

The mechanism of areflexia in patients with Nipah encephalitis.

Nee Kong CHEW MRCP, Khean Jin GOH MRCP, Chong Tin TAN FRCP MD.

Division of Neurology, Department of Medicine, University of Malaya

Abstract

Areflexia was an important and distinctive feature in patients with Nipah encephalitis. It appeared to indicate a poor prognosis. However, the site of the lesion responsible was unclear, as there were no objective signs of peripheral neuropathy in these patients. In order to determine the underlying mechanism of areflexia we carried out electrophysiological studies, nerve conduction study and electromyography in 13 Nipah encephalitis patients with areflexia. Eleven patients were studied in the acute phase while 6 patients were studied in the late phase of illness, of which 4 were repeat studies. Nerve conduction studies were abnormal in all but 2 patients. The late responses (F wave and H reflex) were disproportionately more abnormal compared to other parameters. These were the only abnormal parameters in five patients. Motor nerve conduction velocities and sural sensory responses were normal in all patients. Needle electromyography showed denervation change in the tibialis anterior of only 1 patient. The results suggest a proximal lesion affecting the spinal roots and this was probably secondary to meningeal inflammation, ischaemia and microinfarction from vasculitis. This study suggest that spinal root involvement may contribute to areflexia in Nipah encephalitis.

Keywords : Areflexia, Nipah encephalitis, electrophysiological studies.

INTRODUCTION

Nipah encephalitis occurred as an outbreak in several pig-farming villages in Malaysia in 1998 and 1999. It caused a severe neurological syndrome presenting with fever, headache, giddiness, vomiting and mental obtundation.¹⁻³ In patients seen at the University of Malaya Medical Centre, Kuala Lumpur, 55 percent had reduced conscious level with prominent brainstem dysfunction and the mortality rate was 32 per cent.³ 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.⁴ Histopathological studies revealed widespread microinfarction as a result of vasculitis-induced thrombosis in the brain and spinal cord, with some evidence of direct neuronal involvement.²

Several distinctive neurological signs were observed including segmental myoclonus involving the diaphragm, floor of mouth, face and extremities, severe hypertension and tachycardia at the nadir of their illness and tendon areflexia. Areflexia was found in 56 per cent of patients overall and in 81 per cent of patients with reduced conscious level, and was significantly more common in those who died compared to the survivors (73 per cent versus 48

per cent). It therefore appeared to indicate a poorer prognosis.³

Loss of tendon reflexes normally indicates a peripheral nerve lesion. However, in Nipah encephalitis, it was thought to be primarily central in origin, because of its generalized nature and diffuse occurrence in the presence of relatively normal muscle power.³ As the underlying mechanism for areflexia was uncertain, we carried out electrophysiological studies, nerve conduction studies and electromyography in a group Nipah encephalitis patients with areflexia during the acute and late phase of the disease to evaluate the peripheral nervous system. We report our findings and conclusions.

METHODS

During the outbreak, patients were diagnosed to have Nipah encephalitis based on clinical, epidemiological and laboratory criteria.³ We selected a group of Nipah encephalitis patients with absent or reduced tendon reflexes for electrophysiological studies.

Electrophysiological studies were carried out on a Medelec Sapphire® (Oxford Instruments) electromyography machine. Patients were studied in the acute as well as in the late phase of their illness. We chose ambulant patients for

the late phase studies to minimise the effects of compressive neuropathy in those who were bed-ridden. Surface electrodes were used for stimulation and recording and skin temperature was maintained above 32° Celsius. The following nerve conduction studies were performed unilaterally: motor - median, ulnar, posterior tibial and common peroneal nerves, sensory - median, ulnar, superficial radial and sural nerves. F-wave and the soleal H-reflex studies were also carried out. Abnormal values were defined as 2.5 standard deviation above or below the mean of the normal values of our laboratory. Electromyography (EMG), using concentric needle electrodes, was carried out in the first dorsal interossei, biceps, tibialis anterior and vastus medialis muscles on one side.

