

Electroencephalography in acute Nipah encephalitis

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Abstract

Objectives: To study the electroencephalographic (EEG) changes in acute Nipah encephalitis (NE). **Methods:** Cases were defined to have Nipah encephalitis based on contact with pigs, and clinical, cerebrospinal (CSF) or brain magnetic resonance imaging (MRI) features of the encephalitis. EEG was carried out at different phases of the illness. **Results:** 73 EEGs were carried out on 40 patients with 55 EEGs during the acute phase of illness and 18 on follow-up. 97.5% of the EEGs carried out in the acute phase were abnormal. The most common abnormality was continuous diffuse, symmetrical slowing with or without focal discharges (87.5%). The degree of slowing correlated with severity of disease. Focal discharges were seen in 53.1%. Independent bitemporal periodic complexes (PC) were common among those who were deeply comatose and were associated with 100% mortality. EEG changes did not correlate with focal neurological signs. EEG carried out during follow-up (after recovery from acute illness) showed no correlation with neurological status of the patients. **Conclusion:** EEG was a sensitive investigation in acute phase of Nipah encephalitis. Bitemporal PC were common in comatose patients and was associated with high mortality.

Key words: EEG, Nipah virus encephalitis, Malaysia.

INTRODUCTION

From September 1998 to June 1999, an outbreak of viral encephalitis occurred in several pig-farming villages in Malaysia.¹ Of the more than 200 patients nationwide, 94 were admitted to the University of Malaya Medical Centre (UMMC), Kuala Lumpur. Since then, four other relapse cases were seen. The illness was initially thought to be Japanese encephalitis but a new paramyxovirus related to Hendra virus isolated from the cerebrospinal fluid (CSF) of some of the patients proved to be responsible for the epidemic.² It was named Nipah virus after Kampung Sungai Nipah, the village of the patient from which the virus was first isolated. The disease later spread to Singapore involving 11 abattoir workers with one mortality.^{3,4}

The infection was thought to spread from pig to man through close contact.^{2,5} The clinical features of patients with Nipah encephalitis revealed a short incubation period, within two weeks and the main presenting features were fever, headache, giddiness and vomiting.⁵ Fifty-five percent of the patients had reduced conscious level with prominent brainstem dysfunction. Mortality was 32%. Distinctive features in

severely ill patients were segmental myoclonus involving diaphragm, floor of mouth and extremities; tendon areflexia, hypotonia, severe hypertension and tachycardia. Neurological relapse and late-onset disease occurred. Pathologically there was widespread microinfarction in the central nervous system with evidence of direct neuronal involvement.² Magnetic Resonance Imaging (MRI) of the brain showed widespread small, discrete high signal lesions on T2-weighted imaging mainly in the subcortical and deep white matter of the cerebral hemisphere. These were probably due to microinfarction.⁶ MRI was a sensitive and specific for the diagnosis of the encephalitis.

Electroencephalograms (EEG) were carried out as part of the investigative workup of our patients. EEG features of this new encephalitis and their clinical correlation are described.

MATERIALS AND METHODS

The diagnosis of NE was based on a) clinical, CSF or MRI features of encephalitis in patients who b) come from outbreak areas and c) had close or direct contact with pigs or other animals suspected of being infected. 32-channel EEG

was carried out with Medelec DG 3P Examiner using the International 10-20 system of electrode placement. Due to constraints of time, manpower and equipment not every patient was studied. EEG was carried out in patients during the acute, recovery and convalescent phases of illness as well as in relapsed cases. MRI studies were carried out using a 1.5 Tesla Siemens scanner with T1-weighted, T2-weighted and FLAIR (fluid attenuated inversion recovery) sequences. Data was analyzed statistically using Student's t-test and Chi-square test.

