Serum Cryptococcal Antigen : Diagnostic Value in the Diagnosis of AIDS-Related Cryptococcal Meningitis

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Abstract

Rationale: The incidences of HIV-AIDS patients with opportunistic infections of the central nervous system are increasing. Of these, cryptococcal meningitis is the most important and serious. A simple method for the diagnosis of cryptococcal meningitis is needed despite its variable clinical features and the lack of a capacity in most health facilities in Thailand to exclude it from other diseases especially mass lesions in the brain.

Objective: To identify the capability and cut off point of serum cryptococcal antigen for diagnosis and screening of cryptococcal meningitis in HIV-AIDS patients.

Method: One hundred consecutive cases of HIV-AIDS patients suspected of having central nervous system infections were prospectively recruited for the study. The serum of all patients were examined for cryptococcal antigen by latex agglutination test, the Pastorex *Cryptococcus* manufactured by Sanofi Diagnostic Pasteur, France. If a test was positive, the serum dilution was carried out using 10-fold serial dilution. Every patient went through pre-defined standard investigations to derive at a definite diagnosis. The gold standard for diagnosis of cryptococcal meningitis was the presence of encapsulated yeast forms in the cerebrospinal fluid or a positive culture for cryptococcal neoformans from the cerebrospinal fluid.

Result: Of 100 patients enrolled in this study, 58 patients had cryptococcal meningitis and serum cryptococcal antigen was detectable in 60 patients. If the cut-off point for a positive test was when the serum cryptococcal antigen titer was more than zero, then, the sensitivity of the test was 91.4 per cent, the specificity was 83.3 per cent, likelihood ratio if test positive (LR+) was 5.47, likelihood ratio if test negative (LR-) was 0.1, false positive was 16.7 per cent, false negative was 8.6 per cent.

Conclusion: We conclude that serum cryptococcal antigen is a simple and rapid screening method for diagnosis of cryptococcal meningitis.

Key word : Cryptococcal Meningitis - AIDS-Related - Opportunistic Infection - Diagnosis - Serum Cryptococcal Antigen

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Recent evidence has shown an increasing prevalence of patients infected with HIV[1,2]. When the CD4 count of the HIV or AIDS patients was less than 200 cell/μl, they tended to have a higher tendency to develop opportunistic infections especially *Cryptococcosis* generally considered to be one of the most serious complications[1,3-7]. In 1995, there were 464 HIV/AIDS patients admitted to the Medical Department, Maharaj Nakhon Ratchasima Hospital. Of these cases, 42.2 per cent had central nervous system infections and 32.7 per cent had cryptococcal meningitis. AIDS patients with cryptococcal meningitis have been known to have variable clinical manifestations, frequently not typical of meningitis[6,8,9]. Common symptoms were fever with headache or nonspecific symptoms including nausea, vomiting and malaise, fever and unexplained protracted malaise[8]. Others reported predominant headache, nausea and vomiting[10], only headache but no fever[4]. Overt meningeal symptoms and signs were unusual[6]. In some health care facilities especially in many rural areas, lumbar puncture, the procedure for diagnosis of cryptococcal meningitis, cannot be performed due to the presence of contraindication or to the inadequate facility to rule out mass lesion in the brain.

The objective of this study is to identify the capability and cut off point of serum cryptococcal antigen by latex agglutination test for diagnosis and screening of cryptococcal meningitis in HIV/AIDS patients.

MATERIAL AND METHOD

One hundred consecutive cases of HIV/AIDS patients suspected to have central nervous system infections were prospectively recruited for the study. All were admitted to the Medical Department, Maharaj Nakhon Ratchasima Hospital from October 1995 to March 1996. Serum cryptococcal antigen was examined in all patients by latex agglutination test. After admission, a set of predefined standard investigations for diagnosis of central nervous system infections was carried out. All patients underwent at least one lumbar puncture and a CAT brain scan. The gold standard for the diagnosis of cryptococcal meningitis was the identification of the encapsulated yeast forms of *Cryptococcus neoformans* in the CSF by Indian ink wet preparation and/or a positive culture for *Cryptococcus neoformans* using Sabouraud's glucose agar medium. The India ink wet preparations were examined by clinicians and cultures were done by a technician who did not know the result of the latex agglutination test. Cryptococcal antigen was detected by the latex agglutination test (Pastorex *Cryptococcus* manufactured by Sanofi Diagnostic Pasteur, France). A 120 ul of serum was added to 20 ul of pronase to eliminate interference factors[11,12]. The mixture was then homogenized and heated at 56°C for 30 minutes, then one drop of stepping solution was added. Forty microliters of the treated specimen was applied in a circle on the agglutination card. Next, a ten microliters of *Cryptococcus* Latex was applied on the agglutination card. The card was rotated at 160 rpm for 10 minutes at room temperature. The presence or absence of agglutination was observed by naked eyes. If the latex particles agglutinated, the reaction was positive. To determine the titer of cryptococcal antigen in a positive sample, a series of sample dilutions was carried out using 10-fold serial dilutions started from 1:10. The diluted sample was then processed as described above.