RESULTS

Clinical characteristics of patients

Thirteen Nipah encephalitis patients with absent and reduced tendon reflexes underwent electrophysiological studies. Of these, 11 patients were studied during the early phase of their illness, from the 9th to the 36th day of illness (mean 25th day). Six patients were studied in the late and recovery phase of the disease ranging from 60 to 291 days (mean 178 days) since illness onset, of which 4 were repeat studies of patients examined earlier. Their mean age was

39.6 years (range 28 – 58 years) and the male to female ratio was 1.3:1. The majority were ethnic Chinese (79 per cent) and the rest ethnic Indians (21 per cent). Their clinical features are summarised in Table 1. Most of the patients were severely ill and 10 (71 per cent) had to be ventilated for deepening coma. Eight of these ten patients had evidence of a flaccid tetraplegia. Sensory complaints were difficult to evaluate acutely in severely ill patients but these did not appear to be prominent. However, 4 patients complained of paresthesia affecting the upper limbs after recovery but had no other objective signs of neuropathy.

Other Investigations

Cerebrospinal fluid (CSF) examination was abnormal in 10 (71 per cent), showing lymphocytic pleocytosis, raised CSF protein concentration with normal CSF glucose. MRI of the brain in 9 patients, showed brain stem lesions (pons and midbrain) in five patients and cerebellar lesions in two patients. Eleven patients had serological tests against the Hendra virus antigen and this was positive in 71 per cent and 29 per cent in the serum and CSF respectively.

Progress and clinical outcome

Nine (64 per cent) patients (including the six who had electrophysiological studies at the later

Table 1: Clinical features of Nipah encephalitis patients who underwent electrophysiological studies.

Clinical features	No of patients (%)
GCS* score < 15	11 (79)
Headache	9 (64)
Vomiting	4 (29)
Meningism	4 (29)
Seizures	6 (43)
Segmental myoclonus	5 (36)
Abnormal doll's eye reflex	8 (57)
Abnormal pupils	11 (79)
Cerebellar ataxia	4 (29)
Hypertension (BP >160/90) [#]	7 (50)
Tachycardia (HR > 120/minute) [#]	11 (79)
Flaccid tetraparesis [#]	8 (57)

* Glasgow coma scale

At the nadir of illness

phase of the illness) were ambulating when reviewed at follow up, although the areflexia persisted. Of the patients who had developed a flaccid tetraplegia during the acute illness, only 3 recovered sufficiently to be ambulating while the rest remained bedridden with severe neurological and cognitive deficits. One patient developed upper motor neuron signs after suffering a cardiac arrest.

Electrophysiology

Results of the nerve conduction studies are shown in Table 2 and 3. The F wave latency was abnormal in 61% and 29% in the early and late studies respectively, while the H reflex latency was abnormal in 73% and 67%. On the other

hand, other parameters including distal motor and sensory latency, motor and sensory amplitude, motor and sensory conduction velocities were less severely affected in both sets of studies. In the early phase, 1 patient had an entirely normal result while 2 patients had only abnormal late responses. In the later phase, nerve conduction studies was normal in 1 patient while 3 patients had only abnormal late responses. There was evidence of bilateral carpal tunnel syndrome in one patient. Motor nerve conduction velocities and sural nerve studies were normal in both sets of patients.

Needle electromyography was abnormal in only 1 patient and showed denervation changes in the tibialis anterior muscle only.

Table 2. Percentages of abnormal NCS in the early stage of illness (n=11).

Parameters	Median Nerve	Ulnar Nerve	Radial Nerve	Tibial Nerve	Peroneal Nerve	Sural Nerve	Total
CMAP* amplitude	9	0	n.a	18	27	n.a	14
SNAP** amplitude	64	46	0	n.a	n.a	0	27
Distal motor latency	36	18	n.a	18	18	n.a	21
Distal sensory latency	36	9	0	n.a	n.a	0	4.5
Conduction velocity (motor)	0	0	n.a	0	0	n.a	0
Conduction velocity (sensory)	27	46	0	n.a	n.a	0	18
F wave response	46	64	n.a	55	81	n.a	61
H reflex response	n.a	n.a	n.a	72	n.a	n.a	72

*CMAP = compound muscle action potential

**SNAP = sensory nerve action potential

n.a = not applicable

Table 3. Percentages of abnormal NCS in the late stage of illness (n=6).

