Neuropsychiatric Sequelae of Nipah Virus Encephalitis

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The authors followed nine patients with Nipah virus encephalitis over the course of 24 months. Eight of the nine developed psychiatric features assigned to the encephalitis. Three patients developed major depressive disorder immediately after recovering from the encephalitis, and two developed depression approximately 1 year after the outbreak. Two patients developed personality changes, and two suffered chronic fatigue syndrome. Neuropsychological testing was accomplished in eight of the nine patients. Deficits in attention, verbal, and/or visual memory were substantial in seven of the eight patients tested. Verbal memory was more impaired than visual memory in these patients. Comparison between psychiatric and cognitive impairment and total number of brain lesions showed no discernible trends.

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An outbreak of lethal infectious encephalitis killed more than 100 people in Western Malaysia during 1998–1999. The Nipah virus, a previously unknown paramyxovirus, was discovered to be the cause of the pig-borne epidemic.[1] The outbreak was first noted in late September 1998 and by mid-June 1999, more than 265 encephalitis cases, including 105 deaths, had been reported in Malaysia.[2,3] The virus appeared to be first introduced into pigs, where close contact caused by intensive farming practices led to pig-to-pig transmission, and subsequently pig-to-human transmission. In neighboring Singapore, which imports live pigs from Malaysia for slaughter, the outbreak was also limited to pig workers. Eleven workers in one of two Singaporean abattoirs developed Nipah-virus-associated encephalitis or pneumonia, resulting in one fatality.[4,5]

Neuroimaging studies using magnetic resonance imaging (MRI) have shown unusual multiple small lesions in the cerebral white matter in Nipah virus encephalitis, a pattern unlike other viral encephalitis.[6,7] In the study of late manifestation of Nipah virus infections, Lim et al.[8] found one case of clinical depression as well as evidence of retinal and spinal cord involvement by the virus. Furthermore, there have been reports of relapse among Nipah virus patients in Western Malaysia.[9,10] Information about this novel pathogen is still emerging. Given that Nipah virus is a new cross-species zoonotic pathogen, its natural history and long-term effects are unknown. To our knowledge, this is the first report of the long-term neuropsychiatric sequelae of Nipah virus encephalitis.

METHODS

This is a prospective epidemiological study conducted at the National Neuroscience Institute in Singapore. Case definition is based on epidemiologic and serological diagnosis of Nipah virus infections. Patients underwent psychiatric evaluation and neuropsychological testing 2 years after the outbreak. The neurologic examination and neuroimaging were also reviewed. The research discussed in this article is essentially a late study of viral effect.

Psychiatric Evaluation

Psychiatric interview in all subjects was conducted by one reviewer (B-Y.N.), who was blinded to results of

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neuropsychological testing and MRI studies. Wherever possible, corroborative accounts were obtained from relatives given that many patients had difficulty reporting symptoms as a result of memory impairment. For the psychiatric evaluation, we used the Schedules for Clinical Assessment in Neuropsychiatry (SCAN),[11] a system that covers a much wider range of psychopathology than the Present State Examination and has the clinical advantage of being applied by experienced psychiatrists.

Neuropsychological Testing

Attention, visual, and verbal memory were assessed during a single session by one reviewer (A.Y.). To evaluate attention, digit span subtest from Wechsler Adult Intelligence Scale—Revised[12] was used. For assessment of IQ, Standard Progressive Matrices[13] were used. The Rey Auditory Verbal Learning Test[14] was used to assess verbal memory, which has been found to be reliable and of demonstrated validity in documenting learning and recall processes and in differentiating among relevant clinical groups. For visual memory, we used Visual Reproduction 1 and 2 taken from Wechsler Memory Scale.[15] This subtest allows neuropsychologists to make inferences regarding basic visual perception, visual-constructional, immediate and delayed recall, percent retention, and recognition memory for geometric designs. All tests were performed in the language or dialect the subjects were most conversant in.