RESULTS

Clinical features

Seventy-three EEG tests were carried out in 40 patients with Nipah encephalitis. Their mean age was 39.2 years (range, 15 to 58 years). The male to female ratio was 5 : 1. The racial composition was Chinese (85%), Indians (12.5%) and Malays (2.5%). 52.5% were pig farmers while 27.5% were family members of the pig farmers. Another 20% were not directly involved in pig farming but had contact with pigs and infected animals in the course of their daily activities.

There were two groups of patients in which EEG was carried out: a) those in the acute phase of illness (32 patients), b) those on post-recovery follow up (17 patients).

Those studied during the acute phase of illness had an incubation period of between one to two weeks. Mean duration of symptoms before admission was 3.8 days (range 1 to 7 days). The main presenting symptoms were fever (96.9%), headache (56.3%) and drowsiness or coma (65.6%). 43.8% had epileptic seizures and these were generalized except one patient with partial seizures and secondary generalization. None were in status epilepticus. Focal neurological signs included segmental myoclonus (46.9%), cerebellar ataxia (12.5%) and red nuclear tremor

(6.3%). 84.4% of patients were ventilated due to deepening coma. The mean duration to ventilation was 5.6 days (range 3 to 9 days). 43.8% died in the acute phase, 21.8% remained in coma, 21.9% had residual ataxia and amnesia, while 12.5% recovered completely. One other patient with prolonged coma died after seven months of illness.

Of the 17 patients who had EEGs after clinical recovery, nine had repeat studies after an initial EEG during the acute illness while eight were studied for the first time. Their clinical features at presentation were similar with fever (88.2%), drowsiness (29.4%), segmental myoclonus (5.9%) and generalized seizures (35.3%). Seven patients had been ventilated. At the time of EEG, eight patients had residual neurological deficits (Five had ataxia and three had memory impairment) while nine patients were neurologically normal.

EEG

Fifty-five EEGs were carried out during the acute phase of the illness, 18 during follow-up. Of the 40 patients, 70% had one EEG, 20% had two or three EEGs, while 10% had serial recordings of more than three EEGs.

EEG in acute illness

The first EEG was carried out between the 4th to the 29th day of illness (mean 10th day of illness) and were abnormal in 97.5%. The EEG abnormalities are shown in Table 1. One patient with no impairment of consciousness (but abnormal CSF findings) had a normal EEG. The most common abnormality seen in 87.5% was continuous diffuse, symmetrical slowing with or without focal discharges.

The degree of slowing correlated with the severity of disease (Table 2). There was a clear pattern of EEG changes with progression of disease as observed in three patients who had

TABLE 1: Abnormalities of first EEG in the acute phase of illness

EEG abnormalities	Number of patients (%) (Total number of patient = 32)
Diffuse symmetrical slowing with focal discharges	17 (53.1%)
a) bitemporal periodic complexes	8 (25.0%)
b) other focal discharges	9 (28.1%)
Continuous diffuse, symmetrical slowing (moderate/severe)	11 (34.4%)
Intermittent symmetrical slowing (focal/diffuse)	3 (9.4%)
Normal	1 (3.1%)

TABLE 2: Degree of slowing (with or without discharges) in the first EEG of 32 patients during acute phase of illness.

EEG abnormalities	Patients ventilated (n=27)	Patients not ventilated (5)
Severe continuous diffuse slowing	40.7%	0%
Moderate continuous diffuse slowing	55.6%	20%
Mild continuous diffuse slowing	0%	20%
Intermittent diffuse slowing	3.7%	40%
Normal	0%	20%

serial recordings during the acute phase till recovery. Initially there was intermittent focal or diffuse slowing. Focal discharges appeared later followed by continuous diffuse slowing.

Focal discharges were the other prominent feature seen in 53.1% of first EEGs. Independent bitemporal periodic complexes (PC) were present in eight patients (25%) from day 4 to day 9 of illness. PC were fairly stereotyped (Figure 1 and 2) and consisted of single spike/sharp wave of 50-70 uV amplitude, followed by a slow component, lasting 200-250 milliseconds. It repeated irregularly every 1 to 2 seconds in the background of diffuse symmetrical slowing. PC had equal dominance bilaterally except one case with unilateral predominance alternating from

side to side. The complexes occurred independently on both sides except in one patient where they were temporally related. No unilateral PC was seen.