Parameters	Median Nerve	Ulnar Nerve	Radial Nerve	Tibial Nerve	Peroneal Nerve	Sural Nerve	Total
CMAP* amplitude	17	0	n.a	0	17	n.a	8
SNAP** amplitude	33	17	0	n.a	n.a	0	13
Distal motor latency	33	0	n.a	0	0	n.a	8
Distal sensory latency	50	0	0	n.a	n.a	0	13
Conduction velocity (motor)	0	0	n.a	0	0	n.a	0
Conduction velocity (sensory)	17	0	0	n.a	n.a	0	4
F wave response	17	33	n.a	0	67	n.a	29
H reflex response	n.a	n.a	n.a	67	n.a	n.a	67

*CMAP = compound muscle action potential

**SNAP = sensory nerve action potential

n.a = not applicable

DISCUSSION

Tendon areflexia usually indicates a lower motor neuron lesion. It was remarkable that this sign was a distinctive feature in Nipah encephalitis, a disease in which one would expect a predominant central nervous system involvement. A secondary cause for neuropathy e.g. nerve compression, was unlikely as areflexia was observed early in the course of the illness. Furthermore, there was absence of other objective lower motor neuron signs and sensory loss. The main abnormalities of both the early and late phase electrophysiological studies were in the nerve conduction studies. Late responses (F wave and H reflex) were disproportionately more abnormal compared to other nerve conduction parameters. As these measure the proximal segments of the nerve, the findings point to lesions at the level of the spinal roots. In fact, motor nerve conduction velocities and sural sensory responses were normal and therefore do not suggest a significant distal polyneuropathy.⁵ Furthermore, normal sural studies in the presence of abnormal H reflex responses may indicate a pre-ganglionic lesion of first sacral spinal root.⁶

The probable cause for spinal root involvement in Nipah encephalitis was inflammation of the meninges. Although, meningism was uncommon, suggesting that primary meningitis was not the major mechanism of disease, meningeal inflammation has been noted on pathological studies.² The main pathological change in Nipah encephalitis was widespread vasculitis with microinfarction and ischemia, the site of involvement included spinal cord.² Nipah encephalitis patients seen at University of Malaya Medical Centre with areflexia appeared to have higher CSF white cell count (57.4 per mm³ versus 23.3 per mm³) and protein level (71.9 mg/dl versus 61.7 mg/dl) compared with those with normal reflexes, even though these were not statistically significant ($p=0.244$ and 0.238 respectively, unpublished observation). These values could indicate a more intense meningeal inflammation in patients with areflexia with resultant significant nerve root involvement. A similar situation has been previously reported in a series of patients with cryptococcal meningitis.⁷ Hyporeflexia was present in 36 per cent and electrophysiological studies were abnormal in 93 per cent. The main abnormal parameter was the H reflex (61 per cent) while median F wave latencies were also significantly abnormal (43 per cent). These abnormalities were attributed to spinal root

involvement as part of the chronic meningeal inflammatory process.⁷

In patients who are severely ill, other causes of neuropathy need to be considered. Patients who are bed-ridden are prone to compression neuropathies and this may indeed account for some neurophysiological abnormalities seen in these patients. However, areflexia was observed early in the disease and appeared to be generalised involving all limbs. In addition, it was also noted in patients who were ambulant. This confounding factor was also minimised as we studied patients in the late phase who were ambulant, but who also showed similar electrophysiological findings. Critical-illness polyneuropathy is another diagnosis to be considered in severely ill patients. However, the relative paucity of denervation changes (i.e. spontaneous activity) on needle EMG examination, the preservation of compound muscle action potential amplitudes and the presence of areflexia in relatively mild disease argue against it.⁸

Tendon areflexia appeared to be one of the factors which indicated a poorer outcome. In Nipah encephalitis poor prognosis was associated with signs which indicated severe brainstem dysfunction.³ While this suggests a possible central origin for areflexia, in the light of the electrophysiological studies, spinal root involvement may contribute to areflexia in Nipah encephalitis.

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