Neuroimaging

Initial MRI examinations were acquired at outbreak (days 1–38). The number, size and location of abnormalities were noted by one reader (C.C.T.L.).

RESULTS

In Singapore, 13 patients (12 men and one woman) were affected by the Nipah virus outbreak. One patient died of his disease (mortality rate of 7.7%), and of the 12 surviving patients, three were lost to follow-up or did not present for imaging or psychological assessment. Nine patients underwent neuropsychiatric interview and eight patients underwent neuropsychological testing. Of the nine patients studied, there were eight males and one female; eight Chinese and one Indian; five Singaporeans and four Malaysians. Their ages ranged from 24 to 55 years (mean = 40.8, SD = 10.9). Seven patients worked in the abattoir and were involved either in the slaughtering of pigs or in the cleaning and processing of the carcasses. Two subjects were pig farmers from Malaysia.

Eight of nine patients suffered from neurological deficits, psychiatric sequelae or cognitive impairment; only one made a complete recovery. Table 1 summarizes the number and location of brain lesions on initial MR imaging, the residual clinical signs at 24 months, employment status at 24 months, psychiatric diagnosis, and extent of cognitive impairment detected by neuropsychological testing.

Psychiatric Complications

Five of the nine cases developed major depressive disorder following the encephalitis. These five cases all had cognitive and emotional symptoms of depression, like hopelessness, feelings of worthlessness and suicidal thoughts. Of the five, three became depressed shortly after their discharge from the hospital while two became depressed about 1 year after the outbreak. Four cases responded favorably to antidepressants therapy and supportive psychotherapy, while one patient refused psychiatric interventions and remained chronically depressed. There were two patients who developed personality changes, and two suffered chronic fatigue syndrome. Only one patient had no psychiatric diagnosis. Also, in this study, we found that four patients needed help coping with uncertainty. Although they had survived the initial critical period of viral encephalitis, many of them had complications arising from the illness, both physical and mental. Furthermore, recovering patients faced uncertainty and anxiety over reports of relapsed patients in Western Malaysia, although to date no such cases had been reported in the Singapore cohort.

Neuropsychological Testing

Eight patients were studied by neuropsychological testing. Of the eight subjects, four were estimated to have average premorbid functioning, two of low average functioning and two to be functioning within the borderline range. This estimation was based on their education and occupational background. Intellectually, five of the subjects were assessed to be functioning within their estimated premorbid level while the remaining three subjects were functioning at below the expected level.

Three subjects had impairment of attention. Five sub-

TABLE 1. Number and Location of Brain Lesions on Initial MRI, Residual Clinical Signs at 24 Months, Employment Status at 24 Months, Psychiatric Diagnosis, and Extent of Cognitive Impairment Detected by Neuropsychological Testing

Patient	Sex	Age (years)	Number of Lesions on Initial MRI: White Matter	Number of Lesions on Initial MRI: Other Sites	Residual Clinical Signs at 24 Months	Employment Status at 24 Months	Psychiatric Diagnosis	Cognitive Impairment
1	M	42	20	0	Finger weakness, left arm dysesthesia, delayed Horner syndrome	Working at abattoir (light duties)	Major depression following recovery from encephalitis	Impairment of attention, verbal (immediate, delayed and recognition) and visual (delayed) memory
2	M	37	50	11 (cortex, pons, cerebellar peduncle, thalamus, putamen)	VI nerve palsy	Delivery man	Major depression shortly after discharge from hospital	Impairment in attention, verbal memory (delayed and recognition); no impairment in visual memory
3	M	55	6	16 (cortex, pons, putamen)	Monoparesis, nystagmus	Unable to work because of leg weakness	Major depression (at 1 year postencephalitis)	Not tested
4	M	41	40	12 (cortex, pons, thalamus)	No residual neurological deficits	Does odd jobs	Personality changes	No significant impairment
5	F	51	10	13 (cortex)	No residual neurological deficits	Unemployed for 2 years; was helping on family pig farm, since closed	Personality changes (irritability, poor anger control), chronic fatigue syndrome	Impairment of verbal memory (immediate)
6	M	24	8	3 (cortex)	Blurred vision due to branch retinal artery occlusion	Chicken farmer	Major depression (at 1 year postencephalitis)	Impairment of verbal memory (immediate)
7	M	45	26	10 (cortex, pons, cerebellar peduncle)	No residual neurological deficits	Working at abattoir	Major depression following discharge from hospital	Impairment of verbal memory (immediate and recognition); no impairment in visual memory
8	M	48	30	3 (cortex, caudate)	No residual neurological deficits	Working at abattoir	Chronic fatigue	Impairment of attention and verbal (immediate and delayed) memory
9	M	24	5	2 (cortex)	No residual neurological deficit	Working at abattoir	Nil	No significant impairment