All patients with PC were deeply comatosed. Focal discharges and PC were both associated with higher mortality ($p<0.05$ and $p<0.005$ respectively). All patients with PC died rapidly within five days of admission. PC persisted until death (Fig 2). Diffuse slowing in the acute phase was associated with higher mortality and prolonged coma ($p<0.01$) but not higher mortality *per se* ($p=0.067$).

The EEG changes did not correlate with focal neurological signs. Segmental myoclonus seen in 46.9% of the patients was not time-locked



FIG. 1: Characteristic bitemporal PC seen at day 4 illness of a 51 years old pig farmer with NE.

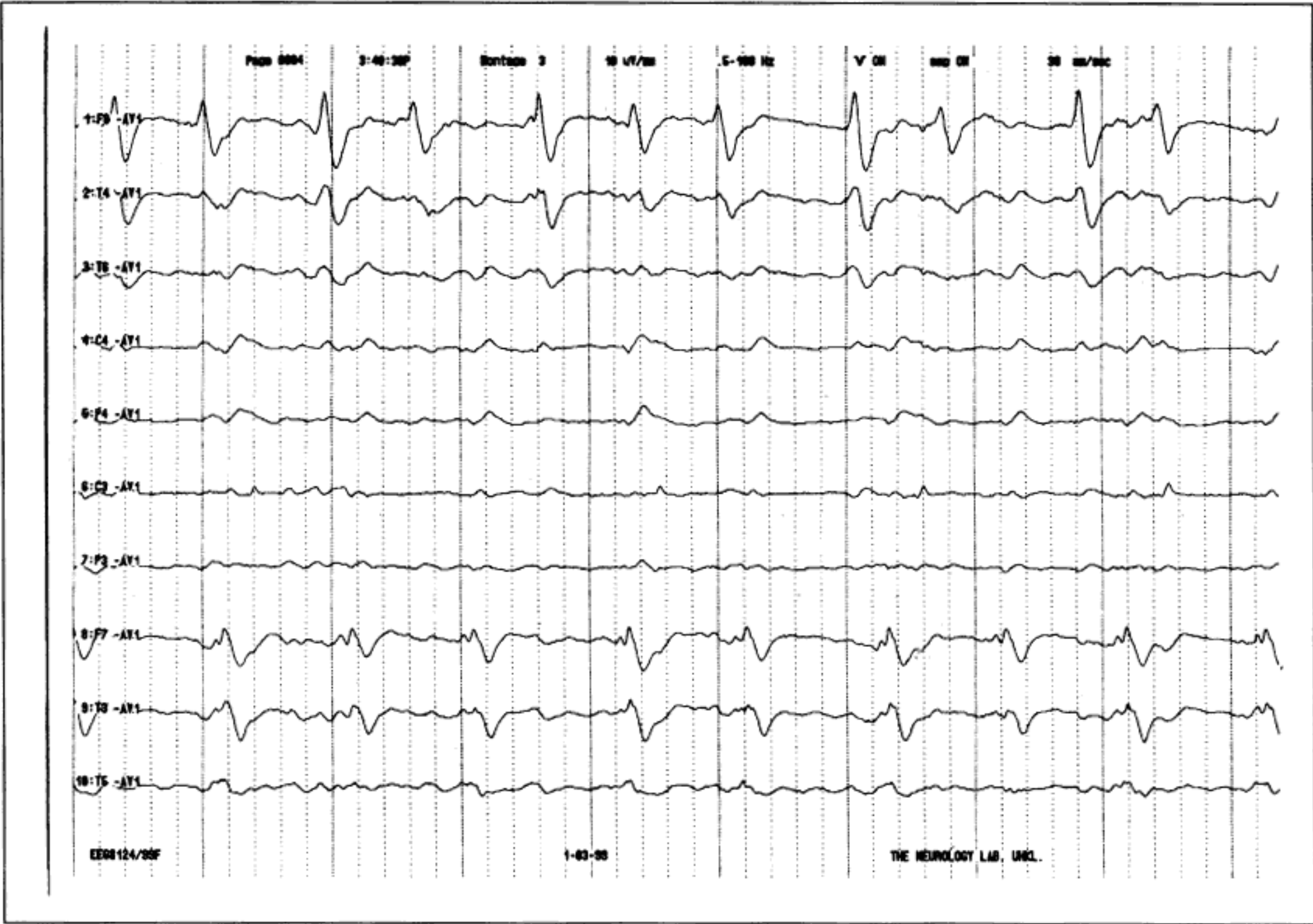


FIG. 2: The same patient as in FIG. 1 at day 6 of illness. The background activity became more attenuated. There was a preponderance of PC on the right side. The patient died on the same day.

with focal discharges or PC. Presence of focal discharges and PC did not predict occurrence of clinical seizure ($p=0.324$ and 0.177 respectively). No episodes of non-convulsive status epilepticus were recorded.

Follow up EEG

Seventeen patients had follow-up EEG between 150 and 240 days after illness onset (mean 194 days). The findings were focal discharges with focal slowing (5.9%), intermittent diffuse slowing (23.5%), intermittent focal slowing (17.6%) and normal (52.9%). EEG did not correlate with the neurological status of survivors (Table 3). Patients with normal neurological status and residual neurological deficits had a similar frequency of normal EEGs.

Neuroimaging

All the 16 CT brain were normal. MRI was performed on 21 patients during acute phase of illness. All MRI scans were abnormal. MRI findings in the acute encephalitis cases showed widespread discrete lesions in subcortical and deep white matter in the cerebrum and brainstem on T2-weighted and FLAIR sequences (Figure 3). Lesions on MRI in the acute phase of illness did not correlate with focal EEG discharges or PC. In the three patients with bitemporal PC who had MRI studies, there were no corresponding temporal lobe lesions seen in the MRI.

Histopathology

Three patients with EEG studies who died were

TABLE 3: Correlation between functional status and EEG during follow up

EEG findings	Residual neurological deficits (n=7)	Normal (n=10)
Normal	57.1%	50%
Intermittent slowing	42.9%	40%
Focal discharges	0%	10%

