyngitis, adenopathy, and atypical lymphocytosis are not features of that condition. A positive Monospot test has been described rarely in disorders other than infectious mononucleosis, but never in herpes infection. Detailed viral antibody studies were not performed during the acute illness because of the compelling nature of clinical and laboratory evidence for infectious mononucleosis as the aetiology. Despite this and the patient's complete spontaneous recovery, the EEG findings of periodic
Fig. (A) EEG showing predominantly left-sided periodic slow wave complexes on a background of diffuse slow activity. The interval between complexes is about 4 seconds. (B) EEG recorded on day 20, showing marked left-sided slow activity. Some slow activity is also present on the right, but activity in the alpha and beta frequency ranges is now conspicuous on this side. The periodic complexes seen previously are no longer present.

complexes led us to seek more definitive support for the diagnosis of infectious mononucleosis encephalitis. The results of viral antibody studies on convalescent serum were suggestive of recent Epstein-Barr viral infection, and not of recent infection with cytomegalovirus or herpes simplex.

The EEG finding of period slow wave complexes was surprising, as such complexes have been previously described in only a single case of encephalitis associated with infectious mononucleosis. In that patient, an EEG obtained 2½ weeks into the illness, and 5 days after the onset of neurologic symptoms, showed synchronous periodic slow wave bursts occurring every 5 seconds. This activity became less prominent with resolution of the illness, and was absent at follow-up 18 months later. In our patient, as well, periodic complexes disappeared in temporal relation to clinical recovery. Recognition of the occurrence of periodic EEG complexes in infectious mononucleosis underlines the difficulty in aetiological diagnosis of acute viral encephalitis. Clinical, radiological and electroencephalographic findings cannot be relied upon to provide a definitive diagnosis. Given the demonstrated efficacy of adenine
arabinoside treatment for herpes encephalitis, and the expectation that specific (and perhaps more toxic) therapies for other viral encephalitides will be developed, brain biopsy and rapid virologic assays are likely to assume increasing importance in the differential diagnosis of these disorders.

References

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