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Presence of CSF IgM do not have protective effect in Nipah encephalitis

Vimalan RAMASUNDRUM, Chong Tin TAN, **Heng Thay CHONG, Khean Jin GOH, Nee Kong CHEW, **Vijayasingham PETHARUNAM, **Tarmizi THAYAPARAN, *Kaw Bing CHUA, *Sai Kit LAM, ***Thomas G KSIAZEK

Department of Medicine and *Microbiology,University of Malaya, Kuala Lumpur. **Department of Medicine, Seremban Hospital, Malaysia, ***Division of Viral and Rickettsial Diseases, Centers forDisease Control and Prevention, Atlanta,Georgia, USA .

Abstract

This is a study to correlate the presence or absence of IgM in the CSF with clinical and cerebrospinal fluid features in Nipah encephalitis. The study subjects consisted of patients with Nipah encephalitis admitted to the University Hospital, Kuala Lumpur and Seremban Hospital. The inclusion criteria was patients from the outbreak area with clinical, CSF or MRI features of encephalitis and a positive serum Nipah IgM serology. The patients were divided into two groups, those with positive or negative CSF Nipah IgM serology. The clinical and cerebrospinal fluid features of the two groups were compared. There were 36 patients with positive CSF serology and 34 patients with negative serology. The two groups were comparable in the demographics features and timing of serology test. The seropositive patients had higher CSF pleocytosis and protein level. There was however no significant difference in the mortality and severity of illness. The latter was indicated by the proportion of patients ventilated and its duration, duration of illness and hospitalisation, and the factors known to be associated with poor prognosis, which were myoclonus, seizures, hypertension and tachycardia. The study indicates that although the presence of CSF IgM is associated with evidence of increased inflammatory activity, it did not have a protective effect on the illness. The humoral immunity probably has a minor role to play in the disease proccess and recovery.

Key words: Nipah encephalitis, cerebrospinal fluid, serology, prognosis

INTRODUCTION

An outbreak of viral encephalitis among pig farmers started in the district of Kinta near Ipoh north of Kuala Lumpur in November 1998. The outbreak later spread to Negri Sembilan State south of Kuala Lumpur in December 1998 till May 1999. A novel virus closely related to Hendra virus, later named Nipah virus was later found to be responsible for the encephalitis.[1,2] The illness in humans had a short incubation period after close contact with pigs. The presenting features were fever, headache, dizziness and vomiting. Reduced level of consciousness and prominent brain-stem dysfunction were common. Distinctive clinical signs included segmental myoclonus, areflexia and hypotonia, hypertension, and tachycardia.[3] Pathological changes were mainly seen in the brain with disseminated microinfarction as a result of vasculitis-induced thrombosis with direct neuronal involvement.[1-3] The mortality rate was in excess of 30%. Many of the factors associated with poor prognosis were indicative of severe brain-stem involvement. These included reduced level of consciousness, vomiting, abnormal doll's-eye reflex, abnormal pupils, hypertension and tachycardia; segmental myoclonus, seizures and periodic temporal epileptiform discharges in electro-encephalogram.[3,4] Serology with IgG and IgM antibody against Hendra, later Nipah antigen were developed as aid to diagnosis.[2,3] The serology was positive in 76% of patients overall.[3] The CSF IgM is the initial humoral response to viral pathogen. The purpose of this study was to correlate the presence of CSF IgM with clinical and CSF features in patients with Nipah encephalitis so as to determine its role in the pathogenesis of the disease.

MATERIALS AND METHODS

The study subjects consisted of all patients with Nipah encephalitis who were admitted to the University Hospital Kuala Lumpur and Seremban General Hospital from February 1999 to June 1999. The two Hospitals were the epicenters

Address correspondence to: Dr Vimalan, Neurology Laboratory, University Hospital, Kuala Lumpur 59100, Malaysia

treating more than four fifth of the patients in the outbreak. The inclusion criteria were: patients from outbreak area, clinical, CSF or MRI evidence of encephalitis, presence of IgM antibody to Hendra in the serum. Patients who did not have cerebrospinal fluid examination was excluded in the study.

For serology, the CSF and serum samples were tested with an IgM-capture enzyme-linked immunoabsorbant assay (ELISA) and indirect IgG ELISA for antibodies against Hendra virus antigen. The antigens were both inactivated by cobalt irradiation.

The data was analyzed with SPSS Version 9.0 using frequency and descriptive statistics and non-parametric test for comparison.

RESULTS

Seventy patients fulfilled the inclusion criteria, 36 patients were seropositive and 34 patients seronegative. The demographic features of the two groups were listed in Table 1. As shown, they were comparable. For the ethnic origin, the "others" were foreign workers who were Myanmase, Nepalese, Indonesians and aborigines. For the occupation, the "others" were patients who worked part-time in the pig farms. The median duration of symptom to date of test was 6.5 days for seropositive patients and 5.0 days for the seronegative patients. There was no statistical difference between the two groups (p=0.111).

Table 2 was the comparison of the CSF changes between the seropositive and the seronegative groups. As shown, the mean CSF protein and white blood cell count were significantly higher for the seropositive group. On the other hand, there was no significant difference in the CSF sugar and red blood cell count between the two groups.