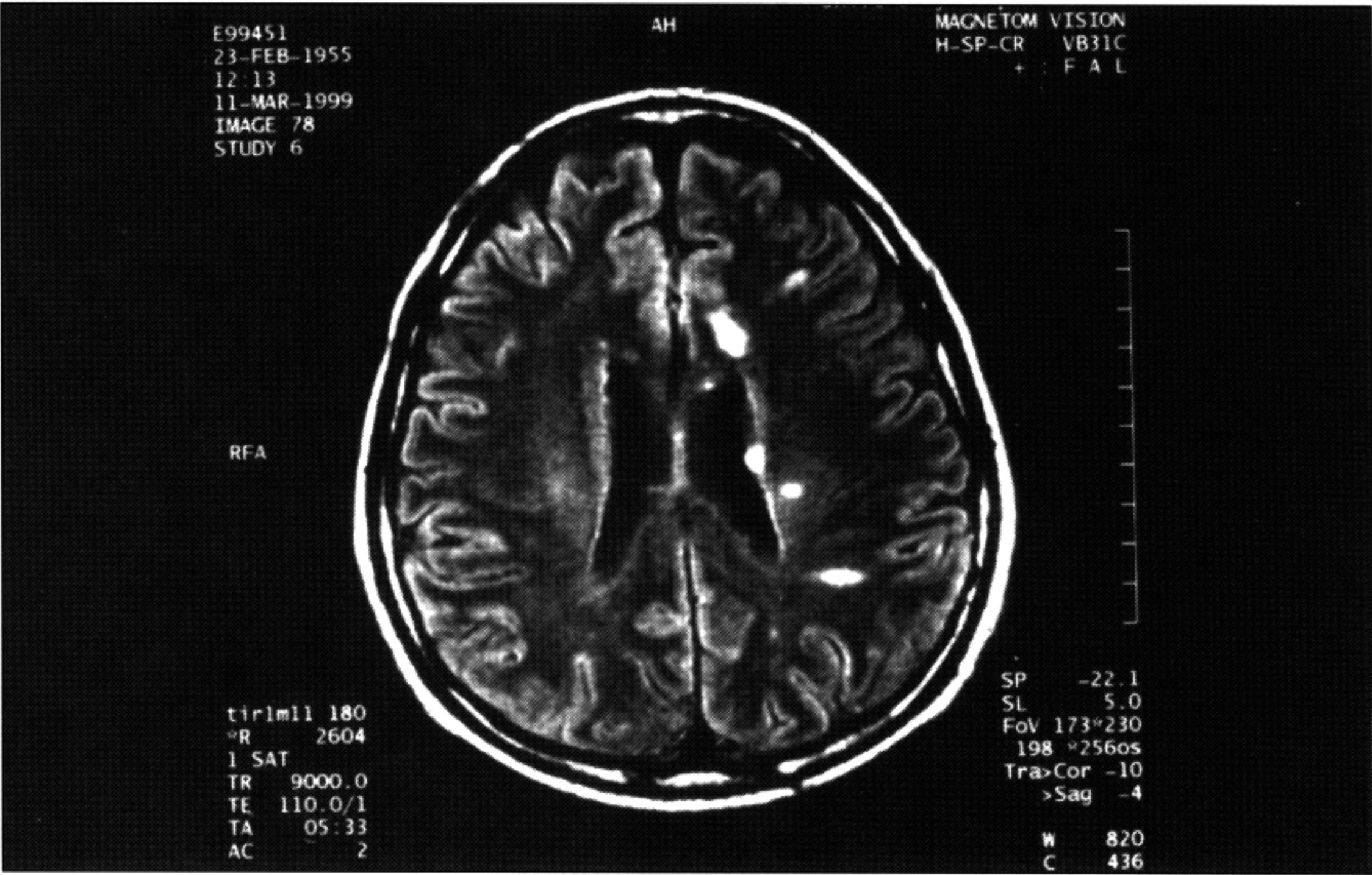


FIG. 3: Typical MRI finding in acute NE showing discrete high signal lesions of 2-7 mm sizes at subcortical region and deep white matter on T2 and fluid-attenuated inversion recovery (FLAIR) sequence.

necropsied. The typical changes of vasculitis induced thrombosis and disseminated micro-infarction in the white and gray matters of the cerebral hemispheres, cerebellum and brainstem were seen.² While two of the patients had bitemporal PC on EEG, there was no predilection of the lesions for the temporal lobes on histopathological examination.

Sensitivity of EEG, CSF, CT Brain and MRI brain in early diagnosis

The sensitivities of CSF findings, CT brain (*as above*), MRI and EEG in Nipah encephalitis are compared in Table 4. Both MRI and EEG were more sensitive than CSF examination in

confirming encephalitis. CT scan of brain was normal in all the cases.

DISCUSSION

The clinical profile of patients who underwent EEG examination in acute illness was more severe than in the overall series of patients.⁵ 84.4% was ventilated and 43.8% died. This would be expected, as more severely ill patients were selected for EEG studies. The high rate of EEG abnormalities (96%) in this group of patients therefore reflect this selection bias. The sensitivity of EEG appeared to be similar to that of MRI and superior to CSF examination and CT scan.