Inclusion criteria

1. HIV/AIDS patients who had any of the following clinical symptoms and signs of central nervous system infections including fever, headache, nausea, vomiting, alteration of consciousness, convulsion, focal neurological deficit and stiffness of neck.

or 2. HIV/AIDS patients suspected of central nervous system infections including those with an organic headache without fever without stiffness of the neck, or nausea, vomiting, alteration of consciousness, or convulsion.

or 3. HIV/AIDS patients who had unexplained clinical symptoms and signs including fever with malaise, nausea, vomiting and no cause of these symptoms and signs could be found despite standard investigations.

RESULTS

All 100 HIV/AIDS patients were enrolled in this study. The age of patients varied from 16 years to 84 years (mean ± SEM = 33.1 ± 10.02 years). Most patients were male (82%) with a mean age of 32.79 (mean ± SEM = 32.79 ± 10.36 years, range = 16-84 years). The mean age of female patients was 34.5 (mean ± SEM = 34.5 ± 8.42 years, range = 24-56 years). A CD4 count was carried out in 35 patients. The CD4 values ranged

from 0 to 660 cells/μl with a mean of 83.14 cell/μl. Most patients (91.4%) had a CD4 value below 200 cell/μl (Table 1).

Table 1. Distribution of CD4 count.

CD4 count (cell/μl)	n	%
0-199	32	91.4
200-399	0	0
400-599	2	5.7
600-799	1	2.9

The occurrences of clinical symptoms and signs are shown in Table 2. Common symptoms were headache (92%), fever (71%), nausea, vomiting (54%), and common signs were stiffness of neck (63%), and fever (56%).

Fifty-eight patients had cryptococcal meningitis and cryptococcal antigen was detected in the sera of 60 patients (Table 3). The result of serum cryptococcal antigen titers are also shown in Table 3. If the test was positive, titer >0 the sensitivity was the highest (91.4%), the specificity was 83.3 per cent, likelihood ratio if test positive was 5.47 and likelihood ratio if test negative was 0.1, false positive was 16.7 per cent, false negative was 8.6 per cent. If test was positive, and titer >1:1000 the specificity was 100 per cent, and no false positive was found but false negative was found in more than 50 per cent. By receiver operating curve (ROC) of serum cryptococcal antigen titer, as shown in Fig. 1, at very low cutting point, the specificity was close to 1 and sensitivity was close to zero. When cutting points increased (titer >1:1000,1:100,1:10), the sensitivity rapidly increased while specificity slowly decreased. Up to a titer >0, the sensitivity stayed remains close to 1 while specificity started to rapidly decrease. Therefore the optimal point was at titer >0.

Table 2. Distribution of clinical symptoms and signs.

Clinical symptoms	n (%)	Clinical signs	n (%)
Fever	71	Fever	56
Headache	92	Stiffness of neck	63
Nausea vomiting	54	Alteration of consciousness	17
Drowsiness	14	Focal neurological deficit	4
Malaise	8	Confusion	3
Confusion	5		
Convulsion	5		
Neck pain	4		
Weakness	3		
Blurring of vision	2		

Table 3. Distribution of serum cryptococcal antigen titers.

