Seizure in Non-HIV Cryptococcal Meningitis

Somsak Tiamkao MD*,
Kittisak Sawanyawisuth MD*, Verajit Chotmongkol MD*

** Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen*

Objective: *The authors studied the prevalence of seizure in non-HIV cryptococcal meningitis.*
Material and Method: *The records of non-HIV adult patients (age > 15 years) diagnosed as cryptococcal meningitis in Srinagarind Hospital (Khon Kaen University) from 1990 to 1994 were reviewed. All subjects were studied for the rate, pattern, and long-term result of seizure.*
Results: *There were 105 cases. Eight patients (7.6%) had seizures at initial presentation. The pattern of seizure of six patients was generalized tonic-clonic seizure (GTC) and the others were focal seizure. Only one case still had seizures after treatment with conventional therapy of cryptococcal meningitis. At ten years follow up, ten cases had died, one patient still had seizures (the same case that had seizures after treatment) and one case with developed GTC after improvement of meningitis.*
Conclusion: *GTC was the common pattern of seizure in non-HIV cryptococcal meningitis and mostly controlled by standard regimen of therapy for cryptococcal meningitis without any antiepileptic drugs.*

Keywords: *Seizure, Non-HIV cryptococcal meningitis*

J Med Assoc Thai 2007; 90 (7): 1298-302
Full text. e-Journal: *http://www.medassocthai.org/journal*

After the spreading of HIV infection, cryptococcal meningitis has markedly increased. Seizure can be presented at initial manifestation in both HIV and non-HIV cryptococcal meningitis. The rate of convulsion was 38% in HIV positive patients[1]. The presence of seizures was strongly associated with therapeutic failure in HIV negative patients[2]. There was a report of cryptococcal meningitis manifesting as epilepsia partialis continua of the abdomen[3]. The authors studied the rate and pattern of seizures, how to treat the seizures, and long-term result of cryptococcal meningitis and seizures in non-HIV cryptococcal meningitis in the authors' hospital.

Material and Method

The authors reviewed records of non-HIV adult patients (age > 15 years) diagnosed as cryptococcal meningitis in Srinagarind Hospital (Khon Kaen University, Khon Kaen, Thailand) from 1990 to 1994. All cases were diagnosed by positive India ink test, culture or cryptococcal antigen in cerebrospinal fluid (CSF). Most of the patients presented with prolonged fever and chronic headache.

All cases that had seizures were reviewed for pattern and frequency of seizure and how to treat the seizures. The authors followed up the patients by clinic visit or letter to evaluate the success of seizure control. All patients were defined into two groups: normal host and immunocompromised host. Continuous variables were express as the mean and standard deviation and were analyzed by Mann-Whitney U-test. Discrete variables were presented with number (N) and percentage and were compared by Chi-Square or Fisher's Exact test. A two tailed p-value < 0.05 was considered significant difference.

Results

There were 105 cases of non-HIV cryptococcal meningitis admitted to the authors' hospital from 1990 to 1994. The authors defined all patients to two groups; normal host and immunocompromised host. Seventy-eight patients (72.2%) were normal host. Baseline characteristics and clinical manifestations are shown as Table 1. The mean age and the number of patients who had headache, acute headache, and

Correspondence to : Tiamkao S, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. E-mail: somtia@kku.ac.th

Table 1. Clinical manifestations of non-HIV cryptococcal meningitis (n = 105)