The severity of illness on presentation was similar in both the groups. Drowsiness was seen in 47.2% of the seropositive group and 52.9% of the seronegative group (p=0.726). Lethargy was seen in 38.9% of the seropositive group and 23.5% of the seronegative group (p=0.152). Meningism was seen in 25% of the seropositive group and 29.4% of the seronegative group (p=0.738). Table 3 was the comparison of the neurological characteristics between the two groups of patients known to be associated with poor prognosis. As shown, there was no significance between the two groups.

Table 4 was the comparison of mortality and severity of illness between the two groups. As shown, there was no significant difference between the two groups. The later is shown by the duration of hospitalization, the rate and duration of ventilation.

DISCUSSION

This study showed that there was higher mean protein level and white blood cell count with

TABLE 1. Demographic characteristics of the patients.

	CSF IgM positive (n=36)	CSF IgM negative (n=34)	
Median age (years)	39.1	39.1	P=0.814
Sex			
Male	88.8%	73.5%	P=0.101
Female	11.2%	16.5%	
Ethnic origin			
Chinese	55.5%	82.3%	P=0.931
Indians	16.6%	2.9%	
Others	27.9%	14.8%	
Occupation			
Pig farmer	83.3%	70.5%	P=0.171
Lorry driver	5.4%	8.8%	
Housewife	8.6%	5.8%	
Others	2.7%	14.9%	

TABLE 2. CSF features of the seropositive and seronegative groups.

	CSF IgM positive (n=36)	**CSF IgM negative (n=34)**	
Protein in mg/dl*	108.1 (0-701)	45.0 (0-129)	P=0.004
Glugose in mmol/l*	3.1	4.2	P=0.062
White blood cell/ul*	11 (0-580)	1.5 (0-240)	P=0.027
Red blood cell/ul*	0.0 (0-848)	0.0 (0-550)	P=0.776

* mean values are shown, with the range in parenthesis.

TABLE 3. Neurological characteristics of the seropositive and seronegative groups.

	CSF IgM positive (n=36)	**CSF IgM negative (n=34)**	
Myoclonus	36.1%	32.4%	p=0.685
Seizures	38.9%	38.2%	P=0.884
Mean maximum systolic blood pressure in mm Hg	160	154	p=0.869
Mean maximum diastolic blood pressure in mm Hg	93	87	p=0.406
Mean maximum pulse rate per minute	114	104	p=0.306

TABLE 4. Mortality and disease severity of the seropositive and seronegative groups.

	CSF IgM positive (n=36)	**CSF IgM negative (n=34)**	
Mortality	50%	68%	P=0.380
Mean duration of hospitalisation in days.	21.2	23.9	P=0.680
Mean duration of illness in days.	25.9	25.9	P=0.920
Coma requiring ventilation	69.4%	61.8%	p=0.502
Mean duration of ventilation in days	6.5	5.0	p=0.342

similar red cell count in the seropositive group as compared to the seronegative group. This suggested that the differences in the protein level and white cell count were not due to the traumatic lumbar puncture, but rather there is more active inflammatory response in the seropositive patients.

In-spite of more active inflammatory response, there was no difference in the disease manifestation, disease severity and mortality between the two groups. Of the neurological features shown to be similar in the two groups, reduced level of consciousness, myoclonus, seizures, hypertension and tachycardia were associated with poor prognosis.[3] As IgM is the earliest antibody response against the pathogen, it appears that in Nipah encephalitis, humoral response does not appear to play a significant role in the body defense against the pathogen. This is consistent with the finding by Chua et al[5], who has shown that there was significant association between positive virus isolation and mortality as well as clinical features associated with poor prognosis of the illness. On the other hand, there was lack of correlation between CSF virus isolation and presence of Nipah-specific antibody in the serum and CSF.[5]

The presence of humoral immunity in the CSF may be due to a break in the blood brain barrier, in particular the blood CSF barrier to allow the seepage of antibodies formed in the serum to pass into the CSF. It could also be from the intrathecal or central nervous system production of the antibodies. There are examples of encephalitis where humoral immunity plays an important role in the pathogenesis. The administration of anti-herpes IgG to rats with herpes simplex myelitis resulted in a 50% reduction in illness rates and the earlier breaching of blood brain barrier integrity results in improved outcome and a limited disease manifestation.[6] Patients with Japanese encephalitis have a milder disease manifestation if they had a positive CSF IgM or IgG to Japanese encephalitis serology.[7]

The timing of IgM production may be important in protective effect of encephalitis. In Japanese encephalitis where CSF antibodies is known to have a protective effect[7], the CSF serology is positive in 68% in day one of illness and 100% in day seven of illness.[8] In this study, the median time for the serology was 5.0 days for the seropositive patients and 6.5 days for the seronegative patients. This falls within the mean duration from the onset of symptom to nadir at 6.9 days.[3] Thus, the timing of CSF IgM production may not be crucial in its lack of protective effect in Nipah encephalitis. Only CSF IgM was investigated in this study. CSF IgG was only positive in 10% of patients in this study, probably due to the timing of the test and its role could not be assessed. CSF IgA was also not investigated in this study. In herpes simplex encephalitis, the antibody was detected as early as 6th day of illness but its significance is uncertain. (reference) The IgA response is also seen in other viral encephalitis such as mumps encephalitis.[9] The lack of protective effect of CSF IgM in Nipah encephalitis may be due to the rapid invasion and cell-to-cell spread of the virus in the brain-stem.

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