Titer	Cryptococcal meningitis YES (n = 58)	NO (n = 42)	sens.	spec.	1-sens.	1-spec.	LR+	LR-
>0	53	7	91.4	83.3	8.6	16.7	5.47	0.1
>1:10	46	3	79.3	92.9	20.7	7.1	11.17	0.22
>1:100	37	1	63.8	97.6	36.2	2.4	26.58	0.37
>1:1000	27	0	46.5	100	53.5	0	-	0.54
>1:10000	3	0	5.2	100	94.8	0	-	0.95

sens. = sensitivity
spec. = specificity
LR+ = likelihood ratio if test positive
LR- = likelihood ratio if test negative

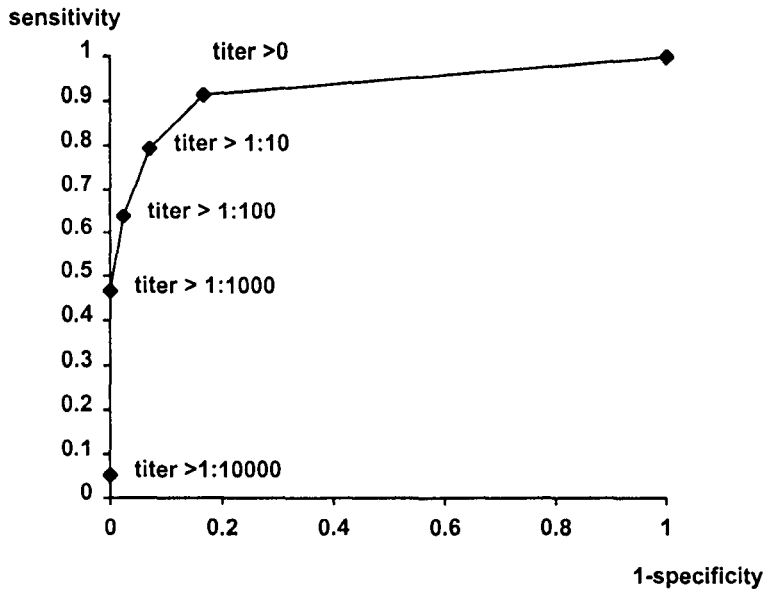

Fig. 1. ROC of positive serum cryptococcal antigen titer.

DISCUSSION

In this study, most HIV/AIDS patients (82%) were male with an average age of 33.1± 10.02 years similar to the study by De Wytt C.N.[10]. However, Tjia T.L. reported no obvious sex predominance[4]. Most patients in the current series (91.4%) had total CD4 counts of less than 200 cell/μl which could predispose them to opportunistic infections including *Cryptococcus neoformans.*

In AIDS patients, the clinical profiles of cryptococcal meningitis varied from general symptoms and signs of non-specific infection to those typical of clinical meningitis such as headache, nausea, vomiting, fever[4,8,10], stiffness of neck, visual disturbance, confusion[10], malaise[6,8], meningism[8]. Powderly noticed that overt meningeal symptoms and signs were unusual[6] and Butler experienced that 15 per cent of his patients had no central nervous system symptoms or if present, did not lead directly to a diagnosis of meningitis[9]. In this study, the clinical features of suspected cryptococcal meningitis included headache (92%), fever (71%), and nausea vomiting (54%), stiffness of neck (63%). These variations in clinical features might be imputed to the variations in the stages and severity of diseases resulting from different immune status and the presence of concomitant treatment. It is important to have a good screening for cryptococcal meningitis particularly in patients with obscure symptoms and signs and those patients who may have some contraindications for lumbar puncture.

Two varieties of *Cryptococcus* organisms have been identified, i.e., *gattii* and *neoformans*, based on biochemical differences. The clinical features of patients affected by the *Cryptococcus gattii* differed from those affected by *Cryptococcus neoformans. Cryptococcus gattii* have been shown to affect immunocompetent hosts in rural area and treatment often resulted in poor outcomes, while cryptococcus neoformans infected immunocompromised hosts and treatment could give rise to good outcomes[13].

For diagnosis of cryptococcal meningitis, the gold standard is either a positive culture for *Cryptococcus neoformans* (which takes several days to get the result) or a positive demonstration of the organism by India ink wet preparations which has a low sensitivity (60%)[14]. In order to make an early diagnosis, many methods were introduced such as latex agglutination test, enzyme immunoassay[15] or enzyme-linked immunosorbent assay[1,16,17]. These methods had different sensitivity and specificity[2,13,18].