Variables	Normal host n = 78	Underlying disease* n = 27	p-value
Age (mean, SD), years	46.8 ± 15.8	39.4 ± 15.4	0.00
Range	16-78	19-70	
Sex (male), n	41 (52.6%)	12 (44.4%)	0.47
Pigeon contact, n	8 (10.3)	0	0.11
Symptoms			
Headache, n	75 (96.2%)	22 (81.5%)	0.03
Duration of headache, days			
Mean, SD	30.0 ± 23.6	38.0 ± 45.1	0.12
Range	1-120	2-250	
Acute, n	5 (6.4%)	6 (22.2%)	0.03
Signs			
Fever (BT ≥ 38°C), n	36 (46.2%)	16 (59.3%)	0.24
Duration, days			
Mean, SD	30.5 ± 28.7	42.4 ± 49.7	0.87
Range	3-120	2-150	
Acute, n	3	3	0.17
Stiffneck, n	65 (83.3%)	17 (63.0%)	0.02
Mental impairment, n	39 (50%)	11 (40.7%)	0.41
Drowsiness, n	14	4	
Confusion, n	16	2	
Stuporous, n	9	5	
Papilledema, n	37 (47.4%)	8 (29.6%)	0.11
6th CN palsy, n	16 (20.5%)	2 (7.4%)	0.15
Unilateral, n	3	2	
Bilateral, n	13	0	
8th CN palsy, n	3 (3.8%)	0	0.57
Decreased vision, n	20 (25.6%)	3 (11.1%)	0.12
Weakness, n	6 (6.7%)	1 (3.7%)	0.67
Hemiparesis, n	2	0	
Paraparesis, n	4	1	
Convulsion, n	8 (10.3%)	0	0.11
Focal, n	2		
Generalized, n	6		
Vomitus, n	27 (34.6%)	5 (18.5%)	0.12
Cervical lymphadenopathy, n	2 (2.6%)	1 (3.7%)	1.00
Skin cryptococcosis, n	2 (2.6%)	2 (7.4%)	0.27
Hepatomegaly, n	0	1 (3.7%)	0.26
Splenomegaly, n	0	0	

* Underlying disease; on corticosteroid or cytotoxic drug (14 cases), pregnancy (2 cases), SLE (2 cases), malnutrition (2 cases), lymphoma (2 cases), thalassemia (1 case), melioidosis (1 case), renal stone (1 case), cirrhosis (1 case), chronic renal failure (1 case)

stiffneck showed significant differences between the two groups. Complete blood count, hemoculture, CXR, CSF analysis, and CT scan of the brain (in indicated cases) were done and shown in Table 2. The mean hematocrit and the number of patients who had CSF opening pressure ≤ 300 mmH_2O and positive CSF cryptococcal antigen test were also significantly different between the two groups.

At initial presentation, there were eight cases (all in the normal host group) who developed seizures.

Table 2. Laboratory findings in non HIV cryptococcal meningitis (n = 105)

Variables	Normal host n = 78	Underlying disease* n = 27	p-value
Complete blood count			
Hematocrit			
Mean, SD (%)	38.0 ± 4.9	30.8 ± 9.8	0.00
Range	24-51	10-48	
White blood cell, cell/mm^3			
Mean, SD	11883.9 ± 8689.4	11867.3 ± 15708.4	0.28
Range	3,900-60,700	1,400-85,400	
Blood culture positive, n	0	1 (3.7%)	0.26
Abnormal CXR, n	24 (30.8%)	11 (40.7%)	0.34
Bilateral interstitial, n	2	1	
Miliary, n	0	0	
Mass or nodule, n	9	4	
Alveolar infiltration, n	10	4	
Cavitary lesion, n	1	2	
Fungal ball, n	2	0	
Abnormal CT brain, n	27/58 (46.5%)	4/12 (33.3%)	0.40
Hydrocephalus, n	14	3	
Infarction, n	4	0	
Cryptococcoma, n	9	1	
CSF profile			
OP** ≥300 mmH_2O, n	49 (62.8%)	8 (29.6%)	0.00
White blood cell			
Mean, SD (cell/mm^3)	306.3 ± 342.1	198.2 ± 232.1	0.10
Range	5-1, 890	0-900	
≤ 5 cell/mm^3, n	1 (1.3%)	3 (11.1%)	0.053
Protein			
Mean, mg/dl	294.0 ± 426.5	178.7 ± 186.0	0.17
Range	24-2,400	26-845	
≤ 45 mg/dl, n	6 (7.7%)	6 (22.2%)	0.07
Glucose ratio (CSF/blood)			
Mean, SD (%)	28.6 ± 15.9	28.9 ± 19.4	1.05
Range	6-80	4-95	
≥ 50%, n	6 (7.7%)	4 (5.1%)	0.28
Positive india ink, n	60 (76.9%)	16 (59.3%)	0.07
Cryptococcal Ag titer, n	65/67 (97.0%)	18/23 (78.3%)	0.01

