

Peripheral nerve involvement in immunocompetent hosts with cryptococcal meningitis: a clinical and electrophysiological study

Wai Keong NG MBBS MRCP, Chong Tin TAN FRCP MD

Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

Abstract

This is a prospective clinical and electrophysiological study on 14 consecutive immunocompetent patients with cryptococcal meningitis over a two year period. Clinically, 36% of the patients had hyporeflexia with or without weakness suggestive of neuropathy. All but one patient (93%) had abnormalities of the electrophysiological test in at least one nerve. 64% of the patients had abnormality in two or more nerves, and 29% of the patients had abnormality in one nerve. The most common abnormalities were: abnormal H reflex (61%), small lateral popliteal compound motor action potential (54%), small posterior tibial compound motor action potential (46%), small median sensory action potential (46%) and delayed median F wave (43%). The abnormalities are best explained by spinal root involvement as part of the meningeal inflammatory process.

Key words: Cryptococcosis, peripheral nerve, neural conduction, electromyography.

INTRODUCTION

Cryptococcus neoformans is a yeast-like fungus that may cause disease in man and animals. The first case of central nervous infection (CNS) of *cryptococcus neoformans* was reported by Zenker in 1861.¹ The most common CNS manifestation of this illness is chronic meningitis often presenting with headache, fever, neck stiffness, visual disturbance and changes in the sensorium.²

We have previously reported 20% of our cryptococcus meningitis patient to have generalized areflexia suggesting the presence of concomitant radiculopathy³. We have further observed several cases of cryptococcal meningitis in immunocompetent patients who have clinical evidence of a predominant motor polyneuropathy involving the lower extremities. The neuropathy may persist and is disabling even after the meningitis has been successfully treated with antifungal agents.

The purpose of this study is to prospectively assess the occurrence of neuropathy in immunocompetent patients with cryptococcal meningitis with nerve conduction studies and electromyography.

MATERIALS AND METHODS

This study was done for two years at the University of Malaya Medical Centre (UMMC) in Kuala Lumpur. The UMMC is one of the

major tertiary referral centers for neurological disease for public patients in Malaysia.

Case ascertainment. All cases of cryptococcal meningitis in immunocompetent hosts admitted at the UMMC from 1994 till 1995 were enrolled into the study. The inclusion criteria were: 1. Clinical history of a chronic meningitis. 2. Cerebrospinal fluid evidence of either a positive culture for *Cryptococcus neoformans* or a positive latex agglutination test for cryptococcal antigen. 3. No evidence of an underlying illness associated with primary or secondary immunodeficiency or drug-induced suppression. 4. Negative serological test for human immunodeficiency virus were.

The patients who satisfy the criteria were assessed by a study neurologist and nerve conduction study and electromyography were performed prior to the commencement of antifungal treatment. Nerve conduction studies were carried on a Neuromatic 2000 electromyography machine (DISA). Surface stimulating and recording electrodes were used. The study was carried out in an open room, and in our country, it is unnecessary to warm the limbs of our subjects to maintain the skin temperature above 32°C. The following nerves were studied bilaterally - median (motor and sensory), ulnar (motor and sensory), radial (sensory), posterior tibial, common peroneal and sural nerves. F waves (minimum latency) of median and ulnar nerves, median-ulnar difference

TABLE 1:

Presenting symptom or sign (n = 14)	Number	Percentage(%)
Headache	14	100
Nausea/Vomiting	12	85.7
Papilledema	12	85.7
Diplopia	11	78.6
Impaired vision	10	71.4
Focal signs	6	42.8
Weakness	6	42.8
Hyporeflexia	5	35.7
Decreased mentation	5	35.7
Seizures	4	28.5
Wasting of limbs	4	28.5
Sensory disturbance	0	0.0

in the same limb and soleal H reflex were also measured bilaterally. Abnormal value was defined as ± 2.5 standard deviation above/below the control mean. Standard concentric needle electromyography of the abductor pollicis brevis and abductor digiti minimi were performed bilaterally. The protocol of this study was approved by the ethical committee of the UMMC.

RESULTS

Patients characteristics. Fourteen patients were identified. The male-to female ratio was 12 : 2. The average age of the patients was 40.3 years (SD 14.4). The age range was 21-59 years. The clinical characteristics upon presentation of the patients are tabulated in Table 1.

Headache, nausea or vomiting, diplopia and impaired vision are the most frequent presenting symptoms. Hyporeflexia was noted in 35.7%,

weakness of limbs in 42.8% and no sensory symptoms were reported among the patients.

The cerebrospinal (CSF) examination is summarised in Table 2.

The latex agglutination test for cryptococcal antigen was positive in all cases. Only 85.7% had a positive indian ink stain and 78.6% were culture positive. Half the patients required shunting of the spinal fluid for raised intracranial pressure.

The results of the nerve conduction study and electromyography are shown in tables 3-7. The result of each nerve studied are categorised into normal, abnormal or absent. The parameter of abnormality in the sensory and motor conduction studies were small motor or sensory potentials, delayed distal latencies and slow conduction velocities.