The presence of serum cryptococcal antigen was first reported by Bloomfield et al in 1963. It was advocated for diagnosis of cryptococcal infections[19], therapeutic evaluation or prediction of prognosis[20]. There were variations in sensitivity and specificity when serum cryptococcal antigen was used for diagnosis of cryptococcal infection[21]. In addition, false-positive reactions occurred if other substances were present in the samples: i.e., rheumatoid factor, agar syneresis fluid, non specific reactivity in HIV-infected patients, hydroxyethyl starch or non-cryptococcal infections such as *Capnocytophaga canimorsus* or *Trichosporon beigelii*[3,5,22]. To reduce false-positive reactions, several procedures have been proposed such as pre-treatment of specimens with heat, incorporation of latex particles coated with normal rabbit globulin, use of pronase, dithiothreitol or 2-mer - captoethanol[5]. Chuck reported that 89 patients were diagnosed as AIDS with cryptococcal meningitis by positive culture and the serum cryptococcal antigen was measured and positive in 70/71 patients. Most patients (87%) had titers more than 1:32[7]. Serum cryptococcal antigen was detected by Desmet in 55 of 450 HIV/AIDS patients (12.2%) by commercial latex agglutination test (IMMY)[23]. Lumbar puncture was performed in 44 patients from the positive serum group (55 patients) and cryptococcal meningitis was confirmed in 29 (66%) of them[23]. Among the patients with serum cryptococcal antigen below 1:64, only 4 out of 16 patients had cryptococcal meningitis but in patients with titers more than 1:64 ,25 out of 28 patients had cryptococcal meningitis[23]. Hoffmann studied the serum from 530 specimens of AIDS/ARC patients were obtained to detect cryptococcal antigen with the Cryptococcal Antigen Latex Agglutination System (Meridian Diagnostics Inc. Cincinnati, OH 45244, U.S.A.) and all were negative. However, stored specimens of serum of 3 cases of cryptococcal meningitis, diagnosed by microscope and culture in HIV-1 infected patients were assayed for cryptococcal antigen and all were positive[24]. Kovacs[25] analyzed the serum of AIDS patients with cryptococcosis in 27 patients and serum cryptococcal antigen was found in 12 out of 16 patients tested with titers ranging from 1:2 to 1:32678. 18 patients were diagnosed as meningitis and encephalitis and all 9 patients tested who presented with neurologic disease. None of the four patients without serum cryptococcal antigen present had meningitis. Nelson[26] reported that serum cryptococcal antigen was measured in 828 febrile HIV-positive patients, 69 of whom had meningism. The antigen assay was positive in 16 patients with meningism and in 1 patient without meningeal symptoms. The 16 patients with meningism and a positive serum cryptococcal antigen assay all underwent a diagnostic LP and all had a positive CSF cryptococcal antigen test result or growth of *C. neoformans* on culture. Srimuang[27] experienced the presence of serum cryptococcal antigen in 4 out of 101 high risk subjects, 3 out of 12 patients with suspicious mycotic infection and 10 out of 11 tested sera from 14 patients with culture proven cryptococcal meningitis.The test was assayed by cryptococcal antigen latex agglutination system (Meridian Diagnostic, Inc, Cincinnatii, Ohio).

In our study, if the cut-off point for a positive titer was a titer more than 0, the sensitivity of the cryptococcal antigen in the diagnosis of cryptococcal meningitis was 91.4 per cent and the specificity was 83.3 per cent, the likelihood ratio if the test was positive was 5.47, the likelihood ratio if the test was negative was 0.1, the false positive rate was 16.7 per cent and the false negative rate was 8.6 per cent. An ROC curve was drawn for the various levels of serum cryptococcal antigen as shown in Fig. 1. The best cut-off point was a serum cryptococcal antigen of more than 0 since the likelihood if test was positive was highest indicating that at this cut-off point the ratio between the true positive rate and the false positive rate was highest. In view of the discussions above, our data could confirm the previous findings about the potential usefulness of serum cryptococcal antigen in screening for cryptococcal meningitis.

SUMMARY

Serum cryptococcal antigen is a simple and rapid method for screening patients suspected to have cryptococcal meningitis or patients with contraindications for lumbar puncture. Serum cryptococcal antigen titer of more than 0 was the cut-off point with the higher likelihood ratio if the test was positive.