* Underlying disease; on corticosteroid or cytotoxic drug (14 cases), pregnancy (2 cases), SLE (2 cases), malnutrition (2 cases), lymphoma (2 cases), thalassemia (1 case), melioidosis (1 case), renal stone (1 case), cirrhosis (1 case), chronic renal failure (1 case)

** OP means opening pressure

The patterns of seizure were generalized tonic-clonic seizure (GTC) in six cases and focal seizure in two cases. On neurological examination, three cases had lateral rectus palsy and five cases had papilledema. The computed tomographys of the brain were done in seven cases (all cases in the GTC group and one in the focal seizure case). In the GTC group, the scans revealed hydrocephalus in two cases and normal findings in the others. Only one patient in the focal seizure group had a CT scan and found cerebral infarction.

Initially, all patients were treated with amphotericin B (0.7 mg/kg/day) with 5 FC (flucytosine 150 mg/kg/day). Two cases needed theco- or ventriculoperitoneal shunt. One case died after one month of treatment, one case had recurrent seizures and controlled seizure by phenytoin 300 mg/day (most of them experienced seizures). The other six cases were free from seizure without any antiepileptic drug use.

The authors followed up cases by letter and hospital visits in 2002, 39 cases completed the evaluation. Ten cases had died, one patient who took phenytoin from the beginning still had seizures, and one case developed GTC after improvement of meningitis. The others seemed to be healthy and experienced no seizures.

Discussion

Cryptococcus neoformans is the common causative pathogen of meningitis in HIV positive patients, but it can be found in a normal host with a lower incidence. The clinical manifestation is mainly neurological symptoms, acute to chronic headache with or without fever.

In HIV positive patients who presented with seizure, the differential causes were as follows; cerebral toxoplasmosis, cryptococcal meningitis, tuberculoma, AIDS dementia complex, progressive multifocal leucoencephalopathy, or unidentified cause[4]. The common type of seizure was GTC[5] but it can be presented with focal seizure.

Headache is still the main presenting symptom in non-HIV cryptococcal meningitis. About 30% of patients had underlying disease such as these on corticosteroid or cytotoxic agents, SLE, malnutrition, etc. Seizure was presented at the initial presentation in only 7.6%. The probable mechanisms are encephalitis, vasculitis, cerebral infarction, hydrocephalus, or cryptococcoma. The type of seizure was similar to the HIV positive group where GTC was the most common pattern. Focal seizure may be associated with parenchymal brain lesion. The radiographic findings revealed normal findings in the majority of cases that may explain GTC by diffuse brain lesion or encephalitis. Magnetic resonance imaging (MRI) was more sensitive than computed tomography (CT) in detection of hydro-cephalus or dilatation of ventricular system[6].

Most patients who developed a single seizure are not taking long-term antiepileptic drug (only one case is still taking phenytoin). HIV positive cryptococcal meningitis cases had a higher rate and recurrent seizure[1,7], and that may be explained by a higher risk of intracerebral lesions. The seizures were mostly controlled by a standard regimen of therapy for cryptococcal meningitis. The authors gave phenytoin to one patient because she developed a cluster of seizures. After the follow up program, twenty-nine cases are still feel free from epileptic episodes.