MRI = magnetic resonance imaging

jects had impaired immediate verbal memory. Three subjects had problems with delayed verbal memory and three of them had recognition memory problems. Of the eight subjects, two had verbal memory problems across the three domains, namely, immediate, delayed and recognition memories.

All of the eight subjects had no difficulty with immediate visual memory and performed within or well within their expected level. Only one subject was impaired on delayed visual memory. Contrasting verbal memory with visual memory, it appears that the subjects had more problems in verbal memory functions than with visual memory functions.

Occupational Status

Of the seven who were gainfully employed at 2 years postencephalitis, four resumed their work at the pig farms or abattoirs. Of the two patients who remained unemployed, one was unable to work because of leg weakness, while the other was severely affected by his fatigue and impaired memory.

Neuroimaging Findings

During the viral outbreak, all patients had multiple small lesions less than 1 cm in maximum diameter within the cerebral white matter. Although lesions were also found in the cortex, brainstem, cerebellum and deep nuclei, most patients had more lesions in the white matter than gray matter. Comparison between psychiatric and cognitive impairment and total number of brain lesions showed no discernible trends.

DISCUSSION

In Nipah virus encephalitis, the diversity and multifocality of neurological manifestations are particularly striking.[5] Histologically, widespread vascular endothelial infection and microinfarction have been demonstrated in Nipah virus infection,[2] and Lim et al.[7] have proposed that the lesions seen on MRI may represent vasculitic small vessel cerebral infarction. Our series of cases would be representative of the population of post-Nipah virus encephalitis patients. There are no selection biases that may have influenced the findings in this case series.

Psychiatric sequelae, especially depression, are common and constitute a major cause of disability following recovery from viral encephalitis caused by other viruses.[16] Depression, cognitive deficits, personality changes and chronic fatigue have been noted months after recovery. In our study, we found patients suffering from depressive symptoms, personality change, and chronic fatigue syndrome. None of our cases had mania, obsessive-compulsive disorder, or psychosis: these have been reported in other postencephalitis syndromes.[17,18]

We find that depression following Nipah virus encephalitis is phenomenologically indistinguishable from an idiopathic depressive disorder. Sadness, anhedonia, loss of energy, weight loss, insomnia, psychomotor agitation or retardation, feelings of worthlessness or hopelessness, diminished ability to concentrate, and thoughts of death or suicide are the characteristic features. In DSM-IV symptoms that are attributable to physical causes are not counted towards a diagnosis of major depression. Our five cases of major depression all had cognitive and emotional symptoms of depression, like hopelessness, feelings of worthlessness and suicidal thoughts. The origins of the mood changes are likely to be multifactorial, including brain dysfunction, functional incapacity, and role changes in society and in the family. The patient's premorbid personality and adequacy of family support and social resources further condition the behavioral response to the brain disorder.