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ซีรัมคริพโตค็อคคัล แอนติเจน คุณค่าในการวินิจฉัยผู้ป่วยโรคเอดส์ที่มีเยื่อหุ้มสมองอักเสบจากการติดเชื้อรา*คริพโตค็อคคัส นีโอฟอร์แมนส์*

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อุบัติการณ์การเกิดโรคติดเชื้อฉวยโอกาสของระบบประสาทส่วนกลางในผู้ป่วยโรคเอดส์มีแนวโน้มเพิ่มมากขึ้น โดยเฉพาะการติดเชื้อราชนิด*คริพโตค็อคคัส*ซึ่งมีความสำคัญและอันตรายมาก วิธีการวินิจฉัยโรคนี้มีความจำเป็นเนื่องจากมีความหลากหลายของลักษณะทางคลินิก และสถานบริการทางด้านสาธารณสุขในประเทศไทยยังขาดเครื่องมือในการวินิจฉัยแยกโรคโดยเฉพาะก้อนเนื้อในสมอง

เพื่อแสดงถึงความสามารถและจุดตัดในการวินิจฉัย และการคัดกรองผู้ป่วยโรคเอดส์ที่มีเยื่อหุ้มสมองอักเสบจากการติดเชื้อราชนิด*คริพโตค็อคคัส นีโอฟอร์แมนส์* ด้วยวิธีตรวจหาคริพโตค็อคคัล แอนติเจนในซีรัมของผู้ป่วย

ได้ทำการศึกษาผู้ป่วยโรคเอดส์ที่สงสัยว่าจะมีการติดเชื้อทางระบบประสาทส่วนกลางจำนวน 100 ราย ผู้ป่วยทุกรายได้รับการตรวจหาคริพโตค็อคคัล แอนติเจนจากซีรัมโดยวิธี ลาเทกซ์แอกกลูติเนชั่น และถ้าการทดสอบให้ผลบวกจะทำการเจือจางซีรัมให้มีความเจือจางเพิ่มขึ้น 10 ส่วนเพื่อหาค่าไตเตอร์ของซีรัมนั้น และผู้ป่วยทุกรายได้รับการตรวจวินิจฉัยหาสาเหตุของโรคตามขบวนการวินิจฉัยโรค การวินิจฉัยโรคเยื่อหุ้มสมองอักเสบจากการติดเชื้อราชนิด*คริพโตค็อคคัส นีโอฟอร์แมนส์*อาศัย การเจาะน้ำไขสันหลังและตรวจหายีสต์โดยวิธีอินเดียอิ้งค์หรือการเพาะเชื้อจากน้ำไขสันหลัง

ผลการศึกษาผู้ป่วยจำนวน 100 ราย พบว่าผู้ป่วย 58 รายได้รับการวินิจฉัยว่าเป็นโรคเยื่อหุ้มสมองอักเสบจากการติดเชื้อราชนิด*คริพโตค็อคคัส นีโอฟอร์แมนส์* ผลการตรวจหาคริพโตค็อคคัล แอนติเจนในซีรัมให้ผลบวก 60 ราย ที่จุดตัดเมื่อค่าไตเตอร์มากกว่า 0 คิดเป็นความไวร้อยละ 91.4 ความจำเพาะร้อยละ 83.3 ค่าผลบวกเท็จร้อยละ 16.7 ผลลบเท็จร้อยละ 8.6 เมื่อการทดสอบให้ผลบวกผู้ป่วยมีโอกาสเป็นโรค 5.47 เท่า และเมื่อการทดสอบให้ผลลบผู้ป่วยมีโอกาสเป็นโรค 0.1 เท่า

สรุปผลการวิจัยนี้ว่าการตรวจด้วยวิธีหาคริพโตค็อคคัล แอนติเจนในซีรัมของผู้ป่วยโรคเอดส์ที่สงสัยว่าจะมีเยื่อหุ้มสมองอักเสบจากการติดเชื้อราชนิด*คริพโตค็อคคัส นีโอฟอร์แมนส์* เป็นวิธีที่ง่ายสะดวกและรวดเร็วในการคัดกรองผู้ป่วย

คำสำคัญ : เยื่อหุ้มสมองอักเสบจากเชื้อรา*คริพโตค็อคคัส* – เกี่ยวเนื่องกับเอดส์ – ภาวะติดเชื้อฉวยโอกาส – การวินิจฉัย – คริพโตค็อคคัล แอนติเจนในซีรัม

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