Conclusion

Single GTC is the most common pattern of seizure in non-HIV cryptococcal meningitis and most could be controlled by a standard treatment for cryptococcal meningitis without any long-term antiepileptic drug.

References

1. Gumbo T, Kadzirange G, Mielke J, Gangaidzo IT, Hakim JG. Cryptococcus neoformans meningoencephalitis in African children with acquired immunodeficiency syndrome. Pediatr Infect Dis J 2002; 21: 54-6.
2. Lu CH, Chang WN, Chang HW, Chuang YC. The prognostic factors of cryptococcal meningitis in HIV-negative patients. J Hosp Infect 1999; 42: 313-20.
3. Chalk CH, McManis PG, Cascino GD. Cryptococcal meningitis manifesting as epilepsia partialis continua of the abdomen. Mayo Clin Proc 1991; 66: 926-9.
4. Chadha DS, Handa A, Sharma SK, Varadarajulu P, Singh AP. Seizures in patients with human immunodeficiency virus infection. J Assoc Physicians India 2000; 48: 573-6.
5. Bartolomei F, Pellegrino P, Dhiver C, Quilichini R, Gastaut JA, Gastaut JL. Epilepsy seizures in HIV infection. 52 cases. Presse Med 1991; 20: 2135-8.
6. Cheng YC, Ling JF, Chang FC, Wang SJ, Fuh JL, Chen SS, et al. Radiological manifestations of cryptococcal infection in central nervous system. J Chin Med Assoc 2003; 66: 19-26.
7. Wong MC, Suite ND, Labar DR. Seizures in human immunodeficiency virus infection. Arch Neurol 1990; 47: 640-2.

อาการชักในผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสที่ไม่ได้เป็นเอดส์

สมศักดิ์ เทียมเก่า, กิตติศักดิ์ สวรรยาวิสุทธิ์, วีรจิตต์ โชติมงคล

การศึกษานี้ต้องการศึกษาถึงอาการชักที่เกิดขึ้นในผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสในผู้ป่วยที่ไม่ได้เป็นเอดส์โดยศึกษาจากเวชระเบียนของโรงพยาบาลศรีนครินทร์ตั้งแต่ปี พ.ศ. 2533 - พ.ศ. 2537 โดยศึกษาถึงความถี่ ลักษณะของการชักและผลการรักษาระยะยาวในผู้ป่วยที่เคยมีอาการชัก พบว่ามีผู้ป่วยจำนวน 8 ราย จาก จำนวน 105 ราย ที่มีอาการชักตั้งแต่เริ่มวินิจฉัย โดยผู้ป่วย 6 ราย ชักทั้งตัวและอีก 2 ราย มีอาการชักเฉพาะบางส่วนของร่างกาย มีผู้ป่วยเพียงหนึ่งรายที่ยังคงมีอาการชักอยู่ทั้งที่ได้รับการรักษาด้วยยา amphotericin B แล้ว เมื่อติดตามการรักษาผู้ป่วยเป็นเวลา 10 ปี มีผู้ป่วยเสียชีวิต 10 ราย ผู้ป่วยที่ยังคงมีอาการชักอยู่ 1 ราย (ผู้ป่วยรายที่มีอาการชักภายหลังจากการรักษา) และผู้ป่วยอีกหนึ่งรายมีอาการชักขึ้นมาใหม่ ภายหลังจากหายจากอาการเยื่อหุ้มสมองอักเสบแล้ว

อาการชักทั้งตัวเป็นชนิดของอาการชักที่พบได้บ่อยที่สุดในผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสที่ไม่ได้เป็นเอดส์ โดยมักจะชักเพียงครั้งเดียวและส่วนใหญ่สามารถควบคุมอาการชักโดยการรักษาโรคเยื่อหุ้มสมองอักเสบจากเชื้อราคริบโตคอคคัสแบบมาตรฐานโดยไม่จำเป็นต้องได้รับการรักษาด้วยยากันชักเป็นระยะเวลานาน