TABLE 2: Results of laboratory test on the CSF

Finding (n = 14)	No. with finding(%)	Mean	Range
Opening pressure > 20cm H ₂ O	12 (85.7)	38.8	12-60
Protein >45mg/dl	13 (92.8)	146	13-334
Glucose < 3.0mmol/l	11 (78.5)	2.14	0.6-4.0
White cell count > 5/ul	10 (71.4)	111.7	0-520
Cryptococcal antigen titre >1:32	14/14 (100)		
Indian ink positive	12/14 (85.7)		
Culture positive	11/14 (78.6)		

TABLE 3: Motor studies

n = 28	Abnormal		Absent	
	n	%	n	%
Compound motor action potential (CMAP)				
Median nerve	3	10.8	0	0
Ulnar nerve	5	17.9	0	0
Posterior tibial	13	46.4	0	0
Lateral popliteal	15	53.6	2	7.1
Distal latency of motor nerves in the upper limb				
Median	3	10.1		
Ulnar	2	8.0		
Nerve conduction velocity of motor nerves in the upper limb				
Median	0	0		
Ulnar	2	7.0		

TABLE 4: Sensory studies

n = 28	Abnormal		Absent	
	n	%	n	%
Sensory action potential (SAP)				
Median nerve	13	46.4	0	0
Ulnar nerve	8	28.6	0	0
Radial nerve	6	27.3	0	0
Sural nerve	4	14.3	0	0
Distal latency of sensory nerves in the upper limb				
Median nerve	4	14.3		
Ulnar nerve	3	10.7		
Radial nerve	3	10.7		
Nerve conduction velocity of sensory nerves in the upper limb				
Median nerve	2	7.1		
Ulnar nerve	5	17.9		
Radial nerve	3	10.7		

TABLE 5: Late response

	Delayed		Absent	
	n	%	n	%
F wave minimal latencies (n = 28)				
median nerve	12	42.9	0	0
ulnar nerve	9	32.1	2	7.1
Comparison of F wave of the same limb				
median-ulnar F wave difference	10	38.5		
H reflex	9	32.1	8	28.5

TABLE 6: Frequency of patients with abnormal nerves

n = 14	Number	%
No. abnormality	1	7.1
One nerve	4	28.5
Two nerves	6	42.8
Three or more nerves	3	21.6

DISCUSSION

The patient characteristics were similar to our previous report.² About 85% of the cases had papilledema and 71.4% had impaired vision which improved with shunting. The elevated intracranial pressure (ICP) seen in 85.7% of our patients correlated well with the high prevalence of papilledema. We have previously reported the raised ICP as important cause of visual failure in cryptococcal meningitis which benefits from shunting, irrespective of whether hydrocephalus is demonstrable in CT scan.⁴ Half of the patients were shunted.

The latex agglutination test for cryptococcal antigen was positive in all cases and only 85.7% had a positive indian ink stain and 78.6% were culture positive. This results is consistent with other studies.⁵

In a large series of *cryptococcal neoformans* isolates in our hospital, the serotype *C. neoformans var gatti* (serotype B/C) was found in 37% and *C. neoformans var neoformans* (serotype A/D) in 63% of isolates.⁶ However, we did not subtype the isolates in this study. As the prevalence of visual symptoms⁵ and raised ICP⁷ is higher in patients with CNS infection from *C. neoformans var gatti*, it is possible that a majority of our patients have been infected with this subtype.

This prospective study shows that 36% of the immunocompetent patients with cryptococcal meningitis has clinical evidence of neuropathy with hyporeflexia with or without weakness. When subjected to electrophysiological test, all

except 1 patient (93%) had abnormality in at least one nerve and 64% had abnormality in two or more nerves. The abnormalities was found in motor and sensory nerve conduction studies, electromyography as well as late response study. Among the parameters studied, the most common abnormality was a small or absent lateral popliteal CMAP (61%) followed by delayed or absent soleal H wave (54%), small posterior tibial CMAP (46%), small median SAP (46%), delayed median F wave's minimal latency (43%), absent or delayed ulnar F wave's minimal latency (39%), abnormal median-ulnar F wave difference in the same limb (39%), small ulnar SAP (29%), small radial SAP (27%), small ulnar CMAP (18%), small sural SAP (14%), delayed ulnar sensory conduction velocity (18%), delayed median sensory distal latency (14%), small median CMAP (11%) and delayed distal latency (10%), delayed ulnar sensory distal latency (11%), delayed radial sensory distal latency (11%) and conduction velocity (11%), delayed ulnar motor distal latency (8%) and conduction velocity (7%), delayed median sensory conduction velocity (7%). The abnormality noted above are mostly of moderate severity. Denervation changes in electromyography was noted in 25-29% of the small hand muscles sampled.

It is possible that the absent or small lateral popliteal CMAP may be partly contributed by compressive neuropathy as the nerve is particularly vulnerable in prolonged bed stay for patient who is paralysed. However, most of the patients were ambulant and the study was conducted soon after diagnosis before the commencement of antifungal treatment.

Compressive neuropathy is thus unlikely to be the predominant cause of the observed widespread abnormalities. Although the observed electrophysiological changes is non-specific, in the context of the patient's illness, the most likely explanation appear to be the spinal root involvement as part of the meningeal inflammatory process.

TABLE 7: Electromyography

Muscle	Fibrillation potentials		Positive sharp waves		Reduced motor units	
	n	%	n	%	n	%
Abductor pollicis brevis	7	29.1	4	16.7	5	20.8
Abductor digiti minimi	6	25.0	3	12.5	4	16.7

A basal meningitic process in cryptococcal meningitis accounts for the cranial neuropathy that manifest as ophthalmoplegia (25%) , facial nerve palsy (15%) , sensorineural deafness (10%) XI and X cranial nerve palsy (5%) of cases.³ The inflammatory process that is present in the basal meninges may extend to the spinal meninges and cause a radiculitis that damages the nerve roots similar to pachymeningitis that occur in tuberculous meningitis. As routine autopsy usually do not include examination of the spinal cord, spinal roots and its meningeal covering, this may explain the lack of attention to the changes in the cord and roots in the medical literature to-date. The spinal pachymeningitis may explain the very high cerebrospinal fluid protein that sometimes occur during the course of cryptococcal meningitis treatment. It may also interfere with the assessment of intracranial pressure by the use of spinal tap.

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