TABLE 4: Sensitivity of various investigations in first two weeks of acute encephalitis

Investigations	Number of patients	Mean day of illness during investigation (range)	Abnormal results
CSF*	32	4.9 (1-8)	23 (71.8%)
CT brain	14	5.4 (4-7)	0
MRI brain	13	6.4 (2-14)	13 (100%)
EEG	28	7.1 (4-14)	27 (96.4)

* CSF = cerebrospinal fluid, CT = computed tomography, MRI = magnetic resonance imaging, EEG = electroencephalography

A lower percentage (80%) of patients with milder disease (no ventilation) had abnormal EEG (Table 2) and the abnormalities detected were mild and nonspecific. Three patients had mild continuous or intermittent diffuse slowing and one patient had moderate continuous diffuse slowing. On the other hand, MRI was abnormal in all 14 patients in the acute phase of NE.⁶ However, there was no correlation between the depth of coma and the degree of MRI abnormality. MRI may therefore be more sensitive than EEG in patients with milder disease.

Drowsiness and coma were prominent features, 55% in the overall series of patients.⁵ There was a close association between coma and signs of brainstem dysfunction and this suggested that severe brainstem involvement resulted in altered consciousness. However, analysis of EEG results in severely ill patients showed that diffuse slowing was common (96% of patients ventilated had moderate to severe continuous diffuse slow waves) (Table 2), suggesting that severe diffuse cortical dysfunction probably due to widespread microinfarction and ischaemia was a contributing cause of coma.⁵

Bitemporal PC was seen in 25% of patients during the acute phase of illness and was a poor prognostic feature. Eight of 14 patients with EEG (57.1%) who died acutely had PC. The mortality of patients with PC was 100%. The patients died within five days of admission. PC occurred as bitemporal spike/sharp wave and slow wave complexes recurring every 1-2 seconds. Bitemporal PC, however, is not specific to Nipah encephalitis. In herpes simplex encephalitis, the EEG complexes are said to repeat every 1 to 3 seconds and appear between 2nd and 15th day of illness. They may be unilateral or bilateral, maximum over the involved temporal lobe.^{7,8} In subacute sclerosing panencephalitis (SSPE), complexes are usually bisynchronous, repeated every 5 to 7 seconds and time-locked to myoclonic jerks.⁹ In Creutzfeldt-Jakob Disease (CJD), the periodic complexes consisted of bisynchronous sharp waves, repeated every 0.5 to 1.6 seconds and had fairly close relationship with myoclonic jerks.¹⁰ Bilateral PC is also seen in hypoxic encephalopathy, and unilateral PC seen in many conditions such as cerebral tumor and infarct.¹¹ The main clinical differential diagnosis of Nipah encephalitis was Japanese encephalitis (JE). Misra & Kalita¹² reported diffuse slowing in 91.7% of patients with JE, with 25% showing focal discharges. PC was not

observed to be a feature. Thus, although bitemporal PC were not specific for Nipah encephalitis, in the context of acute encephalitis among patients in contact with pigs, they strongly support of the diagnosis.

The anatomical origin of bitemporal PC in Nipah encephalitis is uncertain. The absence of predilection of temporal lobe involvement on MRI and histopathology is against a cortical origin. Its close association with coma, high mortality and brainstem dysfunction suggests that it may originate from brainstem.

The myoclonus in Nipah encephalitis was focal and not time-locked to PC or other focal discharges. This indicates that it is non-cortical in origin. The segmental nature of myoclonus was consistent with brainstem and spinal cord location of lesions. This contrasted with SSPE and CJD in which myoclonus was temporally related to PC suggesting cortical origin for the myoclonus.^{9,13}

The degree of EEG abnormality correlated with disease severity and improved with clinical recovery. Serial EEG may be useful for monitoring progress of disease during acute phase of illness. As there is a lack of correlation between EEG and functional status of long term survivors, EEG is less useful when the patient has recovered from the acute illness.

In summary, EEG is a sensitive investigation in acute Nipah encephalitis. Bitemporal PC was common in patients with coma and was associated with high mortality.

ACKNOWLEDGEMENT

We thank the staffs in the Neurology Laboratory of the UMMC for performing the EEG.

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