Two of our patients suffered from chronic fatigue. It seems probable that infection involving the central nervous system has a greater propensity to cause fatigue. Viruses are thought to cause organic brain syndromes in two ways—one is direct action of the virus within the CNS, the other is secondary to an autoimmune or hypersensitivity reaction to the virus either within or outside the CNS.[17]

We found neuropsychological testing helpful in fully delineating the extent of cognitive damage. Formal testing is extremely useful in assessing the patient's cognitive limitations, in following the progress of the disease and in treatment planning. Despite their clinical subtlety, these deficits have significant practical implications for patients' ability to return to their normal lifestyle.[18] It appears that the subjects in our study had more problems in verbal memory functions than with visual memory functions, and this pattern of verbal memory deficits may be a result of Nipah virus infection. However, an alternative explanation is that it could be easier for the subjects to compensate for visual memory loss than verbal memory loss and consequently, they had more problems in verbal memory functions.

The anatomical location of brain lesions in other or-

ganic brain diseases has been shown to be an important factor in determining which patients become depressed. Depression occurs most frequently in patients with lesions affecting the frontal and temporal lobes and the basal ganglia, particularly the caudate nuclei.[16] Additionally, the number and location of MRI lesions did not correlate with the severity of clinical findings in this study.[4] Therefore, the method of measuring lesion burden by counting the number of abnormalities visible on MRI may not be clinically useful in this new disease.

References

1. Goh KJ, Tan CT, Chew NK, et al.: Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. N Engl J Med 2000; 342:1229–1235
2. Chua KB, Goh KJ, Wong KT, et al.: Fatal encephalitis due to the Nipah virus among pig-farmers in Malaysia. Lancet 1999; 354:1257–1259
3. Chua KB, Lam SK, Tan CT, Hooi PS, Goh KJ, Chew NK, Tan KS, Kamarulzaman A, Wong KT: High mortality in Nipah encephalitis is associated with presence of virus in cerebrospinal fluid. Ann Neurol 2000; 48:802–805
4. Lee KE, Umapathi T, Tan CB, et al.: The neurological manifestations of Nipah virus encephalitis, a novel paramyxovirus. Ann Neurol 1999; 46:428–432
5. Paton NI, Leo YS, Zaki SR, et al.: Outbreak of Nipah-virus infection among abattoir workers in Singapore. Lancet 1999; 354:1253–1256
6. Lim CCT, Sitoh YY, Hui F, et al.: Nipah virus encephalitis or Japanese encephalitis? MR findings in a new zoonotic disease. AJNR Am J Neuroradiol 2000; 21:455–461
7. Lim CC, Lee KE, Lee WL, et al.: Nipah virus encephalitis: serial MR study of an emerging disease. Radiology 2002; 222:219–226
8. Lim CC, Lee WL, Leo YS, et al.: Late clinical and magnetic resonance imaging follow up of Nipah virus infection. J Neurol Neurosurg Psychiatry 2003; 74:131–133
9. Wong SC, Ooi MH, Wong MN, et al.: Late presentation of Nipah virus encephalitis and kinetics of the humoral immune response. J Neurol Neurosurg Psychiatry 2001; 71:552–554
10. Tan CT, Goh KJ, Wong KT, et al.: Relapsed and late-onset Nipah encephalitis. Ann Neurol 2002; 51:703–708
11. Wing JK, Babor T, Brugha T, et al.: SCAN: Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990; 47:589–593
12. Wechsler D: Wechsler Adult Intelligence Scale—Revised. New York, Psychological Corp, 1981
13. Raven JC: Guide to the Standard Progressive Matrices. London, HK Lewis, 1960
14. Lezak MD: Neuropsychological Assessment, 2nd ed. New York, Oxford University Press, 1983
15. Wechsler D: Wechsler Memory Scale—Revised. New York, Psychological Corp, 1987
16. Cheyette SR, Cummings JL: Encephalitis lethargica: lessons for contemporary neuropsychiatry. J Neuropsychiatry Clin Neurosci 1995; 7:125–134
17. Lishman WA: Organic Psychiatry: The Psychological Consequences of Cerebral Disorder. Oxford, UK, Blackwell Scientific, 1998
18. Gordon B, Selnes OA, Hart J, et al.: Long-term cognitive sequelae of acyclovir-treated herpes simplex encephalitis. Arch Neurol 1990; 47:646–647